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Date:	2022/04/04 12:58:47
Start Date:	2022/06/17 12:00:00
End Date:	2022/06/17 15:00:00
Priority:	Normal

Type:	Appointment
Location:	https://nasem.zoom.us/j/92914027352
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Dear all,

We are looking forward to tomorrow's virtual meeting of the Standing Committee on Emerging Infectious Diseases and 21st Century Health Threats, taking place from Noon – 3:00 p.m. ET.

Please find attached a final agenda with Zoom information, an updated summary document, and briefing materials.

Topic: June 2022 Meeting of the Standing Committee on Emerging Infectious Diseases and 21st Century Health Threats
Time: June 17, 2021 12:00 PM – 3:00 PM ET
Join from PC, Mac, Linux, iOS or Android (b)(6)
Or iPhone one-tap (b)(6)

Many thanks,
Shalini

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Standing Committee on Emerging Infectious Diseases and 21st Century Health Threats

Health and Medicine Division
Board on Health Sciences Policy
Board on Global Health

Briefing Materials
Meeting 4 – June 17, 2022

Virtual Meeting

For committee use only – Do not circulate

Meeting of the Standing Committee on Emerging Infectious Diseases and 21st Century Health Threats

June 17, 2022

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Meeting of the Standing Committee on Emerging Infectious Diseases and 21st Century Health Threats

Draft Agenda – June 17, 2022, Noon – 3:00 P.M. ET

CLICK HERE TO JOIN

Meeting ID (b)(6)

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International Numbers

FRIDAY, JUNE 17, 2022

Purpose

- Gather a broad array of information and perspectives regarding the development of a medium- (up to five years) and long-term (more than five years) COVID-19 research agenda.
- Understand U.S. Government perspectives on the opportunities, needs, and utility for a coordinated long-term research agenda for COVID-19 to coordinate and align efforts effectively to advance evidence-based practice.
- Scope potential priority topic areas to consider for a comprehensive research agenda.

SESSION I Welcoming Remarks and Sponsor's Reflections

12:00 p.m. **Welcoming Remarks and Overview of the Agenda**

Harvey Fineberg, *Standing Committee Chair*
President
Gordon and Betty Moore Foundation

12:15 p.m. **Welcome and Opening Remarks from the Sponsor**

David (Chris) Hassell
Deputy Assistant Secretary – Senior Science Advisor
Office of the Assistant Secretary for Preparedness and Response
U.S. Department of Health and Human Services

SESSION II Reflections on COVID-19 Long-Term Research Agenda and Research Priorities

12:30 p.m. **Perspectives from Federal Partners**

Objectives:

- Understand U.S. Government perspectives on the opportunities, needs, and utility for a coordinated long-term research agenda for COVID-19;
- Explore how efforts can be coordinated and aligned across federal, state, and local counterparts to advance evidence-based practice; and

- Scope potential priority topic areas to consider for a comprehensive research agenda.

Anthony Fauci *(pre-recorded presentation)*
Director
National Institute of Allergy and Infectious Diseases

Rayvon Fouché
Division Director, Social and Economic Sciences
National Science Foundation

TBD
Centers for Disease Control and Prevention

1:00 p.m. **Committee Perspectives on Research Priorities for a Medium-to-Long-Term COVID-19 Research Agenda**

Objectives:

- Identify initial areas of research priorities or scope of the research agenda
- Solicit input on the key components of such a research agenda.

Harvey Fineberg, *Standing Committee Chair*
President
Gordon and Betty Moore Foundation

2:30 p.m. **Perspectives from Other National Academies Activities**

Objectives:

- Gather information on projects at the National Academies related to a COVID-19 research agenda; and
- Scope potential priority topic areas to consider for a comprehensive research agenda.

Robert M. Groves *(Invited)*
Co-Chair, Societal Experts Action Network

Cinnamon Dixon
Co-Chair, The Action Collaborative on Disaster Research
Forum on Medical and Public Health Preparedness for Disasters and Emergencies

Kevin Anderson
Forum Member, Forum on Microbial Threats

SESSION III MEETING WRAP UP

2:45 p.m. **Committee Debrief, Next Steps, and Future Meeting Planning**

Harvey Fineberg, *Standing Committee Chair*
President
Gordon and Betty Moore Foundation

3:00 p.m. **MEETING ADJOURNS**

Standing Committee on Emerging Infectious Diseases and 21st Century Health Threats

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Standing Committee on Emerging Infectious Diseases and 21st Century Health Threats

COMMITTEE MEMBER BIOSKETCHES

HARVEY FINEBERG, M.D., PH.D. (*CHAIR*)

President
Gordon and Betty Moore Foundation

Harvey Fineberg is president of the Gordon and Betty Moore Foundation. He previously served as president of the Institute of Medicine from 2002 to 2014 and as provost of Harvard University from 1997 to 2001, following 13 years as dean of the Harvard School of Public Health. Fineberg devoted most of his academic career to the fields of health policy and medical decision-making. His past research has focused on the process of policy development and implementation, assessment of medical technology, evaluation and use of vaccines, and dissemination of medical innovations. Fineberg serves on the boards of the Carnegie Endowment for International Peace and the China Medical Board. He helped found and served as president of the Society for Medical Decision Making, previously served on and chaired the board of the William and Flora Hewlett Foundation, and chaired the committee to review the performance of the World Health Organization and the functioning of the International Health Regulations (2005) during the 2009 H1N1 influenza pandemic. Fineberg is co-author of the books *Clinical Decision Analysis*, *Innovators in Physician Education* and *The Epidemic That Never Was*, an analysis of the controversial federal immunization program against swine flu in 1976. He has co-edited several books on such diverse topics as AIDS prevention, vaccine safety, understanding risk in society and global health. He has also authored numerous articles published in professional journals. Fineberg chaired the National Academies committee that produced the 2019 report on *Reproducibility and Replicability in Science*. He earned his bachelor's and doctoral degrees at Harvard and is the recipient of several honorary degrees.

KRISTIAN ANDERSEN, PH.D.

Professor
Department of Immunology and Microbiology
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Kristian Andersen is a Professor in the Department of Immunology and Microbiology at Scripps Research, with joint appointments in the Department of Integrative Structural and Computational Biology, and at the Scripps Research Translational Institute. Over the past decade, his research has focused on the complex relationship between host and pathogen. Using a combination of next-generation sequencing, field work, experimentation, and computational biology he has spearheaded large international collaborations investigating the emergence, spread and evolution of deadly pathogens, including SARS-CoV-2, Zika virus, Ebola virus, West Nile virus, and Lassa virus. His work is highly cross-disciplinary and exceptionally collaborative. Kristian earned his doctoral degree from the University of Cambridge and performed postdoctoral work in Pardis Sabeti's group at Harvard University and the Broad Institute.

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William R. Kenan, Jr. Distinguished Professor
The University of North Carolina at Chapel Hill

(b)(6) (b)(6 is a William R. Kenan, Jr. Distinguished Professor in the Department of Epidemiology at the University of North Carolina. He obtained a Bachelor of Science Degree in Zoology from North Carolina State University in 1977 and a PhD in Microbiology and Immunology from North Carolina State University in 1983. He conducted postgraduate research at the University of Southern California School of Medicine in the department of Microbiology and Immunology between 1983-1986. He is a Harvey Weaver Scholar from the National Multiple Sclerosis Society and an Established Investigator Awardee from the American Heart Association. In addition, he is a World Technology Award Finalist, a fellow of the American Association for Microbiology, a senior editor of PloS Pathogen, and a member of the editorial board of several other specialty journals. He was a member of the National Academy Sciences Working Groups that focused on Gene Sequence Methods for Classification of Select Agents and the Risks and Benefits of Gain of Function Research, an invited speaker to the Institute of Medicine Forum on Emerging Infectious Diseases and an invited panelist for the MERS-CoV Stakeholders Workshop. His group has published over 300 papers, many in highly visible journals like PNAS, Nature Medicine, Science, PloS Medicine and PloS Pathogens. The (b)(6 laboratory uses genetic, immunologic, molecular and biochemical approaches to study the molecular mechanisms regulating virus replication, pathogenesis, molecular evolution and cross species transmission using emerging coronaviruses, flaviviruses (Dengue) and noroviruses as model systems. We have pioneered new strategies for developing reverse genetic approaches for manipulating the SARS-CoV, SAR-CoV-2 and MERS-CoV genomes and are actively studying the role of multiple genes that function in cross species transmission, virulence, pathogenesis, viral transcription and RNA fidelity. The (b)(6 laboratory is also identifying key neutralizing epitopes in emerging coronaviruses, dengue and noroviruses using human monoclonal antibodies and structure guided immunogen design to develop broadly active vaccines and immunotherapuetics against these pathogens. Finally, his group has developed novel animal models of human disease and identified dozens of host susceptibility loci that regulate emerging CoV pathogenesis.

MARY BASSETT, M.D., M.P.H.
New York State Health Commissioner
New York State Department of Health

Mary Bassett is the New York State Health Commissioner at the New York State Department of Health. With more than 30 years of experience in public health, Dr. Mary Travis Bassett has dedicated her career to advancing health equity. Prior to her directorship at the FXB Center, Dr. Bassett served for four years as commissioner of Health for New York City. As commissioner, she worked to ensure that every New York City neighborhood supported the health of its residents, with the goal of closing gaps in population health across the city. Originally from New York City, Dr. Bassett lived in Zimbabwe for nearly 20 years. Previously, she was the Program Director for the African Health Initiative and the Child Well-being Program at the Doris Duke Charitable Foundation. She received her B.A. in History and Science from Harvard University and her M.D. from Columbia University's College of Physicians and Surgeons. She served her medical residency at Harlem Hospital Center, and has a master's degree in Public Health from the University of Washington, where she was a Robert Wood Johnson Clinical Scholar.

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Executive Director

American Public Health Association

Georges Benjamin is well-known as a health leader, practitioner, and administrator. Dr. Benjamin has served as the executive director of the American Public Health Association, the nation's oldest and largest organization of public health professionals, since December 2002. He is a former secretary of Health for the state of Maryland. Dr. Benjamin is a graduate of the Illinois Institute of Technology and the University Of Illinois College Of Medicine. He is board-certified in internal medicine, a Master of the American College of Physicians, a fellow of the National Academy of Public Administration and a fellow emeritus of the American College of Emergency Physicians. He serves on several nonprofit boards such as Research!America, the University of Maryland Medical System and, the Reagan-Udall Foundation. He is a member of the National Academy of Medicine. In April 2016, President Obama appointed Benjamin to the National Infrastructure Advisory Council, a council that advises the president on how best to assure the security of the nation's critical infrastructure.

DONALD BERWICK, M.D., M.P.P., F.R.C.P., KBE
President Emeritus and Senior Fellow
Institute for Healthcare Improvement

Donald M. Berwick is President Emeritus and Senior Fellow at the Institute for Healthcare Improvement (IHI), an organization he co-founded and led as President and CEO for 19 years. He is one of the nation's leading authorities on health care quality and improvement. In July, 2010, President Obama appointed Dr. Berwick to the position of Administrator of the Centers for Medicare and Medicaid Services (CMS), which he held until December, 2011. A pediatrician by background, Dr. Berwick has served as Clinical Professor of Pediatrics and Health Care Policy at the Harvard Medical School, Professor of Health Policy and Management at the Harvard School of Public Health, and as a member of the staffs of Boston's Children's Hospital Medical Center, Massachusetts General Hospital, and the Brigham and Women's Hospital. He has also served as vice chair of the U.S. Preventive Services Task Force, the first "Independent Member" of the Board of Trustees of the American Hospital Association, and chair of the National Advisory Council of the Agency for Healthcare Research and Quality. He is an elected member of the American Philosophical Society, the American Academy of Arts and Sciences, and the National Academy of Medicine (formerly the Institute of Medicine). Dr. Berwick served two terms on the IOM's governing Council, was a member of the IOM's Global Health Board, and currently chairs the NAM Board on Health Care Services. He served on President Clinton's Advisory Commission on Consumer Protection and Quality in the Healthcare Industry. His numerous awards include the 2007 William B. Graham Prize for Health Services Research, the 2006 John M. Eisenberg Patient Safety and Quality Award, and the 2007 Heinz Award for Public Policy. In 2005, he was appointed Honourary Knight Commander of the British Empire by Her Majesty Queen Elizabeth II, the highest honor in the UK for non-UK citizens. He is the author or co-author of over 200 scientific articles and six books. He also serves now as Lecturer in the Department of Health Care Policy at Harvard Medical School.

RICHARD BESSER, M.D.
President and CEO
Robert Wood Johnson Foundation

Richard Besser has been president and CEO of the Robert Wood Johnson Foundation (RWJF) since April 2017. He is the former acting director of the Centers for Disease Control and Prevention and *ABC News'* former chief health and medical editor. At RWJF, Besser leads the largest private foundation in the country devoted solely to improving the nation's health. RWJF's work is focused on building a comprehensive Culture of Health that provides everyone in America with a fair and just opportunity to live the healthiest life possible. In his role, Besser is a leading voice on the importance of health equity, advocating for racial justice, full inclusion of people with disabilities, and a COVID-19 response and recovery that prioritizes those most impacted. Before joining *ABC News* in 2009, Besser worked as director of the Coordinating Office for Terrorism Preparedness and Emergency Response at the CDC. In that role he was responsible for all the CDC's public health emergency preparedness and emergency response activities. He also served as acting director of the CDC from January to June 2009, during which time he led the CDC's response to the H1N1 influenza pandemic.The author or co-author of hundreds of presentations, abstracts, chapters, editorials and publications, Besser has earned many awards for his work in public health and for his volunteer service. He is a member of the National Academy of Medicine. He received the Surgeon General's Medallion for his leadership during the H1N1 response and the Dean's Medal from the Johns Hopkins Bloomberg School of Public Health. In 2012, he received an Overseas Press Club award for coverage of global maternal health issues, and two Peabody Awards for coverage of Hurricane Sandy and Robin Roberts' health journey. In 2017 and 2018, he received an Emmy award for "Outstanding Morning Program" as part of the *Good Morning America* team. His book, "*Tell Me the Truth, Doctor: Easy-to-Understand Answers to Your Most Confusing and Critical Health Questions*," was published in 2013.Besser received his Bachelor of Arts degree in economics from Williams College and medical degree from the University of Pennsylvania. He completed a residency and chief residency in pediatrics at Johns Hopkins University Hospital in Baltimore. He practices as a volunteer pediatrician at the Henry J. Austin Health Center in Trenton, N.J. He and his wife Jeanne, a food writer, have two sons, Alex and Jack.

R. ALTA CHARO, J.D.
Professor Emerita
University of Wisconsin Law School

R. Alta Charo has taught bioethics and biotechnology/medical policy for over 30 years, in both the law and medical schools at the University of Wisconsin. Her work has focused largely on the social implications of emerging technologies, including assisted reproduction; nanotechnology; synthetic biology; and genome editing. She has also worked extensively on stem cell policy, and co-chaired the NAS committee that drafted national voluntary guidelines for that research. Her public health work has centered on vaccine safety and, more recently, again with the NAS/NAM on vaccine allocation. Her familiarity with issues surrounding neurobiology includes service on an NAS committee reporting on organoids and neural chimeras, and service on the NAS Committee on Science, Technology and the Law. From working in the FDA Office of the Commissioner on policy governing novel technologies, she has been involved in looking at the special regulatory and social challenges to research, development and deployment of new drugs and medical devices. At present, she works as a consultant.

PETER DASZAK, PH.D.
President and CEO
EcoHealth Alliance

Peter Daszak is President of EcoHealth Alliance, a US-based organization that conducts research and outreach programs on global health, conservation, and international development. Dr. Daszak's research has been instrumental in identifying and predicting the origins and impact of emerging diseases across the globe. He is one of the founders of the field of Conservation Medicine and has been instrumental in the growth of EcoHealth, One Health, and now Planetary Health. Dr. Daszak is a member of the National Academy of Medicine and Chair of the NASEM's Forum on Microbial Threats. He is a member of the NRC Advisory Committee to the US Global Change Research Program, the Supervisory Board of the One Health Platform, the One Health Commission Council of Advisors, the CEEZAD External Advisory Board, the Cosmos Club, and the Advisory Council of the Bridge Collaborative. He has served on the IOM Committee on global surveillance for emerging zoonoses, the NRC committee on the future of veterinary research, the International Standing Advisory Board of the Australian Biosecurity CRC; and has advised the Director for Medical Preparedness Policy on the White House National Security Staff on global health issues. Dr. Daszak is a regular advisor to WHO on pathogen prioritization for R&D. He received his Ph.D. in parasitic infectious disease from the University of East London.

JEFFREY S. DUCHIN, M.D.
Health Officer and Chief, Communicable Disease Epidemiology & Immunization Section and Professor in Medicine
Public Health – Seattle & King County, WA and University of Washington, Seattle

Dr. Jeff Duchin is the Health Officer and the Chief of the Communicable Disease Epidemiology & Immunization Section for Public Health–Seattle & King County. He holds appointments as Professor of Medicine in the Division of Infectious Diseases and Adjunct Professor in the School of Public Health at the University of Washington. Jeff currently serves as a member of the CDC's Advisory Committee on Immunization Practices' (ACIP) COVID-19 Vaccine Workgroup and represents the Infectious Diseases Society of America (IDSA) as their liaison member to the ACIP. He is a past member of the CDC's Board of Scientific Counselors (Office of Infectious Diseases), the Board of Directors for the IDSA, past member of the IDSA's Pandemic Influenza Task Force, and past chair of the IDSA's Bio-emergencies work group and IDSA's Public Health Committee. Jeff has also been a member of the NASM's Forum on Microbial Threats and Forum on Medical and Public Health Preparedness.Jeff received his medical degree from Rutgers Medical School and trained in internal medicine at Thomas Jefferson University Hospital, completed a fellowship in general internal medicine and emergency medicine at the Hospital of the University of Pennsylvania, and did his infectious disease subspecialty training at the University of Washington in Seattle. Jeff is a graduate of the CDC's Epidemic Intelligence Service (EIS) Officer training where he was assigned to the National Center for Infectious Diseases. He also completed the CDC's Preventive Medicine Residency program. Jeff worked for CDC as a medical epidemiologist in the Divisions of Tuberculosis Elimination and HIV/AIDS Special Studies Branch before assuming his current position. For the past two years, Jeff's work has concentrated on the ongoing COVID-19 outbreak response. As a public health professional and physician, he also recognizes climate change as the overall single greatest global public health threat facing humanity. Jeff's peer review publications and research interests focus on communicable diseases of public health significance. For a complete listing of publications, please see PubMED.

ELLEN EMBREY
President/CEO
Stratitia, Inc.

Ellen Embrey is President/CEO of Stratitia, Inc., a consulting firm focused on developing meaningful and innovative strategies, and delivering supporting tools and partnerships to bring them successfully to life. Ms. Embrey brings deep expertise in health and medical issues, as well as a wealth of other experience gained during her extensive federal service. In her last federal role, she performed the duties of the Assistant Secretary of Defense for Health Affairs and the Director, TRICARE Management Activity during the presidential transition period in 2009-2010. From 2002 to 2009, Ms. Embrey was the Deputy Assistant Secretary of Defense for Force Health Protection and Readiness, leading significant changes in Department of Defense policies and programs affecting deployment and combat casualty medicine, health promotion and preventive medicine, medical readiness and public health emergency preparedness and response. For 9 months in 2001, Ms. Embrey performed the duties of Assistant Secretary of Defense for Reserve Affairs, shaping policies affecting the readiness and use of the National Guard and Reserve in both federal and state status. From 2000 to 2001, she served as Chief of Staff of that office, and from 1998 to 2001, as Deputy Assistant Secretary of Defense for Military Assistance to Civil Authorities, developing policies that shaped the role of the National Guard and Reserve components in supporting homeland security, disaster preparedness, and national disaster response capabilities, including advising the president on such matters in the days and weeks following September 11, 2001. Between 1978 and 1997, Ms. Embrey served in senior-level policy analyst, budget analyst, program analyst, management analyst, and systems analyst positions in the Office of the Assistant Secretary of Defense for Reserve Affairs, the Defense Contract Audit Agency, and the Office of Personnel Management. Ms. Embrey was recognized with the Secretary of Defense's Distinguished Civilian Service Award in 2001 and 2004, and twice received the Meritorious Executive Presidential Rank Award in 2006 and 2009.

BARUCH FISCHHOFF, PH.D.
Howard Heinz University Professor, Department of Engineering and Public Policy
Carnegie Mellon University

Baruch Fischhoff is Howard Heinz University Professor, Department of Engineering and Public Policy and Institute for Politics and Strategy, Carnegie Mellon University (CMU). A graduate of the Detroit Public Schools, he holds a BS (mathematics, psychology) from Wayne State University and a PhD (psychology) from the Hebrew University of Jerusalem. He is a member of the National Academy of Sciences and of the National Academy of Medicine. He is past President of the Society for Judgment and Decision Making and of the Society for Risk Analysis. He has chaired the Food and Drug Administration Risk Communication Advisory Committee and been a member of the Eugene (Oregon) Commission on the Rights of Women, the Department of Homeland Security Science and Technology Advisory Committee and the Environmental Protection Agency Scientific Advisory Board, where he chaired the Homeland Security Advisory Committee. He has received the American Psychological Association (APA) Award for Distinguished Contribution to Psychology, CMU's Ryan Award for Teaching, an honorary Doctorate of Humanities from Lund University, and an Andrew Carnegie Fellowship. He is a Fellow of APA, the Association for Psychological Science, Society of Experimental Psychologists, and Society for Risk Analysis. His books include Acceptable Risk, Risk: A Very Short Introduction, Judgment and Decision Making, A Two-State Solution in the Middle East, Counting Civilian Casualties, and Communicating Risks and Benefits. He has co-chaired three National Academy Colloquia on the Science of Science Communication, as well as its

committees on applying decision science to intelligence analysis and its committee on foundational science for cybersecurity.

DIANE GRIFFIN, M.D., PH.D.
Professor, Department of Molecular Microbiology and Immunology
Johns Hopkins Bloomberg School of Public Health

Diane Griffin is University Distinguished Service Professor and Alfred and Jill Sommer Chair of the W. Harry Feinstone Department of Molecular Microbiology and Immunology at Johns Hopkins Bloomberg School of Public Health. Dr. Griffin is a virologist recognized for her work on the pathogenesis of viral infections. She is known particularly for her studies on measles and alphavirus encephalomyelitis that have delineated the role of the immune response in virus clearance, vaccine-induced protection from infection, tissue damage and immune suppression. Dr. Griffin was born in Iowa City, Iowa, and grew up in Oklahoma City. She graduated from Augustana College, Rock Island, Illinois with a degree in biology and from Stanford University School of Medicine in 1968 with a Ph.D. in immunology and M.D., followed by a residency in internal medicine. She was a postdoctoral fellow in virology and infectious diseases at Johns Hopkins University School of Medicine and joined the faculty in 1974. She has been president of the American Society for Virology and of the American Society for Microbiology and is a member of both the National Academy of Sciences and the National Academy of Medicine.

GIGI GRONVALL, PH.D.
Senior Associate
Johns Hopkins Center for Health Security
Johns Hopkins Bloomberg School of Public Health

Gigi Gronvall is a Senior Scholar at the Johns Hopkins Center for Health Security and an Associate Professor in the Department of Environmental Health and Engineering at the Johns Hopkins Bloomberg School of Public Health. She is an immunologist by training. During the COVID-19 pandemic, she has led the Center's ongoing efforts to track the development and marketing of molecular and antigen tests and serology tests, as well as the development of national strategies for COVID-19 serology (antibody) tests and SARS-CoV-2 serosurveys in the United States. She has also written about the scientific response to the COVID-19 pandemic and implications for national and inte rnational security. Dr. Gronvall is the author of Synthetic Biology: Safety, Security, and Promise. In the book, she describes what can be done to minimize technical and social risks and maximize the benefits of synthetic biology, focusing on biosecurity, biosafety, ethics, and US national competitiveness – important sectors of national security. Dr. Gronvall is also the author of Preparing for Bioterrorism: The Alfred P. Sloan Foundation's Leadership in Biosecurity. Through her description of major grants that represented the foundations investments in civilian preparedness, public health law, law enforcement, air filtering in buildings, influenza preparedness, and business preparedness, she constructed, for a nontechnical audience, a chronicle of early gains in US efforts to confront the threat of bioterrorism. Dr. Gronvall is a member of the Threat Reduction Advisory Committee, which provides the Secretary of Defense with independent advice and recommendations on reducing the risk to the United States, its military forces, and its allies and partners posed by nuclear, biological, chemical, and conventional threats. In 2014-15, she led a preparatory group that examined the US government response to the Ebola outbreak in West Africa as a case study for Department of Defense's strategic role in health security and made recommendations for future Department of Defense actions in response to disease outbreaks. She is also a member of the Novel and Exceptional Technology and Research Advisory Committee, which provides recommendations to the Director of the National Institutes of Health and is a public forum for the discussion of the scientific, safety, and ethical issues associated with emerging

biotechnologies. She served as the Science Advisor for the Commission on the Prevention of Weapons of Mass Destruction Proliferation and Terrorism from April 2009 until the Commission ended in February 2010. She has testified before Congress about the safety and security of high-containment biological laboratories in the United States and served on several task forces related to laboratory and pathogen security. Dr. Gronvall has investigated and presented policy recommendations on the governance of science to the Biological Weapons Convention in Geneva, Switzerland. In addition to being a life member of the Council on Foreign Relations, Dr. Gronvall is an Associate Editor of the journal Health Security (formerly Biosecurity and Bioterrorism). She is a founding member of the Center. Prior to joining the faculty, she worked at the Johns Hopkins University Center for Civilian Biodefense Strategies. She was a National Research Council Postdoctoral Associate at the US Army Medical Research Institute of Infectious Diseases in Fort Detrick, Maryland. Dr. Gronvall received a Ph.D. from Johns Hopkins University for work on T-cell receptor/MHC I interactions and worked as a protein chemist at the Memorial Sloan-Kettering Cancer Center. She received a BS in biology from Indiana University, Bloomington.

ROBERT GROVES, PH.D., M.A.
Executive Vice President and Provost
Gerard J. Campbell, S.J. Professor, Math and Statistics Department & Sociology Department
Georgetown University

Robert Groves is the Gerard J. Campbell, S.J. Professor in the Math and Statistics Department as well as the Sociology Department at Georgetown University where he has served as the Executive Vice President and Provost since 2012. Groves is a Social Statistician, who studies the Impact of Social Cognitive and Behavioral Influences on the quality of Statistical Information. His research has focused on the impact of mode of data collection on responses in sample surveys, the social and political influences on survey participation, the use of adaptive research designs to improve the cost and error properties of statistics, and public concerns about privacy affecting attitudes toward statistical agencies. He has authored or co-authored seven books and scores of peer-reviewed articles. His 1989 book, Survey Errors and Survey Costs, was named one of the 50 most influential books in survey research by the American Association of Public Opinion Research. His book, Nonresponse in Household Interview Surveys, with Mick Couper, received the 2008 AAPOR Book Award. His co-authored book, Survey Nonresponse, received the 2011 AAPOR Book Award. He served as the Director of the US Census Bureau between 2009-2012. Groves serves on several boards and advisory committees including the National Research Council Committee on National Statistics, Pew Research Center Board, the National Science Board, and the Federal Economic Statistics Advisory Committee. He is an elected member of the US National Academy of Sciences, of the National Academy of Medicine, of the American Academy of Arts and Sciences, and of the International Statistical Institute.

MARGARET HAMBURG, M.D.
Foreign Secretary
National Academy of Medicine

Margaret Hamburg is an internationally recognized leader in public health and medicine, and currently serves as foreign secretary of the National Academy of Medicine and chair of the NTI | bio Advisory Group. She is a former Commissioner of the U.S. Food and Drug Administration (FDA), having served for almost six years. As FDA Commissioner she was known for advancing regulatory science, streamlining and modernizing FDA's regulatory pathways, and globalization of the agency. Before joining FDA, Hamburg was founding vice president and senior scientist at the Nuclear Threat Initiative. Previous government positions include Assistant Secretary for Planning and Evaluation, U.S. Department of Health and Human Services, Health

Commissioner for New York City, and Assistant Director of the National Institute of Allergy and Infectious Diseases, National Institutes of Health. She is President-elect of the American Association for the Advancement of Science (AAAS), as well as an elected member of the Council on Foreign Relations and the National Academy of Medicine. Hamburg currently sits on the boards of the Commonwealth Fund, the Simons Foundation, the Urban Institute, the Global Alliance for Vaccines and Immunization, the Parker Institute for Cancer Immunotherapy and the American Museum of Natural History. She is chair of the Joint Coordinating Group for the Coalition for Epidemic Preparedness and Innovation, and a member of the Harvard University Global Advisory Council, the Global Health Scientific Advisory Committee for the Gates Foundation, the Harvard Medical School Board of Fellows, and the World Dementia Council. Dr. Hamburg earned her B.A. from Harvard College, her M.D. from Harvard Medical School and completed her medical residency at Weill Cornell Medical Center. She is the recipient of multiple honorary degrees and numerous awards.

(b)((b)(6) M.D.
Vice President, Technical Staff
In-Q-Tel

(b)((b)(6) is Vice President on the Technical Staff at In-Q-Tel, a non-governmental not-for-profit strategic investor focused on enabling technologies to support national security requirements. He is a board-certified emergency physician practicing at Inova Fairfax Hospital, northern Virginia's Level I trauma center, where he led emergency preparedness response efforts in the aftermath of the 9-11 attacks and the anthrax mailings. He participates as a Medical Team Manager for Virginia Task Force One, a FEMA- and USAID-sanctioned international urban search and rescue team and has deployed to numerous catastrophic disaster events, both domestic and international. Dr. (b)(6) currently serves as the co-chair of the National Academies Forum on Medical and Public Health Preparedness and co-chaired the Institute of Medicine committees responsible for developing the work on "crisis standards of care". Dr. (b)(6) is Clinical Professor of Emergency Medicine at George Washington University. He received an AB in political science from Duke University and was awarded his medical degree from Brown University. He completed an internship in internal medicine at the Miriam Hospital in Providence, Rhode Island, and an emergency medicine residency at George Washington/Georgetown University Hospitals.

JOHN HICK, M.D.
Associate Medical Director for EMS
Medical Director of Emergency Medicine
Hennepin County Medical Center

John Hick is a faculty emergency physician at Hennepin Healthcare and a Professor of Emergency Medicine at the University of Minnesota. Dr. Hick serves as the deputy medical director for Hennepin County Emergency Medical Services and Medical Director for Emergency Preparedness at HCMC. He is also the Vice-Chair of the Clinical Council for Life Link III helicopter service and medical director for MN TF-1 state US&R team. He served the Minnesota Department of Health as the medical director for the Office of Emergency Preparedness until becoming an Advisor to the Director of OEM at ASPR/HHS where he is the lead editor for the TRACIE healthcare disaster preparedness website. He is the founder and past chair of the Minneapolis/St. Paul Metropolitan Hospital Compact, a 32-hospital mutual aid and planning group active since 2002. He is a national speaker on hospital preparedness issues and has published numerous papers dealing with hospital preparedness for contaminated casualties,

personal protective equipment, crisis standards of care, and surge capacity and was honored to serve the Institute of Medicine on their Crisis Standards of Care projects as well as the Forum on Medical and Public Health Preparedness for Disasters and Emergencies. Dr. Hick holds an M.D. from the Mayo Medical School.

KENT E. KESTER, M.D.
Vice President, Translational Medicine
IAVI

Kent Kester is currently Vice President, Translational Medicine at IAVI. During a 24-year career in the US Army, he worked extensively in clinical vaccine development and led multiple research platforms at the Walter Reed Army Institute of Research, the U.S. Department of Defense's largest and most diverse biomedical research laboratory with a major emphasis on emerging infectious diseases, an institution he later led as its Commander/Director. His final military assignment was as the Associate Dean for Clinical Research in the School of Medicine at the Uniformed Services University of the Health Sciences (USUHS). During his military service, Dr. Kester was appointed as the lead policy advisor to the US Army Surgeon General in both Infectious Diseases and in Medical Research & Development. In these capacities, he worked extensively in the interagency environment and developed a variety of Army and DoD medical policies related to infectious diseases, both clinical and research aspects. Dr. Kester holds an undergraduate degree from Bucknell University and an M.D. from Jefferson Medical College, completing his internship and residency in internal medicine at the University of Maryland and a research fellowship in infectious diseases at the Walter Reed Army Medical Center. Currently a member of the US Government Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria (PACCARB) and the Department of Veterans Affairs Health Services Research & Development Service Merit Review Board, he previously chaired the Steering Committee of the NIAID/USUHS Infectious Disease Clinical Research Program, and has served as a member of the FDA Vaccines & Related Biologics Products Advisory Committee (VRBPAC), the NIAID Advisory Council, and the CDC Office of Infectious Diseases Board of Scientific Counselors. He is the Vice Chair of the National Academy of Medicine Forum on Microbial Threats. Board-certified in both internal medicine and infectious diseases, Dr. Kester holds faculty appointments at USUHS and the University of Maryland; and is a fellow of the American College of Physicians, the Royal College of Physicians of Edinburgh, the Infectious Disease Society of America, and the American Society of Tropical Medicine and Hygiene. He is a member of the clinical faculty at the University of Maryland Shock Trauma Center in Baltimore.

PATRICIA KING, J.D.
Professor Emerita
Georgetown University Law Center

Patricia King is Professor of Law emeritus at Georgetown University Law Center and an Adjunct Professor in the Department of Health Policy and Management, School of Hygiene and Public Health at Johns Hopkins University. She is the co-author of Cases and Materials on Law, Science and Medicine. She is a member of the National Academy of Medicine, a member of the American Law Institute, a fellow of the Hastings Center and a faculty affiliate of Georgetown's Kennedy Institute of Ethics. Her scholarship focuses on race and genomics, racial disparities in health and reproductive health. Professor King has served on numerous national advisory bodies formed to address the ethical issues generated by developments in science and technology, including the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (1974-78), which produced the seminal "Belmont Report," the President's Advisory Committee on Human Radiation Experiments (1994-95), the National Institutes of Health's Embryo Research Panel (co-chair for policy, 1994), the Ethics, Legal and

Social Issues Working Group of the NIH's Human Genome Project (1989-95), and the NIH's Recombinant DNA Advisory Committee (1979-81). She has served on numerous boards and Institute of Medicine committees and is currently a member of the Board of Health Sciences Policy of the National Academies. She is also a Director of Mathematica an employee-owned company.She is a graduate of Wheaton College (Massachusetts) and has served as a Trustee and Chair of the Wheaton College Board of Trustees. In 2018 she was designated a Life Trustee by the Wheaton College Board. She graduated from Harvard Law School and is a past member of the Harvard Corporation the governing board of Harvard University. She has received honorary degrees from Wheaton College, Old Dominion University, and Harvard University.

NICOLE LURIE, M.D., M.S.P.H.
U.S. Director
Coalition for Epidemic Preparedness Innovations

Nicole Lurie, is Director of CEPI-US and Strategic Advisor to the CEO at the Coalition for Epidemic Preparedness Innovations (CEPI). She is also a Senior Lecturer at Harvard Medical School, a member of the research faculty at Massachusetts General Hospital and Professor of Medicine at George Washington University School of Medicine. She served an 8-year term as Assistant Secretary for Preparedness and Response at the US Department of Health and Human Services. In that role she led the HHS response to numerous public health emergencies, ranging from infectious disease to natural and man-made disasters and is responsible for many innovations in emergency preparedness and response. She also chaired the Public Health Emergency Medical Countermeasures Enterprise, a government wide organization ultimately responsible for the development of medical countermeasures, including vaccines against pandemics and emerging threats. Dr. Lurie has a long history in health services research. Prior to federal service, she was the Paul O'Neill Professor of Policy Analysis at RAND, where she started and led the public health preparedness program and RAND's Center for Population Health and Health Disparities. She has had leadership roles in academia, as Professor of Medicine and Public Health at the University of Minnesota, as Medical Advisor to the Commissioner, Minnesota Department of Health, and as Principal Deputy Assistant Secretary for Health at the US Department of Health and Human Services. Dr. Lurie received her BA and MD degrees from the University of Pennsylvania, and completed her residency and public health training at UCLA. Her work has focused on access to and quality of care, health system redesign, equity, mental health, public health and preparedness. She is recipient of numerous awards and is a member of the National Academy of Medicine. She continues to practice clinical medicine in a community clinic in Washington DC.

JONNA MAZET, D.V.M., M.P.V.M., PH.D.
Vice Provost of Grand Challenges
Professor of Epidemiology and Disease Ecology
University of California, Davis

Jonna Mazet, is Vice Provost of Grand Challenges and Distinguished Professor of Epidemiology and Disease Ecology at UC Davis. Her main focus has been on identifying and mitigating emerging health threats with an emphasis on bringing diverse disciplines together to address community health issues and disease transmission among wildlife, domestic animals, and people. In 1998, she was appointed to the faculty of the School of Veterinary Medicine and became Co-director of the fledgling Wildlife Health Center and later Executive Director of the One Health Institute, which she took from academic ideas to a more than $40 million per year global research and service unit. Her key accomplishments include discovery of viral health threats in 35 countries, identification of the source and mechanism of zoonotic pathogen

pollution in coastal communities, surveillance for avian influenza in the Pacific Flyway, pioneering approaches to investigate disease transmission at human-animal-environment interfaces, and assisting in the conservation of numerous endangered species through the application of novel and creative epidemiological and ecological methods. She recently completed an eleven-year commitment as Principal Investigator and Global Director of the novel viral emergence early warning project, PREDICT, that has been developed with the US Agency for International Development's (USAID) Emerging Pandemic Threats Program. PREDICT was a more than $200 million multi-institutional, transdisciplinary project in 35 low and middle income countries that continues to contribute to global surveillance for zoonotic diseases emerging from wildlife using geospatial modeling, genomics, molecular virology, and targeted field studies. Mazet led a network of global universities, NGOs, and governmental agencies to build capacity for students and professionals within the PREDICT-engaged countries to develop surveillance methods and complete the necessary research to pre-identify and mitigate the emergence of potentially pandemic viruses, such as SARS-CoV-2, influenza, Ebola, and HIV. Using these projects and others for the research foundation, she has served as the primary mentor for over 80 graduate student and postdoctoral trainees.

PHYLLIS MEADOWS, PH.D., M.S.N., R.N.
Senior Fellow, Health
The Kresge Foundation

Phyllis Meadows currently serves as the Senior Fellow and Program Advisor for the Kresge Foundation Health Team. In this role, she is responsible for supporting the health team in the development and implementation of investment opportunities within and across the Foundation's various programming areas. Her professional career includes leadership roles in philanthropy, academia, community health and governmental public health. She has previously served in the role of Associate Dean for Public Health Practice and Clinical Professor - Health, Management and Policy with the University of Michigan School of Public Health. She has led several initiatives to expand multi-disciplinary practice in communities, designing the University's first certification program on population health and health equity for medical residents. She is currently a Distinguished Towsley Policy Maker in Residence with the University of Michigan's Gerald Ford School of Public Policy. She has taught and developed graduate level and professional continuing education courses to address emerging health issues, including topics on health policy and public health leadership. Dr. Meadows has extensive experience in public health practice having served in various leadership roles in public health. She has held several official appointments in public health leadership at the state, county and local levels. In her most recent appointment, she served as the Chief Health Officer and Director of Health for the City of Detroit, providing leadership for the department of health, environmental health, infectious diseases, child health, clinical and dental services for the residents of Detroit. Her philanthropic experience includes positions as Program Director for the W.K. Kellogg Foundation - Youth, Education and Higher Education; and advisor for several national initiatives of the Robert Wood Johnson Foundation including the Nurse Executive Leadership Program, Partners in Nursing, and the County Roadmaps project. As a registered nurse, she has worked in both community-based health and hospitals. She currently serves as a Board Member and Advisor for several state level organizations and private foundations focusing on health.

TARA O'TOOLE, M.D., M.P.H.
Executive Vice President
In-Q-Tel

Tara O'Toole currently serves as Executive Vice President at In-Q-Tel. Dr. O'Toole was confirmed as the Under Secretary for Science and Technology (S&T) at the U.S. Department of Homeland Security (DHS) and served from November 4, 2009 to September 23, 2013. From 2003 to November 2009, Dr. O'Toole was the CEO and Director of the Center for Biosecurity at the University of Pittsburgh Medical Center (UPMC), and Professor of Medicine and of Public Health at the University of Pittsburgh. The Center for Biosecurity of UPMC is an independent organization dedicated to improving the country's resilience to major biological threats. Dr. O'Toole is internationally known for her work on biosecurity and on health and safety issues related to the U.S. nuclear weapons complex. Her publications in the biodefense field include articles on the response to anthrax, smallpox, and plague biological attacks; containment of contagious disease epidemics; biodefense research and development strategies; and hospital preparedness. She is the founding editor of the journal Biosecurity and Bioterrorism: Biodefense Strategy, Practice, and Science. She was a principal author and producer of Dark Winter, an influential exercise conducted in June 2001 to alert national leaders to the dangers of bioterrorist attacks. She was also a principal writer and producer of Atlantic Storm, an international ministerial-level biosecurity exercise held in January 2005. Prior to founding the UPMC in 2003, Dr. O'Toole was one of the original members of the Johns Hopkins Center for Civilian Biodefense Strategies and served as its director from 2001 to 2003. She has served on numerous government and expert advisory committees dealing with biodefense, including panels of the Defense Science Board; the National Academy of Engineering Committee on Combating Terrorism; and the National Academy of Sciences Working Group on Biological Weapons. She served as chair of the Board of the Federation of American Scientists from 2006 to 2007, and in 2006 she was appointed to the board of Google Foundation's International Networked System for Total Early Disease Detection. From 1993 to 1997, Dr. O'Toole served as Assistant Secretary of Energy for Environment Safety and Health. In this position, she was the principal advisor to the Secretary of Energy on environmental protection and on the health and safety of the approximately 100,000 workers in the U.S. nuclear weapons complex and Department of Energy (DOE) laboratories. She developed the first overall management and safety plan for dealing with the highly enriched uranium, plutonium, spent fuel, and radioactive waste left in place when nuclear weapons production was stopped in the early 1990s. She ran the multi-agency, multimillion-dollar task force that oversaw the government's investigations into human radiation experiments conducted during the Cold War and led the U.S. delegation to Russia to establish the U.S./Russia cooperative effort to study radiation exposure and environmental hazards of the Russian nuclear weapons complex. Prior to her work at DOE, Dr. O'Toole was a senior analyst at the Congressional Office of Technology Assessment, where she directed several projects and studies, including the health impact of pollution resulting from nuclear weapons production. She also served as a consultant to industry and government in matters related to occupational and environmental health; worker participation in workplace safety protection; and organizational change. Dr. O'Toole practiced general internal medicine in community health centers in Baltimore from 1984 to 1988. She is board certified in internal medicine and occupational and environmental health. She has a bachelor's degree from Vassar College, an M.D. from the George Washington University, and a Master of Public Health degree from Johns Hopkins University. She completed internal medicine residency training at Yale University and a fellowship in Occupational and Environmental Medicine at Johns Hopkins University.

ALEXANDRA PHELAN, S.J.D., LL.M., LL.B.
Assistant Professor
Center for Global Health Science and Security
Georgetown University

Alexandra Phelan is an Assistant Professor at the Center for Global Health Science and Security in the Department of Microbiology and Immunology at Georgetown University School of Medicine. Dr. Phelan also holds an appointment as Adjunct Professor of Law at Georgetown University Law Center. Dr. Phelan works on legal and policy issues related to infectious diseases, with a particular focus on emerging and reemerging infectious disease outbreaks and international law. She has worked as a consultant for the World Health Organization, the World Bank, and Gavi: the vaccine alliance, and has advised on matters including international law and pathogen sharing, human rights law and Zika, intellectual property law, and contract law. She previously worked for a number of years as a solicitor at a firm in Melbourne, Australia and was admitted to practice to the Supreme Court of Victoria and High Court of Australia in 2010. Dr. Phelan's doctorate examined how overlap between fields of international law – in particular, global health law, international human rights law, and international environmental law – can serve as the catalyst to progressively develop international law to prevent and respond to infectious diseases. She also holds a Master of Laws, specializing in international law, from the Australian National University and a Bachelor of Biomedical Science/Bachelor of Laws (Honours) double degree from Monash University. She also holds a Diploma of Languages (Mandarin Chinese). Dr. Phelan is a General Sir John Monash Scholar and was recognized as an Associate Fellow of the Royal Commonwealth Society in 2015 for her human rights advocacy during the 2013-16 Ebola outbreak.

DAVID RELMAN, M.D.
Thomas C. and Joan M. Merigan Professor in Medicine, and Chief of Infectious Diseases
Stanford University; VA Palo Alto Health Care System

David Relman is the Thomas C. and Joan M. Merigan Professor in Medicine, and Microbiology and Immunology at Stanford University, and Chief of Infectious Diseases at the Veterans Affairs Palo Alto Health Care System. Dr. Relman is also Senior Fellow at the Freeman Spogli Institute for International Studies (FSI), and served as Science Co-Director at the Center for International Security and Cooperation (2013-2017), at Stanford. He is currently director of a new Biosecurity Initiative at FSI. Relman trained at MIT and then Harvard Medical School, followed by clinical training in internal medicine and infectious diseases at the Massachusetts General Hospital in Boston, and then a postdoctoral fellowship in microbiology at Stanford. His early research focused on molecular methods for pathogen discovery and over the past 20 years, on the human microbiome. He was elected to the National Academy of Medicine in 2011. Dr. Relman served as vice-chair of the National Research Council Committee that reviewed the science performed for the FBI 2001 Anthrax Letters investigation, chair of the Forum on Microbial Threats (2007-2017), and is currently a member of the Intelligence Community Studies Board (2016-) as well as Chair of a Standing Committee tasked with examining the health-related problems of US embassy personnel stationed overseas, all at the U.S. National Academies of Science. He was a founding member of the National Science Advisory Board on Biosecurity (2005-2014), a member of the Working Group on Biodefense for the President's Council of Advisors on Science and Technology (The White House) (2016), and served as President of the Infectious Diseases Society of America (2012-2013). He holds an M.D. from Harvard Medical School.

MARK SMOLINSKI, M.D., M.P.H.
President
Ending Pandemics

Mark Smolinski currently serves as President of Ending Pandemics. Dr. Smolinksi brings 25 years of experience in applying innovative solutions to improve disease prevention, response, and control across the globe. Mark is leading a well-knit team—bringing together technologists; human, animal, and environmental health experts; and key community stakeholders to co-create tools for early detection, advanced warning, and prevention of pandemic threats. Since 2009, Mark has served as the Chief Medical Officer and Director of Global Health at the Skoll Global Threats Fund (SGTF), where he developed the Ending Pandemics in Our Lifetime Initiative in 2012. His work at SGTF created a solid foundation for the work of Ending Pandemics, which branched out as an independent entity on January 1, 2018. Prior to SGTF, Mark developed the Predict and Prevent Initiative at Google.org, as part of the starting team at Google's philanthropic arm. Working with a team of engineers, Google Flu Trends (a project that had tremendous impact on the use of big data for disease surveillance) was created in partnership with the U.S. Centers for Disease Control. Mark has served as Vice President for Biological Programs at the Nuclear Threat Initiative, a public charity directed by CNN founder Ted Turner and former U.S. Senator Sam Nunn. Before NTI, he led an 18-member expert committee of the National Academy of Medicine on the 2003 landmark report "Microbial Threats to Health: Emergence, Detection, and Response." Mark served as the sixth Luther Terry Fellow in Washington, D.C., in the Office of the U.S. Surgeon General and as an Epidemic Intelligence Officer with the U.S. Centers for Disease Control and Prevention. Mark received his B.S. in Biology and M.D. from the University of Michigan in Ann Arbor. He is board-certified in preventive medicine and public health and holds an M.P.H. from the University of Arizona.

DAVID WALT, PH.D.
Hansjörg Wyss Professor of Biologically Inspired Engineering
Harvard Medical School

David R. Walt is the Hansjörg Wyss Professor of Bioinspired Engineering at Harvard Medical School, Professor of Pathology at Harvard Medical School and Brigham and Women's Hospital, Core Faculty Member of the Wyss Institute at Harvard University, Associate Member at the Broad Institute, and a Howard Hughes Medical Institute Professor. Walt is co-Director of the Mass General Brigham Center for COVID Innovation. Walt is the Scientific Founder of Illumina Inc., Quanterix Corp., and has co-founded multiple other life sciences companies. His research is focused on developing and applying new technologies to unmet diagnostics problems including infectious diseases. He has received numerous national and international awards and honors for his fundamental and applied work in the field of optical microwell arrays and single molecules. He is a member of the U.S. National Academy of Engineering, the U.S. National Academy of Medicine, a Fellow of the American Academy of Arts and Sciences, a Fellow of the American Institute for Medical and Biological Engineering, a Fellow of the American Association for the Advancement of Science, a Fellow of the National Academy of Inventors, and is inducted in the US National Inventors Hall of Fame.

Standing Committee on Emerging Infectious Diseases and 21st Century Health Threats

Perspectives on a Long-Term Research Agenda for COVID-19

June 2022 – Draft v2 – June 8, 2022

Outline

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OVERVIEW

The long-term impacts of COVID-19 on individual and population health are yet to be fully understood. The Standing Committee on Emerging Infectious Diseases and 21st Century Health Threats was asked to consider the utility of and the requirements for a comprehensive, evidence-based research agenda on the long-term health impacts and consequences of COVID-19.

