Over the past year, the SARS-CoV-2 pandemic has swept the globe, resulting in more than 113 million persons infected and 2.5 million deaths (1). However, the additional toll resulting from long-term consequences of the pandemic has yet to be tallied. Heterogeneous disease manifestations and syndromes are now recognized among some persons after their initial recovery from SARS-CoV-2 infection. Although a standardized case definition does not yet exist for these manifestations, in the broadest sense they represent a failure to return to a baseline state of health after acute SARS-CoV-2 infection. On 3 to 4 December 2020, the National Institute of Allergy and Infectious Diseases, in collaboration with other Institutes and Centers of the National Institutes of Health, convened a virtual workshop to summarize existing knowledge on postacute COVID-19 and to identify key knowledge gaps regarding this condition.

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**Clinical Observations**

In response to the increasing need to care for patients who do not return to their baseline state of health after COVID-19, specialty clinics have been established in the United States and globally. Observations from clinicians at the workshop provided valuable insights on the vast scope of symptoms, as well as how to begin to differentiate groups of patients by symptoms and structure potential treatment strategies. Clinicians and patients outlined the diverse needs and experiences of affected individuals, including multisystem symptoms (such as fatigue, mental health problems, and pain) and other signs and symptoms pointing toward specific organ systems (for example, renal, cardiac, pulmonary, and gastrointestinal). The diversity of clinical presentations clearly indicates the need for an integrated and multidisciplinary approach to treatment and care.

Postacute manifestations of COVID-19 have been reported among persons of all ages. The clinical presentation of SARS-CoV-2 infection in children differs from that in adults (10); of note, children typically have a mild presentation of acute disease. However, postacute manifestations of COVID-19 have also been reported in the pediatric population, including but not limited to multisystem inflammatory syndrome. Postacute manifestations of COVID-19 may be more challenging to diagnose in the elderly given the increased prevalence of
preexisting cognitive dysfunction and other comorbid conditions. Thus, it will be necessary to study the disease processes in pediatric and geriatric populations, as well as in the general adult population.

Although an association between racial or ethnic background and postacute COVID-19 has not been established, racial and ethnic minority populations in the United States have been disproportionately affected by the pandemic. Furthermore, these populations are affected by structural and socioeconomic inequities that affect access to and delivery of health care for acute and postacute COVID-19. Presentations at the workshop showed that many persons affected by postacute COVID-19 have experienced stigma, and many struggle to be heard and believed by their family, friends, and health care providers about their health conditions. Awareness and understanding of the various manifestations of postacute COVID-19 are insufficient in many communities. Therefore, a comprehensive response to postacute COVID-19 must effectively address structural and socioeconomic inequities and increase communication with historically underserved and vulnerable communities.

Given the diversity of symptoms, patient populations, and scientific and clinical questions that need to be addressed—from pathologic mechanisms to structural barriers to care—postacute COVID-19 must be addressed in partnership with stakeholders, including clinicians, researchers, and patient advocacy groups. Individuals affected by postacute COVID-19 made invaluable contributions to the discussions at the workshop, providing crucial insights on the effects of COVID-19 on multiple organ systems and overall function and quality of life, as well as the stigma associated with SARS-CoV-2 infection and ongoing symptoms. Engagement of clinicians and community stakeholders is crucial for communication to improve public health, reduce stigma, and enhance health care. The National Institutes of Health is committed to building partnerships with academia, the medical establishment, and the patient community to share information and collaborate to better understand, prevent, and treat COVID-19 and postacute manifestations.

**Key Gap: A Need to Define Epidemiology, Clinical Spectrum, and Natural History**

One of the fundamental gaps identified during the workshop is the need to better understand the incidence and prevalence of the diverse manifestations of postacute COVID-19. Reports in the literature often describe only selected patient populations, such as those who were hospitalized, and measure outcomes at varied time points. Studies have examined periods ranging from 3 weeks to 7 months after either onset of symptoms or date of diagnosis (3, 5, 11-13). Workshop discussions highlighted the need for prospective studies that include representative populations of patients with acute COVID-19 to describe the epidemiology of the diverse array of postacute manifestations of COVID-19 at different time points after initial infection or disease onset, and across patient populations with varying characteristics and severity of acute disease. Studies using electronic health records may provide important data to answer certain epidemiologic questions and measure effects on health services; however, these studies may not capture the full spectrum of postacute COVID-19 and may miss important subgroups with postacute disease, such as those who lack access to care or who do not seek care because they believe that no treatment exists.