The dual aim is to help the U.S. respond to COVID-19 over time and to help our nation become more resilient to future public health emergencies.

In preparation for the Standing Committee on Emerging Infectious Diseases and 21st Century Health Threats virtual meeting on June 17, 2022, committee members were asked to reflect on a topic related to their area of expertise and to describe:

- The topic area as it relates to a long-term COVID-19 research agenda
- Current state of what is known about the topic
- Key gaps and priority research questions

Topic areas suggested to committee members included: Public health response management; Patient care, long-COVID impacts, at-risk populations, and strategies for clinical management; Health equity, community engagement, crisis communication, and mis/disinformation management; and Medical countermeasures (including therapeutics, vaccines, and diagnostics) and underlying microbiological characteristics.

This document provides a summary of the insights and perspectives shared by committee members.

***Disclaimer**: This summary was prepared by National Academies staff as a record of feedback provided in preparation for the June 17, 2022, Standing Committee on Emerging Infectious Diseases and 21st Century Health Threats virtual committee meeting. This document was prepared for information purposes only. It has not been through the institution's external peer review and should not be cited or quoted, as the views expressed do not necessarily reflect the views of the National Academies of Sciences, Engineering, and Medicine or the Standing Committee on Emerging Infectious Diseases and 21st Century Health Threats.*

SUGGESTED TOPIC AREAS

***NOTE**: Feedback on research questions for the topic area "Medical countermeasures (including therapeutics, vaccines, and diagnostics) and underlying microbiological characteristics" is pending.

Addressing New Variants

Overview:

Lessons gleaned from the past can inform how we predict, anticipate, and prepare for potential variants of concern that may emerge in the future. A set of questions and priorities to prepare for new variants or other related, rapidly-evolving events will greater enable a coordinated pandemic response.

Research Questions:

- How to better predict need for and effectiveness of variant adapted vaccines when new variants or a SARS CoV 3 arises?
- How to get a better handle on whether new variants are likely to pose problems, more quickly than we have, and to decide if there are additional questions that need to be asked and answered each time things change?

Contributors: Nicole Lurie

Face Mask and Respirator Use

Overview:

There are a large number of studies with methodological weaknesses that prevent firm conclusions on the effectiveness of face masks and respirators. Evidence suggests face mask use and respirator use are beneficial, however additional evidence is needed.

Key Gaps and Research Questions:

- Population level impact under various scenarios of pathogen transmissibility, mask/respirator quality & fit, and level of compliance, is not known.
- What is the population-level impact of face mask (i.e., surgical) and respirator use by public on transmission of viral respiratory disease (incl influenza and CoV-19)?
- Should this be a standard PH recommendation during periods of increased transmission?
- Can the benefit be quantified?

Contributors: Jeff Duchin

Coordination and Stakeholder Engagement

Overview:

A systematic body of knowledge on coordination and stakeholder engagement is potentially lacking.

Key Gaps and Research Questions:

- How do we optimally integrate the clinical healthcare delivery system and public health system at state and local levels during bio-emergency response (including patient evaluation, management, and clinical data collection & transmission, countermeasure administration, support for community-based response needs [field teams for assessment in vulnerable populations, mass testing/vax sites]?
- Healthcare coalitions provide a framework for this activity: How well did healthcare coalitions (that provide a framework for these activities) perform during the CoV-19 pandemic? What needs to be improved to meet future scenarios?
- How do we engage university and private sector assets in the response (e.g., authorization of laboratory-developed tests).
- How can we improve public compliance with non-pharmaceutical interventions?

Contributors: Jeffrey Duchin, Nicole Lurie

Contact Tracing

Overview:

Greater understanding is needed on the role of contact tracing in managing SARS-CoV-2 exposures and COVID positivity. More specifically, how and when contact tracing should be done in a fast moving respiratory infectious disease.

Current State:

Contact tracing as historically practiced was inadequate during the SARS-CoV-2 pandemic because of its asymptomatic spread and rapidly evolving variants. The antiquated nature of our disease reporting systems (speed, accuracy & paper based fax component) as well as the lack of clear reporting guidelines contributed to the problem. New technologies such as proximity apps have promise, but remain in their early stage of development and still have a lag time that to date is often too long for effective doses-axe control. The delay in initial testing followed by the transition to self-testing has complicated this problem creating additional delays in contact tracing even when the self-test is eventually reported. This resulted in abandonment of contact tracing for periods throughout the pandemic during surges and no clear guidelines on when to resume contact tracing when the disease level diminishes to an actionable level.

Key Gaps and Research Questions:

- When should traditional contact tracing be used?
- When should individual contact tracing be abandoned or put on hold and what are the criteria for restarting it?
- How effective are proximity technology apps in disease control?
- Are their new contact tracing and notification models that are more effective for disease control?
- Does effective disease control using contact tracing taper or eliminate the need for community activity (school, business, travel industry) closures?
- What is the fiscal return of investment of a well-functioning disease control system using contacting tracing?
- Do we need to do contact tracing at all anymore for infectious outbreaks like this one? Can these resources then be freed up to do other more productive disease control work? This would be useful for any respiratory pandemic with the characteristics of a virus that passes asymptomatically and continues to evolve rapidly. It is a critical question if the morbidity or mortality increases.
- Does full primary vaccination and boosting alter the need for contact tracing for breakthrough infections? In other words, does full vaccination inhibit viral load sufficiently to negate the need for reporting and tracing?
- When can we normalize COVID management like influenza? If so, what ate the surveillance triggers to resume more aggressive individual reporting and contact tracing. New variants of public health concern, new surges at a certain rate, increased morbidity, increased mortality, etc.

Contributors: Georges Benjamin

Epidemic Modelling

Overview:

Multiple modeling groups produce information that may or may not be harmonized with current public health response needs.

Key Gaps and Research Questions:

- How to optimally integrate academic modeling expertise into public health response in real time?
- How to identify questions existing modeling capacity can inform
- What are realistic time frames for actionable results?
- What is optimal format for communicating results & limitations?
- For example, under prevalent viral transmission dynamics and population immunity, what impact would NPI have under varying assumptions about effectiveness and level of compliance?
- Can one model the impacts of restrictions on public health authorities in state/local jurisdictions might have on impacts of future epidemics or pandemics?

Contributors: Jeffrey Duchin, Nicole Lurie

Health Equity

Overview:

In the United States, COVID-19 has had a disproportionate impact on the health of members or racial, ethnic and underserved communities. Communities of color also suffered disproportionate morbidity and mortality during the CoV-19 pandemic due to long standing health disparities from recognized root causes. Careful attention is needed on health equity, community engagement, crisis communication, etc.

One of the big challenges during this pandemic was related to data equity —- what information was collected, who had access, timeliness, and usability. A focus on equity-centered data systems are needed, given the disparate impact of the pandemic by race, ethnicity, geography, disability, income, to name just some demographics, the lack of granular, real-time data, cost lives.

Key Gaps and Research Questions:

- How to improve public health's role in communication, outreach and increased participation, particularly in underserved communities? - this is a difficult task that desperately requires further research, in light of historically-based mistrust of many communities.
- What policies and community-based capacity and relations with the public health system are necessary to allow optimal bio-emergency response that minimizes health inequities?
- What specific activities, capacity, relationships, and/or structural changes are needed to effect better health outcomes in communities of color?
- Conducting research that sheds light on vulnerabilities (including social determinants of health) and incorporates One Health thinking in solutions and shaping policy.
- Integrating social aspects in understanding risk of emergence in human populations
- Improve employment of human and social sciences and psychology.
- Mapping and characterizing social and regional health inequalities: individual factors and structural aspects of exposure to infection and access to treatment.

Contributors: Richard Besser**,** Jeffrey Duchin, Patricia King, Jonna Mazet

References:

Christopher, G. C., et al. "Charting a course for an equity-centered data system: recommendations from the National Commission to Transform Public Health Data Systems. Robert Wood Johnson Foundation." (2021). https://www.rwjf.org/en/library/research/2021/10/charting-a-course-for-an-equity-centered-data-system.html

Legal Authorities

Overview:

The impact of unwinding and limitation of legal authorities and powers for public health should be urgently considered for public health response management. Public health authorities from the local to the national level have been severely restricted, either through legislative or judicial action. This puts us in a particularly vulnerable position for acting on ongoing and future public health threats: through both actual and perceived restrictions in powers to act to protect public health.

Current State and Key Gaps:

There are groups (such as the National Public Health Law association and our Georgetown Center for Health Science and Security) that have been tracking some of these restrictions, but there is not yet a comprehensive understanding of the implications that this could have for future response. Some legal actions are still pending (e.g. there is an Amicus Curiae brief going to the Federal Court on the CDC mask mandate and the incorrect interpretation of "sanitation"). There are some efforts to create model legislation but these have not been appropriately informed.

Contributors: Alexandra Phelan

One Health Research Needs for Pandemic Preparedness and Mitigation

Overview:

Host and transmission dynamics, impacted by environmental stressors and anthropogenic changes, have implications for future spillover events. Further understanding of the origins, natural hosts, and animal reservoirs of pathogens, coupled with improved surveillance systems and understanding of human behaviors, can inform infection mitigation measures.

Key Gaps and Research Questions:

Surveillance & Data Needs:

- Global viral surveillance at human-animal interfaces to identify and characterize viruses to help prepare for, prevent, and mitigate risks from *Disease X*
- Devise safe and innovative One Health epidemiological surveillance methods useful for implementation by national and regional networks – examples:
    - Continue to evaluate, enhance, and scale wastewater testing
    - Employ wildlife virus surveillance to improve vaccine targets and need inspired medical and technological innovations
    - Improvement of biosafety and biosecurity through automatization of sample collection, storage, testing, etc. (e.g., robots, drones, sensors)
- Improve capacity to monitor animal reservoirs of potentially zoonotic pathogens for shifts in viral diversity and changes in the viruses themselves
- Conceive methods to improve the collection and use of human behavior data, especially high-risk behaviors and compliance with public health safety measures, as well as the perception of risks and willingness to mitigate them through personal action
- Identify and understand geographic zones where emergence of disease is heightened due to regional and global changes, including climate variation
- Optimize syndromic surveillance in medical record systems or other easily implemented tools and integrate that data with real-time genomic data and other methods of passive digital surveillance

- Improve bioinformatics pipelines to handle large volumes of data and their interpretation during a crisis
- Devise systems to strengthen and integrate local, regional, national, and global surveillance systems
- Improve surveillance models to better collect/collate and integrate heterogeneous data

Basic Science to Improve Prevention Policies:

- Pathogen and host biology
    - Identification of hosts from which emerging pathogens can spillover
    - Characterization of potential pathogens from these hosts
    - Host natural history, genetic makeup, and population vulnerability and resilience
    - Host-pathogen dynamics, including immunology
    - Molecular mechanisms essential to the life cycle of the pathogen (including host/pathogen interactions) allowing identification of the best therapeutic targets and/or the development of vaccines
    - Ecology of infectious agents, their interactions with vectors/reservoirs/intermediate hosts, and their secondary spread (e.g., in water and air)
- Drivers of spillover:
    - Animal trade & non-traditional farming (e.g., guano)
    - Expanding human populations
    - Changing land use (agroecological transition, human intrusion in protected areas, intensive urbanization)
    - New animal breeding and agricultural practices
    - Globalization
- Ecosystem stressors that could drive changes in pathogens and hosts (e.g., effect of climate on all hosts and their resilience to infection and shedding in the face of a changing climate)
- Socioeconomic impact of zoonotic diseases (historical & projected)
- How spatial and temporal scales and changes may affect host-pathogen relationships (e.g., biodiversity loss and pathogen circulation)
- Phylodynamics and the use of genomic data for monitoring pathogens in time and space at the molecular level (monitoring of variants; requires shared systems, together with sequencing, bioinformatics, and ad hoc storage platforms)

Human Health, Behavior & Communications:

- Investigate the interconnected determinants of human, animal, and ecological health, including drivers of pathogen emergence and the disproportionate impact of emerging zoonoses on underrepresented communities
- Conduct transdisciplinary research on optimal health communications
- Create knowledge on public perceptions, attitudes, and behaviors with regard to acceptability of prevention practices, as well as vaccines and treatmentsand disaggregate demographically subgroups (by gender, generation, social class, race, community, etc.)
- Increase knowledge on how to influence human actions to reduce impacts on the emergence of zoonotic diseases
- Improve health communication and promotion: production and diffusion of scientific information, role of the media, particularly social networks, building trust, attitudes with regard to science, and the problem of conspiracy theories and fake news
- Assess the costs and benefits of contrasted agro-socio-ecosystems by simultaneously considering farming practices, social and economic well-being, various environmental impacts and emerging disease threats

- Assess the impact of health measures in the different areas of the daily life: exposure to infection, healthcare consumption, personal and family life, mental health, employment and financial resources, living and working conditions, mobility; and at the macroeconomic level: employment, poverty, human capital
- Improve system coordination using cross-sector communication models and by devising organizing principles & conducting trainings
- Increase understanding of the architecture and multi-scalar nature of governance to transform political engagement into positive participation
- Develop short- and long-term strategies for coordinated monitoring, preparation, and mobilization of the academic community, not for profits, and industry in organized public health
- Research emotional/psychological responses to pandemic through art, music, etc.

Mitigation of Exposure/Infection & Pro-active Vaccine Strategies

- Model the spread of potential *Disease X* agents in demographically diverse populations
- Identify the environmental, socio-anthropological, and epidemiological drivers for epidemic spread
- Adapt approaches to monitor and control emerging health threats using scientific data and modeling forecasts
- Assess the risk of emerging resistance to new anti-infective agents and adapt therapeutic strategies
- Search for anti-infectious compounds covering the spectrum of the main viral, bacterial, parasitic, and fungal families infecting vertebrates
- Consider neutralizing monoclonal antibodies from convalescent individuals for target pathogen families, thereby identifying the most cross-reactive, with high potential to protect against new agents liable to emerge in the target family
- Develop vaccine pipelines for emerging and re-emerging agents using a risk-based strategy
- Attempt to determine the target of the most potent neutralizing antibodies for each pathogen family through structural biology studies
- Explore AI approaches to target and track receptor binding for viral families that have spillover potential
- Investigate options to meet the growing food demand by reorienting/designing food systems to reduce the risks of pathogen transmission, while also providing equitable access to nutritious food
    - Develop strategies to reduce wildlife/livestock contact

Diagnostics

- Develop and implement diagnostic instruments and pipelines for all known emerging and re-emerging pathogens, with robust quality standards, compatible with the medical and veterinary diagnostics
- Set up a generic diagnostic capacity that can be rapidly adapted to an emerging event and deployed at the relevant sites for humans and host species
- Organize the collection and map availability of diagnostic reference products (strains, natural and synthetic positive controls, specific antibodies) and biological specimens from human and veterinary clinical research programs on emerging events
- Identify predictive biomarkers of the clinical course of Disease X

Education and Engagement

- Develop One Health curricular offerings for all stages of education from elementary to university and beyond
- Design and implement more in-depth One Health curricula for accredited health programs, including veterinarians, physicians, and other licensed healthcare providers and public health practitioners in training, as well as curricular offerings for K-12 and undergraduates

- Offer collaboration training for researchers and healthcare personnel to improve sharing of knowledge and data and to form best practices in health management
- Conduct participatory research and engage with communities (consider involving patient associations, consumer associations, community based organizations, and citizens) to understand needs and obstacles to public health goals and to help improve scientific literacy and acceptability
- Advance interactions between expert scientific organizations and political/governmental decision makers as part of the public policymaking process to improve the efficient employment of institutions during crisis

Contributors: Jonna Mazet

Post-COVID Conditions and Pediatric Impacts

Overview:

The underlying causes and mechanisms for Long COVID (Post-Acute Sequelae of COVID (PASC)) and Multi-inflammatory Syndrome in Children (MIS-C) have not yet been identified. These conditions have the potential to cause huge burdens on the healthcare system because of their chronic nature. Assuming that COVID-19 becomes endemic, we will continue to see patients presenting with long COVID and MIS-C. If the number of patients affected is in the present range of 10-20%, then this will cause loss of productivity and debilitating symptoms in millions of people.

Any useful investigation of or response to Long COVID (LC), or post-COVID conditions (PCC) must take into account the enormous scale, scope, complexity and urgency of the problems and consequences associated with this syndrome. As was the case during the COVID-19 pandemic, investigations based on individual, disconnected efforts will likely lead to statistically underpowered studies, a bevy of confusing biological endpoints, and a waste of money and time.

A national – or preferably, international - strategy to rapidly and efficiently determine and disseminate an understanding of the underlying biology and effective clinical treatment of Long COVID is essential to success. Scientific studies, clinical investigations and social support schemes pursued as disjointed, independent, business-as -usual efforts are highly likely to fail.

Efforts to prevent Long COVID, and alleviate the suffering of those already afflicted should be granted urgent priority in view of the current scale of the problem and the ongoing nature of COVID-19 infection. Delays in determining the causes, prevention and treatment of Long COVID, failure to rapidly disseminate such findings, or impediments to LC patients accessing effective care will prolong human suffering and incur substantial financial costs to patients, health care systems and the nation.

Thus, an effective approach to Long COVID cannot be business as usual. Instead, a well-coordinated, multi-pronged national effort is needed that establishes clear goals, aligns academic and private sector research efforts, and prioritizes strategic endpoints and approaches. The closest model of such an effort in recent times is probably the Operation Warp Speed (OWS) project, which featured close coordination between government and industry, common goals, extensive sharing of information among participants, federal efforts to de-risk private sector investments, and regulatory speed and flexibility. The obvious shortcomings of OWS, such as failure to adequately communicate the value and safety of COVID-19 vaccines, should also be considered in designing an approach to Long COVID.

Current State:

Scale of the Long COVID Problem

Long COVID is a potentially immense global problem with medical, social and economic impacts possibly playing out over decades. It could even constitute as big a social challenge as the COVID-19 pandemic itself.

Even using conservative estimates of Long COVID cases, the scale of the problem constitutes a major international public health emergency. Current estimates are that 10-30% of those infected with COVID-19 and its variants experience long COVID symptoms. To date, over 83M Americans have been infected with the virus and over 526M have been infected globally. Both numbers are certainly undercounts. Thus, we might expect a rough estimate of 8-17M Americans to be affected by long COVID, and between 52M-175M to be affected worldwide.

Long COVID symptoms are known to occur even in those with mild or no symptoms. A recent study seemed to indicate that risk peaks in middle age, when people have major responsibilities to family and are most economically productive. Thus, LC could pose devastating socioeconomic damage, especially among communities already stressed economically, have less access to health care, and which bear exceptional burdens of infection.

Scope of Long COVID Problem

Long COVID patients face potentially serious, and thus far poorly understood, medical manifestations, (heart, lung and kidney dysfunction);mental health consequences (“cognitive fog”, depression and anxiety, etc.); and possible long-term disability and loss of economic productivity. The costs (monetary and otherwise) of Long COVID to families, employers and governments will likely be extensive and prolonged. Stigma and scapegoating, which occurs in all epidemics, could maim lives, and last for lifetimes.

In some ways, albeit on a much larger scale, long COVID is somewhat analogous to the complicated situation related to Gulf War Syndrome - something that has been variously endorsed or denied as a real problem, with the various research efforts associated with it representing a patchwork of good science and opportunism.

Taming Long COVID will require efforts on many fronts, including those listed below. The potential scope of LC is such that with the right focus (and funding), we might be able to learn something meaningful.

Key Gaps:

Scientific Studies Will Be Extremely Challenging –

Clinical Studies - The absence of an association between clear and consistent clinical presentations or reliable biological markers and a diagnosis of LC will make clinical and biomedical studies especially challenging. It is possible that Long COVID actually encompasses several different or related syndromes.

In addition, the prevalence and burden of Long COVID is likely underestimated. Study cohorts will have to be exquisitely defined, probably quite large, and followed over long periods - likely decades, given what we know about other post-viral syndromes. Standardization of case definitions and endpoints – especially cognitive and mental health-related outcomes, across studies will be essential. Disparities among individuals in study populations in socioeconomic status, health care access, including access to vaccines and treatments for acute COVID, will have to be taken into account.

The complexity, likely costs and urgency of LC clinical studies **mandates centralized design and oversight** of study designs, patient enrollment and measured endpoints, as well as agreements among researchers to share pre-competitive data, use of Master protocols, etc. Consideration should be given to establishing a comprehensive, centralized data base. To ensure fair access to study participation and clinical trials, enrollment of representational sample populations and cost-effective management, use of digital monitoring (which must also be validated and standardized) will be essential.

Investigation of Long COVID Molecular and Biological Disease Mechanisms –

A myriad of identified factors have been associated LC in recent studies, including high levels of RNA virus early in infection; presence of autoantibodies; reactivation of Epstein Barr Virus; and history of type 2 DM, and presence of underlying illnesses generally. But the risk factors and the molecular mechanisms that lead to LC are simply not known. Multiple organ systems can be involved in LC, either directly as a result of the virus or through more indirect interaction with the patient's immune response. A far deeper understanding of the basic science behind human immune responses will likely be necessary to solve the problems LC presents.

International coordination and collaboration strategies that benefited progress in understanding, preventing and treating HIV/AIDs should be considered and incorporated into scientific investigation strategies. For example, rapid and open publication of study results – among researchers and patients - should be a strong feature of LC investigations world-wide. Solutions which can be employed around the world, not just in sophisticated medical settings, should be prioritized.

Patient Treatment and Support will Require New Strategic Approaches

Currently, the needs of LC patients and the clinical capabilities and financial expectations of American health care institutions are not well aligned. The need to formulate and effectively deliver care for Long COVID victims is occurring during a pandemic which has already overwhelmed most health care systems, including those in the U.S.

The financial costs of caring for LC victims are almost certain to be high, while the uncertainties surrounding diagnosis and treatment will likely complicate reimbursement, even among those with insurance. Access to effective care will be a huge problem, particularly among "essential workers". Mechanisms to ensure health care access and to support health care institutions caring for such patients will be needed. Consideration of the (eventual) approaches to care and disability compensation granted to 9/11 First Responders and some military groups (Agent Orange) might be warranted.

LC patients have reported great difficulty finding appropriate health care providers, even in large cities with specialized care. The difficulty diagnosing the disorder, lack of understanding of LC causes, and the confusing range of symptoms it can manifest, and limited knowledge of effective treatment approaches would be difficult in any circumstances. But the need for compassionate and effective medical care for millions of LC victims is happening at a time when physicians are exhausted, hospitals are financially stressed and short-staffed, and physician performance and reimbursement requirements are increasingly rigid and demanding rapid and predetermined patient evaluation and treatment.

Mental Health services, already in dangerously short supply, will be further stressed by LC victims and their families. Beyond diagnosing the mental consequences of LC, which will be necessary for obtaining access to care services as well as financial reimbursement and disability support, provisions will be needed to meet demand for mental rehabilitation services.

Efforts to rapidly educate health care providers about LC and to support the delivery of effective care are essential. National and international efforts to rapidly identify and communicate effective approaches will be essential. It will also be critical to adjust expectations of physician performance to the reality of caring for a very large population of sick people whose underlying illness, biological causes and appropriate treatments will elude us for some time. Access to care, especially in communities hardest hit by the pandemic, including immigrant communities, will be a major problem. Telemedicine and remote monitoring care should be expanded and made available to patients and covered by insurance.

Clinical specialization focused on team-based care to maximize patient care and clinical excellence and efficiency, as evolved during the HIV/AIDs epidemic, will likely be necessary, and should be encouraged, at least until the disease course and effective therapies are better understood.

Realistic insurance and federal reimbursement to clinicians, rehabilitation services and hospitals will be essential.

Since better diagnostic precision will be key to identifying patients, structuring research studies, and devising effective treatments and paying for it all, the federal government should make the **development of diagnostic tools for LC a priority, and should examine financial and regulatory barriers to diagnostic innovation as has been encountered during the pandemic.**

Many LC patients are extremely debilitated by their illness and experience radical disruption of their ability to care for themselves, their families or hold down a job. **Adjustments to employer-based and government disability programs will be needed.** As will epidemics throughout history, social stigma is also likely to impact LC sufferers and should be anticipated and discouraged.

Special Attention Will Need To Be Devoted To Possible Long Term Impacts On Infants And Children

Special attention will be needed on possible long term impacts on infants and children, including, but not limited to, neurodevelopmental effects, physical health and development, and behavioral problems. This will be difficult, because even highly infrequent effects – hard to detect without very large sample sizes – will be objects of concern from parents and the general population.

Of note, the study of long term COVID impacts on infants and children is likely to be emotionally charged in the public arena. As we try to clarify causes and effects, we will encounter doubts about the science, closely held beliefs, misunderstandings of risk, and suspicions (think about autism and vaccines as an analogue), and there will need to be study and planning about communications and public trust and understanding.

Research Questions:

- Underlying mechanism/etiology for PASC and MIS-C
    - What are the underlying causes of PASC (likely multiple)?
    - What are the underlying cause(s) of MIS-C?
    - Are there therapeutic interventions that can prevent PASC and MIS-C either prior to, during, or post infection to prevent PASC and MIS-C?
- Case definition – what is included in the case definition and what is not? This is unlikely to be a uni-factorial process – for those with prolonged hospitalizations it's a mistake to attribute prolonged fatigue and many other symptoms to a new process for example – and each organ system in some ways may need its own definitions / thresholds. In many cases, there is a psychological contribution that is likely primary in some cases and secondary in others – teasing this out is critical.
- Risk factors – there is some evidence on this already, but it needs to be crystallized with additional research.
- Pathogenesis – COVID-19 clearly seems to have some defined effects on the neurologic, respiratory, and cardiac systems – what is the mechanism and why does this happen?
- Treatment – what are promising modalities for treating these symptoms based on the pathogenesis? What is working already and based on pathogenesis what specific targeted treatments may be needed? Is there a need for new therapies? Would these cross over to treat other similar pathologies?
- Prevention – is there a way to predict / prevent these syndromes from occurring? Are there early treatments during the disease process that decrease the incidence? Does vaccination have impact in prevention or attenuation?
- Impact – for those that are / believe they are suffering from long-COVID what has been the physical, social, and economic impact?
- What is the low-hanging fruit and what deserves longer-term investigation / investment? Where is the greatest future return on investment – particularly in understanding pathology and identifying

new treatments that might contribute to broader categories of patients beyond long COVID that have similar impairments.

- What anti-virals do we need to further stockpile/develop to anticipate needs of future pandemics influenza and otherwise?
- What are some of the key viruses with pandemic potential and where do we stand with vaccine development for them?
- How do we continue to improve vaccine development and manufacturing?
- How do we combat disinformation more effectively?
- Can we show that patient transfer / distribution mechanisms in states made a difference in mortality?
- Look at non-COVID-19 excess mortality in urban and rural areas to help define future needs and strategies
- Look at racial and geographic differences in COVID and excess mortality to define intervention populations, as well as examining factors that made persons less likely to seek care / vaccination. What are their trusted sources of information? How do we tap into those?
- How can we improve critical care so that it can be expanded? AI and automated integrated technologies have tremendous promise but we need to figure out the specifics and the levers…
- How do we improve our ability to develop and scale clinical testing?
- What belongs in the public health lane going forward? Many mass vaccination and testing plans that fell on public health prior to the COVID-19 pandemic clearly did not work and healthcare wound up taking this on – in many cases there is no good return on investment here and staffing was difficult (and MRC in many communities failed to meet the needs) – where do we go from here? Can we depend on public health during a biological threat event to do mass prophylaxis? Or should this be done by / with major support from private logistics partners and healthcare?
- Creation of a registry – in fact, the entire topic needs much better definition to begin with – the NIH paper (doi:10.7326/M21-4905) demonstrates that should be a top priority.
- Better characterization of host immunity -- who gets sick? Who doesn't? who gets post- COVID Conditions? Who doesn't?
- Examination of bio-psycho-social links to inflammation and the risk of post Covid conditions
- Correlation to viral load present (is there correlation?); correlation to GI involvement and lymph
- node viral retention; correlation of anosmia to neuro-cognitive sequelae
- Correlation to the use of therapeutics – paxlovid, vaccine, monoclonals and immunomodulators
- What surveillance methods could give us greater certainty about who has COVID and who does not, so as to better be able to attribute long term physical and neurodevelopmental status to the virus?
- Pediatric COVID impacts
    - By what methods could we parse out the effects of COVID on infants and children from background physical and neurodevelopmental problems that are always in this subpopulation?
    - How shall we deal with the likelihood that many COVID cases in infants and children will likely not have been diagnosed? The methodological questions are very important.
    - If patterns of long term consequences for the pediatric population emerge, policy questions will emerge, as well, about coverage and payment for care and for educational and developmental supports. We may do well to anticipate these.
    - What are public health/population health approaches to the mental health impacts of the pandemic, especially for youth, and how to mitigate such effects in future pandemics?

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Risk and Crisis Communication

Overview:

Members of the public need authoritative information about the potential risks and benefits of actions that they can take regarding pandemic diseases (e.g., vaccination, masking, traveling, visiting relatives) and about the policies that officials take on their behalf (e.g., restrictive mandates, testing protocols, insurance guarantees). Effective risk communications lead to better decisions and greater trust in officials (and their science). Effective communications also provide a bulwark against disinformation, by enabling people to rebut it on their own and encouraging reliance on official sources. Conversely, ineffective official risk communications can lead to confusion and frustration, along with reliance on other sources (NASEM, 2020).

Note: "Risk Communication" has become the term of art for communications regarding the outcomes of risk-related decisions, including not just risks, but also expected costs and benefits, some of which come from reducing risks (as with medical procedures).

Crisis and risk communication is also more difficult in underserved communities because of differences in access to new media tools (smart phones in particular); WiFi access, disinformation, misinformation, inadequate numbers of informed trusted messengers and baseline mistrust of authority including health providers/systems.

Current State:

We actually know a lot about how to do risk and crisis communication but not how to get the system to implement best practices early. We know a lot about how best to engage underserved communities.

Risk communication is an iterative process involving interdisciplinary teams that:

- Analyze decision makers' information needs (decision theory)
- Describe their current beliefs and values (behavioral science)
- Draft communications, faithful to scientific understanding (subject matter expertise)
- Test with those drafts with prospective users (evaluation/implementation research)
- Repeat, as necessary.

Risk communication has existed as a distinct field for roughly half a century. It arose to address rising skepticism regarding science and technology (e.g., nuclear power, genetically modified crops, vaccines). It has drawn on advances in behavioral research, delineating heuristics and bias in judgment and decision-making processes. It studies both experts and non-experts. As examples of research results:

Studies of non-experts often find that they:

- Have incomplete mental models of the processes that create and control risks.
- Have an imperfect sense for how much they know, tending to overconfidence when their knowledge is limited, under confidence when it is extensive.
- Have difficulty evaluating the quality of decisions, subject to hindsight bias and outcome bias.
- Are sharply attuned to cues regarding trustworthiness (competence, honesty).
- Can be supported or undermined by their emotions.
- Can learn quickly from well-executed, proactive risk communications.

Studies of experts often find that they:

- Are like non-experts when relying on intuition (e.g., overconfident, when their knowledge is limited).
- Have procedural safeguards against fallible intuitions (e.g., peer review).
- Are insensitive to disciplinary norms that privilege some kinds of information (e.g., readily quantified).
- Are insensitive to social and ethical biases in their practices (e.g., definitions of "risk," treatment of distributional effects, unrepresentative data sets).
- Have poor intuitions regarding lay audiences, especially those with different backgrounds.
- Appear competent, but cold to the public.

Three NASEM colloquia on the sciences of science communication provide introductions to the potential contributions of different social, behavioral, and decision science disciplines (Fischhoff & Scheufele, 2013, 2014, 2019). Articles within these collections also offer narrative overviews (Fischhoff, 2013, 2017; Fischhoff & Davis, 2014). FDA's Risk Communication Advisory Committee produced an edited volume for practitioners (Fischhoff, Brewer & Downs, 2013). An early NASEM consensus report (1989) captures the field at its emergence.

Key Gaps:

Operations Research

Research on why risk and crisis communication comes too late/later in the response is missing. Also, the funding for doing risk and crisis communication always seems like an afterthought and goes to groups that are not the ones that culturally can make the biggest impact. The need is an operations health services research agenda on how best to get the system to engage these communities early with the right messages, messengers and tools that have been informed by evidenced based message testing.

Mental Models of Processes Creating and Controlling Risks

Risk communication research has advanced by addressing fundamental issues arising in applications. For example, researchers have studied how people think about exponential processes in the contexts of invasive species, population growth, and radioactive decay. They have studied lay perceptions of field strength in the context of 60 Hz fields, contamination in the context of food safety, and mutations in the context of genetic counseling.

Research gap 1: How do we translate existing research into terms useful for the professionals charged with communications regarding pandemic risks and control mechanisms (e.g., explaining exponential spread of infectious disease)?

Research gap 2: How do we identify and study phenomena unique to pandemic disease (e.g., cascading transmission pathways, layered protective measures, the implications of uneven global vaccinations)?

Quantitative Estimates

Decisions depend on the size of the risks (and benefit) of choice options. Although non-experts sometimes struggle with quantitative estimates, their confusion is, often, not with the number but with the event to which it is attached. For example, what do weather forecasters mean by "rain" in "the probability of rain Is 70"? They may also be misled by communications that omit critical details that experts know, but fail to convey (e.g., the size of the population in which disease cases were observed, known biases in reporting).

Research gap 3: How do we create clear terminology for terms that are critical to understanding pandemic risks, both when experts agree (e.g., effectiveness, efficacy) and when terms are still in flux (e.g., long COVID)?

Research gap 4: How do we explain the limits to scientific knowledge, so that changes are seen as scientific progress, rather than confusion (broken promises, flipflops, etc.)?

Trust

How people seek and interpret information depends on their trust in sources. Studies of trust in sources of pandemic risk information echo studies in other domains, in terms of the cues they use to assess sources' honesty and competence. Those are found in both what sources say and how they say it. Studies find that once lost, trust is hard to regain, especially after people have turned to other sources. The challenges increase when the parties have different backgrounds and lack direct interaction, reducing the expectation of shared values and opportunities to correct misunderstanding.

Research gap 5: How do we ensure that experts know the information needs and expectations of the diverse publics that depend on them, so that they can secure and retain trust?

Research gap 6: How do we explain the rationale for public health policies (e.g., restricting some groups for the protection of others, delaying or pausing the availability of treatments)?

Research Questions:

The research gaps (above) are formulated as priority research questions. Addressing them will require institutional design, as well as material resources. Effective risk communication requires a research enterprise that can:

- Rapidly assess and consistently monitor the information needs and perceptions of diverse publics.
- Support the community partnerships essential for trusted two-way communications.
- Create the interdisciplinary teams needed for successful applications, with expertise in analyzing decisions, summarizing scientific knowledge, describing lay perceptions, and developing risk communications.
- Provide incentives for basic researchers to work on those teams, contributing their broad knowledge and intellect.
- Work with public health organizations to develop consistent practices and policies, making trustworthy risk communication possible.

Achieving these goals will require innovative research programs. They must support strong basic research, given the difficulty of the problems and the stakes riding on their solution. They must be more agile than conventional proposal and review cycles, in its response speed and flexibility. They must support continuing two-way communication with policy makers and community partners. They must engage risk communication researchers in decisions regarding data collections and analysis, so that those data are as relevant as possible to the decisions that depend on them, as needed for effective communications.

Additional research questions for consideration are:

- Are delayed effective communications a cause of health inequities? The hypothesis is that a well-structured system that is permanently in place, has worked to build trust, has the right messengers and can be quickly informed by good information, and deliver health information that will overcome mistrust, minimize misinformation, and combat disinformation. Such a process will reduce preventable health inequities.

- Can early message testing of underserved communities around health threats better inform public health interventions and improve health disparities? This can be informed by the experiences and research agendas of major health threats every year from severe storms, other environmental emergencies/urgencies, gun violence, food borne outbreaks, etc.
- What is the role of social media mis/disinformation and how is best to counter it?
- What is the best way to combat misinformation and the infodemic?
- What are evidence-based best practices for communicating and building trust during an evolving public health emergency in the setting of extreme political polarization and mistrust of government and institutions?

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Meeting of the Standing Committee on Emerging Infectious Diseases and 21st Century Health Threats

December 9, 2021
Notes from Closed Session Strategic Planning

Exploratory Research Topics and Questions

Topic	Background	Key Questions
COVID-19 vaccine strategy to address new variants of concern	Currently available vaccines may be less effective with the emergence of new COVID-19 variants of concern (VOC). Alternative strategies to address this issue are to develop vaccines that are more specific, provide broader coverage, or a balance between the two.	- What is the timing for new vaccines? - What is the interim strategy? - What are regulatory, production, and deployment considerations for new vaccines? - Do we need a universal or pan-Coronavirus vaccine?
Omicron variant issues and impacts on the US	The Omicron variant is currently surging in the U.S. and there continues to be uncertainty regarding the duration of the surge, the severity of cases to be expected, and populations at greatest risk for infection.	- What are the urgent issues that need to be addressed? - What do we know about the existing variants? - What health impacts can be anticipated with the information available? - How do we address pediatric illness?
Scientific readiness	With any emerging crisis, a core set of scientific capabilities are needed to respond to issues rapidly. Pre-positioning capabilities and defining research priorities toward bringing clarity to these issues allows for quick adaptation in response to the crisis.	- What are the research priorities? - What needs to be done to create standardized capacities and centers? - What capabilities need to be prepositioned? - Where do we anticipate significant scientific roadblocks? - How can we quickly assess the level of risk that a new variant presents? - What can we do now to prepare for the next pandemic?
Anticipating future COVID-19 scenarios	Lessons gleaned from the past can inform how we predict, anticipate, and prepare for potential variants of concern that may emerge in the future. A set of questions and priorities to prepare for new variants or other related, rapidly-evolving events will greater enable a coordinated pandemic response.	- What could future variants look like? - How can we identify scenario-based strategies for potential future variants? - What factors are most important to map out, trace, and monitor (i.e. transmission, severity, etc.)? - Can we use any lessons learned from the flu to anticipate future variants and vaccines that may combat them?

Legal and social readiness* **Potential area of collaboration with the CDC Standing Committee on Public Health Preparedness and Response*	Experiences from COVID-19 have highlighted the importance of having preparedness and readiness for law. Clarity in individual liberties, federal-state relationships, and local-intrastate relationships could reduce confusion and lead to more efficient response.	- What changes in law, regulation, licensure, etc., that were adaptive in handling the COVID pandemic should be retained for the future? How do we effectively communicate these? - How can common understanding of public health laws be fostered during a public health emergency? - How to adapt laws to the needs of a crisis?
Data coordination and integration	Reliable and timely data systems are necessary to maintain trust in public health intuitions and health systems.	- How do we create a data-enabled public health system that builds from healthcare system experiences and data? - How do we create a timely and integrated data system that correlates with state and local monitoring systems?
Strategies for public-private partnership for public health emergencies	Throughout the pandemic, there have been examples of what has gone well and has not gone well to engage public and private sector partners and stakeholders.	- What are the successes in engaging public and private sector for the pandemic response? - What are the meaningful models for partnership? - What are the best practices? - How can we institutionalize public-private engagement to address future crises?
Climate change, compounding hazards, and health	During the COVID-19 pandemic, multiple climate hazards impacted the pandemic response in various regions of the world. The compounding hazards are unique to the 21st century and have global impacts due to the interconnectivity of people.	- What is the effect of climate change on the landscape and future for emerging infectious disease? - What are uniquely 21st century challenges that arise due to compounding climate change impacts? - What other threats should we be considering?
Pandemic Treaty	Member states of the World Health Organization will begin negotiations on an international treaty on pandemic preparedness, prevention, and response.	- What could a pandemic treaty look like? - What topics that must be considered in treaty negotiations?
Re-evaluating past SCEID REC's	The committee has previously worked on many relevant COVID-19 issues, specifically issues of face masks, aerosol transmission, respiratory viruses, and genomic surveillance. Many topics may need to be revisited in light of new variants, new policy questions, and future respiratory pandemics.	- What is the quality of masks that should be recommended for public use? - What requirements around mask wearing should be in place in the US? - What scientific standards for indoor air quality are required? - What system change is required to improve indoor air quality? - What other RECs need to be evaluated?
Trust, communication, and behavior change*	The national pandemic response has suffered from a lack of trust between the public and scientists, politicization of response measures,	- What information does the public need to make an informed decision? - How can experts earn the public's trust?

**Topic will be an ad hoc workshop with the CDC Standing Committee on Public Health Preparedness and Response - https://www.nationalacademies.org/our-work/building-public-trust-in-public-health-emergency-preparedness-and-response-phepr-science-a-workshop*	vaccine hesitancy, and misinformation. With the emergence of new variants, a systematic approach to communicating and building trust with the public is needed.	- How do we develop a systematic risk communication program? - How do we keep pace with need for quick advancements in vaccines and therapeutics but take the time to build trust and communicate? - How can discussions on public health be de-polarized or de-politicized?

***Disclaimer**: This list of research topics was prepared by Health and Medicine Division (HMD) staff as an informal record of issues that were discussed during the public session of the Standing Committee on Emerging Infectious Diseases and 21st Century Health Threats meeting, held on March 11, 2020. This document was prepared for information purposes only. It has not been peer reviewed and should not be cited or quoted, as the views expressed do not necessarily reflect the views of the National Academies of Sciences, Engineering, and Medicine's Standing Committee on Emerging Infectious Diseases and 21st Century Health Threats.*

Standing Committee on Emerging Infectious Diseases and 21st Century Health Threats

Meeting #1: March 11, 2020

Research Topics Discussed

The following research topics were discussed at the first meeting of the Standing Committee on Emerging Infectious Diseases and 21st Century Health Threats with the sponsors (Office of Science and Technology Policy and the Office of the Assistant Secretary for Preparedness and Response). Please note this is a first cut at many of the very important questions regarding the current COVID-19 outbreak, if you would like to submit additional questions or topics, please submit them to SCEID@nas.edu.

Virus Characteristics

- *Virus genetics, origin, and evolution*
    - Examples of short-term research needs
        - Real-time tracking of whole genomes and a mechanism for coordinating the rapid dissemination of that information to inform the development of diagnostics and therapeutics and to track variations of the virus over time.
        - Access to geographic and temporal diverse sample sets to understand geographic distribution and genomic differences, and determine whether there is more than one strain in circulation. Multi-lateral agreements such as the Nagoya Protocol could be leveraged.
    - Examples of long-term research needs
        - Evidence that livestock could be infected (e.g., field surveillance, genetic sequencing, receptor binding) and serve as a reservoir after the epidemic appears to be over.
            - Evidence of whether farmers are infected, and whether farmers could have played a role in the origin.
            - Surveillance of mixed wildlife- livestock farmsfor SARS-CoV-2 and other coronaviruses in Southeast Asia.
            - Experimental infections to test host range for this pathogen.
- *Transmission, incubation, and environmental stability*
    - Examples of short-term research needs

        - Range of incubation periods for the disease in humans (and how this varies across age and health status) and how long individuals are contagious, even after recovery.
        - Prevalence of asymptomatic shedding and transmission (e.g., particularly children).
        - Seasonality of transmission.
        - Physical science of the coronavirus (e.g., charge distribution, adhesion to hydrophilic/phobic surfaces, environmental survival to inform decontamination efforts for affected areas and provide information about viral shedding).
        - Persistence and stability on a multitude of substrates and sources (e.g., nasal discharge, sputum, urine, fecal matter, blood).
        - Persistence of virus on surfaces of different materials (e,g., copper, stainless steel, plastic).
- *Risk factors*
    - Examples of short-term research needs
        - Data on potential risks factors
            - Smoking, pre-existing pulmonary disease
            - Co-infections (determine whether co-existing respiratory/viral infections make the virus more transmissible or virulent) and other co-morbidities
            - Neonates and pregnant women
            - Socio-economic and behavioral factors to understand the economic impact of the virus and whether there were differences.

Diagnostics and Surveillance

- *Systematic, holistic approach to diagnostics (from the public health surveillance perspective to being able to predict clinical outcomes)*
    - Examples of short-term research needs
        - Evaluate how widespread current exposure is to be able to make immediate policy recommendations on mitigation measures. Denominators for testing and a mechanism for rapidly sharing that information, including demographics, to the extent possible. Sampling methods to determine asymptomatic disease (e.g., use of serosurveys (such as convalescent samples) and early detection of disease (e.g., use of screening of neutralizing antibodies such as ELISAs),
        - Efforts to increase capacity on existing diagnostic platforms and tap into existing surveillance platforms.
        - Recruitment, support, and coordination of local expertise and capacity (public, private—commercial, and non-profit, including academic), includinglegal, ethical, communications, and operational issues.
        - National guidance and guidelines about best practices to states (e.g., how states might leverage universities and private laboratories for testing purposes, communications to public health officials and the public).
        - Development of a point-of-care test (like a rapid influenza test) and rapid bed-side tests, recognizing the tradeoffs between speed, accessibility, and accuracy.
        - Rapid design and execution of targeted surveillance experiments calling for all potential testers using PCR in a defined area to start testing and report to a specific entity. These experiments could aid in collecting longitudinal samples, which are critical to understanding the impact of ad hoc local interventions (which also need to be recorded).
        - Separation of assay development issues from instruments, and the role of the private sector to help quickly migrate assays onto those devices.

        - Establish efforts to track the evolution of the virus (i.e., genetic drift or mutations) and avoid locking into specific reagents and surveillance/detection schemes.
        - Latency issues and when there is sufficient viral load to detect the pathogen, and understanding of what is needed in terms of biological and environmental sampling.
        - Use of diagnostics such as host response markers (e.g., cytokines) to detect early disease or predict severe disease progression, which would be important to understanding best clinical practice and efficacy of therapeutic interventions.
        - Policies and protocols for screening and testing.
        - Policies to mitigate the effects on supplies associated with mass testing, including swabs and reagents.
    - Examples of long-term research needs
        - Technology roadmap for diagnostics.
        - Barriers to developing and scaling up new diagnostic tests (e.g., market forces), how future coalition and accelerator models (e.g., Coalition for Epidemic Preparedness Innovations) could provide critical funding for diagnostics, and opportunities for a streamlined regulatory environment.
        - New platforms and technology (e.g., CRISPR) to improve response times and employ more holistic approaches to COVID-19 and future diseases.
        - Coupling genomics and diagnostic testing on a large scale.
        - Enhance capabilities for rapid sequencing and bioinformatics to target regions of the genome that will allow specificity for a particular variant.
        - Enhance capacity (people, technology, data) for sequencing with advanced analytics for unknown pathogens, and explore capabilities for distinguishing naturally-occurring pathogens from intentional.
        - One Health surveillance of humans and potential sources of future spillover or ongoing exposure for this organism and future pathogens, including both evolutionary hosts (e.g., bats) and transmission hosts (e.g., heavily trafficked and farmed wildlife and domestic food and companion species), inclusive of environmental, demographic, and occupational risk factors.

Medical Care

- *Surge capacity and nursing homes*
    - Examples of short-term research needs
        - Resources to support skilled nursing facilities and long term care facilities.
        - Mobilization of surge medical staff to address shortages in overwhelmed communities
- *Efforts to inform allocation of scarce resources*
    - Examples of short-term research needs
        - Age-adjusted mortality data for Acute Respiratory Distress Syndrome (ARDS) with/without other organ failure – particularly for viral etiologies
        - Extracorporeal membrane oxygenation (ECMO) outcomes data of COVID-19 patients; and,
        - Outcomes data for COVID-19 after mechanical ventilation adjusted for age.
        - Knowledge of the frequency, manifestations, and course of extrapulmonary manifestations of COVID-19, including, but not limited to, possible cardiomyopathy and cardiac arrest.

        - Application of regulatory standards (e.g., EUA, CLIA) and ability to adapt care to crisis standards of care level.
- *Personal Protective Equipment*
    - Example of short-term research needs
        - Approaches for encouraging and facilitating the production of elastomeric respirators, which can save thousands of N95 masks.
- *Alternative methods to advise on disease management*
    - Examples of short-term research needs
        - Best telemedicine practices, barriers and facilitators, and specific actions to remove/expand them within and across state boundaries.
        - Guidance on the simple things people can do at home to take care of sick people and manage disease.
        - Oral medications that might potentially work.
    - Example of long-term research needs
        - Use of AI in real-time health care delivery to evaluate interventions, risk factors, and outcomes in a way that could not be done manually.
- *Processes of care*
    - Example of short-term research needs
        - Best practices and critical challenges and innovative solutions and technologies in hospital flow and organization, workforce protection, workforce allocation, community-based support resources, payment, and supply chain management to enhance capacity, efficiency, and outcomes.

Non-Pharmaceutical Interventions

- *Effectiveness*
    - Examples of short-term research needs
        - Guidance on ways to scale up NPIs in a more coordinated way (e.g., establish funding, infrastructure and authorities to support real time, authoritative (qualified participants) collaboration with all states to gain consensus on consistent guidance and to mobilize resources to geographic areas where critical shortfalls are identified) to give us time to enhance our health care delivery system capacity to respond to an increase in cases.
        - Rapid design and execution of experiments to examine and compare NPIs currently being implemented. DHS Centers for Excellence could potentially be leveraged to conduct these experiments.
        - Rapid assessment of the likely efficacy of school closures, travel bans, bans on mass gatherings of various sizes, and other social distancing approaches.
- *Equity and barriers to compliance*
    - Example of short-term research needs
        - Methods to control the spread in communities, barriers to compliance and how these vary among different populations..
    - Examples of long-term research needs
        - Models of potential interventions to predict costs and benefits that take account of such factors as race, income, disability, age, geographic location, immigration status, housing status, employment status, and health insurance status.
        - Policy changes necessary to enable the compliance of individuals with limited resources and the underserved with NPIs. Research on why people fail to comply

with public health advice, even if they want to do so (e.g., social or financial costs may be too high).
        - Research on the economic impact of this or any pandemic. This would include identifying policy and programmatic alternatives that lessen/mitigate risks to critical government services, food distribution and supplies, access to critical household supplies, and access to health diagnoses, treatment, and needed care, regardless of ability to pay.

Vaccines & Therapeutics

- *Research and development and evaluation efforts*
    - Examples of short-term research needs
        - Evaluate/investigate effectiveness of drugs being developed and tried to treat COVID-19 patients.
            - Clinical and bench trials to investigate less common viral inhibitors against COVID-19 such as naproxen, clarithromycin, and minocyclinethat that may exert effects on viral replication.
        - Methods to evaluate potential complication of Antibody-Dependent Enhancement (ADE) in vaccine recipients.
        - From a clinical development perspective, explore use of best animal models and their predictive value for a human vaccine.
        - Capabilities to discover a therapeutic (not vaccine) for the disease, and clinical effectiveness studies to discover therapeutics, to include antiviral agents.
        - Alternative models to aid decision makers in determining how to prioritize and distribute scarce, newly proven therapeutics as production ramps up. This could include identifying approaches for expanding production capacity to ensure equitable and timely distribution to populations in need.
    - Example of long-term research needs
        - Efforts targeted at a universal coronavirus vaccine.

Risk Communication

- *Communicating with high-risk populations*
    - Examples of short-term research needs
        - Modes of communicating with target high-risk populations (elderly, health care workers).
        - Risk communication and guidelines that are easy to understand and follow (include targeting at risk populations' families too).
        - Communication that indicates potential risk of disease to all population groups.
- *Clarify community measures*
    - Example of short-term research needs
        - Clarify misunderstanding around containment and mitigation.

Equity Considerations

- *Problems of inequity*
    - Examples of short-term research needs
        - Action plan to mitigate gaps and problems of inequity in the Nation's public health capability, capacity, and funding to ensure all citizens in need are supported and can access information, surveillance, and treatment.

        - Measures to reach marginalized and disadvantaged populations.
        - Data systems and research priorities and agendas incorporate attention to the needs and circumstances of disadvantaged populations and underrepresented minorities.
        - Understand and mitigate threats to incarcerated people from COVID-19, assuring access to information, prevention, diagnosis, and treatment.
        - Understand coverage policies (barriers and opportunities) related to testing, treatment, and care

Information Sharing & Inter-sectoral Collaboration

- *Data standards and nomenclature*
    - Examples of short-term research needs
        - Methods for coordinating data-gathering with standardized nomenclature.
        - Consistent platform for sharing response information among planners, providers, and others.
        - Understand and mitigate barriers to information-sharing.
- *Governmental public health*
    - Example of short-term research needs
        - Determine how to recruit, support, and coordinate local (non-Federal) expertise and capacity relevant to public health emergency response (public, private—commercial and non-profit, including academic).
    - Examples of long-term research needs
        - Better integration of federal/state/local public health surveillance systems.
        - Value of investments in baseline public health response infrastructure preparedness capacity and capability.

Centers for Disease Control and Prevention

CDC Public Health Science Agenda for COVID-19

Building the Evidence Base for Ongoing COVID-19 Response

Updated May 17, 2022

Priority COVID-19 Public Health Science Questions

As the public health response to the COVID-19 pandemic continues to evolve, considerable progress has been made. We now have more tools than ever to prevent COVID-19 from placing strain on communities and healthcare systems. With current high levels of vaccination and high levels of population immunity from both vaccination and previous infections, the risk of medically significant disease, hospitalization, and death from COVID-19 is greatly reduced for most people (see more on COVID-19 Community Levels). It remains important to collect data-driven information on key priority areas that can help CDC and public health partners continue to fill critical scientific gaps, build on knowledge gained and advances made, and inform evidence-based decision-making for continued intervention through public health surveillance and epidemiologic research.

CDC has developed priority questions around **8** thematic topic areas for *The CDC Public Health Science Agenda for COVID-19:*

- Health equity
- Vaccines
- Variants
- Prevention strategies
- Testing
- Treatment
- Natural history, transmission, breakthrough infections, and reinfections
- Post-COVID conditions and other health impacts

Within these topic areas, **15** priority public health science questions relate to the broad scope of CDC's scientific work, both in the United States and globally, including public health surveillance, epidemiologic research, implementation science, and evaluation. These questions also relate to ongoing work in the broader scientific community (such as other government agencies, academics, the private sector). Other relevant questions are found in the complementary science agendas of other federal agencies, including the National Institutes of Health (NIH), the Food and Drug Administration (FDA), the

Environmental Protection Agency (EPA), and the White House. This Science Agenda is intended to inform efforts by the broader public health research community. It is used to help direct and monitor CDC's scientific activities but is not a commitment by CDC to address every question.

Importantly, these questions also serve to expand the evidence base to accelerate progress toward reducing COVID-19 health disparities and achieving health equity in prevention, testing, treatment, and management of post-COVID conditions. Health disparities are differences in health among groups of people that are linked to social, economic, geographic, and/or environmental disadvantage (social determinants of health), and health equity is achieved when everyone has a fair and just opportunity to attain their highest level of health. Our health equity priority question considers populations experiencing COVID-19-related health disparities including, but not limited to: age, sex, race, ethnicity, sexual orientation, socioeconomic status, disability, underlying medical conditions (especially compromised immune status), education, occupation, place and type of residence (single versus congregate housing and urban versus rural settings), and other social determinants of health that may not necessarily fall within other priority questions. However, health equity science remains a fundamental consideration for all priority questions, and there is some overlap in health equity science activities across questions.

Two priority questions were added in March 2022 to address research gaps in evaluating equitable access to treatments for COVID-19 and the effectiveness of COVID-19 treatments in improving outcomes from COVID-19, post-COVID conditions, and other conditions unrelated to COVID-19.

Key activities of public health importance that fall within the question domain are noted under each question.

Health Equity

1. How can the public health community effectively identify and address health inequities to protect populations disproportionately affected by COVID-19?

Key activities:

- Identifying and monitoring trends in, and effects of, disparities in severe COVID-19 illnesses, hospitalizations, deaths, post-COVID conditions, as well as trends in access to vaccines and other prevention and treatment measures.
- Identifying and monitoring trends in, and effects of, disparities in COVID-19 associated second-order consequences in children (such as orphanhood or caregiver death, poverty, food insecurity, violence, adverse childhood experiences, adverse mental health conditions, and disruptions to education and childcare access)
- Understanding the social determinants of health that may contribute to these disparities in various populations to identify opportunities for interventions
- Evaluating the effectiveness of initiatives and policies, including broad communication and dissemination strategies, in facilitating equitable access to testing, vaccines, and treatments and identifying opportunities for improvement
- Evaluating which initiatives and policies (such as COVID-19 vaccination incentives or mandates) have improved vaccination equity and coverage in communities of varying demographic composition, socioeconomic status, geographic location, policy environment, and population size, both domestically and globally
- Characterizing outpatient and inpatient treatment of severe COVID-19 in populations affected by disparities related to social determinants of health, to identify opportunities for improvement
- Identifying and implementing targeted efforts to protect people with moderate or severe immunocompromising conditions, who might receive less protection by vaccines than others

Vaccines

2. What is the effectiveness and duration of immune protection afforded by COVID-19 primary series and booster vaccines?

Key activities:

- Measuring differences in vaccine effectiveness against symptomatic or severe COVID-19 illness in various populations and settings, including by country or region, single versus congregate settings, age groups, underlying medical conditions (including previous infection with SARS-CoV-2, the virus that causes COVID-19), product type (including mixed doses with more than one vaccine formulation), the number of doses, and the interval between doses
- Measuring effects of vaccination on SARS-CoV-2 transmission and disease burden
- Evaluating effectiveness of primary series and booster vaccines in reducing the likelihood of post-COVID conditions, including MIS-C
- Determining if post-vaccination testing in populations at risk for severe disease can inform the need for additional vaccine boosters, preexposure prophylaxis (such as monoclonal antibodies), treatment, or other clinical interventions

3. What communication approaches are most effective at increasing COVID-19 vaccination access and coverage?

Key activities:

- Evaluating strategies to build trust in CDC recommendations for use of COVID-19 vaccines and to increase vaccine uptake among people who have not yet been vaccinated
- Addressing vaccine hesitancy in communities of varying demographic composition and among special populations, including, but not limited to, adults aged 65 and older, residents of long-term care facilities, pregnant and lactating people, parents or guardians of minor children, adolescents, incarcerated or homeless populations, and healthcare providers, using culturally appropriate messaging
- Evaluating strategies to effectively counter vaccine misinformation and disinformation and encourage effective provider recommendations of COVID-19 vaccination as a part of routine care, especially for pediatric populations
- Tracking and responding to changes in vaccine-related questions, concerns, and reports about adverse events over time, particularly for pediatric vaccination
- Addressing barriers to vaccine providers checking Immunization Information Systems (IIS) prior to vaccination to reduce missed opportunities for vaccination

4. What are the risks associated with COVID-19 primary series and booster vaccines?

Key activities:

- Conducting vaccine safety analyses using various vaccine safety data sources, and developing accurate, timely, and transparent communication on potential adverse events and differences in potential adverse events by vaccine product
- Assessing effects of back-to-back vaccination against COVID-19 and other vaccine-preventable diseases, including seasonal influenza
- Characterizing the effect of COVID-19 vaccination on routine and seasonal vaccinations, domestically and globally
- Assessing potential risks in populations for which vaccination has only recently been approved or is not yet approved but poised to be (such as pediatric populations).

Variants

5. How can the public health community effectively and efficiently enhance surveillance for known and emerging SARS-CoV-2 variants?

Key activities:

- Tracking and measuring the proportion and incidence of emerging variant lineages in various populations and settings
- Using specialized surveillance strategies to identify importation of emerging variants, including testing travelers to the United States
- Improving the timeliness and accuracy of genomic surveillance and regional estimates of variant proportions in circulation in the United States and globally to effectively detect and track variants, including from wastewater surveillance
- Improving data quality of measures for detecting and tracking variants by enhancing genomic surveillance; increasing social and demographic data completeness; integrating epidemiologic and genomic data where available, including travel history; and ensuring a representative sample of specimens
- Effectively communicating health information about variants to the public

6. How do SARS-CoV-2 variants affect the performance of diagnostics, vaccine effectiveness, clinical outcomes, transmissibility, and treatments, and the outcome of public health interventions?

Key activities:

- Measuring changes in effectiveness of COVID-19 vaccines, treatments, and other public health interventions against SARS-CoV-2 variants in various populations and settings
- Measuring differences in the transmissibility of SARS-CoV-2 variants in various populations and settings, and by population vaccination status
- Understanding changes in adherence to recommended prevention strategies and vaccine uptake related to the public's understanding of variants
- Characterizing clinical impact and severity of variants in pediatric and adult populations

Prevention strategies

7. What effective prevention strategies and non-pharmaceutical interventions should be prioritized to reduce transmission of SARS-CoV-2 in various populations and settings?

Key activities:

- Reducing barriers to implementation of effective prevention strategies (such as masking, ventilation, distancing, and other effective interventions) in schools, workplaces, and other congregate settings when they are needed
- Evaluating effectiveness of prevention strategies, including testing, in settings at varying levels of vaccination coverage and varying levels of community transmission
- Evaluating which prevention strategies (jointly with vaccination) can measurably reduce disparities in severe COVID-19 illness, hospitalizations, and deaths

- Developing and communicating evidence-based health recommendations and information on COVID-19 prevention



Testing

8. How effective are at-home/self-testing, rapid diagnostic testing, point-of-care testing, routine screening, and serial testing strategies compared with laboratory-based nucleic acid amplification testing strategies on reducing outbreaks, reducing disease burden, detecting potential surges, and detecting re-introduction of SARS-CoV-2 into low transmission settings?

Key activities:

- Evaluating and identifying the most effective approaches to rapidly expand testing capacity when needed, as indicated by appropriate metrics
- Improving collection of demographic and epidemiologic data associated with testing, including the effect of testing on transmission
- Evaluating cost-effectiveness of testing strategies and developing testing recommendations that are effective for both vaccinated and unvaccinated people and consider the impact of emerging variants
- Evaluating ways to link at-home/self-testing with access to treatment



Treatment

9. What interventions, programs, and communication approaches are most effective at increasing equitable COVID-19 treatment access and coverage?

Key activities:

- Evaluating strategies to assess and build trust in use of SARS-CoV-2 oral antiviral treatment, including strategies to effectively counter oral antiviral misinformation and disinformation
- Tracking and responding to concerns about adverse events related to oral antivirals and other treatments, particularly for pregnant and lactating people and pediatric populations
- Assessing approaches for oral antiviral prescribing and dispensing, including telehealth
- Evaluating the relationship between testing demand and oral antiviral treatment availability
- Evaluating the benefits and risks of dispensing oral antiviral treatment at the time of COVID-19 testing, prior to disclosure of testing outcomes

10. How effective are treatment strategies at reducing disease burden and transmission?

Key activities:

- Addressing needs for expanded and equitable treatment access, and adopting approaches to increasing treatment availability domestically and globally
- Improving collection and analysis of epidemiologic data associated with treatment strategies in various populations and settings
- Conducting laboratory monitoring to rapidly identify oral antiviral resistant SARS-CoV-2 isolates

- Evaluating how SARS-CoV-2 treatments may influence the severity of COVID-19, post-COVID conditions, and other health conditions unrelated to COVID-19



Natural history, transmission, breakthrough infections, and reinfections

11. How does the public health community effectively and efficiently enhance surveillance for SARS-CoV-2 reinfections, breakthrough infections, vaccination, and various health outcomes?

Key activities:

- Measuring incidence of reinfection and associated risks
- Improving data completeness for demographic and social determinants of health variables, and methods for handling missing data
- Evaluating impact of reporting of infections and characterizing risk factors for reinfection in various populations and settings, including those experiencing health disparities related to social determinants of health
- Evaluating the effectiveness of new surveillance strategies to inform policy and personal action
- Characterizing risk factors for breakthrough infections leading to severe illness among vaccinated people
- Evaluating to what extent breakthrough infections contribute to SARS-CoV-2 transmission and whether these transmission rates differ by variant

12. What factors best inform SARS-CoV-2 transmission dynamics and predict surges of community-level infection?

Key activities

- Characterizing how the seasonality of other respiratory viruses (such as influenza) affects SARS-CoV-2 transmission, domestically and globally
- Evaluating whether geography-based data indices on social determinants of health, such as the Social Vulnerability Index and Area Deprivation Index, improve the accuracy of predicted surges in localized COVID-19 incidence
- Understanding the potential role of animal reservoirs of SARS-CoV-2 transmission to humans and sustaining environmental reservoirs
- Characterizing viral load and duration of shedding following infection by different host and virologic factors including age group, immune status, test type, virus variant, or infection and/or vaccine-mediated immunity
- Measuring rates of SARS-CoV-2 transmission and assessing risk of transmission by viral shedding dynamics, variant, and additional host and contact factors

13. What are reliable immune factors contributing to protection from SARS-CoV-2 infection and/or vaccination, and what are accurate ways to measure them?

Key activities:

- Expanding diagnostic capabilities to distinguish infection versus vaccine-mediated immunity
- Measuring differences in strength and duration of protection afforded by infection and/or vaccine-mediated immunity, variant type, disease severity and symptomatology
- Evaluating measures for population-level immunity from initial and booster vaccinations, and changes over time due to waning immunity and other factors

- Measuring variation of serological correlates by demographic and clinical characteristics



Post-COVID conditions and other health impacts

14. How does the public health community effectively conduct epidemiologic research on post-COVID conditions, overall and in various populations and settings?

Key activities:

- Developing standard case definitions for post-acute versus long-term phases of COVID-19
- Measuring and understanding the prevalence and incidence of various post-COVID conditions over time
- Measuring the burden of post-COVID conditions in health systems, to promote equitable access to care and quality of care
- Characterizing risk factors at the individual and population levels, including SARS-CoV-2 infection or reinfection characteristics, underlying biological mechanisms, and variant characteristics
- Assessing prevention measures for post-COVID conditions, including COVID-19 vaccination
- Assessing potential health and economic impacts of post-COVID conditions (such as inability to work or effects on daily activities)

15. What short- and long-term impacts from the COVID-19 pandemic are of the greatest public health importance, and what are the best ways to address them?

Key activities

- Measuring and improving mental health outcomes in the public health workforce and other frontline workforce populations to reduce adverse mental health effects of the COVID-19 pandemic
- Measuring changes to non-COVID-19 health epidemics and illnesses affected by the COVID-19 pandemic
- Understanding how the effect of the pandemic on income, housing, employment, caregiving, childcare, orphanhood, and other factors have exacerbated health and social inequities
- Evaluating evidence-based best practices for pre-pandemic planning and public health agency collaboration with specified sectors (such as healthcare, schools, and high-risk industries) to strengthen the overall public health infrastructure in an effective pandemic response
- Modeling long-term effects and differential burdens by population groups, communities, and countries

Background for the CDC Public Health Science Agenda for COVID-19

The COVID-19 pandemic is a formidable global public health challenge. Since the initial emergence of a novel coronavirus in late 2019, the spread of SARS-CoV-2 has been unrelenting, impacting nearly every aspect of society worldwide. The pandemic has required a substantial response by public health authorities at all levels.

The Centers for Disease Control and Prevention (CDC) is at the forefront of the public health response to the COVID-19 pandemic and is a respected source of data and information used by public health, medical, and policy decision makers. From the beginning of the pandemic, CDC has been working with a wide array of partners to advance understanding of COVID-19.

The CDC Public Health Science Agenda for COVID-19 builds on CDC's ongoing pandemic-related work. Importantly, the COVID-19 pandemic has underscored long-standing health disparities and inequities in the United States. Data-driven strategies are essential to address these disparities and improve the health outcomes of people disproportionately affected by COVID-19.[1] The work set out in *The CDC Public Health Science Agenda for COVID-19* is predicated on the use of culturally and linguistically appropriate approaches and methods and inclusion of populations at increased risk for health disparities and inequities to help reduce the impact of COVID-19 in these communities.

Goal of *The CDC Public Health Science Agenda*

The goal of *The CDC Public Health Science Agenda for COVID-19* is to guide the development of the evidence base needed to strengthen the public health actions, guidance, and policy essential to limit the spread and impact of SARS-CoV-2 and ultimately end the COVID-19 pandemic.

CDC's role and the scope of *The CDC Public Health Science Agenda*

CDC is providing leadership and technical expertise in the prevention and control of the COVID-19 pandemic by:

- employing public health fundamentals, including disease surveillance, laboratory detection, and epidemiologic investigation;
- identifying and implementing public health interventions to reduce disease transmission and the mitigation of its impact on health and well-being;
- developing evidence-based guidance and policies for disease prevention, detection, and control; and
- engaging in effective communication strategies to optimize uptake of protective behaviors and recommended actions.[2]

These key functions underpin *The CDC Public Health Science Agenda for COVID-19.*

Organization of *The CDC Public Health Science Agenda*

The CDC Public Health Science Agenda for COVID-19 was initially organized around a framework of six **Priority Areas**:

- Priority Area I. COVID-19 disease detection, burden, and impact
- Priority Area II. Transmission of SARS-CoV-2
- Priority Area III. Natural history of SARS-CoV-2 infection
- Priority Area IV. Protection in healthcare and non-healthcare work settings
- Priority Area V. Prevention, mitigation, and intervention strategies
- Priority Area VI. Social, behavioral, and communication science

For each of the six Priority Areas, a series of **Objectives** were described.

Priority Area I. COVID-19 Disease Detection, Burden, And Impact

Disease surveillance and laboratory detection are at the heart of CDC's mission and fundamental to the COVID-19 public health response. They underpin CDC's work with federal, state, tribal, local, and territorial (STLT), academic, and commercial partners to better understand the burden of COVID-19 disease and efforts to mitigate its diverse impacts, including the disproportionate impacts of COVID-19 on people at increased risk for health disparities and inequities. CDC supplements surveillance and laboratory methods with the modern tools of viral genomics and mathematical modeling.

- **Objective 1**. Develop new, or modify existing, methods of epidemiologic surveillance for COVID-19
- **Objective 2**. Develop and optimize testing for SARS-CoV-2
- **Objective 3**. Utilize viral genomics to advance understanding of COVID-19 and mitigate its impact
- **Objective 4**. Use mathematical modeling and other technological tools to forecast COVID-19 trends and measure the impact of interventions across a range of populations

- **Objective 5**. Assess and limit the impact of the COVID-19 response on healthcare services and public health programs in domestic and international settings

Priority Area II. Transmission of SARS-Cov-2

Understanding how SARS-CoV-2 is transmitted and the important factors that can facilitate its spread among people in healthcare, workplace, and community settings has been a high priority for CDC since the earliest days of the pandemic. This essential information is used to develop and update guidance about effective strategies to prevent, contain, and mitigate COVID-19.

- **Objective 1**. Refine understanding of SARS-CoV-2 transmission modes
- **Objective 2**. Identify host and virus factors associated with person-to-person transmission
- **Objective 3**. Assess and characterize transmission of SARS-CoV-2 across a spectrum of healthcare settings
- **Objective 4**. Evaluate transmission of SARS-CoV-2 in non-healthcare workplace and community settings/populations
- **Objective 5**. Evaluate transmission of SARS-CoV-2 between people and animals

Priority Area III. Natural History of SARS-Cov-2 Infection

The full spectrum of COVID-19 disease continues to unfold and confound in its clinical manifestations and requires careful study. CDC and its collaborators have been undertaking comprehensive clinical and laboratory investigations of confirmed cases across a range of age groups and populations to learn about the natural history of COVID-19 disease, associated medical complications, and the development of immunity.

- **Objective 1**. Define the spectrum and clinical course of SARS-CoV-2 infection
- **Objective 2**. Characterize the immune response in infected persons

Priority Area IV. Protection in Healthcare and Non-Healthcare Work Settings

Understanding and mitigating risks to patients, HCP, and non-healthcare workers across a range of settings is a high priority focus. CDC works to identify culturally and linguistically appropriate innovative strategies, tools, and practices which can supplement traditional infection control and worker safety measures to protect patients and reduce nosocomial and occupationally acquired SARS-CoV-2.

- **Objective 1**. Improve and assess the effectiveness of personal protective equipment
- **Objective 2**. Assess strategies to reduce transmission of SARS-CoV-2 in healthcare and non-healthcare work settings

Priority Area V. Prevention, Mitigation, and Intervention Strategies

CDC has disseminated a portfolio of prevention, mitigation, and intervention strategies tailored to specific settings and sectors to slow the spread of COVID-19 and protect individuals and communities. Evaluating the effectiveness of these strategies is critical to help refine public health guidance and recommendations. A key responsibility for CDC, in collaboration with STLT public health partners and academic and other researchers is monitoring the coverage, safety, and effectiveness of COVID-19 vaccines.

- **Objective 1**. Evaluate individual- and community-level strategies to limit infection with SARS-CoV-2
- **Objective 2**. Evaluate strategies to limit infection with SARS-CoV-2 in specialized settings or select populations
- **Objective 3**. Develop methods to detect SARS-CoV-2 in the environment

- **Objective 3**. Develop methods to detect SARS-CoV-2 in the environment
- **Objective 4**. Identify the most effective methods for contact tracing, testing, and monitoring
- **Objective 5**. Evaluate travel-related interventions
- **Objective 6**. Optimize the acceptability, coverage, safety, and effectiveness of COVID-19 vaccines

Priority Area VI. Social, Behavioral, And Communication Science

Effective communication requires community engagement; empowerment of individuals to take appropriate measures to reduce their risk; evaluation of risk communication methods and information gaps; and culturally and linguistically responsive materials and messengers. The effectiveness of risk reduction strategies, such as community mitigation or maximizing vaccine uptake, is dependent in part on understanding the barriers to implementation/acceptance, including economic and social determinants of health. Understanding the social, behavioral, and mental health impacts of the COVID-19 pandemic are as important as understanding the impacts to physical health.

- **Objective 1**. Understand where people receive information about the pandemic
- **Objective 2**. Optimize uptake of recommended behaviors and actions
- **Objective 3**. Enhance CDC communication products and information tools
- **Objective 4**. Assess the social and mental health impacts of the pandemic

Footnotes

1. Populations of special focus include racial and ethnic minority populations; people living in rural or frontier areas; people experiencing homelessness; essential and frontline workers; people with disabilities; people with substance use disorders; people who are justice-involved (incarcerated persons); and non-U.S.-born persons.
2. A CDC framework for preventing infectious diseases. See https://www.cdc.gov/ddid/docs/ID-Framework.pdf

Resources

1. CDC Coronavirus Disease 2019 (COVID-19)
2. ACIP COVID-19 Vaccine Recommendations
3. CDC Science Briefs
4. CDC COVID-19 Publications Database
5. MMWR COVID-19 Reports
6. CDC Office of Science
7. CDC Strategy for Global Response to COVID-19

Last Updated May 17, 2022

An official website of the United States government
Here's how you know

COVID-19 Research

EPA researchers are building on an expansive body of world-class research by applying that knowledge to reduce the risk of exposure to SARS-CoV-2, the virus that causes COVID-19. This research will help states, tribes, local, and territorial governments, including public health agencies, guide homeowners, business owners, and workplace managers to reduce the risk of exposure to SARS-CoV-2. This page provides updates on EPA's research efforts, including data and results.

Visit our Emergency Response Webinar Series page <https://epa.gov/emergency-response-research/webinar-series> for the schedule of upcoming COVID-19 research webinars.

Aerosols



- Modeling transport of viral aerosols in an office setting <https://epa.gov/covid19-research/modeling-sars-cov-2-aerosols-and-evaluating-ways-inactivate-aerosolized-sars-cov-2>
- Modeling transport of viral aerosols in mass transit <https://epa.gov/covid19-research/modeling-sars-cov-2-aerosols-and-evaluating-ways-inactivate-aerosolized-sars-cov-2>
- Evaluating pesticide devices and products <https://epa.gov/covid19-research/modeling-sars-cov-2-aerosols-and-evaluating-ways-inactivate-aerosolized-sars-cov-2>

Community Exposure



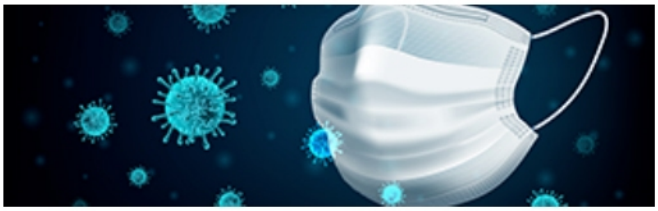
- Monitoring virus levels in sewage <https://epa.gov/covid19-research/assessing-sars-cov-2-virus-levels-sewage>
- Standardizing a method to assess virus in sewage <https://epa.gov/covid19-research/assessing-sars-cov-2-virus-levels-sewage>
- Developing a salivary test to assess community exposure <https://epa.gov/covid19-research/developing-salivary-antibody-test>

Surfaces



- Evaluating residual antimicrobial coatings <https://epa.gov/covid19-research/evaluating-residual-antimicrobial-coatings>
- Developing a rapid viability-reverse transcriptase PCR method <https://epa.gov/covid19-research/development-rapid-viability-reverse-transcriptase-pcr-rv-rtpcr-method-detection>
- Evaluating alternative disinfection devices <https://epa.gov/covid19-research/alternative-disinfection-devices>
- Evaluating effectiveness of electrostatic sprayers <https://epa.gov/covid19-research/evaluating-electrostatic-sprayers-disinfectant-application>

Masks & PPE



- Evaluating masks and facial coverings with and without modifications <https://epa.gov/covid19-research/evaluating-effectiveness-facial-coverings-and-masks>
- Disinfecting PPE for reuse <https://epa.gov/covid19-research/evaluating-disinfection-methods-personal-protective-equipment-ppe-items-intended>

Webinar Recordings

- COVID-19: Aerosol Treatment Devices & Ozone Disinfection <https://epa.gov/emergency-response-research/covid-19-aerosol-treatment-devices-ozone-disinfection-webinar> (August 2021)
- COVID-19: Electrostatic Sprayers and Foggers for Disinfectant Application <https://epa.gov/emergency-response-research/covid-19-electrostatic-sprayers-and-foggers-disinfectant-application> *(July 2021)*
- Reducing Environmental Exposure to SARS-CoV-2 - An Overview of Findings <https://epa.gov/emergency-response-research/reducing-environmental-exposure-sars-cov-2-overview-findings-webinar> *(June 2021)*
- COVID-19: Cleaning & Disinfecting of PPE for Effective Reuse <https://epa.gov/emergency-response-research/covid-19-cleaning-disinfecting-ppe-effective-reuse-webinar> *(April 2021)*
- COVID-19 UV-C Devices and Methods for Surface Disinfection <https://epa.gov/emergency-response-research/covid-19-uv-c-devices-and-methods-surface-disinfection-webinar> *(January 2021)*
- COVID-19 Long Lasting Disinfectants <https://epa.gov/emergency-response-research/covid-19-long-lasting-disinfectants-webinar> *(August 2020)*
- EPA Expands Research on COVID-19 in the Environment <https://epa.gov/emergency-response-research/epa-expands-research-covid-19-environment> *(May 2020)*

Science Matters Newsletter

Evaluating Electrostatic Sprayers for Disinfectant Application <https://epa.gov/sciencematters/epa-researchers-evaluate-electrostatic-sprayers-disinfectant-application>

Evaluating SARS-CoV-2 in the Environment <https://epa.gov/sciencematters/epa-researchers-are-evaluating-sars-cov-2-environment>

Testing Effectiveness of Face Masks, Disinfection Methods Against COVID-19 <https://epa.gov/sciencematters/epa-researchers-test-effectiveness-face-masks-disinfection-methods-against-covid-19>

Aerosol Transport and Mitigation Measures to Reduce COVID-19 Transmission <https://epa.gov/sciencematters/epa-researchers-study-aerosol-transport-and-mitigation-measures-reduce-covid-19>

Assessing Virus Levels in Sewage for Community Level Screening <https://epa.gov/sciencematters/epas-sars-cov-2-research-assessing-virus-levels-sewage-community-level-screening>

Related Resources

- Emergency Response Research Webinar Series <https://epa.gov/emergency-response-research/webinar-series>
- COVID-19 Researcher Profiles <https://epa.gov/healthresearch/covid-19-researcher-profiles>
- Coronavirus Information <https://epa.gov/coronavirus>

Contact Us <https://epa.gov/covid19-research/forms/contact-us-about-covid-19-research> to ask a question, provide feedback, or report a problem.

FDA COVID-19 Pandemic Recovery and Preparedness Plan (PREPP) Initiative

The FDA launched the COVID-19 Pandemic Recovery and Preparedness Plan (PREPP) initiative in 2020 to strengthen the response to the COVID-19 pandemic and resiliency for future public health emergencies. To help achieve these goals, the agency asked an independent, non-government organization to conduct an objective review of the FDA's pandemic response, inventory accomplishments and activities, and identify future opportunities for consideration. The independent organization interviewed FDA leadership, conducted listening sessions with external stakeholder groups, and collaborated with subject matter experts on the FDA staff to produce the summary report (/media/145129/download).

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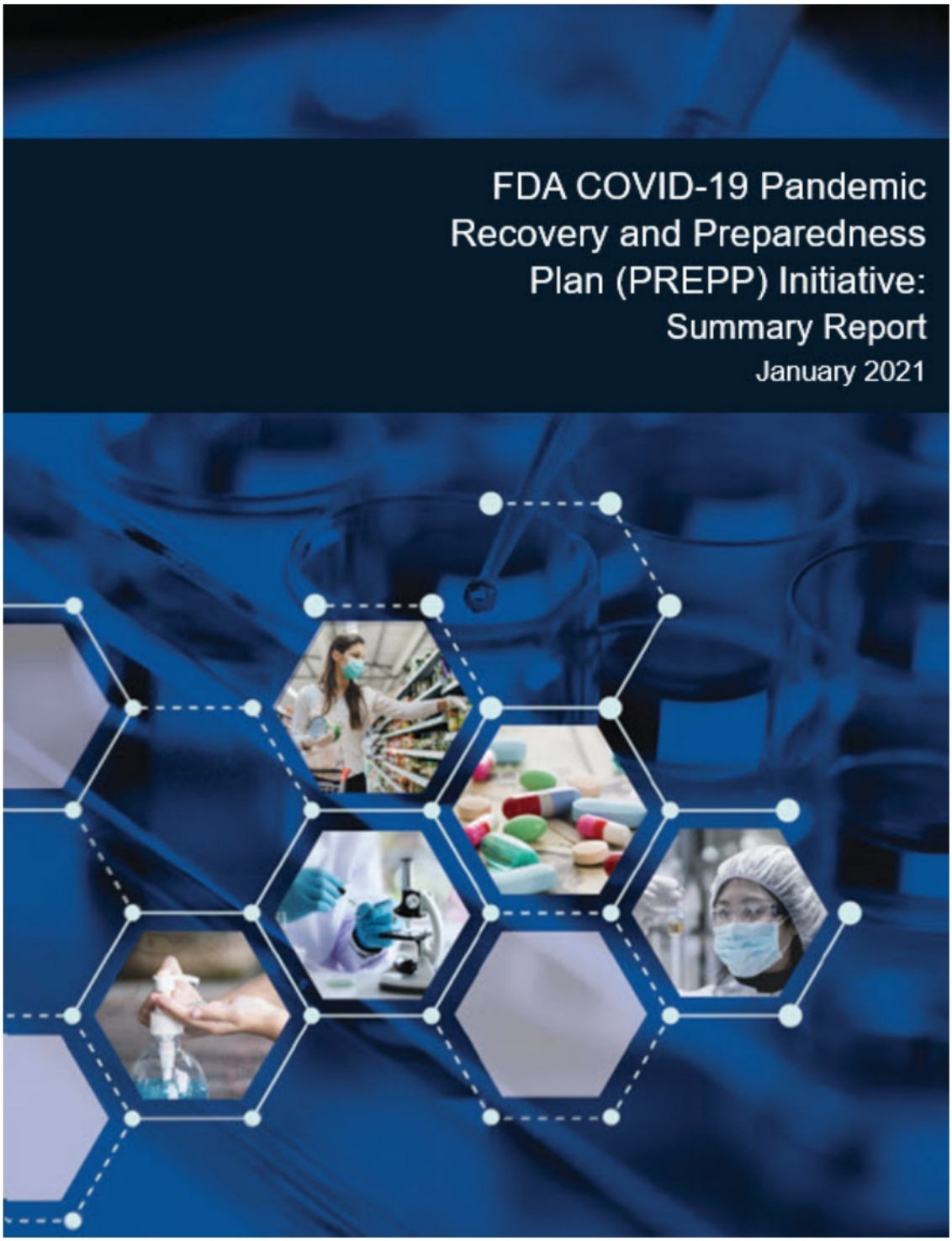

FDA COVID-19 Pandemic Recovery and Preparedness Plan Initiative: Summary Report (PDF-1.31MB) (/media/145129/download)

The report consists of an Executive Summary and detailed Technical Report summarizing the FDA's progress and potential actions to consider going forward. While the report is not a to-do list, the FDA carefully reviewed the options while taking into account its current statutory authorities and available resources. Five areas have been identified for our initial focus; the first one includes two options folded into one:

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- Reviewing aspects of the EUA processes for medical products and identifying areas for potential improvement. The objective is to ensure transparency and facilitate appropriate integration of these products including diagnostics, therapeutics and vaccines, into medical care;
- Reviewing science-based communications to ensure the agency continues to provide timely and accurate communications to the public;
- Evaluating inspectional approaches using next-gen assessment technologies, such as virtual and video-enabled platforms, to further inspectional reach; and
- Evaluating the current supply chain tracking, monitoring and assessment systems to identify gaps and challenges, to help stakeholders improve supply chain resilience.

While our response to the COVID-19 public health emergency is an agency priority, we are also committed to strengthening the agency's public health infrastructure and building the resilience needed to prevent, detect and respond to any emergency.

More Information

- FDA In Brief: FDA Provides Update on COVID-19 Pandemic Recovery and Preparedness Plan (PREPP) Initiative (/news-events/fda-brief/fda-brief-fda-provides-update-covid-19-pandemic-recovery-and-preparedness-plan-initiative)
  This FDA In Brief provides an update on the PREPP initiative (*April 2, 2021*)
- Pandemic Response, Pandemic Preparation (/news-events/fda-voices/pandemic-response-pandemic-preparation)
  FDA Voices piece by former FDA Commissioner Stephen M. Hahn, M.D., and former Deputy Commissioner for Medical and Scientific Affairs Anand Shah, M.D., (*January 13, 2021*)
- FDA Insight: Pandemic Recovery and Preparedness Plan (/news-events/fda-insight/fda-insight-pandemic-recovery-and-preparedness-plan-prepp)
  Listen to this FDA podcast featuring former FDA Commissioner Stephen M. Hahn on FDA's Pandemic Recovery and Preparedness Plan (*January 19, 2021*)
- Coronavirus Disease 2019 (COVID-19) (/emergency-preparedness-and-response/counterterrorism-and-emerging-threats/coronavirus-disease-2019-covid-19)
  Latest news and information about the FDA's response to the COVID-19 pandemic

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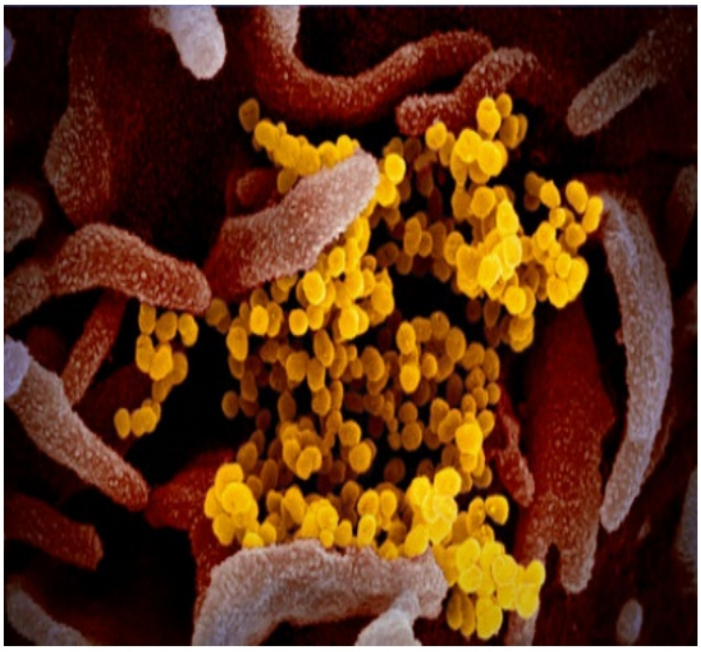

This scanning electron microscope image shows SARS-CoV-2 (yellow), the virus that causes COVID-19, isolated from a patient in the United States, emerging from the surface of cells (pink) cultured in the lab. Credit: NIAID-RML

NIAID STRATEGIC PLAN FOR COVID-19 RESEARCH – **2021 UPDATE**

NIH National Institute of Allergy and Infectious Diseases

DEPARTMENT OF HEALTH & HUMAN SERVICES · USA

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Executive Summary

In response to the unprecedented threat of SARS-CoV-2 and the COVID-19 pandemic, the National Institute of Allergy and Infectious Diseases (NIAID) launched its biomedical research response to safeguard the health of people in the United States and around the world. As delineated in the *NIAID Strategic Plan for COVID-19 Research*, released in April 2020, the response focused on basic research, diagnostics, natural history studies, and the development of safe and effective therapeutics and vaccines. Working with U.S. government agencies, academia, industry, and community partners, NIAID rapidly mounted a comprehensive effort to characterize the virus and develop effective biomedical tools to prevent SARS-CoV-2 infection and treat COVID-19. NIAID supported the most promising candidates through clinical trial testing, prioritizing the inclusion of high-risk and minority populations to ensure broad testing and validation in the most vulnerable populations.

Box 1
NIAID COVID-19 Research Priorities
2021 Update

1. *Advance basic research on SARS-CoV-2 biology, pathogenesis, and transmission*
2. *Identify and test promising COVID-19 therapeutics*
3. *Develop and test next-generation COVID-19 and pan-coronavirus vaccine candidates*
4. *Characterize, prevent, and treat post-acute sequelae of SARS-CoV-2 infection (PASC)*

Building upon the growing knowledge base of SARS-CoV-2 and COVID-19, this update to the *NIAID Strategic Plan for COVID-19 Research* outlines research priorities critical to better understanding, treating and preventing SARS-CoV-2 and COVID-19 and its post-acute sequelae. The plan is structured on four updated strategic research priorities:

- **Advance basic research on SARS-CoV-2 biology, pathogenesis, and transmission** to further evaluate the biology of SARS-CoV-2 and better understand its transmission, epidemiology, pathogenesis, and immunopathogenesis, including the immunologic and clinical markers associated with disease severity. Pursue research to identify and characterize emerging viral variants to understand their epidemiological or clinical considerations and/or their potential impact on vaccines, therapeutics, and diagnostics.

- **Identify and test promising COVID-19 therapeutics,** including the discovery and development of novel antivirals, including SARS-CoV-2–specific and broad-spectrum antivirals; virus-targeted antibody-based therapies (including monoclonal and polyclonal antibody products); and host-directed strategies to treat COVID-19, such as immunomodulators.

- **Develop and test next-generation COVID-19 and pan-coronavirus vaccine candidates** to provide broad and durable protection against SARS-CoV-2 and other coronaviruses with pandemic potential. These include variant-specific vaccine candidates and novel approaches that are designed to increase the breadth or durability of immunity, be given in one dose, or be rapidly scaled up to address the global need.

- **Characterize, prevent, and treat post-acute sequelae of SARS-CoV-2 infection (PASC),** including characterizing the pathophysiology and clinical manifestations of disease and developing treatment and prevention approaches.

To accelerate research, NIAID will continue to leverage current resources and global collaborations, including existing research programs and clinical trials networks. A concerted effort has been made to include at-risk and vulnerable populations in all NIAID-sponsored COVID-19 therapeutic and vaccine clinical trials. With collaboration from agencies within the U.S. government and other key U.S. and global partners, NIAID will continue to rapidly disseminate data from these studies so that the information can be translated into clinical practice and public health interventions to help combat the pandemic.

COVID-19 Research Plan – 2021 Update

Priority 1: Advance basic research on SARS-CoV-2 biology, pathogenesis, and transmission

In 2020, a coordinated research response provided critical knowledge about SARS-CoV-2 and COVID-19 that enhanced the ability to diagnose and treat the disease. This response included the rapid identification of the human cellular receptor for SARS-CoV-2 and characterization of the structure of the viral spike protein that is critical for cell entry. Additional studies revealed areas of the virus surface that are essential to virus neutralization, paving the way for the development of candidate vaccines and therapeutics that hold promise for altering the trajectory of the pandemic. Further studies on basic characteristics of SARS-CoV-2 and COVID-19 remain paramount to developing the tools to prevent SARS-CoV-2 infection and treat COVID-19. These include studies that enhance understanding of SARS-CoV-2 biology, transmission, incidence, and prevalence, and of COVID-19 pathology. To support these efforts, NIAID will continue to source and supply virus isolates, clinical specimens, and reagents in public repositories to the scientific community. In addition, NIAID will continue to support the development of small and large animal models and ensure that well-characterized animal models are made available to the scientific community for the evaluation of promising medical countermeasures.

- **Continue to characterize virus biology and immune responses to infection**
  Continuing to build on the foundational studies of SARS-CoV-2 and COVID-19 is paramount to developing new medical countermeasures to protect public health. Early studies delineating the primary host receptor, angiotensin converting enzyme 2 (ACE-2), and the structure of the virus receptor-binding domain were crucial to the development of promising candidate vaccines and therapeutics that are now publicly available. NIAID will continue to foster research on the interaction between the virus and host immune responses, and on other factors that correlate with severe disease that ultimately may lead to the identification of novel targets for intervention. In addition, NIAID will pursue investigations of SARS-CoV-2 biology and tropism that will enhance the ability to detect, prevent, and treat disease.

- **Assess functional consequences of newly emerging SARS-CoV-2 variants**
  As SARS-CoV-2 circulates throughout the world, a significant number of genetic mutations are occurring within the spike protein of the virus. Although many of these changes are unlikely to have a major impact on the virus or the efficacy of medical countermeasures, several SARS-CoV-2 variants of concern have been associated with increased transmissibility and significant antigenic variation. The presence of these variants underscores the need for continued studies to identify and characterize virus genetic diversity and evaluate the circumstances that lead to their emergence. NIAID will support research on the impact of these variants on transmission, disease severity, and their potential to escape immunity elicited by natural infection or vaccination. Comprehensive *in*

vitro and *in vivo* studies will be performed to rapidly provide a risk assessment of emerging variants, with an emphasis on potential impacts to medical countermeasures.

- **Assess dynamics of disease transmission and progression through natural history and serosurveillance studies**
  Ongoing observational studies conducted and supported by NIAID track COVID-19 disease prevalence, transmission, and pathology. These ongoing studies reveal critical features of how the virus spreads and causes disease. Seroprevalence studies provide crucial data on the prevalence of disease in high-risk populations such as healthcare workers and the elderly. Natural history studies provide insight into the immune response over time, pathogenesis, and biomarkers for severe disease. Identification of early biomarkers or characteristics of infection that lead to severe disease are critical to informing early treatment strategies that may improve clinical outcome. Along with informing our understanding of COVID-19 immunopathogenesis and viral tropisms, data from these longitudinal cohorts may elucidate mechanisms of disease transmission, including the duration of virus shedding during infection and the durability of immune protection after infection or vaccination. Data from these studies will continue to be essential to developing and optimizing prevention and treatment strategies for SARS-CoV-2 infection and COVID-19.

Priority 2: Identify and test promising COVID-19 therapeutics

Since the beginning of the COVID-19 outbreak, NIAID has worked with partners across government agencies, academia, industry, and the community to advance promising therapeutics against COVID-19. This approach involved developing and testing drugs and monoclonal antibodies (mAbs) and has yielded several promising therapeutic interventions. The NIAID Adaptive COVID-19 Treatment Trial (ACTT) demonstrated the safety and efficacy of remdesivir, an RNA polymerase inhibitor developed by Gilead Sciences, for shortening time of COVID-19 recovery. Further studies revealed promising safety and efficacy of additional interventions, including baricitinib, a Janus kinase (JAK) inhibitor, and monoclonal antibodies, including Eli Lilly and Company's, LY-CoV555 (bamlanivimab) for treating various stages of COVID-19. Promising therapeutic candidates will continue to be identified and tested in clinical studies, including those initiated under the NIH Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) public-private partnership.

- **Identify and test new drugs for COVID-19**
  Despite early advances in promising therapeutics, there continues to be an urgent need to identify safe and effective treatments across the spectrum of COVID-19 disease. NIAID will continue supporting basic and translational research efforts to identify promising viral targets and drug classes and generate novel compounds. Leveraging former successful partnerships (as for HIV drug development) and continuing the collaborative interactions that were established in response to the COVID-19 pandemic, NIAID will engage pharmaceutical companies to share compound libraries, medicinal chemistry, and drug development expertise to accelerate internal efforts and ensure that the most promising therapeutic candidates progress rapidly into the clinic. The immediate priority is to identify new SARS-CoV-2 drug targets and expedite the development of direct acting antivirals against SARS-CoV-2, with emphasis on drugs that can be administered orally.

- **Support the identification and testing of mAbs for treatment or prophylaxis**
  SARS-CoV-2 specific mAbs are the only therapeutics currently authorized for emergency use by the U.S. Food and Drug Administration (FDA) for early/mild COVID-19. Additional clinical trials are needed to understand their utility as the pandemic evolves and novel SARS-CoV-2 variants become

increasingly prevalent. New treatment strategies involving mAbs capable of neutralizing viral variants *in vitro* will need to be evaluated in ongoing platform trials to determine clinical efficacy. Furthermore, clinical trials are needed to understand the impact of mAb treatment on convalescent immune responses and immune responses to subsequent vaccination.

- **Evaluate host-directed strategies for treatment**
  Severe cases of COVID-19 have been linked to dysregulated immune responses. Host-directed treatment strategies, such as those that impact inflammation, have shown promise when used in combination with antiviral drugs to accelerate recovery and improve clinical outcomes of patients hospitalized with COVID-19. Building on these findings, NIAID will continue to support investigations of other host-directed strategies, including corticosteroids, kinase inhibitors, or cytokines, alone or in combination with antivirals, mAbs, or other therapeutics, as potential treatments for COVID-19.