The workshop also highlighted the need to recognize the full clinical spectrum of postacute COVID-19, as well as the need to characterize the phenotypes of disease that are beginning to emerge and identify risk factors for their development. Weakness, cognitive dysfunction, and psychological disorders after hospitalization for severe COVID-19 may overlap with the well-described post-intensive care syndrome seen with other critical illnesses (14). Persistent fatigue, cognitive dysfunction, and other multisystemic symptoms after COVID-19 in persons who did not require hospitalization for their acute infection may characterize another distinct phenotype. Autonomic dysfunction and postural tachycardia may represent yet another. Comparisons have been drawn between postacute sequelae of COVID-19 and myalgic encephalomyelitis/chronic fatigue syndrome because many symptoms overlap. Care must be taken not to conflate the 2 conditions because neither is completely understood. Lessons learned from several decades of studying myalgic encephalomyelitis/chronic fatigue syndrome may be applied to studies of postacute COVID-19—and in fact, better understanding of both conditions may be mutually beneficial to patients in both groups.

The expected time course of COVID-19 recovery and what would constitute a “prolonged” or “postacute” manifestation of disease also have not yet been clearly defined. One proposed framework for symptomatic SARS-CoV-2 infection includes an acute stage from weeks 0 to 1 after symptom onset, a phase of postacute inflammatory illness from weeks 2 to 4, and late sequelae occurring beyond week 4 (15). Another framework defines “ongoing asymptomatic COVID-19” as signs and symptoms continuing for 4 to 12 weeks and “post-COVID syndrome” as continuing for more than 12 weeks after initial infection (16). The natural histories, including duration, of various manifestations of postacute COVID-19 also remain uncharacterized.

A detailed understanding of the clinical spectrum and natural history of postacute COVID-19 will require systematic longitudinal assessment of individuals after SARS-CoV-2 infection. Workshop participants noted that studies will need to characterize disease phenotypes across multiple organ systems; collect biospecimens; assess cardiovascular, pulmonary, immune, metabolic, and neurologic function and mental health; and be tailored to evaluate pediatric and elderly populations. Enrollment of participants from diverse populations, including groups disproportionately affected by COVID-19, is critical. Identifying adequate control groups is vital to distinguishing the myriad of individual and contextual factors likely to play a role in COVID-19 recovery. Data

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**SPECIAL ARTICLE**

**Workshop on Postacute COVID-19**
and specimens obtained as close as possible after—or even before—infec-
tion or symptom manifestation would be extremely valuable in this regard. Cohorts from
ongoing therapeutic and prevention trials could be leveraged to answer relevant questions about the effects
of these interventions on the development and natural history of postacute COVID-19.

KEY GAP: A NEED TO UNDERSTAND
PATHOPHYSIOLOGY

The pathophysiology that drives the diversity of post-
acute COVID-19 manifestations is poorly understood. Elucidating the pathophysiology not only will be critical
for developing treatment of postacute COVID-19 but may also improve our understanding of the sequelae of
other viral infections (for example, influenza, chikungu-
nya, Ebola, and Epstein-Barr viruses) or conditions where
viral infection may be suspected but not confirmed (such
as some cases of myalgic encephalomyelitis/chronic fa-
tigue syndrome). Workshop speakers and participants
discussed potential disease mechanisms underlying postacute COVID-19.

A key question identified at the workshop is the extent to which postacute COVID-19 manifestations are
direct effects of the virus as opposed to a host response
to SARS-CoV-2 infection. The relationship of duration,
magnitude, and site of the initial viral infection with timing and type of postacute sequelae needs further investiga-
tion. Because SARS-CoV-2 uses angiotensin-converting
cellular (ACE2) as a receptor to enter host cells, under-
standing the expression and localization of ACE2 in
the body may yield insight into postacute COVID-19.
Numerous tissues and organ systems express ACE2, including in the respiratory, cardiovascular, gastrointesti-
nal, and nervous systems (17). In discussing the pathoge-
nesis of diseases caused by other coronaviruses, speakers
described feline coronavirus, an enteric infection that is
sometimes persistent. Occasionally, viral mutations during
Persistence result will result in macrophage infection, leading to
the severe disease of feline infectious peritonitis. It has
been hypothesized that persistent or prolonged SARS-
CoV-2 infection may contribute to the development of postacute sequelae. One recent study analyzed intestinal
biopsies obtained from asymptomatic persons 4 months
after COVID-19 onset, which revealed the persistence of
SARS-CoV-2 nucleic acids and immunoreactivity in the
small bowel of 7 of 14 participants (18).

The immune response may also play a critical role in
the pathogenesis of certain postacute manifestations of
COVID-19, as it likely does in the pathogenesis of acute
disease. One analysis of B-cell responses in patients with
COVID-19 found that those with severe disease showed
B-cell features previously described in autoimmune
processes, such as activation of the extrafollicular path-
way (19). Another study described the detection of pro-
thrombotic antiphospholipid autoantibodies in 52% of a
cohort of 172 patients hospitalized with COVID-19 (20).
Neutralizing autoantibodies against type I interferons
have been described in some patients with severe
COVID-19, an example of the adaptive immune res-

Table. Key Gaps Identified at the Workshop on Postacute
COVID-19

| Description of clinical spectrum and natural history of various phenotypes |
| Identification of risk factors, including comorbid conditions, severity of initial disease, viral characteristics, host genetics, and host immune response |
| Understanding of pathophysiology |
| Characterization of the influence of therapeutics for acute disease and vaccines in preventing or modulating postacute COVID-19 |
| Identification of therapeutic and preventive strategies for postacute COVID-19 |