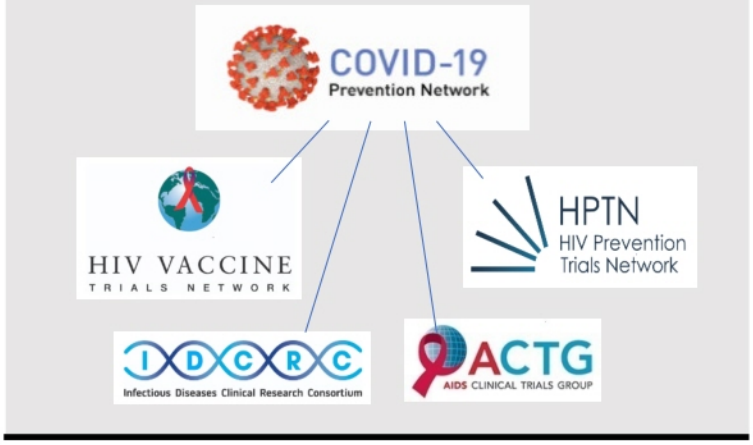
- **Conduct clinical trials to demonstrate the safety and efficacy of lead therapeutic candidates**
  NIAID has developed flexible clinical trial structures to facilitate the evaluation of therapeutic candidates as they emerge, including in special populations, high-risk and minority populations, and pregnant or breastfeeding women. Many potential therapeutic candidates have been identified and are being tested in clinical trials for treating COVID-19. NIAID has developed flexible clinical trial structures to facilitate the evaluation of therapeutic candidates as they emerge, including in special populations, high-risk and minority populations, and pregnant or breastfeeding women. This effort includes the following studies:
  - The ACTT study is testing combinations of therapeutics with remdesivir for improving treatment outcomes of hospitalized patients with COVID-19.
  - The Big Effect Trial (BET), also known as ACTIV5, is conducting smaller studies on putative therapeutics that have existing clinical data and will transition the most promising candidates into larger clinical trials.
  - ACTIV2 continues to investigate promising candidates for the treatment of outpatients with COVID-19, including investigational mAbs developed by multiple companies. Concurrently, ACTIV3 has initiated multiple clinical trials evaluating promising mAbs for treating people hospitalized with COVID-19.

Priority 3: Develop and test next-generation COVID-19 and pan-coronavirus vaccine candidates

The development of safe and effective vaccines is a high priority of the NIAID research response to COVID-19. NIAID has supported the development and testing of several COVID-19 vaccine candidates that hold promise to significantly alter the course of the COVID-19 pandemic. Despite the rapid development and FDA emergency use authorization (EUA) of several vaccine candidates, the SARS-CoV-2 virus is evolving. New variants are associated with increased transmission efficiency and antigenic variation that may diminish the efficacy of authorized vaccines. To maintain progress and ultimately end the pandemic, it is critically important to complete the clinical evaluation of current vaccine candidates across all ages and populations, rapidly develop and evaluate next-generation vaccine candidates to protect against emerging SARS-CoV-2 variants of highest concern, and invest in the fundamental discovery and development of vaccine approaches that provide protection against multiple coronavirus strains. In 2020 NIAID established a new clinical trials network that aims to enroll thousands of volunteers in large-scale clinical trials testing a variety of investigational vaccines and monoclonal antibodies intended to protect people from COVID-19. The COVID-19 Prevention Network (CoVPN) was established by merging four existing NIAID-funded clinical trials networks: the HIV Vaccine Trials Network (HVTN); the HIV Prevention Trials Network (HPTN); the Infectious Diseases Clinical Research Consortium (IDCRC); and the AIDS Clinical Trials Group (Box 2).

- **Continue to advance promising candidates through clinical testing across all ages and populations**
  Although unprecedented progress has been made, much remains to be learned about the vaccine products currently under EUA and in late-stage clinical development, the majority of which are technologies that have not been used extensively in humans. Critical questions to be addressed include understanding: vaccine outcomes across all age groups and demographics, the duration of protection of each candidate vaccine, the impact of vaccination on infection and transmission, the safety and efficacy of vaccination in special populations, and the level of protection afforded by a single dose of certain vaccine products. NIAID is planning or has already initiated studies to confirm the safety of vaccine candidates in pregnant women, children, and immunocompromised individuals. Additional studies are planned to understand whether highly allergic individuals are more prone to allergic reactions to the COVID-19 mRNA vaccines than are non-allergic individuals.

Box 2
NIAID COVID-19 Prevention Network (CoVPN)



- **Identify and characterize immunogens that induce a wide breadth of protection**
  NIAID is supporting the advancement of multiple approaches to identify immunogens with broad protective potential against multiple coronavirus strains. This includes analyses of coronavirus diversity, structural investigations of coronavirus proteins, and identification of broadly reactive B-

and T-cell epitopes. NIAID also supports studies that leverage innovative immunogen identification and design strategies to delineate proteins that elicit broad coronavirus immunity.

- **Develop and evaluate next-generation vaccine candidates that protect against SARS-CoV-2 variants**
  Emerging SARS-CoV-2 variants with multiple changes in critical antigenic regions of the spike protein have the potential to significantly impact vaccine-induced immunity. There is an urgent need to learn the potential impact of these variants on vaccine efficacy and to immediately begin developing next-generation COVID-19 vaccine candidates to protect against emerging variants, should they be needed. NIAID is working with industry, academic, and community partners to develop and evaluate vaccine candidates to protect against currently circulating variants of highest concern. Preclinical *in vitro* studies and studies in animal models are underway. Phase 1 clinical studies for vaccines against current variants are expected to begin in early spring 2021. NIAID will continue to advance novel vaccine candidates that generate potent immune responses against epitopes from multiple SARS-CoV-2 proteins to potentially expand the breadth of protection against viral variants.

- **Provide adjuvants to support vaccine development**
  Identification and selection of appropriate adjuvants is crucial for developing safe and effective vaccines. NIAID is working with multiple collaborators to provide adjuvants to the research community. These adjuvants include compounds that specifically improve SARS-CoV-2 vaccine efficacy in elderly individuals or modulate host immunity toward protective responses while limiting or preventing harmful inflammatory responses.

Priority 4: Characterize, prevent, and treat post-acute sequelae of SARS-CoV-2 infection (PASC)

As millions recover from initial SARS-CoV-2 infections of varying severity, some individuals do not return to baseline health. Reported symptoms involve nearly all organ systems and include fatigue, dyspnea, cognitive dysfunction, anxiety, and depression. Specific case definitions have not been established and PASC may comprise multiple phenotypes. Although the prevalence of these sequelae remains unclear, the public health impact is potentially large given the sheer number of individuals who have been already or will be infected with SARS-CoV-2. NIAID supports efforts to delineate and characterize the clinical spectrum of PASC and launch investigations on promising interventions to prevent and treat the diverse manifestations associated with this condition across demographic groups.

- **Identify and characterize the spectrum and epidemiology of PASC**
  Although multiple clinics have been established in the United States and globally, the clinical spectrum and biology underlying recovery from acute SARS-CoV-2 infection are not well characterized. Multiple factors, including age, sex, existing co-morbidities, and host genetic factors, may impact the breadth of post-acute complications. NIAID is conducting retrospective and prospective studies designed to develop strategies for the prevention and treatment of PASC. In addition to characterizing long-term disease manifestations, a clearer picture of the epidemiology of these outcomes will be critical. NIAID is leveraging new and existing infrastructure, including ongoing natural history cohorts, to characterize the incidence and prevalence of PASC more fully and to understand the long-term impact of SARS-CoV-2 infection.

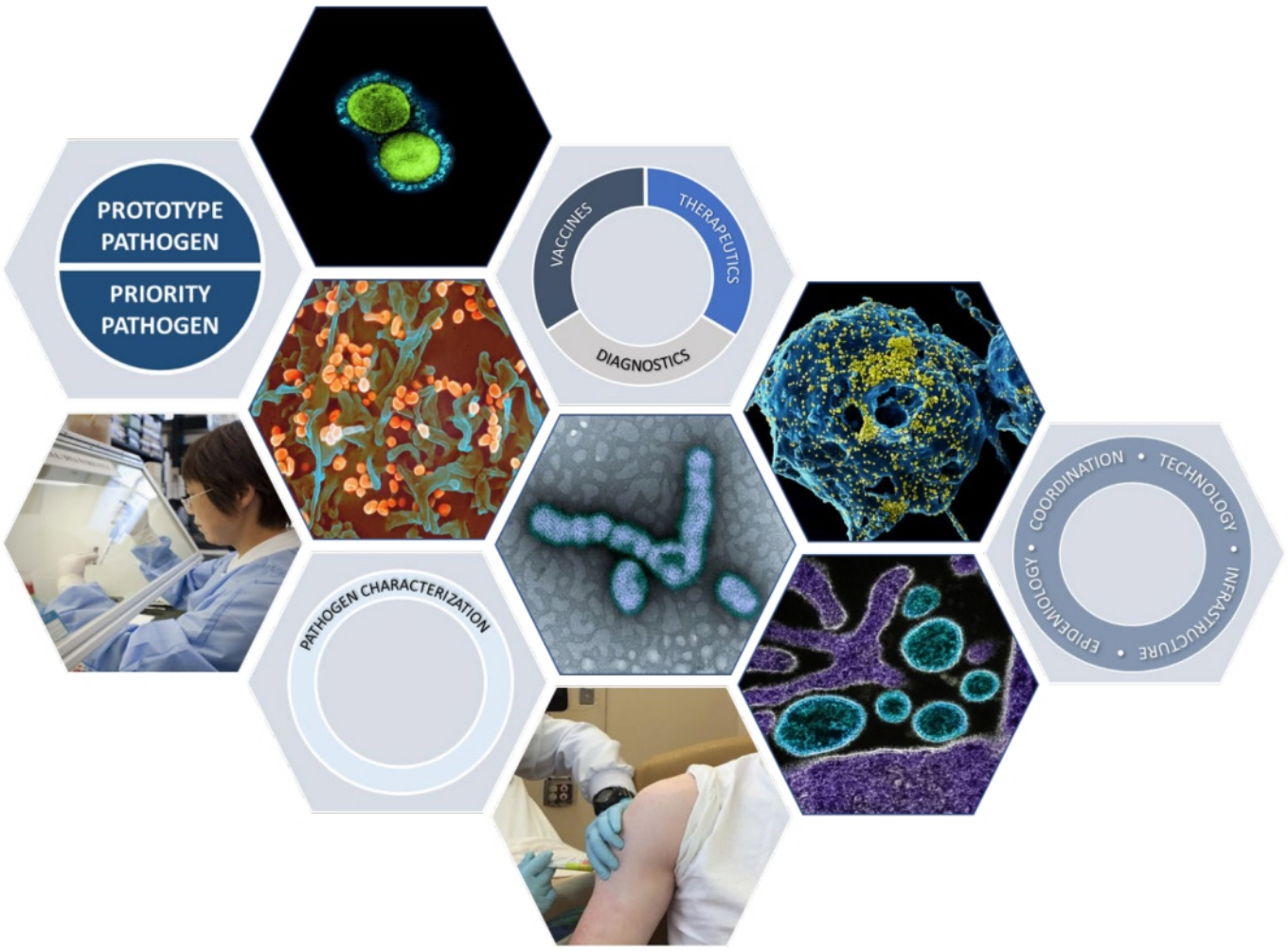
- **Evaluate immune correlates and biomarkers related to long-term outcomes**
  The biological mechanisms underlying the varied long-term effects of SARS-CoV-2 infection are unknown. Although dysregulated immune responses play a key role in progression to severe disease, the factors leading to diverse long-term sequelae are multifactorial, and mechanistic links with immune responses have not yet been identified. NIAID will continue to support research on the immune and inflammatory responses during acute disease and their role in the development of PASC. This includes supporting *in vitro* studies to evaluate cellular responses to SARS-CoV-2 infection and developing animal models of PASC.

- **Identify and adapt treatments and preventative interventions for PASC**
  Characterizing the various manifestations of PASC and their potential underlying causes will suggest novel targets for prevention and treatment. NIAID will support the evaluation of promising interventions, including investigations of existing drugs and testing of novel strategies to address these long-term manifestations.

Conclusion

The unprecedented spread and persistence of COVID-19 has created a daunting public health challenge. Building on early advances in our understanding of SARS-CoV-2 and COVID-19, NIAID is focusing its resources to further characterize virus biology, understand immediate and long-term consequences of disease, and develop safe and effective COVID-19 therapeutics and vaccines. The resulting scientific advances will add to our existing prevention and treatment armamentarium for mitigating the current COVID-19 pandemic, as well as serving as a foundation for the development of prevention, diagnostic, and treatment strategies to address future emerging and re-emerging infectious diseases and protect public health from future pandemics.

National Institute of Allergy and Infectious Diseases



NIAID PANDEMIC PREPAREDNESS PLAN

December 2021

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Background

The National Institute of Allergy and Infectious Diseases (NIAID) is committed to safeguarding the health of Americans and people around the world by conducting and supporting basic and applied research to better understand, treat, and ultimately prevent infectious diseases. NIAID developed this Pandemic Preparedness Plan, which leverages its broad research portfolio, long-standing expertise in product development, capacity to engage both domestic and international partners, and flexible infrastructure to support its mission to respond rapidly to emerging and re-emerging infectious disease threats.

The NIAID pandemic preparedness plan focuses predominantly on viruses that could cause epidemics or pandemics and prioritizes research on prototype-pathogens, representative pathogens from viral families known to infect humans, and high-priority pathogens most likely to threaten human health. Research and development will encompass preclinical research, translational, and early phase clinical studies to evaluate candidate medical countermeasures, such as vaccines, therapeutics, and monoclonal antibodies. Underpinning research and development preparedness efforts are novel epidemiology and surveillance programs, expanded pre-clinical and clinical infrastructure capacity, and a robust and coordinated communication structure. The NIAID Pandemic Preparedness Plan aims to ensure all intramural and extramural NIAID pandemic preparedness efforts are harmonized, and that collaboration will occur across the US Government (USG) and with foreign governments, industry, and international organizations.

Stakeholder engagement is a valuable part of the NIAID preparedness planning efforts. In November 2021, NIAID hosted a workshop that introduced the NIAID pandemic preparedness strategy and facilitated discussions with the scientific community on prioritizing prototype pathogens within viral groups of concern. Moving forward, NIAID will continue to engage the outside scientific community and federal partners to ensure preparedness planning efforts are collaborative, integrative, and aligned with current scientific research.

Introduction

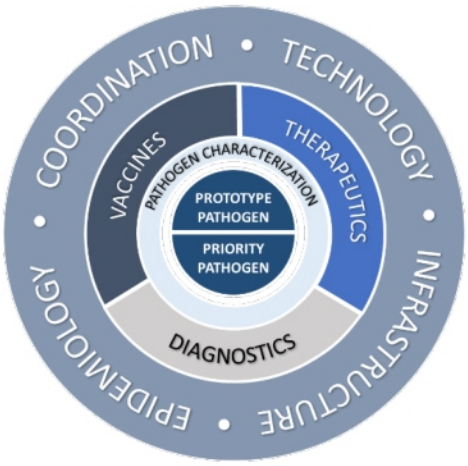
The emergence and re-emergence of infectious diseases continues to threaten the health of Americans and people worldwide. In the past two decades NIAID has mounted major research responses and developed effective countermeasures to emerging infectious diseases including those caused by SARS-CoV-1, the 2009 H1N1 influenza virus, Middle East Respiratory Syndrome coronavirus (MERS-CoV), Ebola virus, Zika virus, and most recently SARS-CoV-2. The ongoing 2020 global pandemic caused by SARS-CoV-2 further has underscored the continual threat of newly emerging and re-emerging pathogens and the critical value of research in pandemic preparedness efforts. To prepare for future public health emergencies caused by infectious diseases, NIAID has developed a Pandemic Preparedness Plan that leverages its broad research portfolio, long-standing expertise in product development, capacity to engage both domestic and international partners, and flexible infrastructure. While it is recognized that pathogens other than viruses could lead to public health emergencies, the NIAID Pandemic Preparedness Plan focuses on viruses that could cause epidemics or pandemics.



Pathogens of concern, for the purposes of the NIAID Pandemic Preparedness Plan, are viruses that have the potential to cause a human epidemic or pandemic.

The goals for the NIAID Pandemic Preparedness Plan are to:

- Systematically **characterize pathogens of concern** and increase research and surveillance to identify threats before they emerge
- **Shorten timelines** between pathogen emergence or outbreak onset and authorization/approval of candidate diagnostics and medical countermeasures, such as therapeutics and vaccines
- **Bridge or eliminate existing gaps** in research, infrastructure, and technology and expand pre-clinical and clinical testing capacity



The NIAID Pandemic Preparedness Plan goals build on a foundation of pathogen-specific research that include advancing research on priority pathogens known to or having the potential for emerging as public health threats. Continuing to build a robust basic research portfolio and advancing translational science on these pathogens is essential for biomedical preparedness. In addition to known threats, effective preparedness must also account for unexpected emerging disease threats, commonly referred to as Pathogen(s) X. To mitigate risks associated with these yet unknown pathogens, NIAID will prioritize preparedness research on prototype-pathogens, which are select pathogens identified from viral families known to infect humans. Viruses are taxonomically organized into families based upon shared functional and structural similarities. Because of this, candidate vaccines developed against a prototype pathogen from a family may similarly work against other members in the same family. Through targeted basic and applied research on these prototype pathogens from each viral family of concern, the accrual of a solid foundation of knowledge and medical countermeasures (MCMs), such as therapeutics, vaccines, and monoclonal antibodies (mAbs), will

enable a rapid response when a Pathogen X emerges from any of the viral families of concern. This anticipatory approach will exponentially increase the preparedness and response portfolio and enable rapid movement of candidate MCMs into clinical trials.

NIAID will support the research, development, and testing of critical MCMs through Phase I/IIa clinical trials where appropriate, in coordination with other entities undertaking similar research worldwide. NIAID also will continue to provide the USG public health infrastructure with a robust pipeline of preparedness resources to shorten the response timeline when human viral disease threats emerge. NIAID, the lead NIH Institute for infectious disease research and MCM discovery, has broad capacity in infectious diseases and immunology and a history of preparing for and responding to domestic and global infectious disease threats. A central NIAID team will facilitate, coordinate, and harmonize preparedness research and development within the Institute. It also will communicate and coordinate with the NIH and other relevant USG agencies as well as appropriate entities outside the U.S., including key international organizations and foreign research partners.

To prevent widespread morbidity and mortality, the early detection of an emerging pathogen threat is essential. Therefore, in partnership with the CDC, USAID and other USG entities concerned with emerging infectious diseases, strategic epidemiological field studies undertaken by NIAID-supported centers and networks will provide key reagents and insights into viruses that have the potential to cause a human epidemic or pandemic. In addition, these efforts will be coordinated with similar global efforts already underway or planned so that informed worldwide surveillance and epidemiology is assured.

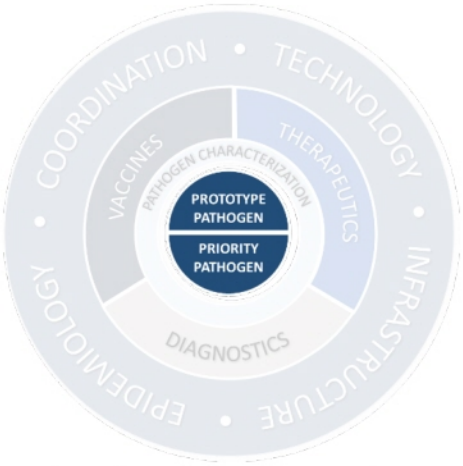
Technological advancements, such as platform technologies for MCMs, will also be crucial to the preparedness effort. The most promising platform technologies will need to be leveraged for development of vaccines, therapeutics, and diagnostics. Their products will also need to be evaluated clinically through an experienced and nimble clinical trial infrastructure that complies with rigorous regulatory standards. Developing and leveraging these cross-cutting elements across the preparedness research pipeline will enable NIAID to support the USG research effort that will underpin an effective response to public health emergencies caused by emerging or re-emerging infectious disease threats.

Preparedness-Response Continuum

Pandemic preparedness and response exist along a continuum, and it is important to operationally distinguish between the capacities associated with each. The extent of preparedness will determine the speed and effectiveness of a response. The NIAID preparedness research efforts will provide the reagents, roadmaps for product development and evaluation, scientific infrastructure, and study capacity needed for a robust research response to a future pandemic.

Conceptual Approach

Preparedness for major infectious disease outbreaks will save lives; rapid deployment of effective diagnostics, vaccines, and treatments can contain an outbreak before it expands into a larger epidemic or pandemic. Obtaining in-depth knowledge and developing MCMs for prototype pathogens within viral families that pose the highest risk for epidemics/pandemics is an effective strategy to prepare for future disease outbreaks. This approach was successfully applied during the global COVID-19 pandemic of 2020 when prior knowledge gained through the study of SARS-CoV-1 and MERS-CoV was leveraged to rapidly design vaccines, diagnostics, and therapeutics against SARS-CoV-2.



Priority and Prototype Pathogen Research

There are multiple virus families for which there are no available licensed vaccines, and many member viruses within families that have potential to cause significant human disease. Since it is not feasible to fully characterize the ~120 viruses known to cause human disease and develop MCMs for each, selection of representative viruses from each family offers a viable pathway to gain knowledge that may be applicable to part or all of a particular virus family. These representative viruses are considered **prototype pathogens.** For example, within the *Arenaviridae* family, Lassa, Junin, or other viruses could be selected as a prototypic pathogen(s). The ideal arenavirus prototype pathogen(s) would not only be a virus with a risk of causing an outbreak, but most importantly, would be one that shares functional and structural properties with viruses across the *Arenaviridae* family. Thus, increasing fundamental knowledge and developing MCMs for the prototype virus(es) not only provides ready potential solutions for these viruses, but also the framework for a rapid research and product development response to other viruses within that family should an outbreak occur. A schematic for how prototype pathogens are selected, studied, and brought to clinical trials is shown in Figure 1.

In addition to the prototype pathogen approach, NIAID will also characterize, develop reagents, and conduct pre-clinical and clinical testing of other pathogens that may not serve as prototypes, but that nonetheless threaten human health and thus are considered a high priority to study. We refer to these as **priority pathogens**. This pathogen-specific research prioritizes viruses most likely to cause significant human morbidity and mortality. While priority pathogens can also be prototype pathogens (e.g., Ebola virus), these two designations do not necessarily overlap. For instance, Zika virus of the Flaviviridae family is known to cause human morbidity, but it does not serve as a good prototype for development of MCMs for other Flaviviridae family members. Thus, NIAID will continue to support Zika virus research in the capacity of a priority pathogen. To ensure adequate coverage of viruses that pose a known threat to human health and Pathogen(s) X, NIAID will support both priority and prototype pathogen research through its pandemic preparedness strategy.

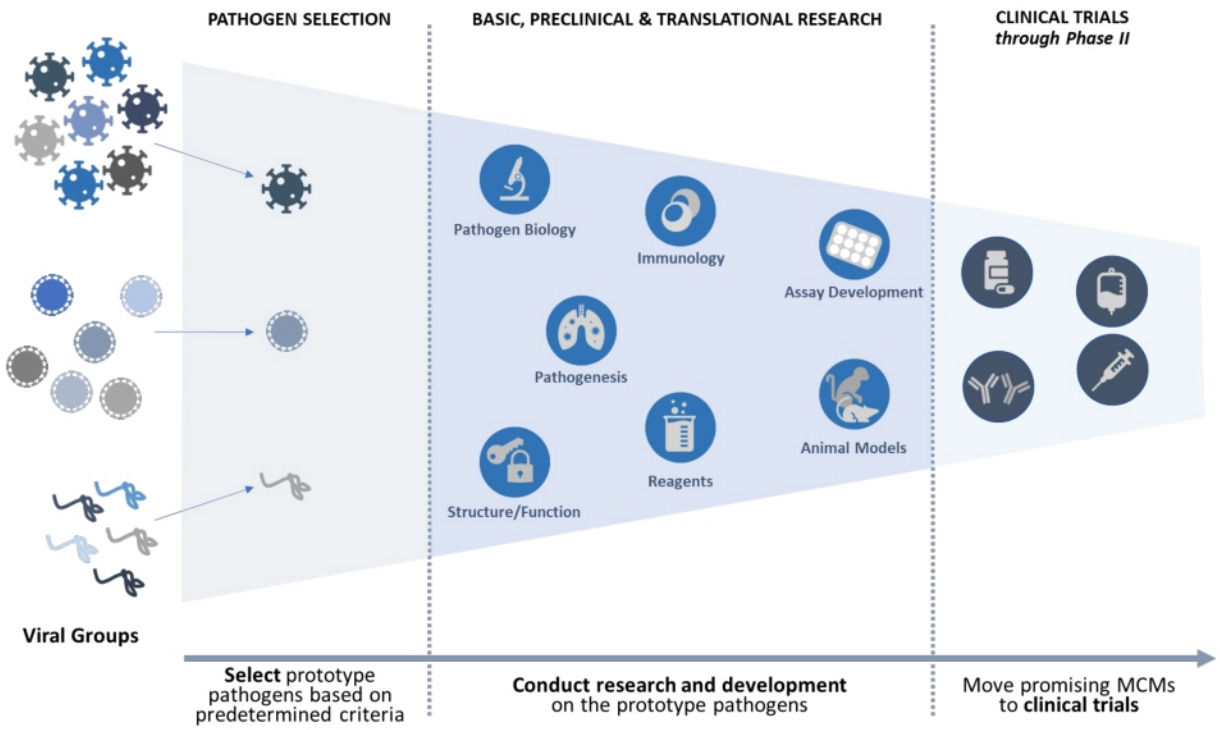
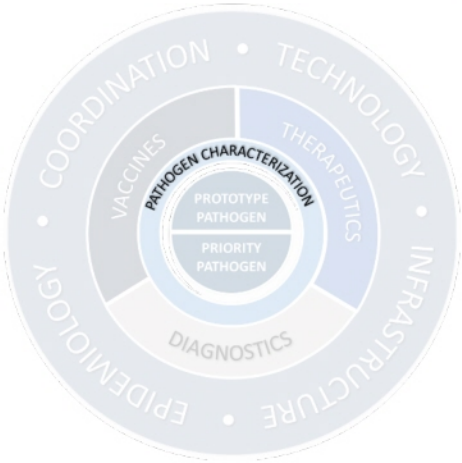


*Figure 1: **Prototype Pathogen Research and Development Process**. Schematic depicts the process by which prototype pathogens will be selected for additional study, preclinical and translational research activities, and clinical trials of promising MCMs.*

Preparedness Research and Development

The Pandemic Preparedness Plan will support critical studies to characterize prototype and priority pathogens, including understanding viral biology and structure, host immune responses, mechanisms of immune evasion, disease pathogenesis, and studies to develop assays and animal models of disease. Research and development will encompass preclinical and translational activities and will include expanded conduct of early phase clinical studies to evaluate candidate countermeasure safety and immunogenicity, or drug profile characteristics. Clinical trials of promising MCMs will include equitable representation of participants from traditionally underrepresented groups, all genders, and individuals across the lifespan.



Preclinical Research

Pathogen Biology, Pathogenesis, and Host Immunity

Developing products that can protect against pathogens of concern is an integrated process that requires basic and applied research. Fundamental knowledge of pathogen biology; structural properties; mechanisms of transmission, including identification of viral vectors; viral lifecycle; viral entry mechanisms and host receptors; tissue tropism; and host immune responses is critical to efforts informing the development of MCMs against new, emerging, or remerging pathogens.

Structure-Function Studies

Understanding the function of essential viral proteins will be necessary to enable structure-guided vaccine design, identify viral targets for the development of effective therapeutic candidates, and develop diagnostic and immunological assays. To facilitate this critical area of research, NIAID will support technologies including x-ray crystallography, nuclear magnetic resonance imaging, cryogenic electron microscopy, and high-throughput technologies, including computational modeling to characterize viral structural components.

Animal Models

Developing animal models that recapitulate human disease is a vital step toward understanding disease pathogenesis and mechanisms of immune protection as well as the assessment of MCM efficacy. Small animal models will be prioritized to enable rapid, scalable studies particularly valuable for screening countermeasure candidates for immunogenicity, drug candidate pharmacokinetics/pharmacodynamics, vaccine and therapeutic efficacy and safety. In parallel, development and characterization of large animal models, including non-human primates that closely recapitulate human disease, is pivotal to advance promising candidates toward clinical evaluation. NIAID will support the development of essential small and large animal models to better understand viral biology and to assist in vaccine and therapeutic development. NIAID also will ensure that well characterized animal models that recapitulate human disease are made available to the scientific community for evaluating priority MCMs.

Immunology and Assay Development

NIAID will support the design and development of serological assays that can serve as useful tools to evaluate MCMs, including evaluating the immunogenicity of promising vaccines and effectiveness of therapeutic candidates. These assays can also identify correlates of protection, identify antigen-specific responses to pathogens, and characterize cross-reactive responses to pathogens.

The design and development of approaches and research tools to assess and enhance cellular and tissue-specific immunity to specific pathogens and pathogen families will also be supported.

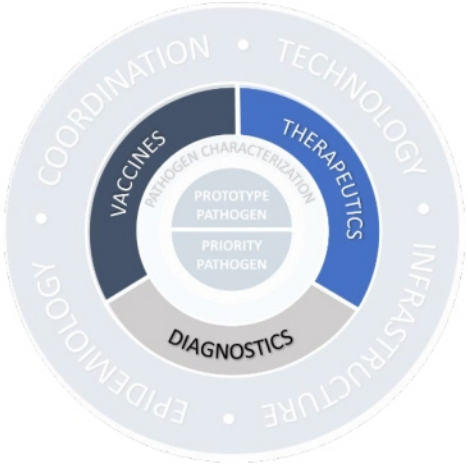
NIAID will provide for the expansion of specialized technologies related to high-throughput cell sorting/cytometry, immunologic assays, and sequencing, and expand support of genetic examination of zoonotic reservoirs that might contribute to emerging infectious diseases of global health importance.

Reagents and Resources

NIAID will support and coordinate the development and sharing of reagents and resources to accelerate fundamental research and the development of vaccines, therapeutics, immunological assays, and diagnostics. Reagent and resource development will include well characterized viral stocks, convalescent serum, and PBMCs to develop assays, protein or nucleic acid standards, mAbs, and animal models. The reagents will be put in NIAID-supported repositories and made available to the scientific research community.

Translational and Clinical Research

Diagnostics



NIAID will leverage its expertise in infectious diseases, genomics, proteomics, bioinformatics, and access to clinical samples to develop rapid-response diagnostics for biological threats and emerging infectious diseases. In close collaboration with other NIH institutes and USG agencies, NIAID will support the development new and improved point-of-care and home-based tests as well as ultrahigh-throughput central reference laboratory testing that can accurately detect signatures of infectious pathogens that are of high public-health consequence. NIAID will develop readiness strategies in collaboration with other USG agencies to ensure immediate authorized deployment of the necessary diagnostic testing as a frontline medical countermeasure following acknowledgement of an imminent public-health threat.

Therapeutics

NIAID will continue to support basic, translational, and clinical research efforts to identify promising targets for intervention and generate novel therapeutics that are both pathogen-specific and have broad-spectrum activity. Leveraging earlier successful partnerships (as for HIV drug development) and continuing the collaborative interactions that were established in response to the COVID-19 pandemic, NIAID will engage pharmaceutical companies to share libraries, medicinal chemistry, and drug development expertise to accelerate internal efforts to ensure the most promising drug candidates progress rapidly into clinical use.

Small Molecule/Antivirals

The Pandemic Preparedness Plan will respond to the pressing need for safe and effective therapeutics by building sustainable platforms for targeted drug discovery through the development of small molecules and antivirals that may be useful against a wide range or class of pathogens of concern. NIAID will evaluate and advance new drug candidates to the stage of being late Phase 2-ready. One existing program through which NIAID will develop safe and effective antivirals is the Antiviral Program for Pandemics (APP). The APP will focus on antivirals that directly act against viral targets, specifically for RNA viruses. Antivirals of interest will have broad use in the outpatient setting, reducing viral burden in the early stages of infection.

As part of the APP, NIAID will establish Antiviral Drug Discovery (AViDD) Centers for Pathogens of Pandemic Concern. The centers will initially focus on novel, oral antivirals for SARS-CoV-2 and other coronaviruses and will expand to other pathogens of pandemic concern in future years.

These Centers will use the tools of structural biology, biochemistry, and systems biology to select essential virus-specific functions for targeting. Further, this platform will provide a means for identifying the conserved structures and functions shared between pathogens of concern that can be targeted for drug development.

Monoclonal Antibodies

Recent advances in mAb technologies have provided scientists with valuable tools to prevent and treat infectious disease. Innovation efforts in the selection and manufacture of mAbs reduced the time needed for their development. Their applicability in either prevention or treatment approaches make mAbs a powerful intervention against infectious disease, particularly essential in the case of an outbreak (as during the Ebola outbreak in central Africa and the COVID-19 pandemic). NIAID will support the development and characterization of panels of mAbs against prototype and priority pathogens. The mAbs that are identified as highly neutralizing or with broadly neutralizing capacity will be further characterized and developed into candidates for effective therapeutics and/or prevention approaches.

Broad-spectrum protection via immunomodulation, trained immunity, and related approaches

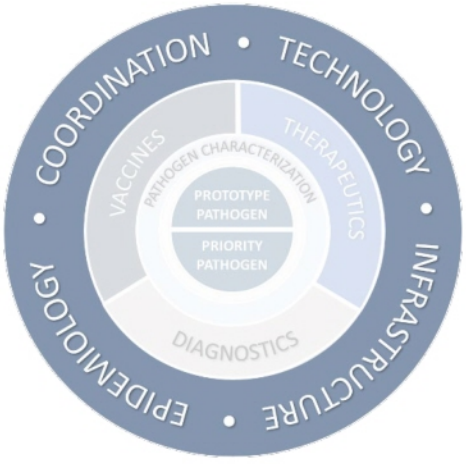
Recent advances in understanding host innate immunity highlight the potential value of non-antigen-specific protection as a bridge during development of antivirals and vaccines. NIAID will support the development and clinical evaluation of short-term, but broadly protective strategies including the use of inhaled or systemic immunomodulators. Research on vaccine-elicited, off-target protection has identified a molecular process termed *trained innate immunity*, by which certain live-attenuated or well-adjuvanted vaccines trigger long-lived epigenetic programs that enhance functions of innate immune cells, including monocytes and macrophages. NIAID will support basic and clinical research with the long-range objective of providing protection from severe disease early in a pandemic (prior to the availability of pathogen specific vaccines) through trained innate immunity.

Vaccines

Successful vaccine design and development can significantly alter the course of a pandemic. To address the need for safe and highly effective vaccines against new and emerging pathogens, NIAID will support work to define the key antigenic targets through the use of the prototype and priority pathogen approaches, solve structures of surface proteins, characterize the immunological response (including epitope mapping), support structure guided vaccine design, identify and characterize novel adjuvants that boost immunity and increase the breadth of immune responses while decreasing vaccine reactogenicity, and identify cellular receptors and tropisms. In addition, comprehensive reagents leading to the development of antigen-specific and serological assays would also provide the necessary tools for vaccine development.

Cross-cutting Preparedness Efforts

The ability of NIAID to prepare for and mount a rapid and effective research response to an emerging pathogen relies on knowledgeable staff, up-to-date facilities and flexible infrastructure, cutting-edge technology, and a robust, centralized coordination hub.



A dedicated preparedness coordination team of NIAID staff and scientists working closely with the NIAID Office of the Director will serve as the coordination hub for the NIAID pandemic preparedness efforts. This team will track the prototype pathogen research portfolio, ensuring adequate pathogen coverage and resource allocation to address scientific gaps. NIAID will continuously engage with leadership in other federal

agencies and international funders with preparedness and response capabilities to inform them on preparedness research progress.

The NIAID Pandemic Preparedness Plan outlines the cross-cutting epidemiology, infrastructure, technology, and coordination and communication approaches necessary to successfully prepare for future pandemics.

Epidemiology and Pathogen Discovery

Underpinning preparedness research and development is a robust global disease discovery and epidemiology program aimed at identifying emerging infectious disease threats, which are crucial for risk assessment, reagent collection, pandemic preparedness efforts and rapid response measures. Early discovery and appraisal of pathogens of concern is a major element of overall pandemic preparedness. Epidemiology and surveillance will ensure that we are able to rapidly identify, characterize, and act upon newly emerging and re-emerging pathogens in zoonotic reservoirs and in geographic regions where outbreaks are likely to occur. The NIAID PREMISE program (Pandemic Response Repository through Microbial and Immune Surveillance and Epidemiology) will contribute significantly to the pathogen discovery mission and overall pandemic preparedness. PREMISE will pair virologic and immunologic surveillance of viruses and facilitate the development of diagnostic tests and MCMs in anticipation of potential pandemic threats. To further pandemic preparedness, NIAID will utilize its global network of research centers to study how and when viruses and other pathogens emerge from wildlife and spillover into humans. The Centers for Research in Emerging Infectious Diseases (CREID) will enable early warnings of emerging diseases, facilitating a rapid response and potentially curbing potential disease threats before they develop into widespread pandemics. In addition, the NIAID Centers of Excellence for Influenza Research and Response (CEIRR) program will focus on the study of influenza in humans and at the human-animal interface and provide international research infrastructure needed to address zoonotic influenza outbreaks in humans or a pandemic.

NIAID will also liaise with other USG agencies and global partners to help support the enhancement of in-country capacity to expand worldwide surveillance, genetic sequencing, epidemiology, virus or viral variant discovery. Such coordination will help prioritize development of diagnostics, reagents, and MCMs.

Technology

NIAID will continue to support and advance platform technologies that can be leveraged to develop MCMs. By investing in research to develop specific MCMs for known threats and utilizing platform-based and prototype-pathogen approaches to allow for adaptation when unexpected outbreaks arise, NIAID and its partners–both domestic and international–can prepare to effectively combat future disease outbreaks. Broad, wide-range platforms that can be used to significantly reduce the time and cost required to bring MCMs to market. For example, mRNA and adenovirus vaccine platform technologies were successfully utilized during the COVID-19 pandemic to develop effective vaccines against SARS-CoV-2; these and other innovative technologies can be leveraged in the NIAID global preparedness efforts. Other examples of platform technologies include screening systems, *in vitro* safety testing, protein expression methodologies, manufacturing technologies, and chemical synthesis designs. The potential to rapidly apply such platform methods to developing new MCMs, particularly when pursued on a global scale, will considerably shorten and streamline the process of countermeasure development.

NIAID will also continue to support and advance technology transfer agreements that attract potential industry partners and shorten the timeframe from discovery to licensure of effective public health tools, such as diagnostics, vaccines, and biologics. Appropriate technology transfer agreements serve to protect publicly funded discoveries while also accelerating the time to commercial availability.

Infrastructure

Preclinical and Clinical Research Infrastructure

Appropriate research infrastructure capacity will enable effective pandemic preparedness and rapid response research. The enhancement and expansion of dedicated USG owned or funded pre-clinical testing facilities with Animal Biosafety Level 3 (ABSL-3) and ABSL-4 capacity can boost the testing of promising candidate drugs and vaccines and mitigate delays in the event of a pandemic.

Global clinical trial networks that provide research capacity for all patient populations against emerging threats are essential to an effective research response. Preparedness includes leveraging and expanding existing domestic and international outpatient and inpatient clinical trial sites, enhancing on-site expertise, and developing the clinical research infrastructure needed to evaluate countermeasures and rapidly respond to infectious diseases. For example, the COVID-19 Prevention Network was a successful example of leveraging several existing clinical trial networks originally established for other purposes, to test vaccines and mAbs quickly and effectively against SARS-CoV-2. Internationally, other networks also were able to adapt to undertake coordinated COVID-19 clinical studies.

Pilot cGMP Manufacturing Capacity and Process Development

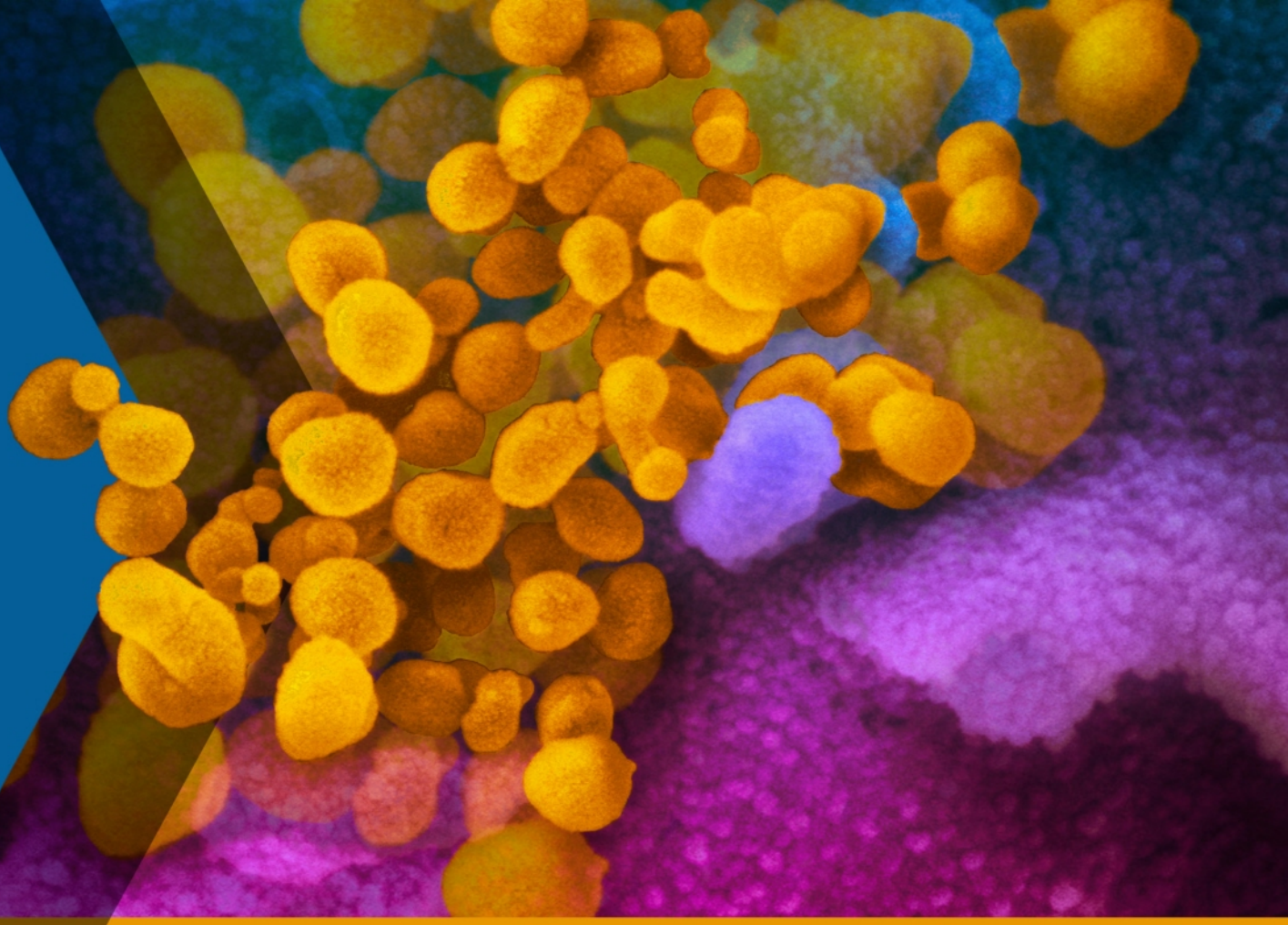
Preparedness efforts will require adequate capacity for process development and pilot Current Good Manufacturing Practice (cGMP) manufacturing of MCMs against prototype and priority pathogens. By manufacturing product and conducting Phase I/II trials, NIAID aims to attract industry partners and shorten the timeframe from scientific discovery to licensure to application of effective public health tools.

Regulatory Science and Strategy Infrastructure

Pandemic preparedness efforts will require close interaction with regulatory authorities and USG partners, particularly the FDA, as well as an understanding of foreign regulatory agencies and processes. Regulatory coordination will ensure that all NIAID-wide pandemic preparedness efforts are harmonized to the extent possible.

Coordination and Communication

Effective coordination and communication are central to effective preparedness research efforts and requires close collaboration both among the NIH ICs and with external partners in the United States, other countries, international organizations, and biomedical research-oriented philanthropies. The NIAID Pandemic Preparedness Plan will ensure that all internal NIAID pandemic preparedness efforts, encompassing intramural and extramural programs, are harmonized and supported by the effective mobilization of logistical, administrative, and technical resources. NIAID will also actively collaborate and integrate its efforts with similar ones undertaken by other USG entities, including CDC, USAID, DoD, and other agencies. Through multiple mechanisms, NIAID also will coordinate its programs with foreign government entities; international organizations, including WHO, the Global Fund, CEPI, GAVI, BMGF, and others; and domestic and international academic, private sector, and NGO entities.



NIH-Wide Strategic Plan for

COVID-19 Research

2021

National Institutes of Health

Updated from July 2020

Cover Image

Coronavirus SARS-CoV-2

This scanning electron microscope image shows SARS-CoV-2 (yellow)—also known as 2019-nCoV, the virus that causes COVID-19—isolated from a patient in the United States, emerging from the surface of cells (blue/pink) cultured in the laboratory.

Credit: Rocky Mountain Laboratories, National Institute of Allergy and Infectious Diseases, NIH

FOREWORD



To the American People,

With the aim of turning discovery into better health for all, the National Institutes of Health (NIH) invests in biomedical research that spurs innovations in science and technology. NIH research has proven its value to the United States and the world over the years by rising to meet the challenges of polio, AIDS, and many other formidable health foes. Most recently, the critical importance of NIH research has been demonstrated by our response to what is likely the greatest public health crisis of our generation: the coronavirus disease 2019 (COVID-19) pandemic.

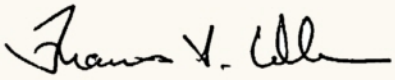
Over the past year, COVID-19 has inflicted a staggering toll on our Nation, claiming the lives of more than a half-million Americans. U.S. science has risen to this daunting challenge and made unprecedented progress in the fight against this swiftly spreading disease caused by the coronavirus SARS-CoV-2.

To address the challenges that COVID-19 poses to our health and economy, NIH has, from the pandemic's outset, worked with all sectors of society in unprecedented ways with unprecedented speed. Enabled by the strong support of Congress and other partners in the public and private sectors, the U.S. biomedical research enterprise has mounted a vigorous response that has given rise to increased testing capacity, innovative therapeutic strategies, and, perhaps most important, safe and effective vaccines. The breathtaking pace and scope of this progress has been made possible by decades of NIH-funded basic research, which built a robust foundation for our continuing efforts to combat COVID-19 and the emerging viral variants that threaten to extend the pandemic's tragic timeline.

Among the out-of-the-box initiatives now underway under NIH's leadership are the following: a highly innovative, competitive effort to expand the capacity and accuracy of testing; a pioneering public–private partnership to accelerate development of therapeutics and vaccines; and a major new push to understand and devise ways to treat or even prevent Post-Acute Sequelae of SARS-CoV-2, or "Long COVID." NIH research also is tackling the disturbing disparities seen in the COVID-19 response, with the aim of developing effective, evidence-based methods to ensure that tests, treatments, and vaccines reach all populations, particularly those disproportionately affected by this devastating disease.

In this updated strategic plan, NIH shares its framework for ensuring that no stone goes unturned in the scientific response to COVID-19. We will carry out this mission by supporting the collective efforts of NIH's researchers, collaborators, and diverse stakeholders to improve, advance, and optimize COVID-19-related research in five key areas: fundamental knowledge, detection and diagnosis, treatment, prevention, and health disparities.

NIH acknowledges that the goals set forth in this plan are very ambitious. Yet we remain optimistic because of our agency's strong record of encouraging ingenuity and delivering biomedical breakthroughs, even in the most difficult of times. We are convinced that pulling together the best minds in science will continue to enable our Nation to meet the twin challenges of closing the door on the COVID-19 pandemic and opening the door to new strategies for confronting future pandemics.



Francis S. Collins, M.D., Ph.D.
Director, National Institutes of Health

NIH-Wide Strategic Plan for COVID-19 Research

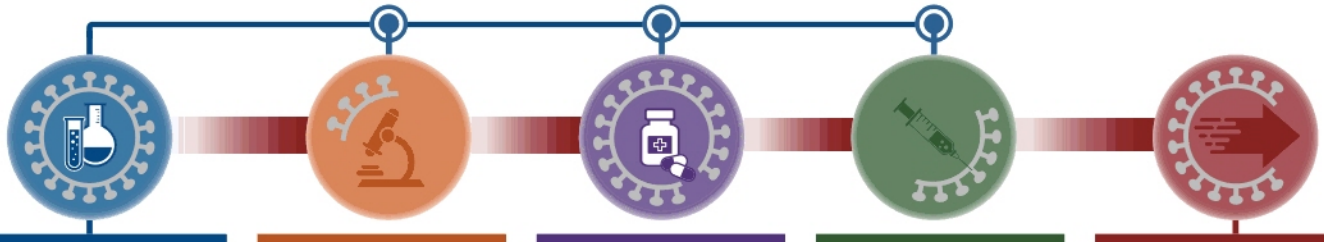
A BOLD COMMITMENT TO AN UNPRECEDENTED HEALTH CHALLENGE



GOALS

- **UNDERSTAND** SARS-CoV-2 and COVID-19
- **PREVENT** SARS-CoV-2 infection
- **DETECT and TREAT** COVID-19
- **MITIGATE** the threat of COVID-19

Guided by FIVE STRATEGIC PRIORITIES



PRIORITY 1

Improve Fundamental Knowledge

of SARS-CoV-2 and COVID-19 disease progression, outcomes, and recovery

PRIORITY 2

Advance Research To Improve Detection

by developing and validating new assays and retooling existing diagnostic platforms

PRIORITY 3

Support Research To Advance Treatment

by evaluating new or repurposing existing treatments and defining implementation strategies

PRIORITY 4

Accelerate Research To Improve Prevention

by developing vaccines, other methods to prevent transmission, and implementation models

PRIORITY 5

Prevent and Redress Poor COVID-19 Outcomes

in health disparity and vulnerable populations

CROSSCUTTING STRATEGIES

PARTNERING to promote collaborative science

SUPPORTING the research workforce and infrastructure

INVESTING in data science

ENGAGING and educating the public

NIH National Institutes of Health

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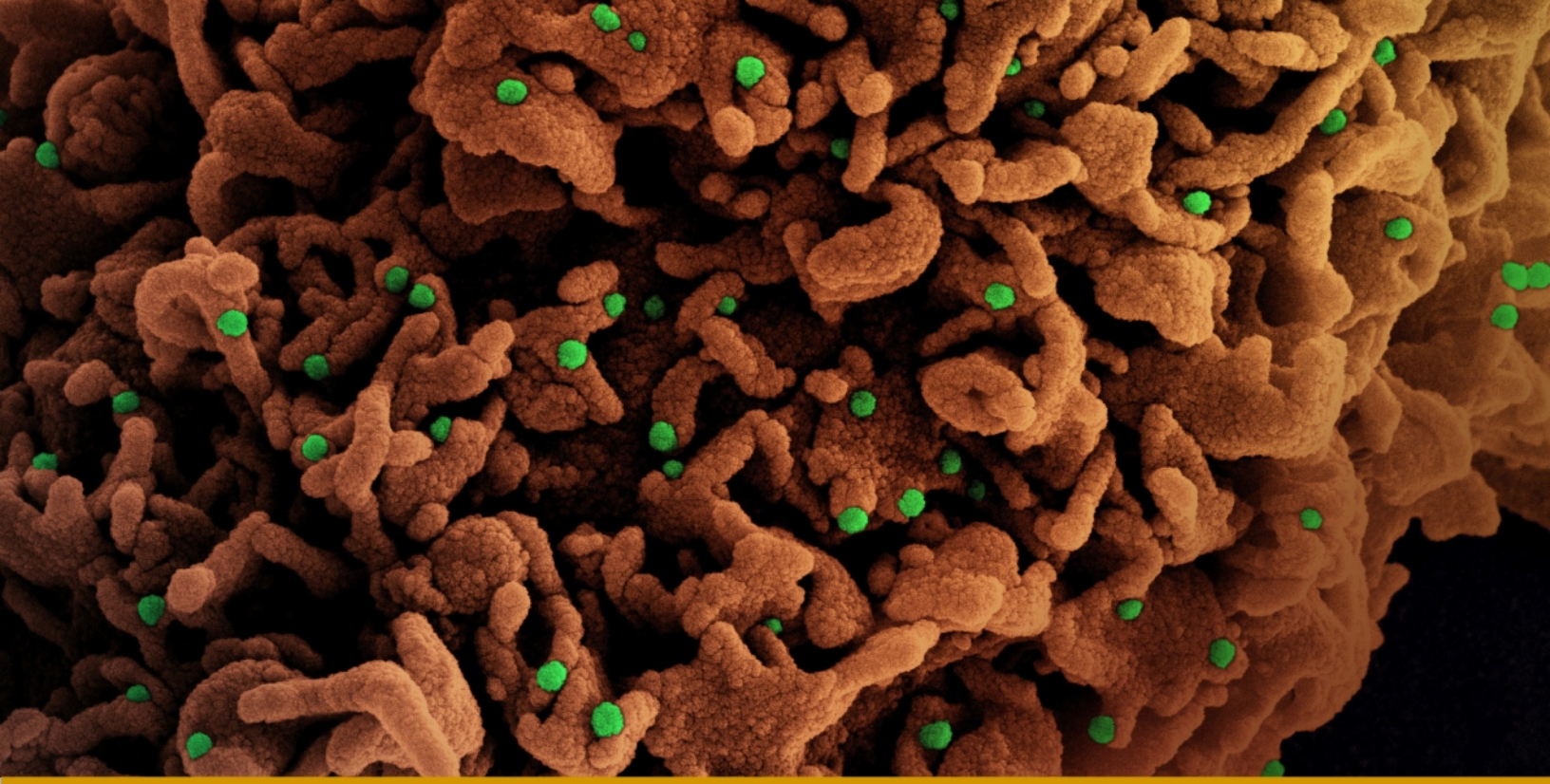


KEY UPDATES

NIH has made incredible progress toward understanding, diagnosing, treating, and preventing SARS-CoV-2 infection and COVID-19 in the past year. However, new challenges have come to light as the pandemic has evolved, necessitating a corresponding evolution in the NIH response, which is reflected in this *NIH-Wide Strategic Plan for COVID-19 Research* (hereafter referred to as the "Strategic Plan"). This second iteration of the Strategic Plan includes updates throughout the document to convey the progress made, new research studies planned, and NIH community outreach efforts. The most significant updates to the Strategic Plan are highlighted below:

- Investigating and treating the long-term health consequences of COVID-19, including Post-Acute Sequelae of SARS-CoV-2 Infection (PASC; also referred to as Long COVID) and pandemic-related impacts on the overall physical and mental health of Americans
- Understanding and responding to new SARS-CoV-2 variants that contain mutations in the spike protein of the virus that may impact the effectiveness of treatments and vaccines against SARS-CoV-2
- Highlighting progress on the development of diagnostic tests, vaccines, and treatments for SARS-CoV-2 infection and developing implementation strategies to determine efficient, effective methods of providing these resources

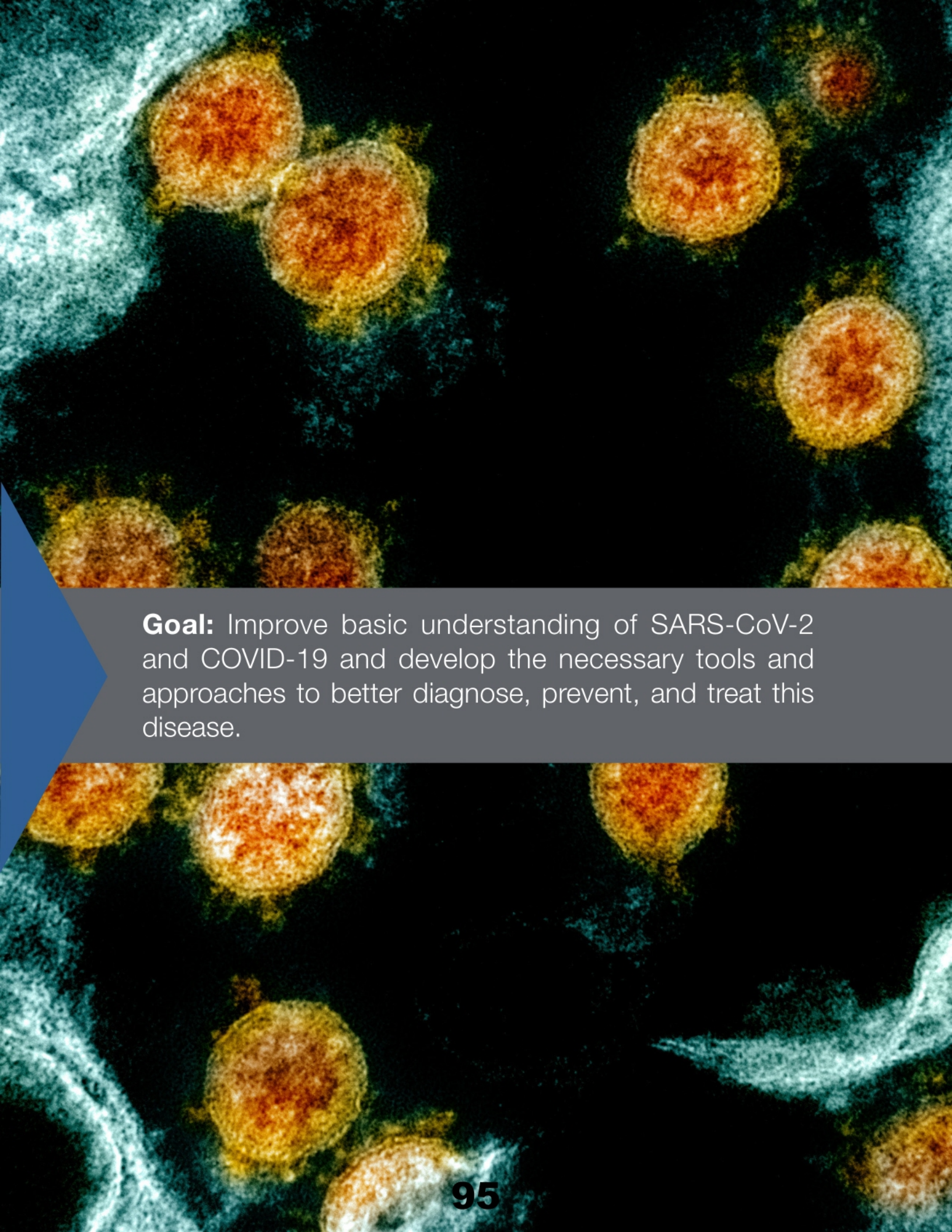
- Understanding and engaging disproportionately impacted and other populations at high risk of SARS-CoV-2 infection to ensure appropriate information, testing, treatments, and vaccines for SARS-CoV-2 and COVID-19 are available to all who need them

These updates and the trajectory of the NIH strategic response take into account input solicited from the public in the *Request for Information* on the *NIH-Wide Strategic Plan for COVID-19 Research* (NOT-OD-21-018). After an open submission period of 6 weeks, NIH staff analyzed and summarized all responses to inform the updates to the Strategic Plan described above. In all, 192 respondents submitted feedback, including respondents from the United States (162 responses), international locations (8), and unknown locations (22). Many of the respondents were from academic institutions (120), the private sector (19), or professional societies (13). The majority of respondents were students and trainees (82), with most of the remaining responses coming from mid-level (42) or senior level leaders (33) within an organization. Twelve responses were submitted anonymously and 51 were submitted on behalf of an organization.

Respondents largely approved of the NIH research response to the COVID-19 pandemic and referenced the scientific initiatives NIH has supported as critical activities for combating the spread of SARS-CoV-2 and preventing COVID-19. They expressed a high level of interest in research included in Priority 1: Improve Fundamental Knowledge of SARS-CoV-2 Infection and COVID-19 (76), Priority 4: Improve Prevention of SARS-CoV-2 Infection (65), and Priority 5: Prevent and Redress Poor COVID-19 Outcomes in Health Disparity and Vulnerable Populations (83) of the Strategic Plan.

Respondents identified scientific gaps (158) and commented on scientific and medical accomplishments mentioned in (87) or missing from (45) the Strategic Plan, health disparities in research or implementation (68), additional resources required (39), and the conduct and stewardship of science (20). Key themes that emerged were the need for research on the long-term impacts of the pandemic and SARS-CoV-2 infection, greater and more inclusive research for at-risk and health disparities populations (including minorities, people with disabilities, and essential worker populations), as well as building research infrastructure and preparing for future pandemics or emergencies. Some responses also mentioned potential collaborations with private organizations and state-level government that could be beneficial to NIH research and tools developed by others to track viral transmission and vaccine uptake.

Some responses also provided input on the Strategic Plan's crosscutting strategies: investing in data science (20), partnering to promote collaborative science (19), and supporting the research workforce and infrastructure (17). Responses emphasized the importance of communicating clearly and effectively with the public to encourage preventive behaviors, like mask wearing and social distancing, and to address questions and concerns about COVID-19 vaccines. Suggestions for new areas of crosscutting focus included a greater emphasis on international collaboration, inclusion of affected populations in research planning processes, and increased support for early-career scientists and clinical care workers.



Goal: Improve basic understanding of SARS-CoV-2 and COVID-19 and develop the necessary tools and approaches to better diagnose, prevent, and treat this disease.



INTRODUCTION

Coronavirus disease 2019 (COVID-19) is caused by a naturally arising virus—the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The virus spreads easily from person to person through respiratory droplets, and infection typically causes fever, loss of taste or smell, shortness of breath, a dry cough, gastrointestinal symptoms, and other symptoms and complications. The ease with which the virus spreads and its ability to be transmitted by asymptomatic individuals have caused possibly the most severe worldwide infectious disease pandemic of the modern age. The COVID-19 pandemic was the third leading cause of death in the United States in 2020, resulting in approximately 375,000 deaths.

NIH is leading a swift, coordinated research response to this public health crisis. By leveraging existing funding mechanisms and establishing new programs, NIH is rapidly mobilizing the disbursement of emergency government funding to the biomedical research community while

still maintaining a scientifically and ethically rigorous review process and strong scientific stewardship to support the most promising and meritorious science in the face of a public health emergency.



Researchers are continuing to build on an immense foundational knowledge base on viruses and their effects on humans drawn from decades of NIH-supported research. Leveraging the most modern technologies and techniques—as well as a rich reservoir of existing diagnostics, prevention strategies, and treatment options used to combat viruses—researchers are rapidly identifying characteristics of SARS-CoV-2 and its mutations of concern and human responses to infection to speed the development of sorely needed interventions to prevent and treat COVID-19. This work includes studying how people infected with COVID-19 develop Long COVID syndrome, clinically termed Post-Acute Sequelae of SARS-CoV-2 Infection (PASC), in which symptoms caused by SARS-CoV-2 infection linger past the usual recovery time for a respiratory virus or emerge and persist after the acute phase of infection seems to be over (See Box 1).

To hasten the development of interventions, NIH is capitalizing on the strengths of its extramural and intramural research infrastructure (domestic and international) and working in close collaboration with its partners in industry, academia, nonprofit organizations, the public, and other government agencies and offices. NIH's intramural scientists are engaging in fundamental studies, creating models, and identifying or screening existing therapeutic drugs against SARS-CoV-2, as well as developing and modifying existing vaccine and diagnostic platforms to prevent and detect the virus. Likewise, NIH's alignment and coordination with other Federal agencies as part of the *National Strategy for the COVID-19 Response and Pandemic Preparedness* (referred to as the National Strategy hereafter) are forging groundbreaking approaches to ramp up the identification, development, evaluation, and manufacture of promising candidate therapeutics and vaccines. The National Strategy also incorporates a plan for distribution of diagnostics, vaccines, and therapeutics proven accurate, safe, and effective.

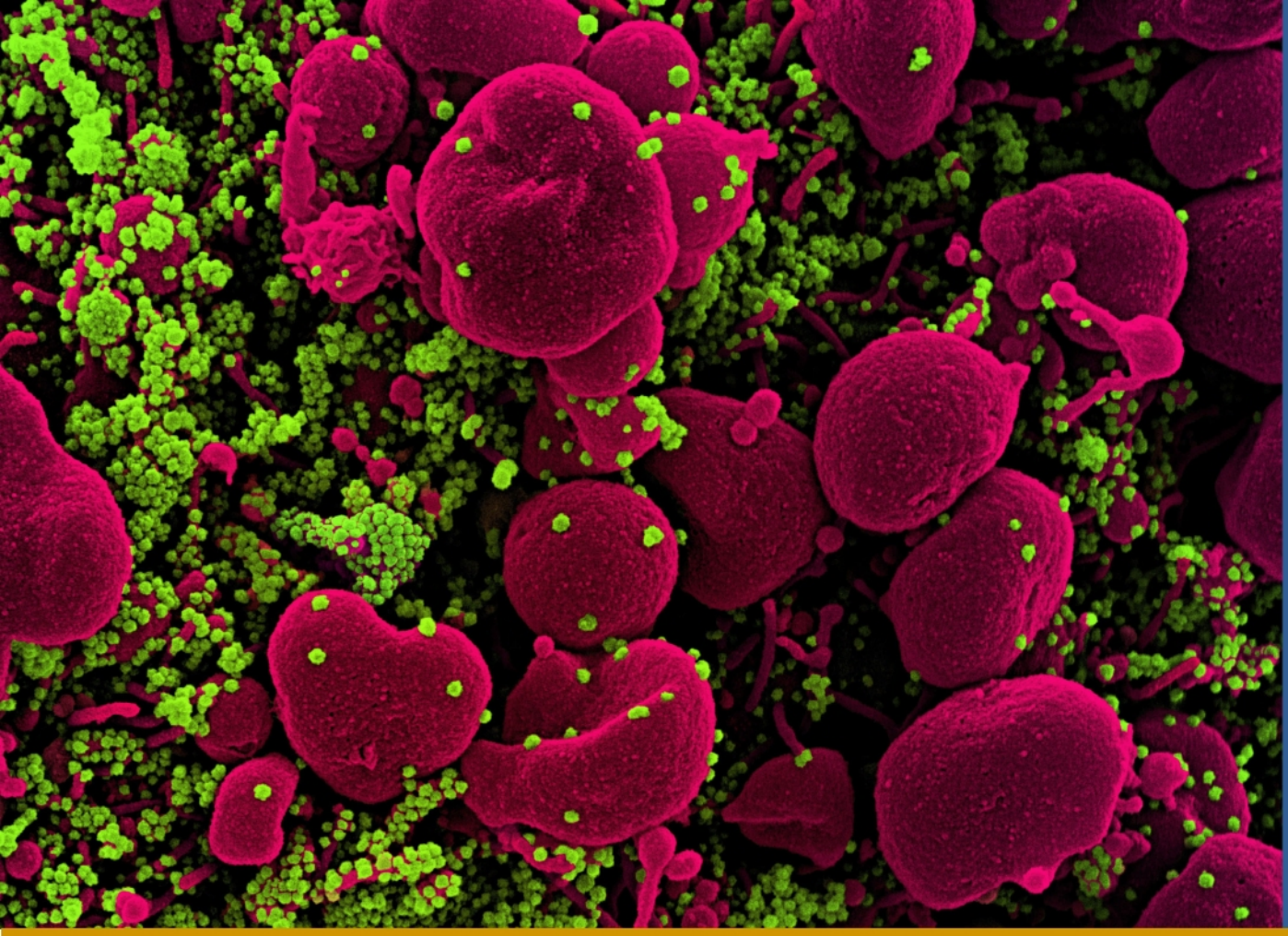
Recognizing the disproportionate impact on health disparity and specific populations that are at high risk of COVID-19, NIH-funded researchers are working to identify the underlying factors and barriers that contribute to the staggering losses of life in these communities.



Inclusion of these populations in clinical trials for diagnostics and interventions is a critical part of NIH's pandemic response, as is exploring effective communication strategies and ways to reduce barriers and improve access to care and interventions for all populations, especially populations at a higher risk of developing COVID-19.

In keeping with the urgency of the pandemic, NIH is rapidly communicating findings to the scientific community, health care providers, and the public. For the scientific community, NIH is moving as quickly as possible to disseminate data in multiple data-sharing platforms. Preprint and peer-reviewed publications relevant to all aspects of the research effort are available, including literature compendiums and analysis tools, such as LitCovid and *iSearch* COVID-19 Portfolio. For health care providers, NIH continues to convene a panel of experts who develop treatment guidelines that continue to evolve as new data and clinical expertise become available. Last, NIH is providing the latest information about NIH efforts and research results to the public through the NIH COVID-19 website and also investing in research to identify the best methods for disseminating scientific findings to the communities and populations who need them most, especially underserved and other populations at high risk of SARS-CoV-2 infection and COVID-19.

NIH is responding to the COVID-19 pandemic by supporting research to understand SARS-CoV-2 and mitigate the threat of COVID-19 for the health of all people. NIH is building on existing research initiatives and accelerating the development of new ones that are focused on the five research priorities detailed in this strategic plan. Through its pursuit of research in these priority areas, NIH hopes to achieve the vision of a world safe from COVID-19 by improving basic understanding of SARS-CoV-2 and COVID-19 and developing the necessary tools and approaches to better diagnose, prevent, and treat this devastating disease.



PRIORITY 1

Improve Fundamental Knowledge of SARS-CoV-2 and COVID-19

NIH-supported researchers continue to work with their partners to understand the biology of SARS-CoV-2 infection, acute COVID-19, and PASC, as well as the impact that the infection and disease have on individuals, communities, and public health. As fundamental knowledge of SARS-CoV-2 and COVID-19 grows, it will be used to identify novel approaches and improvements to existing diagnostics, prevention strategies, and treatments. Importantly, it also will be leveraged to better prepare for future infectious disease outbreaks.

Objective 1.1: Advance fundamental research for SARS-CoV-2 and COVID-19

NIH-supported researchers are building on an already strong foundation of knowledge to understand SARS-CoV-2 infection and COVID-19, including the research priorities outlined

in the National Institute of Allergy and Infectious Diseases' *NIAID Strategic Plan for COVID-19 Research*. For example, researchers are working to understand essential host and SARS-CoV-2 proteins and host-virus interactions, including for SARS-CoV-2 variants, to understand how they mediate infection and disease. Researchers also are working to understand fundamental aspects of how host tissues—such as the heart, lung, blood, and blood vessel wall—respond to the virus. NIH will continue to support research to better understand the mechanisms of infection and how infection contributes to disease in different tissue and organ systems, including the eyes and mouth, the latter of which may play a role in transmitting SARS-CoV-2 to the lungs or digestive system. This knowledge of the virus and host tissue response will enable the development of more effective treatment and prevention strategies.

The immune system plays a critical role in preventing and fighting infections. Researchers are advancing knowledge of the body's immune response to SARS-CoV-2 infection through

Box 1. Addressing the Post-Acute Sequelae of SARS-CoV-2 Infection or "Long COVID"

A significant number of people sickened by COVID-19 report symptoms that may persist for several months or longer after the acute illness has passed, a condition often referred to as "Long COVID" and now clinically referred to as the Post-Acute Sequelae of SARS-CoV-2 infection (PASC). Examples of commonly reported symptoms include fatigue, shortness of breath, "brain fog," sleep disorders, fevers, gastrointestinal symptoms, anxiety, and depression. Symptoms may involve multiple organs and systems throughout the body and can significantly affect overall function and quality of life. The long-term public health implications and impact on Americans' lives of PASC are still unknown, but soon after the first reports arose, NIH began a **study** to track COVID-19 survivors and held a **workshop** to determine the best path forward, actions that informed the development of the **NIH PASC Initiative** launched in February 2021.

The goal of this initiative is to rapidly improve understanding of recovery after SARS-CoV-2 infection and to prevent and treat PASC. Studies will focus on characterizing the biological and clinical spectrum of recovery from SARS-CoV-2 infection, including the subset of patients who have symptoms of disease beyond the standard course, the impact of treatments for acute COVID-19 or for post-acute symptoms on the duration and severity of symptoms, and factors that affect outcomes for patients infected by SARS-CoV-2.

Key features of the initiative include the **SARS-CoV-2 Recovery Cohort and Investigator Consortium**, which will leverage existing and new clinical studies to chart recovery from infection and to assess the full range of PASC symptoms and findings in diverse adult and pediatric populations. The Initiative also will support a data science and biorepository core and leverage a variety of NIH clinical platforms, including large-scale electronic health records and other real-world data-based approaches, existing clinical studies and networks, COVID-19 clinics, registries, and observational studies.

efforts such as the Serological Sciences Network for COVID-19 (SeroNet), the Nation's largest coordinated effort to study immune responses to COVID-19 and the Immunophenotyping Assessment in a COVID-19 Cohort (IMPACC) study. Antibodies, blood proteins produced by the immune system to fight viruses, are a key component of the immune system and, in some cases, prevent future infection from the same virus. Recent studies have shown that patients with COVID-19 develop SARS-CoV-2-specific antibodies capable of neutralizing virus that can last for many months in the blood. Another immune system cell that plays a role in the immune response to viruses, the T cell, also may be beneficial in long-term protection against SARS-CoV-2. Additional research is needed to fully understand how the immune response to SARS-CoV-2 affects the wide range of symptoms and disease outcomes experienced by people with COVID-19. The immune system, although typically protective, sometimes can overreact and contribute to tissue and vascular damage, as observed in COVID-19. Thus, patients with severe COVID-19 may benefit from therapies that turn down the immune response or directly target the virus.

Understanding SARS-CoV-2 transmission—how the virus spreads—and why some individuals are more susceptible to severe disease or long-term effects is an important piece of the COVID-19 response. To gain new insight on these topics, NIH is supporting research to identify potential animal reservoirs, understand animal-to-human and human-to-human transmission, and characterize the genetic diversity of the virus. Studies to examine biological factors that influence individual susceptibility to infection—such as age, sex and gender, genetics, and environmental exposures—already are in progress. Through the COVID Human Genetic Effort, an international project spanning more than 50 genetic sequencing hubs and hundreds of hospitals, NIH researchers discovered that 10 percent of patients with life-threatening COVID-19 pneumonia had, at the start of their infection, autoantibodies that attack a vital component of the immune system, greatly impairing their ability to fight off the virus. Because 95 percent of these patients were men, the findings may provide the first explanation for why more men than women die from COVID-19. Researchers also are examining social and structural factors related to COVID-19, such as health disparities based on race and ethnicity, including their influence on biological factors. This information will be critical to understanding infection and disease progression and outcomes, and it may inform the development of interventions and vaccines.

Objective 1.2: Support research to develop preclinical models of SARS-CoV-2 infection and COVID-19

Animal models, particularly those that replicate human disease, are essential to understanding the basic biology of coronaviruses, including transmission, incubation periods, and host immune responses to infection. Such models also are critical to testing potential preventive and therapeutic strategies. Researchers are using mice, hamsters, ferrets, and

other animal models to study responses to experimental therapeutics and vaccines. NIH has established resources to leverage existing animal models of infection with other coronaviruses to develop preclinical models to study and understand SARS-CoV-2 infection and COVID-19. Given the major impact of underlying cardiovascular, pulmonary, and hematologic conditions on morbidity and mortality among patients with COVID-19, NIH is supporting research to develop model systems to rapidly test and advance the development of innovative therapeutics to prevent damage to critical host tissues and organs.

Previous experience with related coronavirus diseases suggests that replicating COVID-19 in animal models may be challenging. Thus, researchers are exploring new ways to increase access to validated animal models and enhance the comparison of approaches to identify informative assays. NIH is developing and validating human microphysiological systems—engineered 3D platforms that support living human cells and tissues—that can be used to study viral infections in relevant human tissue models—such as the lung, kidney, gut, or brain—and more clinically predictive assay systems to test new treatments. Systems biology and computational techniques are being used to complement preclinical models and aid in evaluation of therapeutic effects against SARS-CoV-2 and COVID-19. Scientists have accelerated COVID-19 modeling research by creating computer-generated maps and models of SARS-CoV-2 biological pathways throughout the infection cycle and are pursuing strategies to ensure the widespread discovery and use of such data to address the pandemic with novel computation modeling efforts.

Objective 1.3: Advance the understanding of SARS-CoV-2 infection risk and COVID-19 dynamics at the population level

Gaps exist in our understanding of the dynamics of virus transmission in different populations over time and the factors that influence a population's susceptibility to severe disease. Researchers continue to work toward understanding the progression of SARS-CoV-2 infection through natural history studies. These studies may reveal why some groups, such as older adults and people with preexisting conditions, are at higher risk of severe COVID-19 than others. NIH is supporting studies and online dashboards to describe the extent to which SARS-CoV-2 has spread throughout the United States and to provide insights into which communities and populations are most affected, including racial and ethnic minorities, underserved rural populations, socioeconomically disadvantaged populations, and sexual and gender minorities. For example, one study is leveraging an existing program that monitors threats to the U.S. blood supply to analyze the prevalence of SARS-CoV-2 antibodies in blood donors in six cities with high incidence of COVID-19.



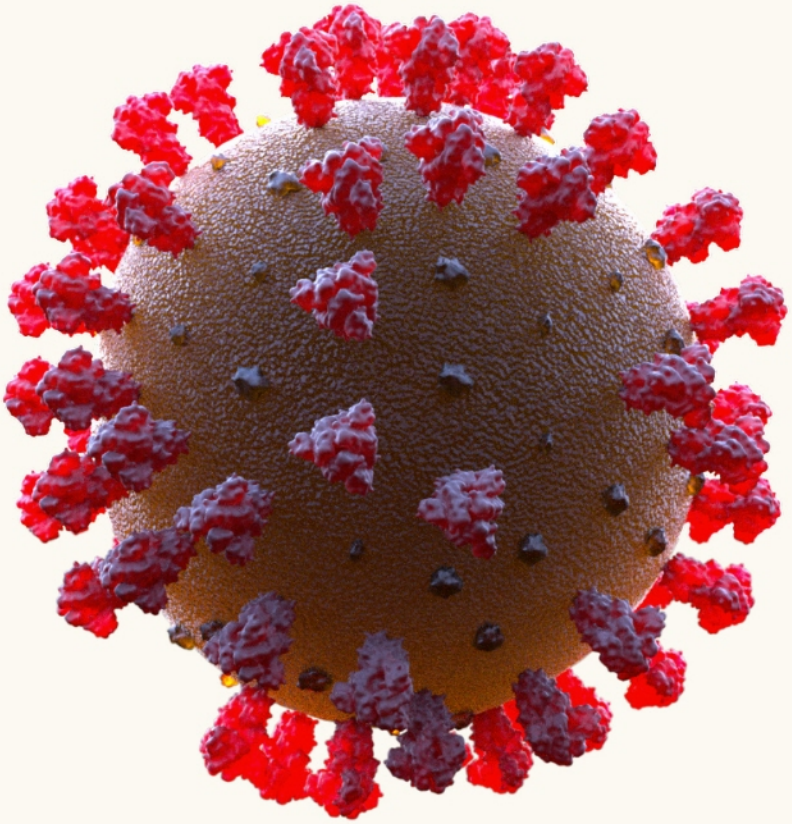
NIH also is supporting research to understand and address the behavioral and social factors that affect the spread of the virus. NIH-supported clinical epidemiology programs are leveraging existing clinical and community-based research platforms to characterize the clinical features and disease course of COVID-19. Population-level studies are being used to explain the role of different factors in driving disease severity and outcomes—including, but not limited to, older age; sex; social and structural determinants of health; and such comorbidities as diabetes, cancer, cardiovascular disease, kidney and digestive diseases, rare diseases, pain, substance use, and substance use disorders. For example, the Collaborative Cohort of Cohorts for COVID-19 Research (C4R) study combines existing diverse cohort studies—such as the Framingham Heart Study (HS), Jackson HS, and Strong HS—to examine COVID-19-related outcomes and factors that affect resilience and risk. Studies are ongoing to monitor mortality trends across the United States to better understand the patterns of death over part of 2020—those from COVID-19 and other causes.

Objective 1.4: Understand the short- and long-term health consequences of SARS-CoV-2 infection and COVID-19

As the United States and countries around the world respond to the COVID-19 pandemic, the negative impact of social, behavioral, and economic factors on people and their health is becoming clearer. Studies have shown that the pandemic has taken a disproportionate toll on people with intellectual and developmental disabilities and populations facing existing health disparities. Researchers are working to understand the pandemic's effect in additional populations, such as the rare diseases community, adults with fetal alcohol spectrum disorders, people with HIV, and health care workers. Studies aim to understand the effects of the COVID-19 pandemic across the lifespan and in different populations, especially populations that are at higher risk for the disease itself or who may experience complications related to measures taken to contain the pandemic.

NIH is supporting research to understand and address the impacts of the virus and public health measures used to prevent its spread—such as physical distancing, shelter-in-place orders, quarantining, school closures, and mask mandates—on social epigenomic pathways (how social experiences affect genes and biology); mental and physical health; child development; pregnancy; substance use; and well-being, illness, and recovery. In addition, studies are exploring the health consequences from delayed care, not only for COVID-19, but also for routine preventive practices (e.g., vaccinations) and detection and treatment of diseases and conditions (e.g., cancer).

Researchers also are investigating the long-term effects of SARS-CoV-2 infection, with or without acute COVID-19, as well as the influence of physical, environmental, neurobiological, social, and behavioral factors. Studies are underway to understand COVID-19's effects on various parts of the nervous system, such as the brain and eyes, and how the effects of COVID-19 on physical and mental health are influenced by alcohol, tobacco, and other substance use. A new NIH-wide initiative was launched recently to understand, treat, and prevent PASC. Additionally, because many of the lingering effects of infection are neurological in nature—such as the common complaint of "brain fog"—NIH has established a database and biobank specifically to collect information on the neurological symptoms, complications, and outcomes of COVID-19 across the lifespan, including pregnancy and old age.



Advance Detection of SARS-CoV-2 Infection and Diagnosis of COVID-19

As Americans return to public spaces, a vital component of the National Strategy is detecting, diagnosing, and surveilling the population to identify and quarantine COVID-19 cases and track the spread of the virus. Although NIH has made significant contributions to increase the number of tests available, current testing capacity is insufficient to meet the Nation's needs—both in terms of the number of tests available and their ability to deliver answers in a timely manner at the point of care. Additionally, as the pandemic has evolved, new testing challenges have surfaced in the form of new viral variants, reinforcing the continued need for tests that can help accurately detect and track SARS-CoV-2, including variants of concern as they arise. To develop more accurate, rapid, scalable, affordable, and accessible tests, NIH is aggressively accelerating the development, validation, and commercialization of innovative SARS-CoV-2 testing technologies, focusing efforts both on viral tests—which indicate whether a person

has a current infection—and on antibody, or serological, tests—which indicate if a person has had a previous infection. To this end, NIH is advancing a wide range of initiatives to improve or repurpose current technologies and advance new ones.

Objective 2.1: Support research to develop and validate new diagnostic technologies

NIH is supporting the development and validation of new diagnostics, including nucleic acid tests and viral antigen detection tests, that can identify the presence of the virus in biospecimens. Most current testing for the virus depends on detection of the viral RNA using a polymerase chain reaction (PCR) test. These tests are accurate, but generally require a laboratory with expert technical staff and specialized equipment. Newer alternatives may be able to carry out this kind of nucleic acid detection with a simple point-of-care device.

Another alternative that NIH-supported researchers are pursuing is called viral antigen testing, which detects the virus protein capsule. Antigen tests are traditionally less sensitive, but new approaches for at-home use enable easier and more frequent testing, which may help maintain overall accuracy. Preliminary findings suggest that screening using rapid antigen tests on a regular cadence every two to three days achieves sensitivity comparable to reverse transcription–PCR tests. In February 2021, NIH launched a study to assess the performance and usability of the smartphone app, MyDataHelps, paired with the Quidel QuickVue At-Home OTC COVID-19 Test, which has now been authorized by the U.S. Food and Drug Administration (FDA) for over-the-counter use without a prescription.

To address the need for better diagnostics, NIH launched the Rapid Acceleration of Diagnostics (RADx℠) initiative to speed innovation in SARS-CoV-2 testing technologies, with the potential of delivering widely accessible, rapid testing strategies to the public (see Box 2). The RADx Tech arm of RADx aims to speed the development, validation, and commercialization of innovative point-of-care and home-based tests (including the Quidel QuickVue test referenced above), as well as improve clinical laboratory tests that can detect the virus directly. RADx Tech expanded the existing Point-of-Care Technology Research Network and is using a flexible approach to infuse funding and enhance technology designs at key stages of development. New technologies may employ less invasive sampling techniques, such as saliva collection, or other approaches, such as viral antigen testing to detect the virus protein capsule, and are designed to meet the needs of various settings, such as hospitals, schools, and places of business. Together with RADx Advanced Technology Platforms (RADx ATP), which focuses on scaling up promising technologies, RADx Tech supported more than 150 companies and contributed more than 180 million tests to the national testing capacity through April 2021 with additional capacity being added monthly. As of April 2021, the FDA has authorized 17 tests supported by RADx Tech/ATP for emergency use, including a rapid antigen home test that provides results in 15 minutes, point-of-care molecular tests that provide results in

Box 2. RADx℠: Rising to the Challenge of Widespread Testing

Over the last century, advances in biotechnology have improved medical treatment and saved lives. As the United States continues to fight a devastating public health threat, the **Rapid Acceleration of Diagnostics** (RADx℠) initiative calls on scientists and engineers to put forward their most promising biomedical technologies and implementation strategies to answer the pressing need for SARS-CoV-2 testing. The RADx initiative is a nationwide program aimed at speeding the development and commercialization of rapid, easy-to-use diagnostic tests. The program supports innovative approaches for implementation, expansion, accessibility, and acceptance of existing diagnostic testing. The initiative consists of five key components:

- **RADx Tech and RADx Advanced Technology Platforms (RADx-ATP)** use a phased approach to support the early development of point-of-care SARS-CoV-2 diagnostics and improved laboratory-based tests via RADx Tech. RADx-ATP focuses on reducing barriers for scaling up advanced technologies to increase the capacity for rapid, high-throughput testing infrastructure. As of April 2021, these programs have supported more than 150 companies, and 31 projects have been scaled up for manufacturing, with 27 still active. Seventeen tests have been authorized by the FDA for emergency use. Combined, these programs have increased testing capacity by more than 180 million tests through April 2021.
- **RADx Radical (RADx-rad)** advances nontraditional, but potentially transformational, approaches and repurposing of existing approaches for SARS-CoV-2 testing. With longer development timelines, 49 RADx-rad projects are addressing gaps in SARS-CoV-2 testing through technology platforms that can be used in future outbreaks of COVID-19 and that could be applicable to other, as yet unknown, infectious organisms.
- **RADx Underserved Populations (RADx-UP)** leverages existing community partnerships to build community-engaged demonstration projects focused on identifying effective implementation strategies to enable and enhance testing for populations at high risk of SARS-CoV-2 infection and address the unique needs of different communities. In Phase 1, RADx-UP provided 70 awards to 55 institutions across 33 states, including a Coordination and Data Collection Center, a collaborative network of clinical research centers across the country, and a program studying the social, ethical, and behavioral implications of testing.
- **RADx At-Home Testing** is supporting an innovative community health initiative called "**Say Yes! COVID Test**" to improve testing accessibility by providing communities with access to free, rapid antigen tests that individuals can administer to themselves at home. The study will use such technologies as the RADx Tech/ATP-supported Quidel QuickVue At-Home COVID-19 Test recently tested in a **pilot at-home study** and evaluate if frequent self-administered COVID-19 testing helps residents reduce community transmission of SARS-CoV-2.
- **RADx Data Management** supports researchers in their studies to develop new and novel testing devices and collects, standardizes, and harmonizes the resulting data. The data management team interfaces with coordinating centers across the RADx program to develop and implement common data elements and models, to facilitate harmonized data sharing in a secure cloud-based data platform, and to provide a research data repository of curated and de-identified RADx COVID-19 data.

Box 2. Continued

The RADx initiative supports innovative technologies and, since its inception, has enabled the development of millions of additional rapid, easy-to-use, diagnostic tests for the United States. RADx identifies and employs evidence-based implementation strategies to increase accessibility and acceptance in those populations most affected by this deadly pandemic. By calling on the ingenuity and inventiveness of U.S. scientists and engineers, NIH will continue to advance diagnostic tools to prevent the spread of SARS-CoV-2, improve health, and save lives.

30 minutes, and technologies to increase the throughput of laboratory-based molecular tests. Through the RADx initiative, NIH is now assessing testing technologies for their ability to detect SARS-CoV-2 variants.

The RADx Radical (RADx-rad) arm of RADx is supporting new and nontraditional approaches that address gaps in COVID-19 testing, as well as adapting applications of existing approaches to make them more usable, accessible, or accurate. RADx-rad projects include a diagnostic breathalyzer, smell and taste tests, biosensors for the skin and mouth, community wastewater detection, and artificial intelligence applications for various diagnostic uses, such as predicting long-term risk of disease severity in children.

Other NIH intramural and extramural activities are focusing on the development of diagnostic approaches that include wearable, implantable, and remote sensors; medical imaging technologies combined with informatics solutions and artificial intelligence for detection and monitoring; and noncontact sensing and imaging for rapid mass screening and vital sign assessment. To characterize the different approaches to diagnostics, NIH data scientists developed the COVID-19 Portfolio Tool, using artificial intelligence and machine learning methodologies to provide a curated source of publications coupled with a user-friendly portfolio analysis interface for querying the contents of these publications.

Objective 2.2: Support research to retool existing diagnostic technologies

In addition to catalyzing the development of novel COVID-19 diagnostic technologies, NIH is supporting efforts by scientists to repurpose, modify, or improve diagnostic tools currently available or under development. Researchers are shifting their focus to repurpose diagnostic technologies and improve the speed, sensitivity, accuracy, and utility of available tests, including the use of imaging technologies for early detection of COVID-19 in the lungs and the use of artificial intelligence to improve image-based diagnosis. To further this approach, NIH launched the Medical Imaging and Data Resource Center (MIDRC), an ambitious effort that unites expertise from academia, professional societies, industry, and government. The first data set of images is now available for researchers to use.

Objective 2.3: Support research to develop and validate serological assays

Serology tests—also called antibody tests—detect the presence of antibodies in a person's blood. Someone who has antibodies to a virus, such as SARS-CoV-2, was infected at some point in time. However, because antibody tests do not look for components of the virus itself, they cannot be used to diagnose SARS-CoV-2 infection or determine if someone is infectious. Currently, the extent to which the presence of SARS-CoV-2 antibodies correlates with lasting immunity is unclear, as is how durable and protective these antibodies might be. Serology tests are crucial for determining the efficacy of promising therapeutic or vaccine candidates and for studies of disease prevalence and virus spread through communities.

NIH's focus on accelerating the availability of high-quality serology tests is a key part of its response to the pandemic. To address this need, NIH is supporting the SeroNet, which will study immune responses to COVID-19, establish a U.S. SARS-CoV-2 serology standard, develop new serological tests, collaborate with Federal partners to assess tests developed by industry and academic organizations, and expand the national serological testing capacity. The Recipient Epidemiology and Donor Evaluation Study (REDS) Program also is establishing a repository for sharing blood samples and data with government, academic, and industry scientists to advance serological testing and vaccine development. As part of the REDS Program, the REDS RESPONSE study is leveraging access to the blood supply and blood donors to help evaluate new serology tests. Other efforts underway by NIH-supported and intramural investigators are adapting platforms used to test for antibodies resulting from other infections to detect SARS-CoV-2 and identifying SARS-CoV-2 antibodies that may be able to be detected sooner after infection.

Objective 2.4: Support research on scale-up and implementation of testing

Widespread, frequent, and timely testing leading to early identification and quarantine of infected individuals is a critical facet of the National Strategy to stop the spread of SARS-CoV-2 infection. To help ensure that the national testing capacity scales to meet the demand of testing needs, NIH implemented RADx-ATP as part of the RADx program (see Box 2). RADx-ATP seeks to scale up existing technologies, such as high-throughput platforms; expand the use of platforms suitable for testing centers providing access to underserved populations; further develop point-of-care tests for at-home test use; and identify next-generation diagnostic testing platforms that could be scaled to population-level testing. NIH also is leveraging intramural research resources to help alleviate potential supply chain issues. For example, to address potential shortages in swabs used for testing, the NIH intramural program is developing and evaluating several variations of 3D-printed swabs.



NIH is committed to supporting research on dissemination and implementation models of testing that are effective, accessible, and inclusive. RADx-Underserved Populations (RADx-UP) is supporting community-engaged research on implementation of testing in underserved and other communities at high risk of COVID-19, including projects to support research on approaches to enable safe return to schools in these communities. RADx Tech supported the development of the COVID-19 Testing Impact Calculator, a free online resource that shows how different approaches to testing and other mitigation measures can curb the spread of the virus in schools and businesses. The website also provides a playbook for K–12 education to help guide schools on implementing testing strategies and a step-by-step Implementation Guide to help business leaders plan and implement a testing strategy to meet their organizations' needs. Researchers planning studies of in-home testing as an intervention also are using NIH-supported online platforms, such as the COVID-19 Pandemic Vulnerability Index (PVI) Dashboard, to help select local communities to study.

Because research indicates that transmission may be happening through contact with individuals who are not showing symptoms, traditional containment strategies—testing of only people with symptoms, contact tracing, quarantine—may not be enough to stop the spread. NIH is supporting research into alternative strategies that harness digital health solutions using such tools as smartphone apps, wearable devices, and software that can identify and trace contacts of infected individuals, keep track of verified SARS-CoV-2 test results, and monitor the health status of infected and potentially infected individuals, while still protecting personal privacy. In March 2021, NIH announced the launch of "Say Yes! COVID Test," a collaboration with the Centers for Disease Control and Prevention (CDC) to provide up to 160,000 residents of Pitt County, North Carolina, and Hamilton County, Tennessee, with free, rapid antigen tests to evaluate the effectiveness of self-administered testing.



PRIORITY 3

Advance the Treatment of COVID-19

When the COVID-19 pandemic began, FDA-approved treatments for coronaviruses did not exist. Normally, the discovery and development of a new therapeutic is a years-long process. The unprecedented need brought on by the COVID-19 pandemic has compelled a paradigm shift in the process to enhance the sharing of knowledge, resources, and infrastructure among academics, Federal agencies, and industry. Through such a shift, NIH was able to expedite the selection and testing of interventions to treat COVID-19, while continuing to apply rigorous standards to ensure safety and efficacy. To this end, NIH assembled the Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) partnership (see Box 3) and continues to work closely with other government agencies organized through the National Strategy.

NIH has made great strides in treating COVID-19 in a short amount of time, and the chances of surviving this disease have significantly improved since the beginning of the pandemic.

Box 3. ACTIV: An Unprecedented Partnership for Unprecedented Times

The rapid spread of COVID-19 and limited resources highlighted the need to coordinate and streamline research processes to optimize biomedical research and testing of potential therapeutic and vaccine candidates. In April 2020, NIH launched the Accelerating COVID-19 Therapeutic Interventions and Vaccines (**ACTIV**) public–private partnership to develop a coordinated research strategy for prioritizing and speeding the clinical evaluation of the most promising treatments and vaccines. Led by expert working groups, ACTIV is pursuing four fast-track focus areas that are most ripe for opportunity: (1) developing a collaborative, streamlined forum to standardize and share evaluation methods and testing of preclinical therapeutics and vaccines; (2) prioritizing and accelerating clinical testing of the most promising treatments for all stages of the disease; (3) leveraging clinical trial capacity and effectiveness; and (4) accelerating the evaluation of vaccine candidates to enable rapid authorization or approval. The coordinated efforts of the working groups have fed into six clinical trials:

ACTIV-1: Tests promising immune modulator compounds, a class of drugs that help minimize the negative effects of an overactive immune response to SARS-CoV-2 infection.

ACTIV-2: Evaluates the safety and efficacy of monoclonal antibodies and other therapies in outpatient settings. The trial tests if treatments can reduce the duration of symptoms and increase the proportion of participants with undetectable virus.

ACTIV-3: Examines the safety and efficacy of monoclonal antibodies and other therapies for hospitalized patients. The trial evaluates if investigational treatments can reduce the time to recovery and studies treatment effects on complications associated with COVID-19 and lung function.

ACTIV-4: Evaluates the safety and efficacy of different types of blood thinners to treat adults with COVID-19. The trial seeks to prevent and treat the effects of COVID-19-associated clotting and understand its effects in hospitalized, outpatient, and convalescing individuals.

ACTIV-5: Assesses if approved therapies or investigational drugs in late-stage clinical development show promise against COVID-19. Compounds that do not demonstrate efficacy based on interim evaluations are dropped, whereas those that demonstrate efficacy move forward into additional clinical trials.

ACTIV-6: Evaluates prescription and over-the-counter medications previously approved for other indications for people to self-administer to treat symptoms of COVID-19. The trial aims to provide evidence-based treatment options for the majority of adult patients with COVID-19 who have mild to moderate symptoms and are not sick enough to be hospitalized.

See the ACTIV website for a list of **therapeutics currently under investigation** in ACTIV clinical trials. In addition to trials conducted under the ACTIV partnership, NIH has prioritized and tested additional therapeutics in ACTIV-associated trials. These are **NIH-funded, randomized, placebo-controlled clinical trials** with one or more industry partners. NIH and its ACTIV partners will continue to work intensively to develop new and better treatments with the ultimate goal of ending the pandemic as soon as possible.



However, much work remains to improve the treatment of this disease. Orally administered drugs are needed for use as early-intervention strategies in primary care and outpatient settings that could potentially lessen the severity and duration of disease, as Tamiflu® does for influenza. Host-targeted treatments also are needed to prevent and address symptoms associated with COVID-19 that can cause lasting injury to the body and overall health of people with COVID-19. Candidates for such treatments include antivirals, host-targeted immune modulators, monoclonal antibodies (mAb), and symptomatic/supportive agents, including anticoagulants.

Treatment scenarios likely will become more complex and require additional studies as the pandemic continues to evolve, vaccines become more available, and viral variants continue to arise (e.g., treatments for reinfected people, immunocompromised individuals, vaccinated people who become infected, people whose symptoms persist longer than is typical for recovery from a respiratory virus). Through continued NIH-wide efforts and Federal, academic, and industry partnerships—such as ACTIV and ACTIV-associated trials—NIH is continuing to prioritize and test therapeutics to meet the changing needs of COVID-19 treatment and expand the populations eligible for treatment.

Objective 3.1: Identify and develop new or repurposed treatments for COVID-19

NIH has established a multipronged approach to discover or repurpose promising candidate therapies for COVID-19 using advanced screening methods—such as human cell–based models and animal models—to identify promising therapies that may interfere with the production of the virus or its ability to infect cells. These efforts will remain essential even in the context of vaccine availability as new viral variants arise that may be resistant to the currently available vaccines and therapeutics.