1. Common terminology and case definitions
2. Characterization of epidemiology (including incidence and prevalence of various phenotypes in the full spectrum of patients in and diverse communities)
In vitro studies are a valuable tool for understanding cellular responses to SARS-CoV-2 infection. In particular, workshop participants discussed the value of stem cell-derived human tissues and organoids. Benefits of using stem cell-derived human tissues include their ability to grow indefinitely in vitro, maintain a normal genetic makeup, and differentiate into a wide range of somatic tissues. Several stem cell-derived tissues and organoids have successfully been infected with SARS-CoV-2 (30, 31). These in vitro studies complement investigations using animal models and can be used to answer basic research questions, including which cells are infected by SARS-CoV-2, how they recover after acute infection, and what happens after infection.

Conclusions

Workshop presentations and discussions identified fundamental gaps that must be addressed in knowledge about postacute COVID-19 (Table). An initial need is for clear, common terminology to describe the condition. Accepted case definitions are also essential to advancing the field, harmonizing research, conducting surveillance, and developing and providing relevant treatment and prevention strategies. Developing such terminology and definitions will require ongoing communication with all stakeholders, including clinicians, researchers, and advocacy and patient community groups.

In addition, we need to describe the epidemiology of postacute COVID-19, characterize the various phenotypes and their clinical spectrum, delineate natural histories, and identify risk factors for development. Studying the effects of vaccination, as well as therapeutics given during the acute phase of disease, on the development of postacute COVID-19 will also be informative. Delination of the pathogenesis of various manifestations of postacute COVID-19 is another fundamental knowledge gap, and findings from these studies will inform the development and evaluation of safe and effective methods of treatment and prevention. In addition, the effects, if any, of SARS-CoV-2 variants on the development of postacute COVID-19 need to be explored.

As the number of reports of postacute COVID-19 continues to increase, fundamental questions must be answered. We urgently need a collaborative research approach that includes harmonized case definitions; delineation of epidemiology, natural history, and pathophysiology; and strategies to address longtime health disparities. This will enable the optimum implementation of evidence-based diagnostic, therapeutic, and preventive strategies essential to help mitigate the pain and suffering of individuals with postacute COVID-19.

From the National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland (A.M.L., D.A.R., L.Y., C.F.W., L.M.N., J.J.B., R.W.E., J.S.S., E.J.E.), and The University of North Carolina at Chapel Hill, Chapel Hill, North Carolina (A.A.A.).

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Corresponding Author: Andrea M. Lerner, MD, Immediate Office of the Director, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Building 31, Room 7A10A, 31 Center Drive, Bethesda, MD 20892; e-mail, Andrea.lerner@nih.gov.

Current author addresses and author contributions are available at Annals.org.

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**Current Author Addresses:**

Drs. Lerner and Eisinger: Immediate Office of the Director, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Building 31, Room 7A10A, 31 Center Drive, Bethesda, MD 20892.

Drs. Robinson, Yang, and Schneider: Policy Planning and Evaluation, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Building 31, Room 7A46C, 31 Center Drive, Bethesda, MD 20892.

Dr. Williams: Division of AIDS, National Institute of Allergy and Infectious Diseases, National Institutes of Health, 5601 Fishers Lane, Room 9G60, Bethesda, MD 20892.

Dr. Newman: Division of Microbiology and Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, 5601 Fishers Lane, Room 8E45, Bethesda, MD 20892.

Dr. Breen: Division of Allergy, Immunology and Transplantation, National Institute of Allergy and Infectious Diseases, National Institutes of Health, 5601 Fishers Lane, Room 7B41, Bethesda, MD 20892.

Dr. Adimora: Division of Infectious Diseases, CB #7030, 130 Mason Farm Road, UNC School of Medicine, The University of North Carolina at Chapel Hill, Chapel Hill, NC 27599-7030.

Dr. Erbelding: Division of Microbiology and Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, 5601 Fishers Lane, Room 7G51, Bethesda, MD 20892.

**Author Contributions:**

Conception and design: A.M. Lerner, D.A. Robinson, L. Yang, C.F. Williams, L.M. Newman, J.J. Breen, R.W. Eisinger, A.A. Adimora, E.J. Erbelding.

Drafting of the article: A.M. Lerner, D.A. Robinson, L. Yang, C.F. Williams, L.M. Newman, J.J. Breen, R.W. Eisinger, J.S. Schneider.

Critical revision of the article for important intellectual content: A.M. Lerner, D.A. Robinson, L. Yang, C.F. Williams, L.M. Newman, J.J. Breen, R.W. Eisinger, J.S. Schneider, A.A. Adimora, E.J. Erbelding.

Final approval of the article: A.M. Lerner, D.A. Robinson, L. Yang, C.F. Williams, L.M. Newman, J.J. Breen, R.W. Eisinger, J.S. Schneider, A.A. Adimora, E.J. Erbelding.