NIH-supported researchers are continuing to seek out and characterize candidate therapeutics that target the viral and host proteins that play an important biological role in SARS-CoV-2 infection, including candidates that inhibit viral replication or that block binding to ACE-2, the receptor through which the virus enters human cells. Data science tools are critical to this endeavor; NIH intramural and NIH-supported researchers already are creating complex computer-generated models of SARS-CoV-2 and its biological processes to determine key interactions and pathways to target for therapeutics development, as well as to predict resistance of newly arising virus mutants to currently available therapeutics.

Other therapeutic approaches under investigation involve passively boosting the immunity of people infected with SARS-CoV-2 by infusing convalescent plasma from patients recovered from COVID-19, pooling such blood products into hyperimmune blood proteins (alone or in combination with antiviral drugs), and using monoclonal antibodies designed to target and



neutralize the virus. NIH researchers and partners around the globe are continuing to develop and test new monoclonal antibodies for mild to moderate COVID-19 and hospitalized COVID-19 patients, and clinicians have begun treating patients in outpatient settings with monoclonal antibodies that already have demonstrated beneficial effects for mild to moderate COVID-19, including bamlanivimab (note that this treatment is not effective against some SARS-CoV-2 variants) and the combination antibody treatments casirivimab/imdevimab and bamlanivimab/etesevimab. In related work, NIH intramural scientists are exploring the potential use of nanobodies, a special type of antibody naturally produced by camelids (a group of animals that includes camels, llamas, and alpacas) to prevent or treat COVID-19.

In addition to new therapeutics, researchers are looking for ways to repurpose drugs approved for other indications and use them to treat COVID-19. NIH-supported and intramural researchers and their partners are screening existing FDA-approved therapeutics for activity against SARS-CoV-2, strategically targeting pathways identified in foundational coronavirus research studies as essential to virus production or infection. Within a few months of the pandemic's beginning, NIH collaborated with industry partners to show that the antiviral remdesivir, a drug formerly tested for the treatment of Ebola, accelerates the recovery of hospitalized, oxygen-supplemented patients with severe COVID-19. NIH now is testing remdesivir in combination with other new or repurposed drugs for treatment of patients with severe COVID-19. One combination treatment of remdesivir with a drug used to treat rheumatoid arthritis, baricitinib, reduces the time to recovery for people hospitalized with COVID-19 and now is being used to treat patients. Additional clinical trials are planned or are underway to evaluate the efficacy of other repurposed drugs through ACTIV and ACTIV-associated clinical trials or by leveraging ongoing NIH therapeutic clinical trials for other diseases to add measures to evaluate the efficacy of their target therapeutic against COVID-19 (see Box 3). NIH has taken steps to ensure that information about COVID-19 related clinical trials is swiftly shared through its ClinicalTrials.gov platform.

Objective 3.2: Evaluate new or repurposed treatments and treatment strategies for COVID-19

The multiorgan, multisystem involvement of moderate to severe COVID-19 prompts critical questions about its immediate and long-term impact, particularly in people with preexisting conditions. The severity of COVID-19 varies widely and can involve a number of different systems, including the cardiovascular, nervous, renal, and respiratory systems. NIH is supporting clinical trials to investigate whether existing antiviral drugs can be repurposed for early treatment of COVID-19 with a hope of preventing progression to severe disease and longer-term effects, but therapies to treat various COVID-19 complications are still needed.

The multifaceted nature of the impact of COVID-19 on multiple body systems necessitates evaluating a wide range of therapies that target disease processes resulting from SARS-CoV-2



infection. As part of this broad approach to therapy, NIH is evaluating treatment strategies that target the body's response to the virus, as well as evidence-based integrative health approaches. Clinical trials in progress include approaches to address disease processes resulting from SARS-CoV-2 infection, such as tissue injury, blood clotting, overreaction of the immune system, and inflammation. Some of these therapeutics under investigation have already demonstrated benefits in clinical trials.

To facilitate the testing of both antiviral and disease process-targeted treatments for COVID-19 and its complications, NIH created new research networks and is leveraging other clinical trial networks supported by Institutes, Centers, and Offices across NIH, including the Clinical Center. These networks are conducting a variety of flexible, adaptive clinical trials and support clinical trials designed in real-world hospital settings, called pragmatic clinical trials. NIH is collaborating with Federal, industry, and academic organizations through such partnerships as ACTIV to increase the capacity to conduct clinical trials across all phases, from pilot studies to large safety and efficacy trials. These partnerships are helping streamline recruitment and hasten the collection of data needed for FDA authorization to ensure that new or repurposed interventions will be advanced as quickly as possible.

Objective 3.3: Identify and evaluate new or repurposed treatments for the long-term effects of SARS-CoV-2 infection



Recovery from SARS-CoV-2 infection is extremely variable, with many patients recovering quickly but others experiencing longer-term illness. A significant number of COVID-19 survivors develop PASC (See Box 1). The magnitude of the public health impact of PASC is currently unknown but potentially profound, given the numbers of individuals across the age spectrum who have been and will be infected with SARS-CoV-2. It is imperative that we better understand and develop strategies to prevent and treat PASC and learn how to differentiate the general psychosocial impacts of the pandemic from the biological effects of the virus on cognitive function and mental health. Developing treatment strategies for all of these scenarios will be key to improving the well-being and functioning of the American people.

NIH has announced a research initiative to learn about the clinical spectrum of and biology underlying recovery from acute SARS-CoV-2 infection over time, across diverse populations, and throughout the lifespan. Through clinical and laboratory studies, including analyses of electronic health records, these research opportunities will help provide understanding of why most patients recover quickly but others have lasting or develop new symptoms after SARS-CoV-2 infection. This research will lay the foundation for clinical trials to identify safe and effective treatments to enhance the recovery of patients with persistent and new symptoms and identify interventions which, if initiated early, could prevent end-organ and systems damage and other symptoms. NIH also will evaluate medical care strategies that seek to improve COVID-19 outcomes, recognizing that individuals who receive critical care interventions, in particular, may require ongoing rehabilitation during recovery.

Objective 3.4: Investigate strategies for access to and implementation of COVID-19 treatment

The resolution of the COVID-19 pandemic will depend on the expeditious and broad dissemination of treatment strategies and care practices for use by health care practitioners and acceptance of these practices and strategies by communities to ensure that all members of the public have access to appropriate COVID-19 treatment. Delays in the adoption of up-to-date clinical practices could result in unnecessary prolongation of the pandemic, additional lives lost, and increased economic burden.

NIH is building on existing dissemination and implementation science research, both by testing the adaptation of strategies that have been successful in other disease areas, such as HIV and tuberculosis treatment, and by supporting new studies that examine methods to disseminate, provide access to, and facilitate uptake of interventions for COVID-19. Community-engaged research strategies and sex- and gender-focused approaches are essential to the success of implementing interventions, particularly for underserved and other populations at high risk of SARS-CoV-2 infection. These populations are disproportionately affected by COVID-19, experiencing the highest infection rates and risks for complications or poor outcomes. Equitable access to and uptake of treatments among these populations is of the utmost importance and critical to resolution of the COVID-19 pandemic. Community-engaged research seeks to use local communication channels, resources, and social infrastructure that can aid the design of tailored, local strategies to mitigate implementation barriers for underserved populations, such as barriers resulting from social determinants of health.

Essential to these goals is the consideration of cultural, ethical, social, behavioral, historical, and economic factors in the collection, storage, and dissemination of health-related data, as well as in evaluation of interventions. NIH is supporting in-depth examinations of factors that relate to barriers to and implications of treatment; stigma and financial burden associated with COVID-19 treatment and follow-up care; and issues of privacy, confidentiality, and data sharing.

PRIORITY 4



Improve Prevention of SARS-CoV-2 Infection

Critical to resolving the current COVID-19 pandemic and preventing future outbreaks is the development of countermeasures to stop transmission of the virus and prevent new infections. By supporting the development of new vaccines, behavioral and community interventions, and effective strategies for implementing these countermeasures, NIH is creating preventive interventions with the potential to reduce the incidence of new SARS-CoV-2 infections across the country. The NIH approach leverages existing knowledge, tools, networks, and infrastructure—in addition to developing and implementing novel approaches—to prevent new SARS-CoV-2 infections.

Objective 4.1: Develop novel vaccines for the prevention of COVID-19

To prevent outbreaks of COVID-19, safe and effective vaccines for SARS-CoV-2 needed to be developed and distributed as quickly as possible. The NIH intramural program played an important role in the early testing and development of several vaccine candidates, including the Moderna mRNA vaccine, developed by NIH and ModernaTX, Inc., (see Box 4) and the AstraZeneca vaccine, developed in a partnership between NIH and Oxford University. As of April 2021, the Moderna vaccine and another mRNA vaccine developed by Pfizer and BioNTech—as well as a recombinant vector vaccine developed by Johnson & Johnson's Janssen Pharmaceuticals—have received FDA emergency use authorization for administration in adults. Two additional vaccines developed by AstraZeneca and Novavax have ongoing Phase 3 clinical trials. NIH is continuing to support research and development of effective COVID-19 vaccines, including novel vaccine platforms such as a cage of sticky nanoparticles, which are ultrafine particles sized between 1 and 100 nanometers that have the potential to combat multiple strains of coronaviruses. NIH also is pursuing research on a universal coronavirus vaccine that would offer protection from multiple coronavirus strains and variants in an effort to prevent future outbreaks from occurring, as well as a clinical trial for the SARS-CoV-2 B.1.351 variant.

Similar to its role for therapeutics, ACTIV (see Box 3) has played a critical role in coordinating research efforts and clinical trials for vaccines across the NIH, FDA, and industry. To coordinate and accelerate clinical testing, NIH and its partners are leveraging existing clinical trial networks, such as the HIV Vaccine Trials Network; the HIV Prevention Trials Network; the Infectious Diseases Clinical Research Consortium; and the Prevention and Early Treatment of Acute Lung Injury Network (PETAL Network), which conducts trials to improve prevention and treatment of acute respiratory distress syndrome. NIH created the COVID-19 Prevention Network (CoVPN), which is coordinating clinical research sites for Phase 3 efficacy trials and providing centralized data coordination and novel epidemiological disease tracking tools to speed the evaluation of vaccine candidates. These data help inform the decision-making process for expanding vaccine testing to new populations, including groups at higher risk of SARS-CoV-2 infection. For example, based on the success and safety of vaccines in healthy adults, clinical studies to test the safety and efficacy of COVID-19 vaccines in children, adolescents, and pregnant individuals are now underway.

Objective 4.2: Develop and study other methods to prevent SARS-CoV-2 transmission

Until COVID-19 vaccines are widely available and we know more about how effective they are against newly arising variants of SARS-CoV-2, alternative methods to slow the spread of



the virus will continue to be necessary. NIH is supporting studies on preventive treatments, behavioral and community prevention practices, and policies to rigorously study and determine the most effective approaches to promote individual and community safety. These approaches are informed by NIH basic research into the mechanisms of viral survival, infection, and transmission.

Antibody treatments, in addition to their potential therapeutic use, hold promise as a method to prevent COVID-19 in individuals exposed to SARS-CoV-2 and those who are at high risk of serious illness. Clinical trials supported by NIH demonstrated that the monoclonal antibody bamlanivimab can prevent COVID-19 symptoms in SARS-CoV-2 positive patients and reduce the risk of SARS-CoV-2 infections in nursing home residents by up to 80 percent. Additional studies for the use of other monoclonal antibodies as preventive treatments are underway.

Research into the survival of SARS-CoV-2 in the environment and its transmission through respiratory droplets has guided the understanding of how physical distancing and personal protective equipment (PPE) can be applied to prevent viral spread. Modifiable risk factors, such as environment and nutrition, and interactions with preexisting biological mechanisms, such as epigenetics and metabolomics, that may contribute to a person's susceptibility to SARS-CoV-2 infection are being studied to better understand a broad range of prevention methods. The Community Prevalence of SARS-CoV-2 Study (COMPASS) will inform the development of future SARS-CoV-2 prevention research and provide valuable information on the effectiveness of prevention practices by assessing knowledge, attitudes, behaviors, and beliefs about the COVID-19 pandemic and modeling the potential impact of prevention strategies.

NIH also is supporting research into effective practices for PPE use and reuse, as well as the development of new PPE to protect health care workers, caregivers, and the public. NIH prioritizes the safety of health care workers and caregivers and seeks to build scientific knowledge of the best decontamination methods and other safety measures specific to the needs of health care environments, such as nursing homes, dental practices, and hospitals. The NIH Worker Training Program has supported 31 grants to create virtual trainings for COVID-19 essential and returning workers. As of April 2021, more than 8,200 health care workers, first responders, community-based organization staff, death care industry professionals, and other essential workers have completed these online trainings. NIH also supported research into the development of practices and innovative decontamination technologies and procedures—such as the use of ultraviolet light, heat, and chemical procedures—to decontaminate and reuse N95 respirator masks.

Objective 4.3: Develop effective implementation models for preventive measures

NIH and its funded scientists are leveraging existing and new collaborations to determine the best possible methods for developing, implementing, and distributing vaccines and behavioral prevention methods against SARS-CoV-2. As vaccines are becoming widely available, rigorous research is needed to answer critical questions about the most effective distribution practices. Ensuring vaccines are delivered equitably to at-risk individuals in high-need areas, with proper access and administration techniques, is critical to preventing further outbreaks. Key to this research is identifying methods to address social, ethical, and behavioral factors likely to influence the use of vaccines and other prevention practices. Implementing effective

Box 4. Groundbreaking Vaccine Development to End the Pandemic

The development of multiple safe and effective vaccines against COVID-19 is critical to ending the pandemic. As soon as the SARS-CoV-2 genetic sequence became public in January 2020, NIH-funded scientists began working at an unprecedented pace to identify, develop, and test promising vaccine candidates. Previously, new vaccines took, on average, longer than 10 years to develop, and many candidates were ultimately unsuccessful. Building on previous coronavirus vaccine research at NIH and the intense collaboration and dedication of NIH-supported and intramural scientists and its industry and Federal partners, several vaccine candidates have successfully been developed and deployed in one year without sacrificing standards for safety or scientific rigor. This extraordinary effort and record-breaking pace represent countless scientific and logistical advances in vaccine development made both before and during the current pandemic; these advances—and others to come—will help us better prepare for the rapid creation and testing of vaccines against future emergent viruses.

NIH ensured needed resources and supplies were available for researchers and vaccine developers, **leveraged existing clinical trial networks** to rapidly advance the testing of vaccine candidates, and coordinated across the U.S. Department of Health and Human Services to focus resources and standards on vaccine candidates moving through the development pipeline. Advancing candidates through preclinical study, clinical testing, and regulatory approvals required extraordinary coordination of Federal and industry partners via collaborations and partnerships, such as ACTIV (**see Box 3**). In one collaboration, ModernaTX, Inc., and the Biomedical Advanced Research and Development Authority developed the **mRNA-1273 vaccine** (called the Moderna vaccine). NIH provided funding and technical support for the Phase 3 efficacy trial that enrolled more 30,000 participants at 100 research sites across the country. As one of the first vaccines to receive **FDA emergency use authorization** in the United States, it is being delivered to millions of Americans daily. NIH and ModernaTX already have pivoted to address emerging SARS-CoV-2 variants and now are testing a **vaccine targeted toward the B.1.351 variant**.



and responsive prevention strategies in populations at high risk of SARS-CoV-2 infection is a principal priority for NIH (see Priority 5).

Leveraging testing technology and new knowledge of SARS-CoV-2 transmission is critical to preventing the spread of the virus. The COVID-19 Testing Impact Calculator (see description in Priority 2) provides clear guidance for schools and businesses to promote risk-reducing behaviors and navigate evolving conditions on a local level. NIH is using the SAFER COVID app—which tracks symptoms, assesses risky activities, and assists with at-home testing and reporting—to inform its own employees' safe return to work. A pilot study to determine if frequent at-home testing can reduce viral transmission began in March 2021.

NIH recognizes the need to communicate and partner with the public to help increase uptake of preventive measures, including vaccines, and address vaccine hesitancy. To help ensure development of vaccines that would work for all Americans, NIH worked to achieve diversity in vaccine clinical trial participants through the Community Engagement Alliance (CEAL) Against COVID-19 Disparities initiative. The initiative provides trustworthy information through active community engagement and outreach in disproportionately affected communities. In another effort, partners across NIH compiled evidence-informed communication strategies for prevention measures tailorable to the needs and concerns of diverse communities. NIH also has solicited research proposals for community-engaged research to evaluate strategies to increase vaccine uptake and address barriers to increasing vaccinations among populations experiencing health disparities and vaccine hesitancy.



PRIORITY 5

Prevent and Redress COVID-19 Outcomes in Health Disparity and Other Populations at High Risk of SARS-CoV-2 Infection

The impact of COVID-19 on populations that are underserved and experiencing health disparities[1] must be urgently addressed. There are consistent differences in COVID-19 prevalence and mortality across different age, racial, and ethnic groups, and among specific populations (e.g., people with asthma or diabetes).[2] The underlying causes are complex and include social

[1] Health disparity populations include Black/African American populations, Hispanics/Latinos, American Indians/Alaska Natives, Asian Americans, Native Hawaiians and other Pacific Islanders, socioeconomically disadvantaged populations, underserved rural populations, and sexual and gender minorities.

[2] Populations with increased risk of COVID-19 include residents of chronic care and assisted living facilities; community-dwelling older adults; individuals with rare diseases; individuals with cognitive impairment or dementia; homeless populations; incarcerated populations and those involved with the criminal justice system; adults with medical comorbidities; pregnant individuals; children and adolescents; individuals with substance use disorders or severe mental illness; those living in congregate housing; persons who are deaf or with disabilities, including visual, hearing, communication, or mobility impairment; detainees in immigration centers; migrant communities; individuals living on Tribal lands or reservations; and communities that are exposed to high rates of air pollution or other toxic exposures. Individuals who are on the frontlines of health care during the COVID-19 pandemic and those working in essential business operations also are at higher risk for COVID-19.

and structural determinants of health—such as social, economic, and political mechanisms that generate inequalities in society (e.g., discrimination, economic and educational disadvantages) and differences in health care access and quality. These concerns are amplified in densely populated urban areas where physical distancing is not possible; rural areas where access to testing and vaccines may be delayed or inadequate due to limited transportation networks and access to hospital and specialty care; communities with high rates of chronic health conditions; and lower- and middle-income countries with fragile health care systems. An in-depth understanding of the underlying causes that may exacerbate the spread and morbidity or mortality of COVID-19 in the United States, as well as different countries around the globe, allows the scientific, public health, and clinical communities to efficiently implement interventions to mitigate negative outcomes through better prevention, testing, and treatment of COVID-19. NIH aims to address key questions related to the differential impacts of the COVID-19 pandemic, including the long-term health consequences. These include understanding barriers to adherence to different mitigation strategies, including vaccine misinformation, distrust, and hesitancy among populations; and differences in risk and resilience based on biological factors, gender, race and ethnicity, socioeconomic status, disability, and other social and structural determinants of health. Ultimately, the United States cannot control the pandemic alone. NIH will continue to collaborate with the global scientific community, such organizations as the World Health Organization, and foundations, partnerships, and nongovernmental organizations engaged in research response not only to understand the spread of SARS-CoV-2, but also to develop and distribute the diagnostics, treatments, and vaccines needed to control the COVID-19 pandemic on a global scale.

Objective 5.1: Understand and address COVID-19 as it relates to health disparities and populations at higher risk for COVID-19 in the United States

As part of the RADx initiative (see Box 2), NIH is funding a series of interlinked community-engaged projects to enhance SARS-CoV-2 testing in underserved, under resourced, and rural populations across the United States. This initiative has developed infrastructure to assess and expand evidence-based testing capacity and address the social, cultural, ethical, and behavioral implications associated with SARS-CoV-2 testing for those populations that are most at risk for infection and adverse outcomes from contracting the virus. RADx Underserved Populations (RADx-UP) projects are conducting pragmatic and traditional clinical trials at multiple sites across the country to investigate a variety of testing methods and approaches to better understand the uptake, acceptance, and effectiveness of testing in specific populations. These projects are undertaken in partnership with community health centers (e.g., Tribal health centers, Health Resources and Services Administration–funded community health centers, Federally Qualified Health Centers), medical libraries, houses of worship, homeless shelters,



group care homes, jails and prison systems, and other community resources to address the unique needs of different communities. The implementation and evaluation of new community interventions to prevent SARS-CoV-2 transmission and its immediate and long-term adverse psychosocial, behavioral, and socioeconomic consequences on health disparity populations is crucial. In April 2021, NIH released funding opportunities to expand testing efforts in underserved communities and schools; address testing and vaccine hesitancy and social, ethical, and behavioral factors associated with testing and vaccination; and build partnerships with CEAL to ensure that communities have access to the best strategies to increase vaccine and testing uptake and address COVID-19.

The CEAL initiative also works to address the disproportionate burden of COVID-19 in underserved populations. CEAL connects researchers with trusted local leaders and organizations in hard hit communities to provide accurate, accessible information about COVID-19, preventive measures (including vaccines), and opportunities to participate in research. The initiative also develops and disseminates free culturally tailored educational resources in English and Spanish about ongoing clinical trials and emerging vaccines and treatments in the United States. Continued dialogue and engagement with communities at high risk of SARS-CoV-2 infection through RADx-UP, CEAL, and other NIH programs will be critical to the success of the national vaccination campaign. Vaccine hesitancy and mistrust are prevalent in underserved communities and could slow vaccination efforts in the communities that would benefit from vaccines the most. To that end, NIH launched a research initiative to promote vaccine acceptance, uptake, and implementation among populations that experience health disparities. Related efforts include holding an NIH Tribal Consultation on COVID-19 Research to seek input from Tribes about programs focused on enhancing testing capacity to better understand the best strategies for effectively addressing the COVID-19 pandemic in these populations. NIH will continue engagement efforts with Tribal leaders to assist the national vaccination campaign.

Multiple factors determine vulnerability and case fatality rates, including preexisting conditions, disabilities, and sex and gender disparities. This pandemic underscores the imperative to consider the entirety of the American population and social determinants of health to strengthen our collective capacity to respond equitably to COVID-19 and ensure study findings are relevant to everyone. NIH will fund mechanistic studies on the interaction between SARS-CoV-2 infection susceptibility, routes of infection, the course of COVID-19, and morbidity and mortality in people with preexisting conditions (e.g., obesity). Equitable distribution of resources, access to care, and accommodations related to disabilities and other transportation and mobility issues will be critical to ensure health care and resources are available to all who need them. NIH is supporting the development of tools that provide access to COVID-19 incidence information and help people with visual impairments plan their travel activities. With the goals of promoting scientific rigor and enhancing health equity, NIH developed guiding principles to

urge systematic examinations of sex and gender influences in COVID-19 research. The guidance addressed how NIH policies on sex as a biological variable and inclusion could inform study designs, analysis, and result reporting to improve health outcomes amid the COVID-19 crisis and public health emergency.

NIH is committed to including individuals who have been traditionally underrepresented in biomedical research in clinical trials for treatments and vaccines to understand how interventions may affect these populations differently and ensure the applicability of findings to all. For example, the trans-NIH INCLUDE (INvestigation of Co-occurring conditions across the Lifespan to Understand Down syndromE) initiative is supporting research that explores the effects of COVID-19 on individuals with Down syndrome. Similarly, the RADx-UP and NIH's Helping to End Addiction Long-term℠ (HEAL) programs are supporting research into the best implementation strategies to test for SARS-CoV-2 infection in children with intellectual and developmental disabilities and communities most heavily affected by the opioid epidemic, respectively.

Objective 5.2: Understand and address COVID-19 maternal health and pregnancy outcomes

Pregnancy is associated with alterations in the immune system—resulting in increased susceptibility to certain viral, bacterial, and parasitic infections—which may adversely impact maternal health, preterm birth, and infant health. More specifically, other respiratory viral infections, such as influenza, are associated with more severe disease outcomes in pregnant individuals and an increased risk of pregnancy-related and neonatal complications. Yet, information about SARS-CoV-2 infection and disease in pregnant individuals is scarce. Independent of COVID-19, individuals in the United States from underserved populations face substantially higher rates of pregnancy-related complications (i.e., severe maternal morbidity) and pregnancy-related death than non-Hispanic white women. Up to 60 percent of pregnancy-related deaths are preventable, highlighting inequities in health care access and quality-of-care factors that contribute to racial disparities in maternal mortality and severe morbidity. NIH will leverage existing research on maternal morbidity and mortality to investigate questions related to



pregnancy and COVID-19, including the effects of SARS-CoV-2 infection and treatment of COVID-19 on maternal and fetal health during pregnancy, as well as pregnancy outcomes. Populations at higher risk for COVID-19, including pregnant individuals, also are included in RADx-UP programs, to coordinate improved strategies for diagnostic testing.



NIH has initiated large-scale studies to investigate the effects of COVID-19 on such factors as pre-, peri- and postnatal care; rate of Cesarean section delivery; and maternal and infant health outcomes. Early results from the Maternal Fetal Medicines Unit Network's Gestational Research Assessments for COVID-19 (GRAVID) show that pregnant individuals who experienced severe symptoms of COVID-19 had a higher risk of complications during and after pregnancy, but women in the third trimester are unlikely to pass the infection on to their infants. Additional studies will examine neurodevelopmental issues in children whose mothers were infected with SARS-CoV-2 during pregnancy, while others will address neurological complications of COVID-19 in pregnant individuals, children, and newborns exposed to the virus. NIH-supported researchers also have created a repository of recent peer-reviewed journal articles on COVID-19, breastfeeding, infant feeding, and breast milk. NIH recognizes the need to determine the safety and efficacy of COVID-19 therapeutics for pregnant and breast-feeding individuals—a clinical trial to evaluate the use of remdesivir during pregnancy launched in February 2021.

Objective 5.3: Understand and address age-specific factors in COVID-19

Certain age groups are at higher risk for serious complications from SARS-CoV-2 infection, such as older adults (65 years and older). NIH is supporting studies of neurological and neurocognitive symptoms in COVID-19 and complications associated with SARS-CoV-2 infection in older adults. In addition, NIH is funding research to explore the role of inflammation in older populations with COVID-19 and subsequent progression to more severe disease, including lung pathology. NIH also is developing aged animal or *in vitro* models suitable for studies on pathogenesis of the virus or preclinical testing of investigational therapeutics and vaccines against SARS-CoV-2.

Although the majority of children and young adults have mild, moderate, or asymptomatic cases of COVID-19 compared with adults, studies are needed to address the dynamics of the virus and the immune response in children and adolescents, as well as short- and long-term outcomes. For example, the NIH Human Epidemiology and Response to SARS-CoV-2 (HEROS) study will help determine what percentage of children infected with SARS-CoV-2 develop symptoms of the disease. Data also suggest that undiagnosed infections in children may present later as a pediatric inflammatory syndrome similar to Kawasaki disease called multisystem inflammatory syndrome in children (MIS-C). It is known that many children with MIS-C either were infected with SARS-CoV-2 or were exposed to someone with COVID-19. Trans-NIH efforts known as the Collaboration to Assess Risk and Identify Long-term Outcomes for Children with COVID (or CARING initiative) and the RADx-rad Predicting Viral-Associated Inflammatory Disease Severity in Children with Laboratory Diagnostics and Artificial Intelligence (or PreVAIL kIds) studies are part of a research plan to investigate MIS-C. These and other studies aim to describe the spectrum of pediatric SARS-CoV-2 infection and why some children are more likely to get infected, understand long-term outcomes for patients, identify MIS-C risk factors, and define other critical research questions to impact patient health. In another effort, the Pediatric Trials Network is using more than 50 established research sites to evaluate drugs given to children diagnosed with COVID-19. Researchers are analyzing blood samples collected from routine medical procedures to understand how these drugs act in children, refine dosing, and improve safety.

The long-term socioeconomic and health impacts of the COVID-19 pandemic on children remain to be seen, but the potential exists for profound and lasting detrimental consequences for the well-being, education, and mental health of children, particularly among underserved populations. Researchers funded by the Environmental influences on Child Health Outcomes (ECHO) program rapidly developed parent- and child-specific COVID-19 questions to study the impact of changes in environmental exposures resulting from the COVID-19 pandemic on child health outcomes. These tools are now available to researchers and clinicians through the NIH Public Health Emergency and Disaster Research Response COVID-19 Collection Tools and the PhenX Toolkit COVID-19 Protocol Library. Additionally, the RADx-UP program is supporting the study of school-based COVID-19 diagnostic testing approaches in high-risk communities to facilitate a return to in-person school for disproportionately affected and underserved populations, including racial and ethnic minorities and students with disabilities.

Objective 5.4: Address global health research needs revealed by COVID-19

NIH recognizes that a global pandemic requires a global response and is working with international partners to improve fundamental knowledge of SARS-CoV-2 and COVID-19, as well as optimize the development and delivery of diagnostic tests, treatments, and vaccines

to populations most in need. Much of the initial knowledge regarding the basic science, epidemiology, and disease characteristics of COVID-19 was gained from or developed in collaboration with the international scientific and medical communities. Collaborations with scientists around the globe have been essential to piecing together the emergence and spread of SARS-CoV-2, and they have helped identify the populations most severely affected. Critical to these efforts are open lines of communication and a collaborative approach among the international biomedical community. NIH continues to foster international collaborations to address the COVID-19 public health response on a global level, drawing on a worldwide network of grantees and former trainees, many of whom have leadership roles in global and national responses.

Robust international scientific collaboration is critical to the development and distribution of diagnostics, treatments, and vaccines needed to control COVID-19 on the global scale necessary for full social and economic recovery. NIH is coordinating efforts with other international COVID-19 product development accelerators to share best practices and information about clinical trials and the advancement of promising new medical countermeasures. For example, the NIH-supported Global Network for Women's and Children's Health Research is examining antibody testing at delivery to compare maternal, fetal, and neonatal outcomes of women infected with SARS-CoV-2 with those of noninfected women in different countries. Academic and industry collaborations outside the United States are providing critical perspective on SARS-CoV-2 transmission, tracking molecular changes in the virus, establishing epidemiological tools to help monitor outbreaks and new infection patterns, and developing countermeasures against the virus. Fogarty International Center in-house researchers have been collaborating with partners in Asia and Africa to use mathematical modeling to study the disease dynamics of COVID-19 in the United States and abroad. Fogarty scientists also have trained international partners in Africa, Asia, and South America to use genomic epidemiology to track local emergence of SARS-CoV-2 variants of concern. By applying lessons learned from implementation and dissemination science studies in low- and middle-income countries, NIH is employing its international clinical infrastructure to create new collaborations that ensure timely distribution of these diagnostics and interventions to the populations that would benefit from them the most.

- **Partnering to promote collaborative science**
- **Supporting the research workforce and infrastructure**
- **Investing in data science**
- **Engaging and educating the public**

CROSSCUTTING STRATEGIES

To support the five strategic priorities, NIH is pursuing crosscutting strategies that build on its existing strengths as the Nation's premier biomedical research agency. Specific examples of these strategies have been provided throughout this plan.

Partnering to promote collaborative science

NIH will continue fostering collaborative efforts to build an interactive, multidisciplinary scientific workforce in the United States and internationally to accelerate research on COVID-19. By leveraging existing NIH-funded global research networks, coordinating closely with its Federal partners, and creating new public–private partnerships, NIH continues to employ every opportunity to deepen the understanding of and develop interventions for COVID-19.

Many NIH-funded research networks already have been mobilized to address COVID-19—including those focused on specific practice areas, particular demographics, or otherwise at-risk populations—such as the PETAL Network.

NIH continues to expand collaborations with its fellow agencies and offices within the U.S. Department of Health and Human Services (HHS) (e.g., Biomedical Advanced Research and Development Authority, CDC, FDA) and beyond (e.g., U.S. Department of Defense) to ensure efficient and rapid dissemination of diagnostics, treatments, and vaccines to the public. Furthermore, NIH and its Federal partners are working closely and recognize the importance of collaboration with the private sector, scientific societies, nonprofit organizations, patient communities, and health care providers.

Supporting the research workforce and infrastructure

The COVID-19 pandemic has the potential to have a substantial negative impact on the livelihood and diversity of the scientific workforce, particularly for women and underrepresented groups, such as racial and ethnic, sexual, and gender minority populations. NIH has assessed the effects of COVID-19 on the scientific workforce at NIH and the extramural community at an individual and institutional level, including underrepresented groups, and is using these preliminary survey results to inform the best course forward for promoting a diverse and inclusive scientific community. Already, NIH has specified opportunities for extending fellowship and career development awards impacted by COVID-19, and investigators adversely impacted by COVID-19 can request an extension of their early-stage investigator status via the electronic Research Administration (eRA) Commons. NIH also provides substantial administrative flexibilities for researchers who have been adversely affected by the COVID-19 pandemic.

Despite challenges presented by the pandemic and measures put in place to limit its spread, NIH is working with the scientific community to advance SARS-CoV-2 and COVID-19 research. By adapting its processes to work within the physical distancing constraints of the pandemic, NIH continues to process proposals and fund research projects in a timely manner. For example, NIH has expanded its use of virtual meetings to conduct peer reviews to protect the health of reviewers and NIH staff while facilitating the funding of COVID-19 and other research.

NIH continues to support researchers by providing such resources as tools, reagents, and sequencing tools. For example, NIH provides validated biosamples and access to animal models of SARS-CoV-2 infection. Furthermore, NIH is continuing to solicit innovative ideas to aid the COVID-19 response, potentially from investigators outside of infectious disease or virology research, through such mechanisms as the NIH Common Fund High-Risk, High-Reward Program.



In addition to funding COVID-19 research in the extramural community, NIH continues to mobilize its Intramural Research Program and the Clinical Center in support of COVID-19 research. Talented investigators are using NIH's specialized infrastructure that provides access to unique patient cohorts and clinical trials networks, as well as its state-of-the-art equipment, to deliver one-of-a-kind services relevant to COVID-19. These efforts take advantage of a unique and wide range of research and technological expertise, as well as partnerships and collaborations with extramural investigators. Projects are underway to evaluate and validate serology tests, design and assess PPE, and complete onsite clinical trials and basic science research. NIH continues to maximize the capacity and use of its vaccine treatment and evaluation units to enroll participants rapidly and evaluate vaccine response in a safe and effective manner.

Investing in data science

The ability of researchers to rapidly access and use pandemic-related data, from viral sequences to infection rates, has been critical to the ground-breaking speed of the U.S. response. NIH supports multiple data science efforts to ensure that COVID-19 research data are findable, accessible, interoperable, and reusable (the FAIR principles). Artificial intelligence and machine learning approaches are being incorporated into studies across the spectrum of research to support data-driven decision-making and improve scientific stewardship. By enhancing

existing and creating new data science resources and analytical tools, NIH is facilitating the use of COVID-19 data to the greatest extent possible, both by those generating the data and by other researchers. These investments support the development of diagnostic tools, survey instruments, risk assessment models, public health surveillance tools, and portals to share data (e.g., National COVID Cohort Collaborative (N3C), NIH Repository of COVID-19 Research Tools, OpenData Portal, PhenX, Systemic Harmonization and Interoperability Enhancement for Laboratory Data Collaborative (SHIELD), SARS-CoV-2 Sequencing for Public Health Emergency Response, Epidemiology, and Surveillance, and the COVID-19 SeroHub). NIH's investments in these and other tools and infrastructure continue to grow as the pandemic progresses, signaling NIH's commitment to the development of shared metrics and terminologies across research projects to facilitate and maximize the use of a wide breadth of data, from chemical structures to clinical trial results.

Through these approaches, NIH continues to explore and implement innovative ways to leverage its domestic and global infrastructure to address the needs of the COVID-19 pandemic and speed its resolution. Looking forward, NIH will build on the lessons learned regarding strategic data and information assets and data sharing infrastructure from this pandemic for use in streamlining future responses to health-related emergencies.

Engaging and educating the public

NIH has made considerable advances in the detection, treatment, and prevention of SARS-CoV-2 in the first year of the COVID-19 pandemic. To truly capitalize on these research advances, NIH must also focus on ensuring that the public is aware of and engaged in NIH research. This will help secure equitable impact across the Nation, as outlined by the National Strategy. To work toward reaching as many different audiences as possible, NIH is placing an emphasis on communication through different mediums—from television to social media to print. The NIH COVID-19 public website is serving as a central hub for the public to learn about and participate in COVID-19 research across all of NIH. NIH COVID-19-focused initiatives also have developed informative, engaging websites to communicate with the public, including specific audiences. For example, NIH has created the Women, Science, and the Impact of COVID-19 webpage and established a virtual speaker series on this topic. NIH's new Spanish COVID-19 website brings health information to the Spanish-speaking public. NIH also has collaborated on the HHS Combat COVID website, also available in Spanish.

Community engagement efforts are needed to foster public confidence in science and cultivate an informed public equipped to prevent the spread of SARS-CoV-2, particularly within communities hardest hit by the COVID-19 pandemic. CEAL has been instrumental to this endeavor, providing trustworthy information about vaccines and clinical trials through active community engagement and outreach to communities at high risk of SARS-CoV-2 infection (see description in Priority 5). These efforts are already beginning to pay off, with 37 percent of the volunteers in the NIH-Moderna vaccine trial coming from communities of color.



CONCLUSION

At the start of the COVID-19 pandemic, NIH and the biomedical community launched an unprecedented effort to diagnose, prevent, and treat this rapidly spreading disease. NIH has collected innovative and creative ideas from across the country, built new partnerships, and undertaken a bold and ambitious plan for protecting the American people from the novel coronavirus. These efforts already have shed light on the virus and its biology and have led to a number of approaches to save lives and mitigate the pandemic. Building on this knowledge and research infrastructure will prepare the world for future epidemics, and enhancing response capacity will be a vital legacy of this work.

The discoveries made by NIH scientists and NIH-funded investigators have built on countless scientific and technological advances in biomedical science. Genome sequencing, imaging technologies, data science and bioinformatics, and implementation science all have contributed to our knowledge of SARS-CoV-2 and COVID-19. To meet current needs, the approach to biomedical research has shifted in groundbreaking ways. By bringing together teams across a range of sectors and scientific disciplines and building on discoveries of the past, NIH will continue to take a crosscutting, integrative view of public health to put forward creative and bold strategies to end the COVID-19 pandemic.

The COVID-19 pandemic is the latest reminder of the constant threat to the health of the American people of emerging and reemerging infectious diseases. These pathogens require constant surveillance as they evolve and adapt to environmental pressures. Likewise, NIH must maintain a flexible, adaptable infrastructure to support research programs that aim to understand the foundational biology of new organisms and emerging diseases, the role of behavioral and social factors, and their potential impact on human health. These efforts will prepare scientific groundwork to protecting life from this and future public health threats. Under these extraordinary circumstances, NIH will continue to act swiftly to turn discoveries into health.




NIH
National Institutes of Health

National COVID-19 Preparedness Plan

Today, the U.S. government is releasing the National COVID-19 Preparedness Plan – which will enable America to move forward safely, sustaining and building on the progress we've made over the past 13 months. This plan lays out the roadmap to help us fight COVID-19 in the future as we begin to get back to our more normal routines. We look to a future when Americans no longer fear lockdowns, shutdowns, and our kids not going to school. It's a future when the country relies on the powerful layers of protection we have built and invests in the next generation of tools to stay ahead of this virus.

The President's National COVID-19 Preparedness Plan focuses on four key goals:



Protect Against and Treat Covid-19



Prepare for New Variants



Prevent Economic and Educational Shutdowns



Continue to Vaccinate the World



Protect Against and Treat COVID-19

The United States has experienced five waves of the pandemic since 2020, including three in the past year that were driven by new variants. America experienced a wave of COVID-19 cases driven by the Alpha variant in early Spring 2021 – a time when the U.S. vaccination program was administering a record number of vaccines every day. The Delta variant, which was more than twice as contagious as the original coronavirus strain, then swept across the country starting in Summer 2021, beginning in the South and spreading to the Midwest and Rocky Mountain regions.

Omicron represented another step in the virus's evolution, and has been one of the most contagious viruses in history, causing record numbers of infections around the world over the past three months. However, because of both lower severity of the Omicron variant and a stronger level of population immunity from vaccinations, Omicron has caused relatively fewer cases of severe COVID-19. Compared to prior waves of COVID-19 in the United States, the Omicron wave has had a lower proportion of cases resulting in hospitalization or death.

America has weathered the current Omicron wave with minimal disruption – schools and businesses largely remained open. As the country emerges from the Omicron wave, our path forward relies on maintaining and continually enhancing the numerous tools we now have to protect ourselves and our loved ones – from vaccines, to tests, to treatments, to masks, and more.

In January 2021, Americans had very few tools to protect against COVID-19, and the tools we did have were in limited supply. Over the last year, together, with states, localities, and public and private partners, the Administration has mobilized an unprecedented, whole-of-society effort to give Americans the tools they need to protect themselves.

The Administration has put vaccines at the center of our COVID-19 response because vaccines are the best tool we have to prevent hospitalization and death. We stood up the largest free vaccination program in our country's history – mobilizing 90,000 vaccination locations, standing up dozens of federally-run mass vaccination sites with the ability to administer more than a combined 125,000 shots a day, and deploying over 9,000 federal personnel to support vaccinations nationwide – including over 5,000 active duty troops.

As a result, today, the vast majority of Americans have the protection of a vaccine – with 215 million Americans fully vaccinated, and an estimated two-thirds of eligible adults having received their booster shot. Vaccinated and boosted people are 41 times less like to die of COVID-19 than unvaccinated individuals. And America's unprecedented vaccination campaign has saved lives: a December 2021 estimate suggested that vaccines saved over 1 million American lives and successfully prevented over 10 million hospitalizations.

The Administration has also expedited the development, manufacturing, and procurement of COVID-19 treatments, building a diverse medicine cabinet filled with more treatments now than at any point in the pandemic. Today about 4 million treatment courses are available to Americans, with 1 million *additional* courses of the Pfizer antiviral available in March, and another 2.5 million *additional* courses of the Pfizer antiviral available in April. In total, we have secured 20 million courses of Pfizer's life-saving antiviral pills, which have been shown to reduce the risk of hospitalization or death by 89%.

The nation's testing supply has increased dramatically. We now have free testing sites at 21,500 locations around the country. In January 2021, there were no rapid, at-home tests on the market available to Americans; during January 2022, there were more than 480 million at-home tests available to Americans on top of all other testing options. And we stood up COVIDtests.gov so Americans could order tests that shipped directly to their homes — for free. Private insurance and Medicaid now cover rapid at-home tests for free, and Medicare will fully cover these at-home tests starting this spring.

And the U.S. government has successfully put equity at the heart of a nationwide public health response. Hispanic, Black, and Asian adults are now vaccinated at the same rates as White adults. This is the result of an all-of-society effort that got America to where it is today: employers who offered paid time off for their employees; child care providers who offered drop-in services for caregivers to get vaccinated; public transit authorities and ride-sharing companies that provided free rides to vaccination sites; churches, civic organizations, barbershops, and beauty salons, who opened their doors to be trusted spaces for vaccinations; and the families who made vaccination a family affair.

The path forward in the fight against COVID-19 is clear: we must maintain and continually enhance the tools we have to protect against and treat COVID-19. The Administration looks forward to working with Congress to ensure that we have the resources to do just that.

Because we have these tools, we can begin to get back to our more normal routines safely and the use of public health mitigation measures like masking can be less frequent. The Centers for Disease Control and Prevention (CDC) has updated its framework for recommendations on preventive measures like masking, so masks are recommended when and where they matter the most and Americans will be wearing masks less often.

Make no mistake, as America moves forward we will leave no one behind. Equity will remain at the very center of our path forward in the fight against COVID-19. And we will be there to support Americans with the long-term impacts of COVID-19, including people experiencing Long COVID or mental and behavioral health challenges; as well as families suffering from the tragedy of losing someone they loved.

The Administration will work with Congress to secure the necessary funding to:

Launch an effort to vaccinate America's youngest children as soon as the U.S. Food and Drug Administration (FDA) authorizes and the CDC recommends a vaccine for that age group.

Ensure that Americans – of all ages – can get the protection of an effective vaccine.

Increase American manufacturing capacity to reliably produce an additional 1 billion vaccine doses per year – three times the U.S. population – and accelerate research and development of a single COVID vaccine that protects against SARS-CoV-2 and all its variants, as well as previous SARS-origin viruses.

Continue vaccination outreach and education efforts and combat misinformation and disinformation.

Ensure there are enough treatments for every American who needs them.

Launch a nationwide Test to Treat Initiative so Americans can rapidly access treatment, including by visiting a “one-stop” location to get a free test and free treatment pills.

Update the framework for recommendations on preventive measures like masking to reflect the current state of the disease.

Launch a one-stop-shop website that allows Americans to easily find public health guidance based on the COVID-19 risk in their local area and access tools to protect themselves.

Sustain and increase American manufacturing of COVID-19 tests, so we can continue to have a robust supply of tests.

Prioritize protections for the immunocompromised and take new actions to protect people with disabilities and older adults.

Help Americans with the long-term impacts of COVID-19.

Ensure equitable access to COVID-19 health care and public health resources.



Prepare for New Variants

As we work to keep ourselves protected against COVID-19, America must remain prepared for any new variant that may come our way. To do so, the Administration has developed a comprehensive plan for how we monitor this virus to stay ahead of it, adapt our tools swiftly to combat a new variant, and deploy emergency resources to help communities.

Before January 2021, the federal government had insufficient data and sequencing capabilities and was ill-equipped to respond to new variants. Electronic case reporting was in place for only a handful of states in 2020 and the country could sequence only 3,000 viral isolates per week. America had no plan for responding to a new variant or standing up comprehensive efforts to respond to a surge in COVID-19 cases.

The Administration has enhanced our collection, production, and analysis of data, and expanded electronic case reporting to all 50 states, Washington D.C., Puerto Rico, and thousands of health care facilities. The CDC now tracks a range of key COVID-19 response metrics including cases, tests, vaccinations, and hospital admissions in real-time. Additionally, the CDC launched – and is continually enhancing – the National Wastewater Surveillance System (NWSS) to track the presence of SARS-COV-2 in wastewater samples collected across the country. And America has established a world-class sequencing operation, sequencing up to 90,000 isolates a week. The CDC's sequencing efforts can now reliably detect variants that account for as little as 0.1% of all COVID-19 cases circulating in the United States. And when new variants are identified, the federal government has a network of researchers – federal, academic, and commercial – who are able to study the sequence and assess mutations rapidly, allowing the government to respond quickly to concerning variants.

The Administration has also successfully built a robust emergency response infrastructure. Our surge response – led by the Federal Emergency Management Agency (FEMA) and HHS – developed capabilities to stand up over 100 federal mass vaccination sites and federal surge testing sites; distribute millions of critical supplies; and deploy thousands of federal clinical and non-clinical personnel to support states, Tribes, and territories. Since July 2021, the federal government has deployed over 4,000 military and non-military personnel including doctors, nurses, and paramedics; sent over 3,400 ventilators, ambulances, and other critical supplies; and shipped over 115 million pieces of PPE. And over the last year, FEMA has invested $300 million in state hospital preparedness to expand hospital capacity in 38 states.

Moving forward, the Administration will maintain our proven data, sequencing, variant response, and surge response capabilities. The CDC will continue to improve COVID-19

data collection, reporting, and analysis so America is better informed and ready to respond to new variants. And if new variants emerge, the federal government will leverage established playbooks to assess a new variant's impact on our vaccines, treatments, and tests, and rapidly deploy the tools, personnel, and resources Americans need. America will also retain a significant stockpile of tools to combat COVID-19 that remain ready for deployment.

The Administration will work with Congress to secure the necessary funding to:

Improve our data collection, sequencing, and wastewater surveillance capabilities to immediately identify and detect new and emerging variants; and strengthen pandemic preparedness.

Leverage a COVID-19 Variant Playbook to determine the impact of a new variant on our vaccines, treatments, and tests, and shore up and update our tools, if needed.

Utilize new FDA processes to expedite regulatory review of variant-specific versions of vaccines and treatments, so America can get them in place, if needed.

Support new FDA processes to expedite regulatory review of variant-specific versions of vaccines and treatments, so Americans can get them quickly if needed.

Leverage a proven COVID-19 Surge Response Playbook.

Add at-home tests, antiviral pills, and masks for the general population to America's stockpile for the first time.

The U.S. government has established a permanent logistics and operational hub at HHS to ensure accelerated development, production, and delivery of COVID-19 vaccines and treatments.



Prevent Economic and Educational Shutdowns

Our path forward relies on giving schools and businesses the tools they need to prevent economic and educational shutdowns, so that our students can remain safe in school, our workers can be safe at work, and our economy can continue to grow.

At the beginning of last year, America was experiencing widespread school and business shutdowns: only 46% of K-12 schools were open for in-person learning, and millions of businesses had closed and tens of millions of Americans had lost their jobs in 2020. Throughout the last year, the Administration worked to provide schools, child care providers, and businesses with the necessary tools and resources to safely open, while keeping our children, students, and workers safe.

The Administration provided a historic investment of $130 billion from the American Rescue Plan to reopen schools by improving school ventilation, accessing tests, and hiring more teachers, nurses, and staff. To protect workers and keep our businesses open, the Administration launched the largest vaccination campaign in history – working hand-in-hand with the business community; and requiring vaccinations where we could, including for federal workers.

Today, about 99% of K-12 schools are open for in-person learning. And since President Biden took office, there has been historic job growth. The U.S. economy created 6.6 million jobs in 2021 – the strongest job growth of any year on record – and grew 5.7% in 2021, the fastest pace of economic growth in nearly four decades. The U.S. was also the first major economy to exceed its pre-pandemic economic output.

The path forward in the fight against COVID-19 is clear: schools, workers, and workplaces have resources and guidance to prevent shutdowns.

The Administration will work with Congress to secure the necessary funding to:

Give schools and businesses guidance, tests, and supplies to stay open, including tools to improve ventilation and air filtration.

Work with Congress to provide paid sick leave to workers who need to miss work due to a case of COVID-19 or to care for a loved one who has COVID-19.

Update guidance for employers to ensure safer workplaces.

Engage early care and education providers to help them remain safely open and help parents return to work with peace of mind.

With the vast majority of federal workers at their workplaces, substantially expand levels of services at public-facing federal offices (like local Social Security offices).



Continue to Lead the Effort to Vaccinate the World and Save Lives

Fighting this virus abroad is key to America's effort to protect people and stay ahead of new variants. To do so, we will continue to lead in providing vaccines to the world, helping to get those vaccines into arms, and deploying emergency supplies to countries experiencing surges in COVID-19. We will also continue to advance sustainable capacity and financing for health security to fight COVID-19 variants.

The President committed that the United States would be the world's arsenal for vaccines – both because it's the right thing to do and in our collective interest. And America is delivering on that commitment. The United States stands alone in procuring 1 billion vaccines for the sole purpose of donating them. And overall, the Administration has committed to donating 1.2 billion doses to other countries – for free, with zero strings attached, which represents the largest commitment of any single country or group of countries in the world. As of today, the U.S. government has delivered over 475 million free doses to 112 countries around the world – four times the number of free doses shared with the world than any other country.

In addition, the U.S. government has delivered life-saving resources like oxygen, treatments, PPE, and other essential supplies worth more than $1 billion to countries experiencing outbreaks. U.S. government public health experts from the CDC, U.S. Agency for International Development (USAID), the U.S. Department of State (State), HHS and the President's Emergency Plan for AIDS Relief (PEPFAR) and other entities are working side-by-side with on-the-ground providers, providing technical assistance in vaccine program implementation, care provision, and outbreak investigation. We have increased the world's capacity to manufacture vaccines and have fostered an enabling environment for innovation, including by spurring African manufacturing.

Over the last year, the Biden Administration pioneered the model to donate and deliver surplus vaccines to the rest of the world. America was the first country to announce a purchase of doses solely for donation to other countries; the first country to give up our place in line for vaccines – allowing the African Union to immediately start receiving up to 110 million doses of Moderna at a reduced rate negotiated by the United States; and the first country to negotiate a deal to send vaccines directly to humanitarian settings and conflict zones to vaccinate displaced persons. The path forward in the pandemic will require doubling down on our commitment to help vaccinate the globe and to save lives by making tests, treatments, and PPE widely available.

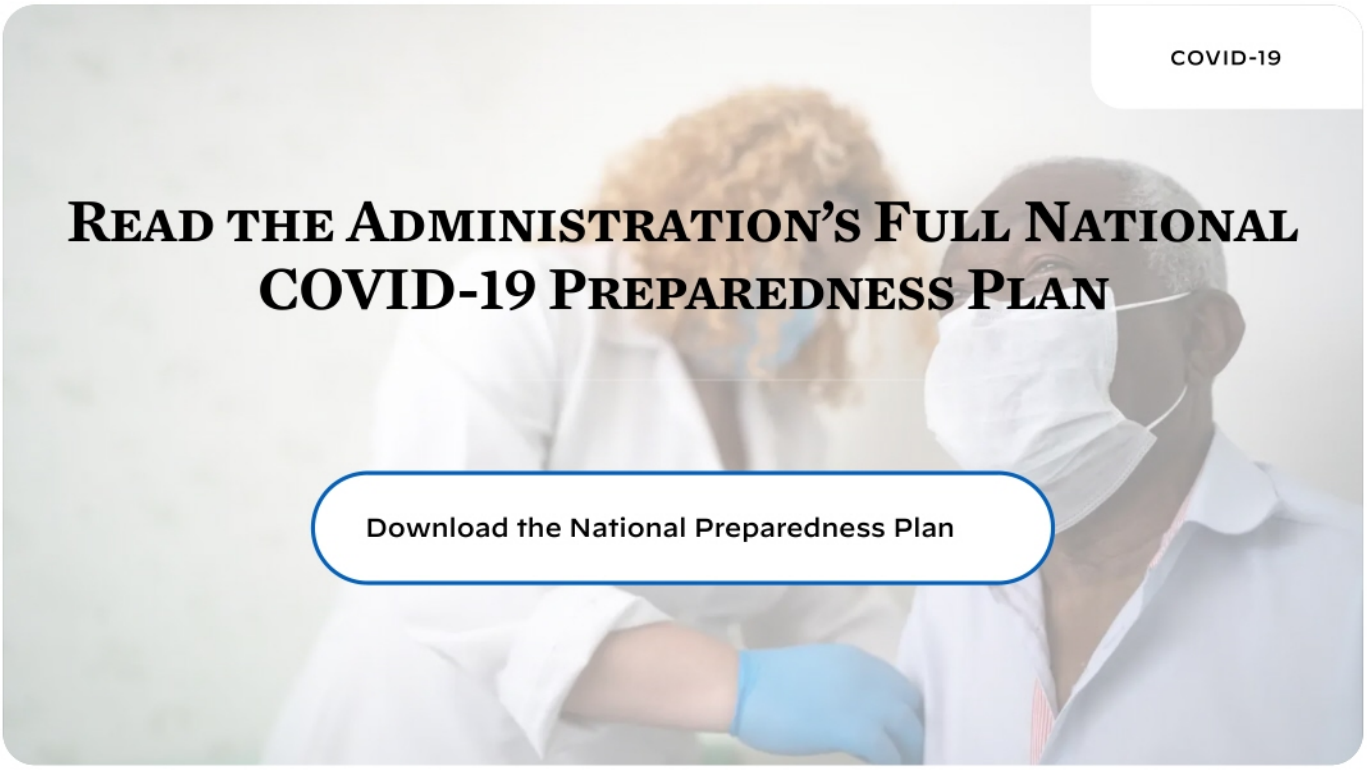
The Administration will work with Congress to secure the necessary funding to:

Leverage the vaccine donation model America pioneered to deliver the 1.2 billion doses we committed to donate to the rest of the world.

Increase efforts to get shots in arms around the world.

Save lives by solving the oxygen crisis and making emergency supplies widely available.

Continue global leadership on the COVID-19 response and build better health security for the future.



National Science Foundation (NSF) COVID-19 Efforts

CORONAVIRUS FACTSHEETS

- Utilizing NSF-funded Research in the Fight Against COVID-19
- Harnessing Computing Power to Fight COVID-19

SELECT BLOG POSTS

- RAPID responders: How NSF support is enabling the fight against COVID-19 in real time
- Small business, big impact: How NSF-funded startups are joining the fight against COVID-19
- Why are supercomputers so important for COVID-19 research?
- Once Considered Too High-Risk, Supercomputer Simulations of 'Wiggling and Jiggling' Atoms Could Help Stop Coronavirus
- Yesterday's research, today's innovation

AMERICAN RESCUE PLAN & COVID-19 RESPONSE UPDATES

"This update spotlights recent awards funded by the American Rescue Plan and research programs stood up by NSF to support the scientific research community. It is a snapshot of the essential research and support NSF is able to invest in thanks to the support from Congress and the Administration." Direct Link

NSF PANDEMIC COMPETITIONS

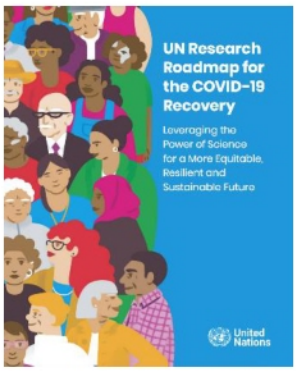
- Impact of public health guidance, in partnership with Social Science Research Council (May 2022)
- Incorporating Human Behavior in Epidemiological Models (IHBEM) (March 2022)
- Predictive Intelligence for Pandemic Prevention Phase I & FAQ (October 2021)

ARTICLES

- Research news about NSF-supported work related to COVID-19 (links to Google search)
- "From Camden, South Carolina, to Chelsea, Massachusetts, behavioral science helps community leaders save lives" – NSF & National Academies SEAN Collaboration (August 2021)

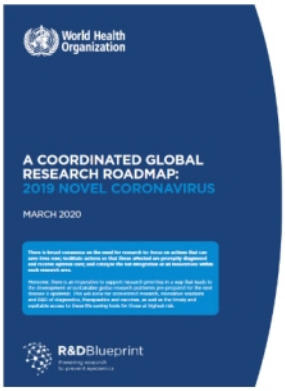
Select Global COVID-19 Research Agenda Materials

UN RESEARCH ROADMAP FOR THE COVID-19 RECOVERY (2020)



"This UN Research Roadmap for the COVID-19 Recovery provides a framework for leveraging the power of science in support of a better socio-economic recovery and a more equitable, resilient and sustainable future. Designed to complement the UN framework for the immediate socio-economic response to COVID-19, this Roadmap identifies 25 research priorities and key scientific strategies to support a recovery that benefits everyone, as well as actions that researchers, research funding agencies, governments, civil society organizations and UN entities can take to act upon it". Direct Link

A COORDINATED GLOBAL RESEARCH ROADMAP: 2019 NOVEL CORONAVIRUS (2020)



"On 11-12 February 2020, WHO, in collaboration with the Global Research Collaboration for Infectious Disease Preparedness and Response (GLOPID-R) – an international network of funders to facilitate coordination and information-sharing, organized a Global Forum on research and innovation for COVID-19 ('Global Research Forum'). This is a strategy which aims to coordinate and accelerate global research work to target diseases that threaten humanity, develop diagnostics, medicines and vaccines fast, and promptly respond to outbreaks thereby preventing epidemics". Direct Link

POLICY PAPER: RESEARCH AND DEVELOPMENT PRIORITIES FOR COVID-19 IN AFRICA (2021)

"The African Academy of Sciences (AAS), together with various partners including the African Union Development Agency (AUDA-NEPAD), conducted a series of priority setting engagements for R&D for COVID-19 with over 1400 African scientists contributing to a consolidated list of priorities. This qualitative and quantitative exercise started with a webinar attended by over 275 scientists on 26 March 2020. They built on the original WHO/GLOPID-R research roadmap with emphasis on the needs of the African continent." Direct Link



Select Global COVID-19 Research Agenda Materials (cont.)

HOW GLOBAL RESEARCH CAN END THIS PANDEMIC AND TACKLE FUTURE ONES (2022)



"In the course of the pandemic, the World Health Organization (WHO) has hosted three critical forums of world experts on research and innovation that have helped shape the global research agenda for COVID-19 – including a coordinated R&D Roadmap at the very start of this emergency. The most recent of these forums (24-25 February 2022) reviewed core thematic areas of research, highlighting knowledge gaps and research priorities in the next research phase." Direct Link

LIVING MAPPING REVIEW FOR COVID-19 FUNDED RESEARCH PROJECTS (2022)

"UK Collaborative on Development Research (UKCDR) and Global Research Collaboration for Infectious Disease Preparedness (GloPID-R) produce a quarterly Living Mapping Review of COVID-19 funded research projects, which analyses globally funded COVID-19 related research." Direct Link



- Snapshot of funded research activity focused on the indirect health impacts of COVID-19.
- Snapshot of funded research activity focusing on various aspects of Long COVID.
- Snapshot of funded research activities with capacity strengthening as an objective.

POLICY A research and policy agenda for the post-pandemic world

Authors: Chris Yiu,[A] Benedict Macon-Cooney[B] and Henry Fingerhut[C]

ABSTRACT

The COVID-19 pandemic response has engaged the academic, public, private and health sectors in the real-time development of technologies and practices to enable predictive, preventive, personalised and participatory (P4) health. Myriad cases of collaborative innovation across these sectors have emerged throughout the pandemic response (despite certain observed technical, social and institutional barriers) that serve as examples to address post-pandemic health system challenges. In this paper, we propose a joint research and policy agenda to generate the knowledge and practices to identify and extend these acute gains toward chronic health system challenges in the post-pandemic era. We identify three key themes for post-pandemic research and policy: the dialectic between novel and traditional techniques, the tension between centralised and local decision-making, and cooperation across academic disciplines, sectors and borders. Going forward, attention to these three themes by researchers and policymakers will help align our health, policy, academic and technological systems to provide better health for all.

KEYWORDS: health systems, health policy, COVID-19, healthcare delivery, innovation policy

DOI: 10.7861/fhj.2021-0082

Introduction

The technological revolution of the 21st century is re-orientating the world. New paradigms are being created, with new risks and new opportunities, with consequences that will be far greater in depth than the industrial revolution of the 20th century. The COVID-19 pandemic response has demonstrated the opportunities but also the technical, social, and institutional challenges of developing and applying predictive, preventive, personalised and participatory (P4) health technologies, harnessing this revolution to work for all on a rapid timescale that corresponds to that of the challenges we face.[1,2] Some of the shape of the future economy has been revealed by the current pandemic: internet era companies continued to thrive as much of the world around them faltered. And in health, the potential of breakthroughs in biotech have been laid out before us in the most profound way. Many lives will ultimately be saved by the speed at which vaccines were developed.

But as nations confront the task ahead, there is a clear need to go faster in supporting the application of technology to address our most pressing health challenges.[3] The need for policymakers to invest in networked technological infrastructure for healthcare provision, take a platform approach to support decentralised health innovators and build trust in emerging health technologies to support their adoption is more urgent than ever.

A little more than a year since the onset of the pandemic, advances have been made in all three domains that would not have been politically or culturally possible in 2019. But the unequal access to services and vaccines at the local, national and global scales, and the sheer scale of illness and mortality demonstrate just how far we have yet to go.

Three related themes to support health technologies have also emerged for the management of health research priorities and the application of research to policy more broadly as we emerge from the pandemic (Table 1). Where Blair and Yiu identify the challenge of trust in emerging health technologies, the pandemic has raised more broadly the *dialectic between novel and traditional techniques*.[3] The pandemic has demonstrated the tension between *centralised and local decision making*, to which, the authors' platform approach to decentralised innovation responds. In addition to the challenge of coordinating between levels, the pandemic has identified the need for *cooperation across academic disciplines, sectors and borders*, to which, the authors' call for networked technological infrastructure responds.

Here, we present successes and ongoing challenges from across three domains in which these themes have emerged during the pandemic: evidence generation and use in decision making, health system operations, and public health. This agenda is critical and, as our recent history has shown, will require a broad coalition. It requires us to engage researchers from across academic disciplines and policymakers from across public sector agencies and roles, as well as those working at the forefront of technology today. COVID-19 should be a collective wake-up call that we need deeper and more concerted action to improve the resilience of our health systems to future shocks. We must ensure that our health,

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Table 1. Opportunities and future challenges for generating and applying health research evidence to policy and practice

Novel vs existing techniques	> Use of non-traditional data sources (search queries, Twitter sentiment, smartphone mobility or wearables). > Predictive, preventive, personalised and participatory (P4) precision medicine. > Digital contact tracing.
Centralised vs local decision making	> Coordination challenges among research groups. > Incentives, mechanisms and structures for largescale open data sharing. > Knowledge management and preprints.
Cooperation across disciplines, sectors, and borders	> Ad hoc interdisciplinary research collaborations (eg COVID19 Dispersed Volunteer Research Network). > Rapid funding mechanisms. > Data journalism, public communication and transparency. > Government science advisory committees. > Realtime evaluation and collaboration among hard scientists, ethicists and economists to inform human challenge trial debate; UK Human Challenge Consortium.

policy, academic and technological systems are aligned to provide better health for all.

Novel vs established data, methods and techniques

The COVID-19 pandemic required innovation from within the academic, public, private and health sector communities. In record speed, researchers developed new theory, methods and ways of working, and these three aspects interacted to produce new knowledge about biological and social systems and processes affecting disease dynamics. In near real time, researchers sequenced the coronavirus genome, developed tests and validated vaccines via novel mechanisms including the novel mRNA platform and the vaccine platform mechanism more broadly.[4] In terms of methods, time dynamics of testing required the use of novel data sources and valid methods for including them in both policymaking and academic theory development.[5,6] Novel datasets and new testing have been essential to identifying emergent trends quickly, informing both theory generation and policy, and enabling governments to reduce a 5-week decision cycle imposed by disease and testing dynamics. These advances were made while most researchers adapted to remote work in response to the pandemic, opening new opportunities for interaction and collaboration across institutions and borders.[7]

Novel techniques nevertheless present challenges from both ethical and validity standpoints. Leslie offers five steps for responsible data use and privacy-preserving innovation to respond to the COVID-19 pandemic; these steps fit more broadly into a research agenda going forward, providing a third way between the false choice of compromising privacy on the one hand and pandemic response on the other.[8] From a validity standpoint, novel mechanisms such as the use of non-traditional data sources for near real-time epidemiological modelling also have their limitations, one notable example being the use of Google search queries for flu prediction.[9] It is essential to maintain evidence standards for both theory generation and policymaking purposes, not by dismissing these techniques out of hand but by continuing to refine research methods such that they can be used responsibly within a suite of indicators to provide valid, near real-time insights. Anticipatory innovation models provide a structured process to consider the technical, biological, temporal, spatial and political uncertainties and possible futures that may arise and to systematise the technical, political and knowledge management mechanisms that have enabled digital health innovation at speed that have emerged during the pandemic. These approaches, bringing together technologists, interdisciplinary academics, policymakers and citizens, are increasingly important to engage digital transformation toward democratic ends.[10]

Coordination between levels: centralised vs local decision making

Across fields, hierarchical top-down/bottom-up models have given way to networked organisations. Indeed, the pandemic has demonstrated the longstanding tension between centralised and local decision making; administrations juggled the coordination and standardisation benefits of centralised decision making with the need for agility, adaptation to local conditions and experimentation that decentralised decision making brings, to varying degrees of success.[11,12] The UK government has laid out guiding principles for local authorities in the interest of a coordinated set of decision-making criteria across levels of government.[13]

In the academic sphere, research coordination quickly became an issue; researchers moved quickly to adapt their research agendas to address the pandemic but, in doing so, left important gaps, such as the study of COVID-19 in children.[14] Further, the commendable rush to contribute to pressing COVID-19 research nevertheless threatened to slow important, existing research in other areas of public health.[15] In the public sector, countries moved quickly to establish the data infrastructure necessary to aggregate disparate epidemiological, health systems and economic data; the different approaches they have taken to data collection, user journeys that generate data, organisations involved and aggregation, and analysis will indicate best practices going forward for the aggregation and use of disparate, real-time data in health policy.[16,17] The design and use of intersectoral data systems contributes to the 'situational awareness' necessary for the precision policy decisions that represent a third way between overly permissive policies that allow the virus to propagate and burden health systems and overly restrictive policies that burden the economy and constrain civil liberties.[18]

Funding mechanisms like the EU Coronavirus Pledging Conference created necessary support and coordinating signals that helped align the disparate international research groups contributing to COVID-19 research to ensure research was allocated to necessary areas.[19] Data portals similarly enabled researchers to centralise data to enable open science and rapid advancement of the knowledge generation and peer review processes.[20] Whole-genome sequences were available to international researchers on GISAID as early as January 2020 and

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the open access it provides to over 450,000 genome sequences was essential to vaccine development; similarly, the COVID-19 Genomics UK Consortium centralises over 370,000 sequences identified through UK testing programmes and coordinates genomic analysis contributing to regular reports to SAGE on virus mutation.[21,22]

Coordination across organisations, disciplines, sectors and borders

Academics have greatly expanded the use of new mechanisms of collaboration across organisations and disciplines, as well as communicating research to policymakers and the public. Researchers developed ad hoc research collaborations across disciplines, institutions and borders (such as the COVID-19 Distributed Volunteer Research Network) to quickly develop cross-cutting research that addressed the biological, epidemiological, legal and ethical aspects of disease dynamics and interventions.[7]

Mechanisms, such as preprints, fast-track publishing and scientific advisory committees (eg the UK government's SAGE), also acted as portals for policymakers and journalists to quickly acquire and act on knowledge from the academic sphere. But while preprints enabled academics to collaborate and policymakers and journalists to track research findings in real time, these external communities were not necessarily equipped to understand the theoretical context and communication for an academic audience, leading to calls for strategies to govern the use of preprints, particularly as scientific debate has played out in the public in real time.[23–25]

An interdisciplinary response is essential for this pandemic, in which macro policy choices were quickly framed as a trade-off between economic and health outcomes, ethical considerations of privacy and equity have come to the fore, and individual behaviour is paramount to disease dynamics. The UK government's Scientific Pandemic Insights Group on Behaviours (SPI-B) designed principles for co-production of guidance between policymakers and governed populations to equitably establish local behavioural standards and policies, increasing acceptability and effectiveness of resulting policies.[26] The question of vaccine challenge trials brought together researchers, health system administrators, private companies and governments to consider both the scientific and ethical merits, resulting in the approval of the Human Challenge Programme in the UK.[27] We would argue that a joint letter from leading researchers (including virologists, epidemiologists, economists, philosophers and ethicists) actually represents a promising achievement in its own right, as a rapid, interdisciplinary policy proposal that unites expert opinion on the scientific and ethical concerns.[28]

However, these policy trade-offs are particularly challenging because, despite admonitions to 'follow the science', under evidence-based policymaking, policymakers trade off policy priorities (an inherently value-driven and political process that depends on scientist navigation of the policy process) informed by available evidence.[29,30] However, the interdisciplinary nature of these decisions means that they are also implicitly trading off silos of academic knowledge and disparate groups of scientific advisors with different expertise and norms.

Similarly, as public compliance with preventive behavioural measures is essential to mitigating this respiratory pandemic, public understanding of and confidence in scientific findings is a critical component of pandemic response. Innovative public communication and transparency tools (such as the GOV.UK dashboard) and novel approaches to data journalism were developed in short order to communicate the breadth of relevant epidemiological and operational data and visualisations interactively, in real time, and at scales that enable individuals to both hold government to account and make informed behavioural decisions.[31,32] As the public engages with these resources, effects such as 7-day moving averages, test sensitivity/specificity, timeseries lags and demographic or geographic multimodality are routinely covered, data literacy, numeracy and susceptibility to cognitive biases are likely to change. The pandemic will not itself resolve a trend of low numeracy in the general public, but advances in data journalism over the past year have gone a long way toward integrating these concepts into common policy discourse.[33] Scientists themselves have also taken to social media to establish collaborations with a wider sphere of academics and to engage directly with the public on the scientific process and their own field, correcting popular misperceptions (or deliberate misrepresentations) of the scientific record and narrowing the gap between the academic and public spheres.

Academic institutions have increasingly partnered with private sector and healthcare organisations to improve translation of their research and inform the design of promising innovations. Collaborations like the new partnership between the P4 Precision Medicine Accelerator (an ecosystem for precision medicine startups) with Nuffield Health bring together private start-ups, healthcare organisations and academics to co-design and test promising innovations, improving their relevance to practice and reducing time to development.[34] These initiatives, along with the advancement of the implementation science field, help systematise the design of practice-relevant technologies and their adoption across settings to close the implementation gap and improve health service quality.[35]

At the international level, coordination across countries and regions is a key example of the limits of centralised decision-making, as multilateral institutions rely on coordination among member states in the absence of hard power. While multilateral institutions, notably the World Health Organization, had a coordinated pandemic response plan in place, they had few mechanisms or hard power to compel nations to act together.[36] Most recently, the EU vaccine distribution strategy further demonstrated the challenges of achieving international consensus to vet, procure and distribute specific vaccines.[37] While COVID-19 drew exceptional attention because it impacted the world's population, the restrictions on mobility have also impeded efforts to address continuing global health and sustainable development challenges that disproportionately or exclusively impact low- and middle-income countries, doubly impacting these populations.[38]

Recommendations: a joint research and policy agenda

As Blair and Yiu argue, in setting the agenda for future health policy: 'the specific technologies matter less than the shift in mindsets and approaches that the modern operating environment makes possible.'[3] We recommend a cross-cutting shift in mindsets and approaches that will strengthen our capacity for health research and its relevance for public policy. The pandemic has laid bare the challenges and opportunities in applying research

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to policy, and a concerted effort across academia and the public sector is necessary to create the structures, mechanisms and norms for effective evidence-based policymaking.

To this end, we propose the following recommendations to shape global health research policy over the immediate, medium and long term, including target outcomes and illustrative initiatives to achieve them.

Mechanisms to support interdisciplinary, problem-focused research

Interdisciplinary research has been gradually increasing and is particularly prominent in the health disciplines, however interdisciplinary studies take longer to gain traction.[39] But true interdisciplinary research, effectively melding traditional disciplines to create knowledge that would not have been possible otherwise because it spans the boundary assumptions of separate disciplines, takes hard intellectual work, investment in a shared mission and engagement norms, and is under-incentivised by traditional academic norms, institutional structures and likelihood of funding.[40,41] Government funders, donors, academic institutions and learned societies should create incentives for the conduct of interdisciplinary research that support both problem-oriented findings and the development of systematic research methods to combine cross-disciplinary approaches.

- Formal training in interdisciplinary methods for PhD students.
- Research prizes to honour problem-focused interdisciplinary achievements.
- Experimental funding mechanisms to support ambitious interdisciplinary research and incentivise collaboration across disciplines, building on the USA's DARPA and UK's ARIA models.

Mechanisms to improve co-creation of applied research / policy agendas

Most scientists are untrained in the policy process and focus on packaging and communicating evidence based on scientific standards, resulting in a form of information that may not be relevant for policymakers.[30] Further, scientists are disincentivised from contributing applied, policy-relevant analysis within the policy sphere due to competitive funding, publishing and tenure mechanisms that value teaching, research and academic service contributions. In one study, academics were particularly attentive to incentives to provide monetary support, professional recognition, academic promotion and capacity enhancement, particularly relevant to expand access to science advice beyond the majority white, male and, in the UK, London-based 'usual suspects'.[42,43]

- Governments should consider creating an 'academic reserve,' a standing funding mechanism for academics to contribute applied analysis to support public service design and policy.
- Universities should develop public policy units (eg University College London's Science, Technology, Engineering and Public Policy department and Massachusetts Institute of Technology's Joint Program on the Science and Policy of Global Change) to provide a point of entry to facilitate policy advice based on scientists' research and to educate scientists on the policy process.
- Governments should extend the use of expert groups in government (eg SAGE, SPI-B and HDR UK) beyond crisis periods and expand access to these groups to include diverse academics across disciplines, institutions, personal backgrounds and geographic settings. They should also add experts in public policy, evidence-based policymaking and ethics to scientific advisory groups to facilitate the application of science within the policy process.

A strategy for science communications

Despite advances by scientists, journalists and government agencies in data communication methods throughout the pandemic, statistical and data literacy is increasingly important to engage the public in response to pressing health policy challenges. Individuals and organisations at the local, national and international levels have developed myriad resources for educating the general public in the basic statistical literacy and numeracy skills necessary to interpret data that impacts their health.[44–46] Going forward, it is more important than ever to coordinate and adapt these resources to the local cultural and educational contexts (through both formal curricula and informal general communication campaigns) to improve awareness and help students, journalists and the general public develop statistical comprehension skills in a meaningful and engaging way.

- Individual scientists should expand their efforts to communicate their own research and the current state of their field on social media in order to engage other academics across disciplines and the general public.
- Scientists, journalists and civil servants should continue to experiment to devise novel communication techniques to improve scientific, statistical and data literacy among policymakers and the general public.
- Public sector, academic and media institutions should collaborate to design a numeracy and statistical literacy education campaign for children and adults. This campaign should focus on novel, light-touch and age-appropriate approaches to engage the general public in everyday statistical thinking, complementing dedicated science, technology, engineering and mathematics (STEM) curricula in schools and universities.

Health technology development, implementation and evaluation

While the pandemic has accelerated progress toward the health technology agenda proposed by Blair and Yiu, more research and public investment will be necessary to evaluate these advances, advise on their use in non-crisis times and adapt health technologies to ensure they work for all.

- Researchers should partner with health systems to conduct a ground-up, post-pandemic technology audit, in order to identify critical health technology infrastructure and innovations that should be integrated into national health systems going forward. Technologies should be used equitably and responsibly to ensure they improve health outcomes for all.
- Academic institutions should expand translational research initiatives (including collaborations with private companies, accelerators and healthcare systems) to develop promising precision and predictive health technologies and complement these initiatives with implementation research programmes to enable uptake at scale.

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These recommendations are not intended to replace existing research and policy approaches, it is essential to maintain basic and applied research that is rightly independent of government's policy priorities for the purposes of knowledge creation, horizon setting and holding policymakers to account. Rather, these recommendations are intended to align those research initiatives meant to align with policy priorities to be conducted to greatest effect, and to provide indications as to where the research enterprise can be expanded.

Conclusion

As we emerge from this global public health challenge, it is more important than ever for academics and policymakers to work together to evaluate and improve our health systems and policy. We should draw lessons and inspiration from innovative successes in knowledge generation, policymaking, technology development and ways of working, while acknowledging the magnitude of loss and unequal outcomes across communities and working to resolve limitations in preparedness, system design and policy that have contributed to those adverse outcomes.

Now more than ever, the health research, policy and operations communities are in the spotlight for the critical work they have done to stem this global pandemic. Working together across disciplines, sectors and borders, we will be well-positioned both to protect against future shocks and to improve long-term health outcomes for all. ■

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Meeting of the Standing Committee on Emerging Infectious Diseases and 21st Century Health Threats

Agenda – June 17, 2022, Noon – 3:00 P.M. ET

CLICK HERE TO JOIN

Meeting ID (b)(6)

Phone Only (b)(6)

International Numbers

FRIDAY, JUNE 17, 2022

Purpose

- Gather a broad array of information and perspectives regarding the development of a medium- (up to five years) and long-term (more than five years) COVID-19 research agenda.
- Understand U.S. Government perspectives on the opportunities, needs, and utility for a coordinated long-term research agenda for COVID-19 to coordinate and align efforts effectively to advance evidence-based practice.
- Scope potential priority topic areas to consider for a comprehensive research agenda.

SESSION I — Welcoming Remarks and Sponsor's Reflections

12:00 p.m. — **Welcoming Remarks and Overview of the Agenda**

Harvey Fineberg, *Standing Committee Chair*
President
Gordon and Betty Moore Foundation

12:15 p.m. — **Welcome and Opening Remarks from the Sponsor**

David (Chris) Hassell
Deputy Assistant Secretary – Senior Science Advisor
Office of the Assistant Secretary for Preparedness and Response
U.S. Department of Health and Human Services

SESSION II — Reflections on COVID-19 Long-Term Research Agenda and Research Priorities

12:30 p.m. — **Perspectives from Federal Partners**

Objectives:

- Understand U.S. Government perspectives on the opportunities, needs, and utility for a coordinated long-term research agenda for COVID-19;
- Explore how efforts can be coordinated and aligned across federal, state, and local counterparts to advance evidence-based practice; and

- Scope potential priority topic areas to consider for a comprehensive research agenda.

Anthony Fauci *(pre-recorded presentation)*
Director
National Institute of Allergy and Infectious Diseases

Rayvon Fouché
Division Director, Social and Economic Sciences
National Science Foundation

Jay C. Butler
Deputy Director for Infectious Diseases
Centers for Disease Control and Prevention

1:30 p.m. **Committee Perspectives on Research Priorities for a Medium-to-Long-Term COVID-19 Research Agenda**

Objectives:

- Identify initial areas of research priorities or scope of the research agenda
- Solicit input on the key components of such a research agenda.

Harvey Fineberg, *Standing Committee Chair*
President
Gordon and Betty Moore Foundation

2:30 p.m. **Perspectives from Other National Academies Activities**

Objectives:

- Gather information on projects at the National Academies related to a COVID-19 research agenda; and
- Scope potential priority topic areas to consider for a comprehensive research agenda.

Robert M. Groves
Co-Chair, Societal Experts Action Network

Cinnamon Dixon
Co-Chair, The Action Collaborative on Disaster Research
Forum on Medical and Public Health Preparedness for Disasters and Emergencies

Kevin Anderson
Forum Member, Forum on Microbial Threats

SESSION III MEETING WRAP UP

2:45 p.m. **Committee Debrief, Next Steps, and Future Meeting Planning**

Harvey Fineberg, *Standing Committee Chair*
President
Gordon and Betty Moore Foundation

3:00 p.m. **MEETING ADJOURNS**

Standing Committee on Emerging Infectious Diseases and 21st Century Health Threats

Perspectives on a Long-Term Research Agenda for COVID-19

June 2022

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OVERVIEW

The long-term impacts of COVID-19 on individual and population health are yet to be fully understood. The Standing Committee on Emerging Infectious Diseases and 21st Century Health Threats was asked to consider the utility of and the requirements for a comprehensive, evidence-based research agenda on the long-term health impacts and consequences of COVID-19.

The dual aim is to help the U.S. respond to COVID-19 over time and to help our nation become more resilient to future public health emergencies.

In preparation for the Standing Committee on Emerging Infectious Diseases and 21st Century Health Threats virtual meeting on June 17, 2022, committee members were asked to reflect on a topic related to their area of expertise and to describe:

- The topic area as it relates to a long-term COVID-19 research agenda
- Current state of what is known about the topic
- Key gaps and priority research questions

Topic areas suggested to committee members included: Public health response management; Patient care, long-COVID impacts, at-risk populations, and strategies for clinical management; Health equity, community engagement, crisis communication, and mis/disinformation management; and Medical countermeasures (including therapeutics, vaccines, and diagnostics) and underlying microbiological characteristics.

This document provides a summary of the insights and perspectives shared by committee members.

***Disclaimer**: This summary was prepared by National Academies staff as a record of feedback provided in preparation for the June 17, 2022, Standing Committee on Emerging Infectious Diseases and 21st Century Health Threats virtual committee meeting. This document was prepared for information purposes only. It has not been through the institution's external peer review and should not be cited or quoted, as the views expressed do not necessarily reflect the views of the National Academies of Sciences, Engineering, and Medicine or the Standing Committee on Emerging Infectious Diseases and 21st Century Health Threats.*

SUGGESTED TOPIC AREAS

***NOTE**: Feedback on research questions for the topic area "Medical countermeasures (including therapeutics, vaccines, and diagnostics) and underlying microbiological characteristics" is pending.

Addressing New Variants

Overview:

Lessons gleaned from the past can inform how we predict, anticipate, and prepare for potential variants of concern that may emerge in the future. A set of questions and priorities to prepare for new variants or other related, rapidly-evolving events will greater enable a coordinated pandemic response.

Research Questions:

- How to better predict need for and effectiveness of variant adapted vaccines when new variants or a SARS CoV 3 arises?
- How to get a better handle on whether new variants are likely to pose problems, more quickly than we have, and to decide if there are additional questions that need to be asked and answered each time things change?
- Developing vaccines that induce broader coverage and more durable immunity to infection. Boosting every 4 months is not a viable long-term approach mRNA was great for rapid development, but now we probably need a different platform that generates B and T cell immunity to multiple viral proteins (not just the spike) and stimulates a more durable response - a live virus vaccine? Or maybe the recombinant protein vaccines. There are lots of candidates out there so some organized analysis of how they compare on these parameters would be useful.

Contributors: Diane Griffin, Nicole Lurie

Face Mask and Respirator Use

Overview:

There are a large number of studies with methodological weaknesses that prevent firm conclusions on the effectiveness of face masks and respirators. Evidence suggests face mask use and respirator use are beneficial, however additional evidence is needed.

Key Gaps and Research Questions:

- Population level impact under various scenarios of pathogen transmissibility, mask/respirator quality & fit, and level of compliance, is not known.
- What is the population-level impact of face mask (i.e., surgical) and respirator use by public on transmission of viral respiratory disease (incl influenza and CoV-19)?
- Should this be a standard PH recommendation during periods of increased transmission?
- Can the benefit be quantified?

Contributors: Jeff Duchin

Coordination and Stakeholder Engagement

Overview:

A systematic body of knowledge on coordination and stakeholder engagement is potentially lacking.

Key Gaps and Research Questions:

- How do we optimally integrate the clinical healthcare delivery system and public health system at state and local levels during bio-emergency response (including patient evaluation, management, and clinical data collection & transmission, countermeasure administration, support for community-based response needs [field teams for assessment in vulnerable populations, mass testing/vax sites]?
- Healthcare coalitions provide a framework for this activity: How well did healthcare coalitions (that provide a framework for these activities) perform during the CoV-19 pandemic? What needs to be improved to meet future scenarios?

- How do we engage university and private sector assets in the response (e.g., authorization of laboratory-developed tests).
- How can we improve public compliance with non-pharmaceutical interventions?

Contributors: Jeffrey Duchin, Nicole Lurie

Contact Tracing

Overview:

Greater understanding is needed on the role of contact tracing in managing SARS-CoV-2 exposures and COVID positivity. More specifically, how and when contact tracing should be done in a fast moving respiratory infectious disease.

Current State:

Contact tracing as historically practiced was inadequate during the SARS-CoV-2 pandemic because of its asymptomatic spread and rapidly evolving variants. The antiquated nature of our disease reporting systems (speed, accuracy & paper based fax component) as well as the lack of clear reporting guidelines contributed to the problem. New technologies such as proximity apps have promise, but remain in their early stage of development and still have a lag time that to date is often too long for effective doses-axe control. The delay in initial testing followed by the transition to self-testing has complicated this problem creating additional delays in contact tracing even when the self-test is eventually reported. This resulted in abandonment of contact tracing for periods throughout the pandemic during surges and no clear guidelines on when to resume contact tracing when the disease level diminishes to an actionable level.

Key Gaps and Research Questions:

- When should traditional contact tracing be used?
- When should individual contact tracing be abandoned or put on hold and what are the criteria for restarting it?
- How effective are proximity technology apps in disease control?
- Are their new contact tracing and notification models that are more effective for disease control?
- Does effective disease control using contact tracing taper or eliminate the need for community activity (school, business, travel industry) closures?
- What is the fiscal return of investment of a well-functioning disease control system using contacting tracing?
- Do we need to do contact tracing at all anymore for infectious outbreaks like this one? Can these resources then be freed up to do other more productive disease control work? This would be useful for any respiratory pandemic with the characteristics of a virus that passes asymptomatically and continues to evolve rapidly. It is a critical question if the morbidity or mortality increases.
- Does full primary vaccination and boosting alter the need for contact tracing for breakthrough infections? In other words, does full vaccination inhibit viral load sufficiently to negate the need for reporting and tracing?
- When can we normalize COVID management like influenza? If so, what ate the surveillance triggers to resume more aggressive individual reporting and contact tracing. New variants of public health concern, new surges at a certain rate, increased morbidity, increased mortality, etc.

Contributors: Georges Benjamin

Epidemic Modelling

Overview:

Multiple modeling groups produce information that may or may not be harmonized with current public health response needs.

Key Gaps and Research Questions:

- How to optimally integrate academic modeling expertise into public health response in real time?
- How to identify questions on existing modeling capacity?
- What are realistic time frames for actionable results?
- What is optimal format for communicating results & limitations?
- For example, under prevalent viral transmission dynamics and population immunity, what impact would NPI have under varying assumptions about effectiveness and level of compliance?
- Can one model the impacts of restrictions on public health authorities in state/local jurisdictions might have on impacts of future epidemics or pandemics?

Contributors: Jeffrey Duchin, Nicole Lurie

Health Equity

Overview:

In the United States, COVID-19 has had a disproportionate impact on the health of members or racial, ethnic and underserved communities. Communities of color also suffered disproportionate morbidity and mortality during the CoV-19 pandemic due to long standing health disparities from recognized root causes. Careful attention is needed on health equity, community engagement, crisis communication, etc.

One of the big challenges during this pandemic was related to data equity —- what information was collected, who had access, timeliness, and usability. A focus on equity-centered data systems are needed, given the disparate impact of the pandemic by race, ethnicity, geography, disability, income, to name just some demographics, the lack of granular, real-time data, cost lives.

Key Gaps and Research Questions:

- How to improve public health's role in communication, outreach and increased participation, particularly in underserved communities? - this is a difficult task that desperately requires further research, in light of historically-based mistrust of many communities.
- What policies and community-based capacity and relations with the public health system are necessary to allow optimal bio-emergency response that minimizes health inequities?
- What specific activities, capacity, relationships, and/or structural changes are needed to effect better health outcomes in communities of color?
- Conducting research that sheds light on vulnerabilities (including social determinants of health) and incorporates One Health thinking in solutions and shaping policy.
- Integrating social aspects in understanding risk of emergence in human populations
- Improve employment of human and social sciences and psychology.
- Mapping and characterizing social and regional health inequalities: individual factors and structural aspects of exposure to infection and access to treatment.

Contributors: Richard Besser**,** Jeffrey Duchin, Patricia King, Jonna Mazet

References:

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Legal Authorities

Overview:

The impact of unwinding and limitation of legal authorities and powers for public health should be urgently considered for public health response management. Public health authorities from the local to the national level have been severely restricted, either through legislative or judicial action. This puts us in a particularly vulnerable position for acting on ongoing and future public health threats: through both actual and perceived restrictions in powers to act to protect public health.

Current State and Key Gaps:

There are groups (such as the National Public Health Law association and our Georgetown Center for Health Science and Security) that have been tracking some of these restrictions, but there is not yet a comprehensive understanding of the implications that this could have for future response. Some legal actions are still pending (e.g. there is an Amicus Curiae brief going to the Federal Court on the CDC mask mandate and the incorrect interpretation of "sanitation"). There are some efforts to create model legislation but these have not been appropriately informed.

Contributors: Alexandra Phelan

One Health Research Needs for Pandemic Preparedness and Mitigation

Overview:

Host and transmission dynamics, impacted by environmental stressors and anthropogenic changes, have implications for future spillover events. Further understanding of the origins, natural hosts, and animal reservoirs of pathogens, coupled with improved surveillance systems and understanding of human behaviors, can inform infection mitigation measures.

Key Gaps and Research Questions:

Surveillance & Data Needs:

- Global viral surveillance at human-animal interfaces to identify and characterize viruses to help prepare for, prevent, and mitigate risks from *Disease X*
- Devise safe and innovative One Health epidemiological surveillance methods useful for implementation by national and regional networks – examples:
    - Continue to evaluate, enhance, and scale wastewater testing
    - Employ wildlife virus surveillance to improve vaccine targets and need inspired medical and technological innovations
    - Improvement of biosafety and biosecurity through automatization of sample collection, storage, testing, etc. (e.g., robots, drones, sensors)
- Improve capacity to monitor animal reservoirs of potentially zoonotic pathogens for shifts in viral diversity and changes in the viruses themselves

- Conceive methods to improve the collection and use of human behavior data, especially high-risk behaviors and compliance with public health safety measures, as well as the perception of risks and willingness to mitigate them through personal action
- Identify and understand geographic zones where emergence of disease is heightened due to regional and global changes, including climate variation
- Optimize syndromic surveillance in medical record systems or other easily implemented tools and integrate that data with real-time genomic data and other methods of passive digital surveillance
- Improve bioinformatics pipelines to handle large volumes of data and their interpretation during a crisis
- Devise systems to strengthen and integrate local, regional, national, and global surveillance systems
- Improve surveillance models to better collect/collate and integrate heterogeneous data

Basic Science to Improve Prevention Policies:

- Pathogen and host biology
    - Identification of hosts from which emerging pathogens can spillover
    - Characterization of potential pathogens from these hosts
    - Host natural history, genetic makeup, and population vulnerability and resilience
    - Host-pathogen dynamics, including immunology
    - Molecular mechanisms essential to the life cycle of the pathogen (including host/pathogen interactions) allowing identification of the best therapeutic targets and/or the development of vaccines
    - Ecology of infectious agents, their interactions with vectors/reservoirs/intermediate hosts, and their secondary spread (e.g., in water and air)
- Drivers of spillover:
    - Animal trade & non-traditional farming (e.g., guano)
    - Expanding human populations
    - Changing land use (agroecological transition, human intrusion in protected areas, intensive urbanization)
    - New animal breeding and agricultural practices
    - Globalization
- Ecosystem stressors that could drive changes in pathogens and hosts (e.g., effect of climate on all hosts and their resilience to infection and shedding in the face of a changing climate)
- Socioeconomic impact of zoonotic diseases (historical & projected)
- How spatial and temporal scales and changes may affect host-pathogen relationships (e.g., biodiversity loss and pathogen circulation)
- Phylodynamics and the use of genomic data for monitoring pathogens in time and space at the molecular level (monitoring of variants; requires shared systems, together with sequencing, bioinformatics, and ad hoc storage platforms)

Human Health, Behavior & Communications:

- Investigate the interconnected determinants of human, animal, and ecological health, including drivers of pathogen emergence and the disproportionate impact of emerging zoonoses on underrepresented communities
- Conduct transdisciplinary research on optimal health communications
- Create knowledge on public perceptions, attitudes, and behaviors with regard to acceptability of prevention practices, as well as vaccines and treatments and disaggregate demographically subgroups (by gender, generation, social class, race, community, etc.)
- Increase knowledge on how to influence human actions to reduce impacts on the emergence of zoonotic diseases

- Improve health communication and promotion: production and diffusion of scientific information, role of the media, particularly social networks, building trust, attitudes with regard to science, and the problem of conspiracy theories and fake news
- Assess the costs and benefits of contrasted agro-socio-ecosystems by simultaneously considering farming practices, social and economic well-being, various environmental impacts and emerging disease threats
- Assess the impact of health measures in the different areas of the daily life: exposure to infection, healthcare consumption, personal and family life, mental health, employment and financial resources, living and working conditions, mobility; and at the macroeconomic level: employment, poverty, human capital
- Improve system coordination using cross-sector communication models and by devising organizing principles & conducting trainings
- Increase understanding of the architecture and multi-scalar nature of governance to transform political engagement into positive participation
- Develop short- and long-term strategies for coordinated monitoring, preparation, and mobilization of the academic community, not for profits, and industry in organized public health
- Research emotional/psychological responses to pandemic through art, music, etc.

Mitigation of Exposure/Infection & Pro-active Vaccine Strategies

- Model the spread of potential *Disease X* agents in demographically diverse populations
- Identify the environmental, socio-anthropological, and epidemiological drivers for epidemic spread
- Adapt approaches to monitor and control emerging health threats using scientific data and modeling forecasts
- Assess the risk of emerging resistance to new anti-infective agents and adapt therapeutic strategies
- Search for anti-infectious compounds covering the spectrum of the main viral, bacterial, parasitic, and fungal families infecting vertebrates
- Consider neutralizing monoclonal antibodies from convalescent individuals for target pathogen families, thereby identifying the most cross-reactive, with high potential to protect against new agents liable to emerge in the target family
- Develop vaccine pipelines for emerging and re-emerging agents using a risk-based strategy
- Attempt to determine the target of the most potent neutralizing antibodies for each pathogen family through structural biology studies
- Explore AI approaches to target and track receptor binding for viral families that have spillover potential
- Investigate options to meet the growing food demand by reorienting/designing food systems to reduce the risks of pathogen transmission, while also providing equitable access to nutritious food
    - Develop strategies to reduce wildlife/livestock contact

Diagnostics

- Develop and implement diagnostic instruments and pipelines for all known emerging and re-emerging pathogens, with robust quality standards, compatible with the medical and veterinary diagnostics
- Set up a generic diagnostic capacity that can be rapidly adapted to an emerging event and deployed at the relevant sites for humans and host species
- Organize the collection and map availability of diagnostic reference products (strains, natural and synthetic positive controls, specific antibodies) and biological specimens from human and veterinary clinical research programs on emerging events
- Identify predictive biomarkers of the clinical course of Disease X

Education and Engagement

- Develop One Health curricular offerings for all stages of education from elementary to university and beyond
- Design and implement more in-depth One Health curricula for accredited health programs, including veterinarians, physicians, and other licensed healthcare providers and public health practitioners in training, as well as curricular offerings for K-12 and undergraduates
- Offer collaboration training for researchers and healthcare personnel to improve sharing of knowledge and data and to form best practices in health management
- Conduct participatory research and engage with communities (consider involving patient associations, consumer associations, community based organizations, and citizens) to understand needs and obstacles to public health goals and to help improve scientific literacy and acceptability
- Advance interactions between expert scientific organizations and political/governmental decision makers as part of the public policymaking process to improve the efficient employment of institutions during crisis

Contributors: Jonna Mazet

Post-COVID Conditions and Pediatric Impacts

Overview:

The underlying causes and mechanisms for Long COVID (Post-Acute Sequelae of COVID (PASC)) and Multi-inflammatory Syndrome in Children (MIS-C) have not yet been identified. These conditions have the potential to cause huge burdens on the healthcare system because of their chronic nature. Assuming that COVID-19 becomes endemic, we will continue to see patients presenting with long COVID and MIS-C. If the number of patients affected is in the present range of 10-20%, then this will cause loss of productivity and debilitating symptoms in millions of people.

Any useful investigation of or response to Long COVID (LC), or post-COVID conditions (PCC) must take into account the enormous scale, scope, complexity and urgency of the problems and consequences associated with this syndrome. As was the case during the COVID-19 pandemic, investigations based on individual, disconnected efforts will likely lead to statistically underpowered studies, a bevy of confusing biological endpoints, and a waste of money and time.

A national – or preferably, international - strategy to rapidly and efficiently determine and disseminate an understanding of the underlying biology and effective clinical treatment of Long COVID is essential to success. Scientific studies, clinical investigations and social support schemes pursued as disjointed, independent, business-as -usual efforts are highly likely to fail.

Efforts to prevent Long COVID, and alleviate the suffering of those already afflicted should be granted urgent priority in view of the current scale of the problem and the ongoing nature of COVID-19 infection. Delays in determining the causes, prevention and treatment of Long COVID, failure to rapidly disseminate such findings, or impediments to LC patients accessing effective care will prolong human suffering and incur substantial financial costs to patients, health care systems and the nation.

Thus, an effective approach to Long COVID cannot be business as usual. Instead, a well-coordinated, multi-pronged national effort is needed that establishes clear goals, aligns academic and private sector research efforts, and prioritizes strategic endpoints and approaches. The closest model of such an effort in recent times is probably the Operation Warp Speed (OWS) project, which featured close coordination between government and industry, common goals, extensive sharing of information among participants, federal efforts to de-risk private sector investments, and regulatory speed and flexibility. The obvious

shortcomings of OWS, such as failure to adequately communicate the value and safety of COVID-19 vaccines, should also be considered in designing an approach to Long COVID.

Current State:

Scale of the Long COVID Problem

Long COVID is a potentially immense global problem with medical, social and economic impacts possibly playing out over decades. It could even constitute as big a social challenge as the COVID-19 pandemic itself.

Even using conservative estimates of Long COVID cases, the scale of the problem constitutes a major international public health emergency. Current estimates are that 10-30% of those infected with COVID-19 and its variants experience long COVID symptoms. To date, over 83M Americans have been infected with the virus and over 526M have been infected globally. Both numbers are certainly undercounts. Thus, we might expect a rough estimate of 8-17M Americans to be affected by long COVID, and between 52M-175M to be affected worldwide.

Long COVID symptoms are known to occur even in those with mild or no symptoms. A recent study seemed to indicate that risk peaks in middle age, when people have major responsibilities to family and are most economically productive. Thus, LC could pose devastating socioeconomic damage, especially among communities already stressed economically, have less access to health care, and which bear exceptional burdens of infection.

Scope of Long COVID Problem

Long COVID patients face potentially serious, and thus far poorly understood, medical manifestations, (heart, lung and kidney dysfunction);mental health consequences (“cognitive fog”, depression and anxiety, etc.); and possible long-term disability and loss of economic productivity. The costs (monetary and otherwise) of Long COVID to families, employers and governments will likely be extensive and prolonged. Stigma and scapegoating, which occurs in all epidemics, could maim lives, and last for lifetimes.

In some ways, albeit on a much larger scale, long COVID is somewhat analogous to the complicated situation related to Gulf War Syndrome - something that has been variously endorsed or denied as a real problem, with the various research efforts associated with it representing a patchwork of good science and opportunism.

Taming Long COVID will require efforts on many fronts, including those listed below. The potential scope of LC is such that with the right focus (and funding), we might be able to learn something meaningful.

Key Gaps:

Scientific Studies Will Be Extremely Challenging –

Clinical Studies - The absence of an association between clear and consistent clinical presentations or reliable biological markers and a diagnosis of LC will make clinical and biomedical studies especially challenging. It is possible that Long COVID actually encompasses several different or related syndromes.

In addition, the prevalence and burden of Long COVID is likely underestimated. Study cohorts will have to be exquisitely defined, probably quite large, and followed over long periods - likely decades, given what we know about other post-viral syndromes. Standardization of case definitions and endpoints – especially cognitive and mental health-related outcomes, across studies will be essential. Disparities among individuals in study populations in socioeconomic status, health care access, including access to vaccines and treatments for acute COVID, will have to be taken into account.

The complexity, likely costs and urgency of LC clinical studies **mandates centralized design and oversight** of study designs, patient enrollment and measured endpoints, as well as agreements among researchers to share pre-competitive data, use of Master protocols, etc. Consideration should be given to establishing a comprehensive, centralized data base. To ensure fair access to study participation and clinical trials, enrollment of representational sample populations and cost-effective management, use of digital monitoring (which must also be validated and standardized) will be essential.

Investigation of Long COVID Molecular and Biological Disease Mechanisms –

A myriad of identified factors have been associated LC in recent studies, including high levels of RNA virus early in infection; presence of autoantibodies; reactivation of Epstein Barr Virus; and history of type 2 DM, and presence of underlying illnesses generally. But the risk factors and the molecular mechanisms that lead to LC are simply not known. Multiple organ systems can be involved in LC, either directly as a result of the virus or through more indirect interaction with the patient's immune response. A far deeper understanding of the basic science behind human immune responses will likely be necessary to solve the problems LC presents.

International coordination and collaboration strategies that benefited progress in understanding, preventing and treating HIV/AIDs should be considered and incorporated into scientific investigation strategies. For example, rapid and open publication of study results – among researchers and patients - should be a strong feature of LC investigations world-wide. Solutions which can be employed around the world, not just in sophisticated medical settings, should be prioritized.

Patient Treatment and Support will Require New Strategic Approaches

Currently, the needs of LC patients and the clinical capabilities and financial expectations of American health care institutions are not well aligned. The need to formulate and effectively deliver care for Long COVID victims is occurring during a pandemic which has already overwhelmed most health care systems, including those in the U.S.

The financial costs of caring for LC victims are almost certain to be high, while the uncertainties surrounding diagnosis and treatment will likely complicate reimbursement, even among those with insurance. Access to effective care will be a huge problem, particularly among "essential workers". Mechanisms to ensure health care access and to support health care institutions caring for such patients will be needed. Consideration of the (eventual) approaches to care and disability compensation granted to 9/11 First Responders and some military groups (Agent Orange) might be warranted.

LC patients have reported great difficulty finding appropriate health care providers, even in large cities with specialized care. The difficulty diagnosing the disorder, lack of understanding of LC causes, and the confusing range of symptoms it can manifest, and limited knowledge of effective treatment approaches would be difficult in any circumstances. But the need for compassionate and effective medical care for millions of LC victims is happening at a time when physicians are exhausted, hospitals are financially stressed and short-staffed, and physician performance and reimbursement requirements are increasingly rigid and demanding rapid and predetermined patient evaluation and treatment.

Mental Health services, already in dangerously short supply, will be further stressed by LC victims and their families. Beyond diagnosing the mental consequences of LC, which will be necessary for obtaining access to care services as well as financial reimbursement and disability support, provisions will be needed to meet demand for mental rehabilitation services.

Efforts to rapidly educate health care providers about LC and to support the delivery of effective care are essential. National and international efforts to rapidly identify and communicate effective approaches will be essential. It will also be critical to adjust expectations of physician performance to the reality of caring for a very large population of sick people whose underlying illness, biological causes and appropriate treatments will elude us for some time. Access to care, especially in communities hardest hit

by the pandemic, including immigrant communities, will be a major problem. Telemedicine and remote monitoring care should be expanded and made available to patients and covered by insurance.

Clinical specialization focused on team-based care to maximize patient care and clinical excellence and efficiency, as evolved during the HIV/AIDs epidemic, will likely be necessary, and should be encouraged, at least until the disease course and effective therapies are better understood.

Realistic insurance and federal reimbursement to clinicians, rehabilitation services and hospitals will be essential.

Since better diagnostic precision will be key to identifying patients, structuring research studies, and devising effective treatments and paying for it all, the federal government should make the **development of diagnostic tools for LC a priority, and should examine financial and regulatory barriers to diagnostic innovation as has been encountered during the pandemic.**

Many LC patients are extremely debilitated by their illness and experience radical disruption of their ability to care for themselves, their families or hold down a job. **Adjustments to employer-based and government disability programs will be needed.** As will epidemics throughout history, social stigma is also likely to impact LC sufferers and should be anticipated and discouraged.

Special Attention Will Need To Be Devoted To Possible Long Term Impacts On Infants And Children

Special attention will be needed on possible long term impacts on infants and children, including, but not limited to, neurodevelopmental effects, physical health and development, and behavioral problems. This will be difficult, because even highly infrequent effects – hard to detect without very large sample sizes – will be objects of concern from parents and the general population.

Of note, the study of long term COVID impacts on infants and children is likely to be emotionally charged in the public arena. As we try to clarify causes and effects, we will encounter doubts about the science, closely held beliefs, misunderstandings of risk, and suspicions (think about autism and vaccines as an analogue), and there will need to be study and planning about communications and public trust and understanding.

Research Questions:

- Underlying mechanism/etiology for PASC and MIS-C
    - What are the underlying causes of PASC (likely multiple)?
    - What are the underlying cause(s) of MIS-C?
    - Are there therapeutic interventions that can prevent PASC and MIS-C either prior to, during, or post infection to prevent PASC and MIS-C?
- Case definition – what is included in the case definition and what is not? This is unlikely to be a uni-factorial process – for those with prolonged hospitalizations it's a mistake to attribute prolonged fatigue and many other symptoms to a new process for example – and each organ system in some ways may need its own definitions / thresholds. In many cases, there is a psychological contribution that is likely primary in some cases and secondary in others – teasing this out is critical.
- Risk factors – there is some evidence on this already, but it needs to be crystallized with additional research.
- Pathogenesis – Determining the pathogenesis of long COVID or PASC that would provide guidance for prevention or treatment. COVID-19 clearly seems to have some defined effects on the neurologic, respiratory, and cardiac systems – what is the mechanism and why does this happen? How important is viral RNA persistence? Would/does antiviral treatment for acute disease decrease the likelihood of this complication?

- Treatment – what are promising modalities for treating these symptoms based on the pathogenesis? What is working already and based on pathogenesis what specific targeted treatments may be needed? Is there a need for new therapies? Would these cross over to treat other similar pathologies?
- Prevention – is there a way to predict / prevent these syndromes from occurring? Are there early treatments during the disease process that decrease the incidence? Does vaccination have impact in prevention or attenuation?
- Impact – for those that are / believe they are suffering from long-COVID what has been the physical, social, and economic impact?
- What is the low-hanging fruit and what deserves longer-term investigation / investment? Where is the greatest future return on investment – particularly in understanding pathology and identifying new treatments that might contribute to broader categories of patients beyond long COVID that have similar impairments.
- What anti-virals do we need to further stockpile/develop to anticipate needs of future pandemics influenza and otherwise?
- What are some of the key viruses with pandemic potential and where do we stand with vaccine development for them?
- How do we continue to improve vaccine development and manufacturing?
- How do we combat disinformation more effectively?
- Can we show that patient transfer / distribution mechanisms in states made a difference in mortality?
- Look at non-COVID-19 excess mortality in urban and rural areas to help define future needs and strategies
- Look at racial and geographic differences in COVID and excess mortality to define intervention populations, as well as examining factors that made persons less likely to seek care / vaccination. What are their trusted sources of information? How do we tap into those?
- How can we improve critical care so that it can be expanded? AI and automated integrated technologies have tremendous promise but we need to figure out the specifics and the levers.
- How do we improve our ability to develop and scale clinical testing?
- What belongs in the public health lane going forward? Many mass vaccination and testing plans that fell on public health prior to the COVID-19 pandemic clearly did not work and healthcare wound up taking this on – in many cases there is no good return on investment here and staffing was difficult (and MRC in many communities failed to meet the needs) – where do we go from here? Can we depend on public health during a biological threat event to do mass prophylaxis? Or should this be done by / with major support from private logistics partners and healthcare?
- Creation of a registry – in fact, the entire topic needs much better definition to begin with – the NIH paper (doi:10.7326/M21-4905) demonstrates that should be a top priority.
- Better characterization of host immunity -- who gets sick? Who doesn't? Who gets post- COVID Conditions? Who doesn't?
- Examination of bio-psycho-social links to inflammation and the risk of post Covid conditions
- Correlation to viral load present (is there correlation?); correlation to GI involvement and lymph
- node viral retention; correlation of anosmia to neuro-cognitive sequelae
- Correlation to the use of therapeutics – paxlovid, vaccine, monoclonals and immunomodulators
- What surveillance methods could give us greater certainty about who has COVID and who does not, so as to better be able to attribute long term physical and neurodevelopmental status to the virus?
- Pediatric COVID impacts
    - By what methods could we parse out the effects of COVID on infants and children from background physical and neurodevelopmental problems that are always in this subpopulation?

- How shall we deal with the likelihood that many COVID cases in infants and children will likely not have been diagnosed? The methodological questions are very important.
- If patterns of long term consequences for the pediatric population emerge, policy questions will emerge, as well, about coverage and payment for care and for educational and developmental supports. We may do well to anticipate these.
- What are public health/population health approaches to the mental health impacts of the pandemic, especially for youth, and how to mitigate such effects in future pandemics?

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Risk and Crisis Communication

Overview:

Members of the public need authoritative information about the potential risks and benefits of actions that they can take regarding pandemic diseases (e.g., vaccination, masking, traveling, visiting relatives) and about the policies that officials take on their behalf (e.g., restrictive mandates, testing protocols, insurance guarantees). Effective risk communications lead to better decisions and greater trust in officials (and their science). Effective communications also provide a bulwark against disinformation, by enabling people to rebut it on their own and encouraging reliance on official sources. Conversely, ineffective official risk communications can lead to confusion and frustration, along with reliance on other sources (NASEM, 2020).

Note: "Risk Communication" has become the term of art for communications regarding the outcomes of risk-related decisions, including not just risks, but also expected costs and benefits, some of which come from reducing risks (as with medical procedures).

Crisis and risk communication is also more difficult in underserved communities because of differences in access to new media tools (smart phones in particular); WiFi access, disinformation, misinformation, inadequate numbers of informed trusted messengers and baseline mistrust of authority including health providers/systems.

Current State:

We actually know a lot about how to do risk and crisis communication but not how to get the system to implement best practices early. We know a lot about how best to engage underserved communities.

Risk communication is an iterative process involving interdisciplinary teams that:

- Analyze decision makers' information needs (decision theory)
- Describe their current beliefs and values (behavioral science)
- Draft communications, faithful to scientific understanding (subject matter expertise)
- Test with those drafts with prospective users (evaluation/implementation research)
- Repeat, as necessary.

Risk communication has existed as a distinct field for roughly half a century. It arose to address rising skepticism regarding science and technology (e.g., nuclear power, genetically modified crops, vaccines). It has drawn on advances in behavioral research, delineating heuristics and bias in judgment and decision-making processes. It studies both experts and non-experts. As examples of research results:

Studies of non-experts often find that they:

- Have incomplete mental models of the processes that create and control risks.
- Have an imperfect sense for how much they know, tending to overconfidence when their knowledge is limited, under confidence when it is extensive.
- Have difficulty evaluating the quality of decisions, subject to hindsight bias and outcome bias.
- Are sharply attuned to cues regarding trustworthiness (competence, honesty).
- Can be supported or undermined by their emotions.
- Can learn quickly from well-executed, proactive risk communications.

Studies of experts often find that they:

- Are like non-experts when relying on intuition (e.g., overconfident, when their knowledge is limited).
- Have procedural safeguards against fallible intuitions (e.g., peer review).
- Are insensitive to disciplinary norms that privilege some kinds of information (e.g., readily quantified).
- Are insensitive to social and ethical biases in their practices (e.g., definitions of "risk," treatment of distributional effects, unrepresentative data sets).
- Have poor intuitions regarding lay audiences, especially those with different backgrounds.
- Appear competent, but cold to the public.

Three NASEM colloquia on the sciences of science communication provide introductions to the potential contributions of different social, behavioral, and decision science disciplines (Fischhoff & Scheufele, 2013, 2014, 2019). Articles within these collections also offer narrative overviews (Fischhoff, 2013, 2017; Fischhoff & Davis, 2014). FDA's Risk Communication Advisory Committee produced an edited volume for practitioners (Fischhoff, Brewer & Downs, 2013). An early NASEM consensus report (1989) captures the field at its emergence.

Key Gaps:

Operations Research

Research on why risk and crisis communication comes too late/later in the response is missing. Also, the funding for doing risk and crisis communication always seems like an afterthought and goes to groups that are not the ones that culturally can make the biggest impact. The need is an operations health services research agenda on how best to get the system to engage these communities early with the right messages, messengers and tools that have been informed by evidenced based message testing.

Mental Models of Processes Creating and Controlling Risks

Risk communication research has advanced by addressing fundamental issues arising in applications. For example, researchers have studied how people think about exponential processes in the contexts of invasive species, population growth, and radioactive decay. They have studied lay perceptions of field strength in the context of 60 Hz fields, contamination in the context of food safety, and mutations in the context of genetic counseling.

Research gap 1: How do we translate existing research into terms useful for the professionals charged with communications regarding pandemic risks and control mechanisms (e.g., explaining exponential spread of infectious disease)?

Research gap 2: How do we identify and study phenomena unique to pandemic disease (e.g., cascading transmission pathways, layered protective measures, the implications of uneven global vaccinations)?

Quantitative Estimates

Decisions depend on the size of the risks (and benefit) of choice options. Although non-experts sometimes struggle with quantitative estimates, their confusion is, often, not with the number but with the event to which it is attached. For example, what do weather forecasters mean by "rain" in "the probability of rain Is 70"? They may also be misled by communications that omit critical details that experts know, but fail to convey (e.g., the size of the population in which disease cases were observed, known biases in reporting).

Research gap 3: How do we create clear terminology for terms that are critical to understanding pandemic risks, both when experts agree (e.g., effectiveness, efficacy) and when terms are still in flux (e.g., long COVID)?

Research gap 4: How do we explain the limits to scientific knowledge, so that changes are seen as scientific progress, rather than confusion (broken promises, flipflops, etc.)?

Trust

How people seek and interpret information depends on their trust in sources. Studies of trust in sources of pandemic risk information echo studies in other domains, in terms of the cues they use to assess sources' honesty and competence. Those are found in both what sources say and how they say it. Studies find that once lost, trust is hard to regain, especially after people have turned to other sources. The challenges increase when the parties have different backgrounds and lack direct interaction, reducing the expectation of shared values and opportunities to correct misunderstanding.

Research gap 5: How do we ensure that experts know the information needs and expectations of the diverse publics that depend on them, so that they can secure and retain trust?

Research gap 6: How do we explain the rationale for public health policies (e.g., restricting some groups for the protection of others, delaying or pausing the availability of treatments)?

Research Questions:

The research gaps (above) are formulated as priority research questions. Addressing them will require institutional design, as well as material resources. Effective risk communication requires a research enterprise that can:

- Rapidly assess and consistently monitor the information needs and perceptions of diverse publics.
- Support the community partnerships essential for trusted two-way communications.
- Create the interdisciplinary teams needed for successful applications, with expertise in analyzing decisions, summarizing scientific knowledge, describing lay perceptions, and developing risk communications.
- Provide incentives for basic researchers to work on those teams, contributing their broad knowledge and intellect.
- Work with public health organizations to develop consistent practices and policies, making trustworthy risk communication possible.

Achieving these goals will require innovative research programs. They must support strong basic research, given the difficulty of the problems and the stakes riding on their solution. They must be more agile than conventional proposal and review cycles, in its response speed and flexibility. They must support continuing two-way communication with policy makers and community partners. They must engage risk communication researchers in decisions regarding data collections and analysis, so that those data are as relevant as possible to the decisions that depend on them, as needed for effective communications.

Additional research questions for consideration are:

- Are delayed effective communications a cause of health inequities? The hypothesis is that a well-structured system that is permanently in place, has worked to build trust, has the right messengers and can be quickly informed by good information, and deliver health information that will overcome mistrust, minimize misinformation, and combat disinformation. Such a process will reduce preventable health inequities.
- Can early message testing of underserved communities around health threats better inform public health interventions and improve health disparities? This can be informed by the experiences and research agendas of major health threats every year from severe storms, other environmental emergencies/urgencies, gun violence, food borne outbreaks, etc.
- What is the role of social media mis/disinformation and how is best to counter it?
- What is the best way to combat misinformation and the infodemic?
- What are evidence-based best practices for communicating and building trust during an evolving public health emergency in the setting of extreme political polarization and mistrust of government and institutions?

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From: Caneva, Duane (b)(6)

To: (b)(6)
(b)(6)
Dr. (b)(6)
(b)(6) MD (b)(6)
(b)(6) (b)(6)
You, Edward H. (WMD) (FBI) (b)(6)
Dr. (b)(6)
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Subject:	RE: Red Dawn Rhapsodizing Begin July 2, 2020
Date:	2020/07/24 13:51:42
Priority:	Normal
Type:	Note

Attachments:

1. • Current updated MQL from DHS S&T
2. • Current Chemical News Report.
3. • (b)(daily COVID-19 Report.

On attachment 2, I just wanted to highlight *our "other" current Public Health Emergency that continues to rage—opioid overdoses*. While we're deep in response to COVID-19, and our law enforcement agencies are being dragged into demonstrations in many cities across the nation, let us not lose sight of this worsening scourge on the country:

DDPHE: Fentanyl-related overdose deaths up 282% in Denver this year. July 22, 2020 (The Denver News Channel). Fentanyl-related overdose deaths are up a staggering 282% in Denver from January of this year to May, compared to the same time period in 2019, according to new data released Wednesday

from the Denver Department of Public Health & Environment (DDPHE). The data shows 48 people have died from fentanyl overdose as of Friday, July 17 of this year. That's compared to a total of 58 deaths related to the drug for the entire year of 2019, a 341% increase from the previous year (2018). The majority of drug overdose deaths in Denver involve multiple substances found in the deceased's system. In 2020 so far 62% of deaths involved 3 or more drugs in the deceased's system: 19% of deaths involved 5 or more drugs in the deceased's system. The overwhelming majority of probable overdose deaths — 83% — occurred in populations outside the homeless community, according to the Denver Office of the Medical Examiner. https://www.thedenverchannel.com/news/local-news/ddphe-fentanyl-related-overdose-deaths-up-282-in-denver-this-year

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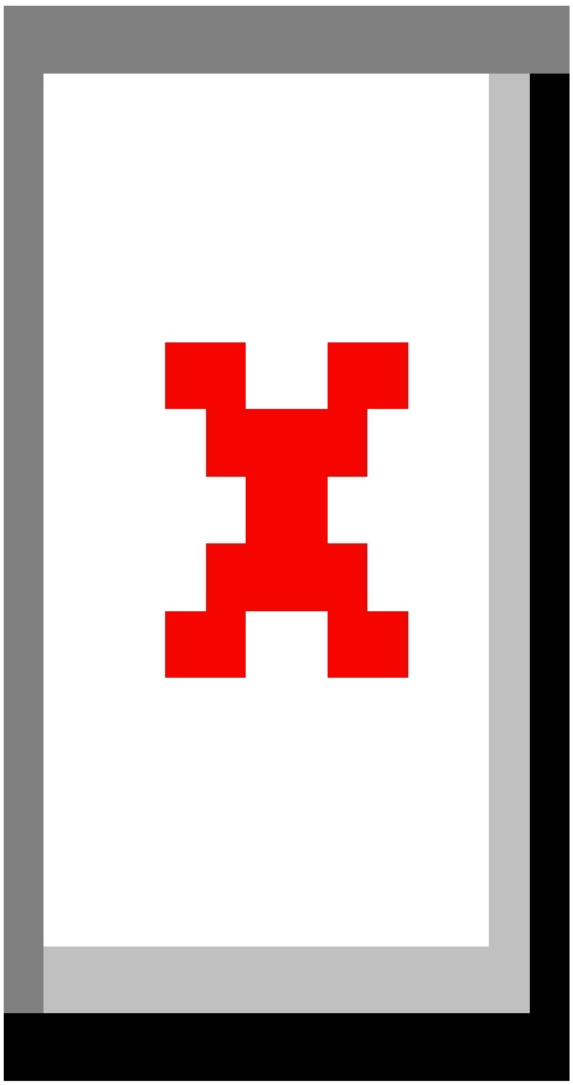
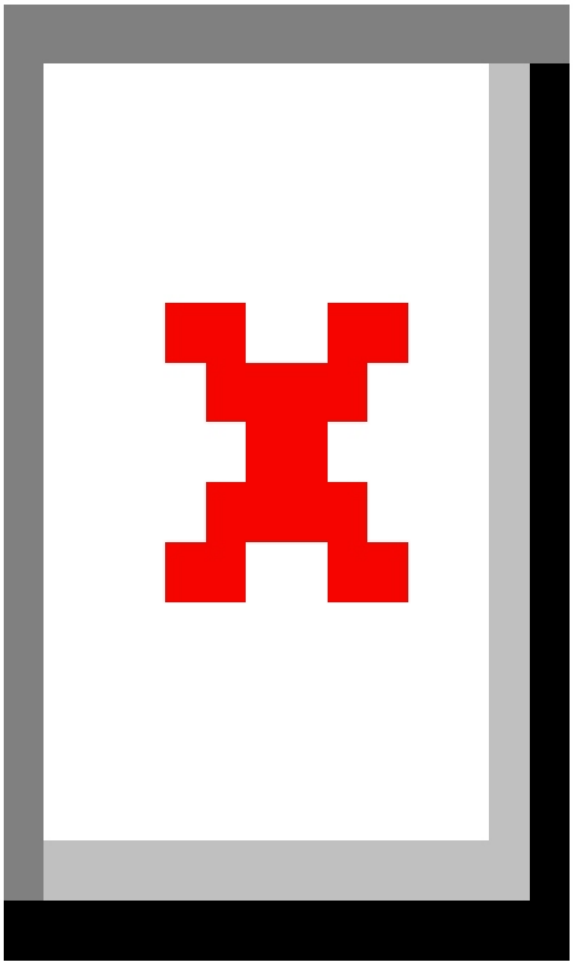
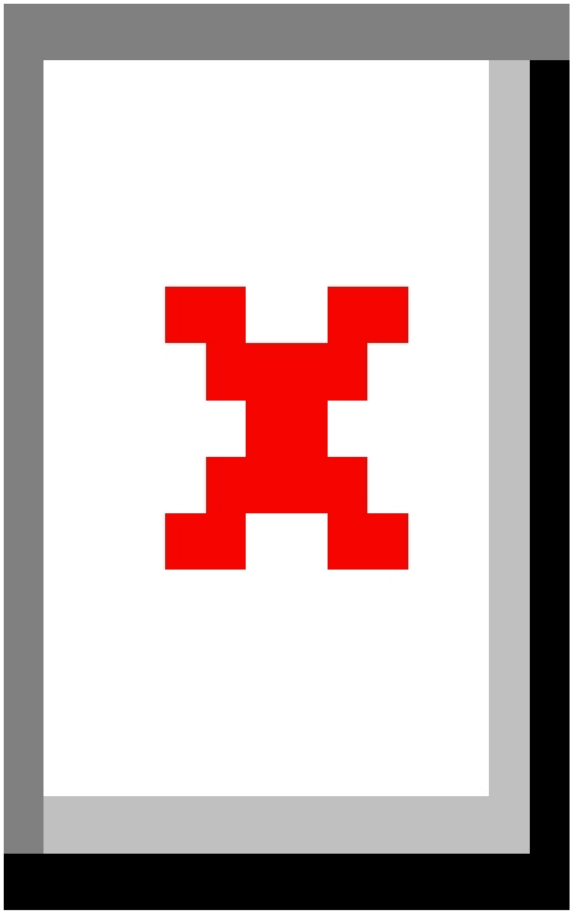
From: (b)(6) (b)(6) (b)(6)
Sent: Thursday, July 23, 2020 10:06 PM
To:
Subject: RE: Red Dawn Rhapsodizing Begin July 2, 2020

Kaiser Foundation is now updating its LTC report every two weeks. The latest report came out this evening. Attached is an updated summary of the reports since April 23.

Here is a graphical comparison of states. I highlighted CA, FL and TX (dashed lines in graphs).







Sent from Mail for Windows 10

From: Dr. [redacted]
Sent: Thursday, July 23, 2020 9:28 PM
To: [redacted]
Cc: [redacted] MD; [redacted] You, Edward H. (WMD) (FBI); Dr. [redacted] (DSHS); Caneva, Duane; [redacted] Keim, MD MBA; [redacted] W; [redacted] (HMFP - Emergency Medicine); [redacted] BOURNE, ALEXANDRA; [redacted] McDonald, Eric; [redacted] V.,M.D.; [redacted] S; [redacted] McGinn, [redacted] Kellermann; [redacted] Eastman, [redacted] LLogandakar; Walters, [redacted] DC; [redacted] JtCIVtUSARMY (USA); [redacted] MD; Fantinato, Jessica (USDA.GOV); Martin, Greg [redacted] KAUSHIK, SANGEETA; [redacted] Larry G; Ignacio, Joselito; [redacted] Hassell, [redacted] (Chris) (OS/ASPR/IO); [redacted] WILKINSON, THOMAS; WOLFE, HERBERT; [redacted] Marinissen, Maria (HHS/OS/OGA); Sutter, [redacted] Krohmer, Jon (NHTSA); [redacted] (APHMFP - Emergency Medicine); [redacted]
Subject: Re: Red Dawn Rhapsodizing Begin July 2, 2020

[redacted] what a coincidence that you mentioned this (about high school and about early undetected cases). A priest and a professor talked to me about covid-19 last Tuesday about an early outbreak in January, from her grand-daughter. I also want to include a comment on grocery stores.

High Schools: Anecdotally, her grand-daugher, Ava, may be one of the Links.There were a couple of new Chinese exchange students in her school in early January, and seeing that they were socially isolated, Ava befriended them. By the end of the month the entire high school was in the grip of what was then called flu. At one point, Ava said only 1000 of the 3000+ school community were actually in attendance. That is Wachusetts Regional High School in Holden, Massachusetts, if you want to do some preliminary research. She says no-one died from the infection. Her own progress closely matched the “hypoxic injury/tissue damage/proceeding rot respiratory infection" model: first symptoms were shortness of breath, followed by fever and flu-like symptoms. She recovered in about 3.5 weeks, she said; others took longer. I suspect we have a clear, undocumented case of a significant Covid eruptiion at least six weeks before its presence in the US was officially acknowledsged.

I modeled Patient 0 in New York City starting early January. So, all these timelines seem to be very accurate. We might even have some in late December, since people were traveling back to the States for winter break. It's just a perfect travel time!

These students knew they're exposed to covid-19 later as they're being tested positive on the serologic tests.

This also gives us an idea what to expect when schools re-open. Clearly we can't afford to have so many kids get sick, so every countermeasures must be established to protect them, and that in turns, protect everyone they come in contact with.

Grocery Stores: Although the mayor and the Governor are standing still in their facemask debate, businesses are requiring face-mask and that is good. However, I urge that grocery stores provide hand sanitizers and position them conveniently everywhere. This is extremely critical for both the workers and the customers. Also it is absolutely not feasible to use self-checkout unless such hygiene is being put in place. I was at Kroger, there're 6 self-checkout in one lane. Everyone touches everything and there's not a single thing to wipe or clean before each customer. You don't need a model, nonetheless, I did some time-motion study and then built a model to characterize the contact, unbelievable, the contact is over 90%!!

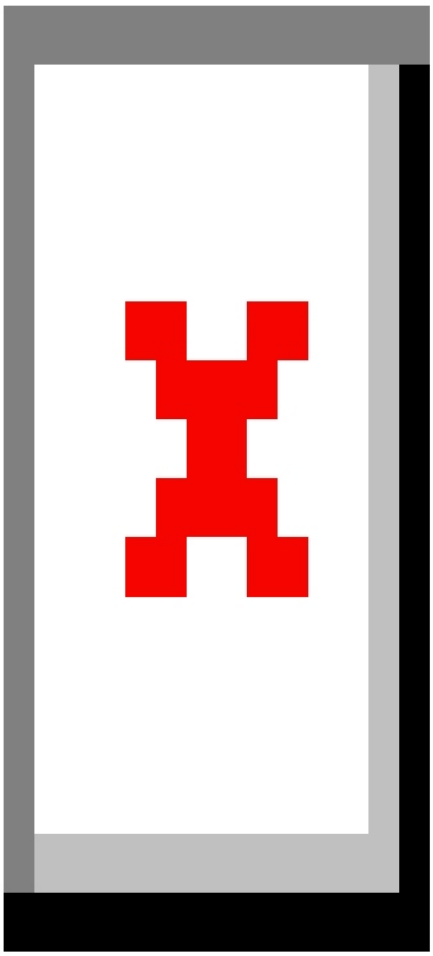
Please, sanitizers everywhere and self-checkout must be safeguard with all necessary cleaning. If there're hand sanitizers there, they can do magic. It is easy and a must-have.

It is a system and everything counts.

I will send the graphs for the other 40 States tonight.

On Thu, Jul 23, 2020 at 8:00 AM (b)(6) (b)(6) <cmecher@charter.net> wrote:
(b) shared a seroprevalence study from JAMA.
https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2768834

The most interesting aspect of the seroprevalence data is the seroprevalence of age group 0-18. Match the age distribution of seroprevalence to the distribution of cases by age reported by NYC and these states (note that this seroprevalence data is from earlier in the pandemic before the recent surge in the young). There is a mismatch. Disproportionately low case ascertainment in children. Suspect COVID went thru this young age group (age 0-18) during the very early stages of the pandemic when the schools were open and we weren't testing (late January thru February). Combine this data with the recent study from South Korea on household transmission with children as the index case in the household. Implications for school reopening?



Sent from Mail for Windows 10

From: (b)(6) (b)(6)
Sent: Thursday, July 23, 2020 7:47 AM
To: Dr. (b) (b)
Cc: (b) (b)(6) MD; (b)(6) (b)(You, Edward H. (WMD) (FBI); Dr. (b) (b) (b)(6) (DSHS); Caneva, Duane; (b)((b)(6) (b)(6) (b)((b)(Keim, MD MBA; (b)(6 (b)(6) (b)(6) (b)(6) (b)((b)(6) (b)(6 ((b)(6) W; (b)(6) (HMFP - Emergency Medicine); (b)(6) (b)((b)((b)(6) BOURNE, ALEXANDRA; (b)((b)(6) McDonald, Eric; (b)(6 (b)(6) (b)(6) , (b)(6) V.,M.D.; (b)((b)(S; (b)(6) (b)(McGinn, (b)((b)(6) (b)(6) (b)(6) Kellermann; (b)(6) (b)((b)(6 (b)(((b)(6) (b)(6) Eastman, (b)(6) (b)(6) (b)(6) ((b)(6) (b)(6) LLogandakar; Walters, (b)(6) (b)(6) (b)((b)(6) DC; (b)(6) JtCIVtUSARMY (USA); (b)((b)(6) MD; Fantinato, Jessica (USDA.GOV); Martin, Greg (b)(6) (b)((b)(6) KAUSHIK, SANGEETA; (b)(6) (b)(6) (b)(6) (b)(6) (b)(6 (b)(6) (b) ((b)(6) (b)(6) (b)(6) Larry G; Ignacio, Joselito; (b)(6 Hassell, (b)((Chris) (OS/ASPR/IO); (b) (b)(6) (b)(6) (b)(6) (b)(6) (b)(6)); (b)(6) (b)(6) (b)(6 (b)(6 (b)((b)(6) WILKINSON, THOMAS; WOLFE, HERBERT; (b)(6) Marinissen, Maria (HHS/OS/OGA); Sutter, (b)(6 (b)(6) (b)(6) (b)((b)((b) (b)(6 Krohmer, Jon (NHTSA); (b)(6) (b)(6) (APHMFP - Emergency Medicine); (b)(6) (b)(6) (b)(6) (b)((b)(6) (b)((b)(6) (b)(6)
Subject: RE: Red Dawn Rhapsodizing Begin July 2, 2020

Some LTC data from the leading edge states. Given this growth, expect deaths to continue to soar in those two states.

Percent increase in COVID+ residents/COVID deaths/COVID + staff since 7/15 (1 week)
FL (LTC) 36%/?/14%
GA (LTC) 8%/8%/11%
CA (SNFs) 7%/5%/?
TX (Nursing Homes) 27%/28%/?
TX (ALFs) 26%/25%/?

Here are graphics.

Sent from Mail for Windows 10

Sent from Mail for Windows 10

From: Dr. (b) (b)
Sent: Tuesday, July 21, 2020 6:02 PM
To: (b)(6) (b)(6) (b) (b)
Cc: (b) (b)(6) MD; (b)(6) (b)(You, Edward H. (WMD) (FBI); Dr. (b) (b) (b)(6) (DSHS);

Caneva, Duane; (b)((b)(6) (b)(6) (b)((b)(Keim, MD MBA; (b)(6 (b)(6) (b)(6) (b)(6) (b)((b)(6) (b)(6 ((b)(6) W; (b)(6) (HMFP - Emergency Medicine); (b)(6) (b)((b)((b)(6) BOURNE, ALEXANDRA; (b)((b)(6) McDonald, Eric; (b)(6 (b)(6) (b)(6) , (b)(6) V.,M.D.; (b)((b)(S; (b)(6) (b)(McGinn, (b)((b)(6) (b)(6) (b)(6) Kellermann; (b)(6) (b)((b)(6 (b)(((b)(6) (b)(6) Eastman, (b)(6) (b)(6) (b)(6) ((b)(6 (b)(6) LLogandakar; Walters, (b)(6) (b)(6) (b)((b)(6) DC; (b)(6) JtCIVtUSARMY (USA); (b)((b)(6) MD; Fantinato, Jessica (USDA.GOV); Martin, Greg (b)(6) (b)((b)(6) KAUSHIK, SANGEETA; (b)(6) (b)(6) (b)(6) (b)(6) (b)(6 (b)(6) (b) ((b)(6) (b)(6) (b)(6) Larry G; Ignacio, Joselito; (b)(6 Hassell, (b)((Chris) (OS/ASPR/IO); (b) (b)(6) (b)(6) (b)(6) (b)(6) (b)(6)); (b)(6) , (b)(6) (b)(6 (b)(6 (b)((b)(6) WILKINSON, THOMAS; WOLFE, HERBERT; (b)(6) Marinissen, Maria (HHS/OS/OGA); Sutter, (b)(6 (b)(6) (b)(6) (b)((b)((b) (b)(6 Krohmer, Jon (NHTSA); (b)(6) (b)(6) (APHMFP - Emergency Medicine); (b)(6) (b)(6) (b)(6) (b)((b)(6) (b)((b)(6) (b)(6)

Subject: Re: Red Dawn Rhapsodizing Begin July 2, 2020

I summarise my comments below:

> (b) you might want to scan something shared by the COVID-19 Healthcare Coalition.
> Virus Diffusion Classroom Design:
> (b)(6) -
> d56726d2eb9a3a6c&u=http://www.cassbeth.com/covid-19/return-to-life/index.html#Virus-Diffusion-Classroom-Design
>
> Full Analysis:
> (b)(6) -
> 241e2b3c9e03ec14&u=http://www.cassbeth.com/covid-19/return-to-life/index.html

Another good read. Interesting, many radiation models. For radiation, there are meters/sensors that people wear to get alerted if the concentration is at certain level of harm. I know some of you are building the mini next generation sensors that can become handy in detecting covid-19 viral counts in the environment in real time. Looking forward for that layer of real-time detection and monitoring.

> My concern is that the US outbreak is much too large to bring back under control thru the use of testing and contact tracing alone (the numbers are just too large). That is what I meant about needing a third chance in reference to (b)(6) oped in April where he talked about how we might have a second chance to transition from the lockdown to a strategy similar to what South Korea had done and what Germany is now doing. This is Puyeo's "Hammer and the Dance." We failed in the transition from the hammer to the dance stage. Perhaps a few states could make that transition, but not most of the US. We are stuck in a transition zone between the hammer and the dance. We no longer are using the hammer and we aren't dancing very well. The result is an outbreak that is partially mitigated (with an R>1) and as a result the outbreak goes on, and on, and on.

Yes, (b)(6) we have talked about this "hammer-and-dance" a few months ago. I was worried at that time -- what if people don't know how to dance? Truly, the hammer was lifted too early, and the dance is random.

South Korea, Hong Kong, Singapore call it "Suppress-and-lift". We can see that even South Korea tip-toed on their re-opening and delayed when they had a local outbreak. In the same way Singapore closed up everything and allowed only 1 person to go out at any time for grocery shopping when they have to deal with the community spread. Consider Singapore (5.6 million) a city in the US. They seem to have good control now (it's been a long time since they closed up in early April), and their suppress is still on. I call it "restrict-and-relax". Can't use a hammer now, but let's make it a localized restriction tailored to the local disease and risk posture.

My email from Germany's update is just an understanding on how we can reopen next time (when we have a chance) in terms of the testing and contact-trace and social distancing, and everything combined. We can't just test and contact-trace now to contain, it cannot be, because we are way beyond containment. We have wide-scale community spread and we will need to have NPI measures. Again, some counties/cities are ready to open schools and they are fine since they have no visible community spread. But majority sites have local community spreads. They will need:

1) Cost-effective evidence-based approach to treat covid-19 patients. If they do need field hospitals, they must ensure that those hospitals will accept patients so they won't repeat the same situation as in NYC where the field hospitals only accepted patients from private hospitals, while others did not coordinate well. Either the field hospitals are used to help treat patients, or they won't be needed.

[Separate covid-19 patients, protect healthcare workers, getting personnel surge from other places or outpatient providers, and optimize clinical environment and shift hours to improve safety. Everything we have shared in great detail back in March.]

We need to know what types of treatment work best for what types of patients and when to intervene, and when to hospitalize, etc. If we can have remote patient monitoring, then we can monitor people's vitals (oxygen level, etc) so it can help hospitalization at the right time for the best intervention and treatment success.

2) Determine the most cost-effective and safe way for businesses to open or close out to maintain business continuity and economics -- bars, theatres, malls, nail salons, gyms, should all be closed for those high-risk cities/counties. Make diners into a table of 4, or close after 6pm and allow only take-out. This minimizes the number of new cases and community spread.

One of the most essential businesses to open is healthcare for all Americans. So outpatient clinics and elective surgeries, there're reasons they need to reopen because some patients simply need all those medical care. We need to provide a very safe environment for them to operate.

Essential workers and factory workers: we must protect them with PPE and we must stagger work hours and minimize infection in their working environment. All issues must be taken care of.

Private sectors, same thing, they can open if they have good means on disease control and prevention. Clearly environment, personnel, timeline, and safety steps must all be optimized to get the safest operations.

There are many screening tools to self-check, as Art has pointed out Emory has one.

Leaders can look at the business lists w.r.t. tradeoffs, GDPs, and risk factors and determine which ones should re-open and which ones can be shut down temporarily to blunt the local community transmission.

Bars and nightclubs seem very popular, even for students, there're happy hours. I don't drink nor smoke, so sorry if I feel that it is so important to close them. But how can people practice social-distance when they are drunk? I did a little econ-tradeoff analysis on alcohol consumption, it actually has a 2-7% GDP burden (negative consequence).

3) Early detention/monitoring, and test, isolate, and contact-trace.

I think every business can do waste-water/sewage testing as a means to monitor their environment. It is cheap and easy to do, and it should give us results even for asymptomatic transmission. I have suggested every business do that -- this is another MUST do.

I actually did a study on how mass dispensing of cipro and doxycycline (after responding to anthrax events) would affect our waste water, the level of antibiotics in it and how it goes to the main streams and gets back to the food chain. So tracking water is a very good idea.

We will need to test regardless if we can contain or not. Testing is the cornerstone for pandemic response, so we better optimize the process. If isolation beds/low acuity beds are needed for those positive patients, get them.

I know I am 200 years-old and a broken record because I keep asking about testing. But we can't avoid it and we can't push it aside. We must confront it head-on and continue to fix the testing and delay along the entire process. They are not the only means, but they are one of the means as part of the holistic system approach to combat covid-19 or any pandemic.

Pooling is good, and optimal pool size is important since it offers efficiency and accuracy. But truly, I fear that even with pooling, we are still running out of time and testing kits.

4) Safe space and safe actions: Individual actions regarding wearing face-mask, practicing social distancing, avoiding crowns, working in staggered shifts, disinfect and all, those we need every citizen to take part in and contribute. It is everyone's responsibility. Their incentive -- the more people buy-in and practice social distancing and wearing masks, the more business we can open and the faster we can get back to :"normal".

***School re-open is a local is*sue,** because every local has its own (covid-19) risk posture, so it is clearly not one-size-fit-all.

Take Harvard as an example, it is going to conduct all classes online. Freshman will live in dormitories. They will live in their own single cell or multiple people in a cell, and they take-out and dine together in that same quarter, and they all do things with the same group and they will sign a contract to agree that they will not venture out of all the requirements. This can work for some students, but not for others who will feel very restrictive. There are a lot of restrictions. Among students who are depressed in university (about 52% across US), 8% of them are freshmen due to adjusting to a new life, new school, new friends, etc. So we don't know how it will work for these new students. They can be happy or they may have other issues, all these waiting for us to discover.

There're workers who will serve them (physically working on campus), and so the layers of protections go far beyond lectures. We also need to keep in mind many workers are under-served minorities so their health risk is higher. It's a ton of things students do on campus, off campus, and all those have to be considered as a system to make it work.

This is what we have talked about for school re-opening: a) we test the waste water to monitor the school environment, b) we test by sampling to see how the people's risk factors are to establish the disease prevalence in the school setting, and c) we have 1/2 students take 3 days of classes, and ioff the rest and the next week, and another group take 3 days next week and off (alternating week). The wait is good for two purposes: the test takes so long to get results, so we may as well test and just send them home, like quarantine, and of course the time will be 14 days - 3, and so 11 days, maybe that will be sufficient for an asymptomatic individual to cool off. Ok, these 3 steps, plus many other steps and measures.

Now you go to nursing homes. Current nursing homes run as large-scale manufacturing systems. The process is streamlined to take advantage of economies of scale. E.g., You streamline so that a group of workers are dedicated to provide baths, and other groups are dedicated to cleaning the rooms, etc. By doing so, every resident is exposed to a list of workers that serve a large number of residents. Hence, easy transmission across the site, because nursing homes are like community living. Now, add PPE on all workers ,ok, we can reduce that cross containment. Better yet, make it into dedicated service -- assign a set of workers to take care of a small set of residents. Break them into groups, now, the residents no longer are exposed to so many workers, but just the few dedicated ones who take care of more tasks for a smaller set of clients.

It may not be the best way for mass production (service), but it can reduce as much as 54% interaction. And that directly reduces intra-facility infection.

By doing so, workers may not need to do the same tasks across multiple sites, and thus reduce inter-facility infection also.

Basically you reduce the circle of interactions to a traceable and manageable size. Now this is kind of like those cozy small family practice businesses. In the old days, that is how it's run. And people do enjoy those types of interactions. Large-scale is created to streamline for bigger profit and more efficiency. In both cases, regulations have to be placed. It is harder to inspect 150 small businesses of nursing homes, instead of 40 large-scale ones. However, if we separate the large-scale ones now into separate wings, then we can get back the small framework that is needed for the best disease control.

I run a model to analyze this and it doesn't deplete the efficiency while at the same time improving the quality and reducing the infection probability (54%-69%).

Prisons close quarters with so little space.. and they are going to spread, can't avoid it. Look, even if they don't have high mortality, they will in turn infect the wardens and someone old,naturally. But the mortality can be high because of the demographics.

> The resurgence began with younger age groups but we are now seeing acceleration in older age groups (just look at the age specific data for FL, CA, and GA). Many do not appreciate the time lag.

What is concerning is that we are seeing an acceleration in cases in LTC staff and residents in places like FL, GA, and TX. If we are seeing there, it is likely happening or going to happen everywhere else. I'm already hearing about challenges with the demand for testing and interest in using pooled specimens. I'm surprised that wastewater surveillance of nursing homes, detention centers, prisons and schools (if they plan on reopening) isn't taking off in anticipation of increasing demand for testing (would be much more efficient and sensitive).

Right, yes, all of these. I have no doubt transmission in China was spread within Wuhan and out of Wuhan (to other parts of China) by some younger asymptomatic patients. That's January. We catch some through testing, and we miss some and they interact (just like Seattle patient 0) and somehow infects someone who works in LTC, and then the aged population is infected rapidly again.

Germany's major community spread is nursing homes and slaughter farms, Hong Kong has now it's community spread and first nursing home infection.

The population is aging, and many live in communities with services. As such, the disease is brought to them.

Sorry, very long.... (b) pause.

Here is the latest LTC data for FL, GA, and TX.

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From: Dr. (b) (b)
Sent: Tuesday, July 21, 2020 7:07 AM
To: (b)(6) (b)(6)
Cc: (b) (b)(6) MD; (b)(6) (b)(You, Edward H. (WMD) (FBI); Dr. (b) (b) (b)(6) (DSHS); Caneva, Duane; (b)((b)(6) (b)(6) (b)((b)(Keim, MD MBA; (b)(6 (b)(6) (b)(6) (b)(6) (b)((b)(6) (b)(6 ((b)(6) W; (b)(6) (HMFP - Emergency Medicine); (b)(6) (b)(6 (b)((b)(6) BOURNE, ALEXANDRA; (b)((b)(6) McDonald, Eric; (b)(6 (b)(6) (b)(6) (b)(6) V.,M.D.; (b)((b)(S; (b)(6) (b)(McGinn, (b)((b)(6) (b)(6) (b)(6) Kellermann; (b)(6) (b)((b)(6 (b)(((b)(6) (b)(6) Eastman, (b)(6) (b)(6) (b)(6) ((b)(6 (b)(6) LLogandakar; Walters, (b)(6) (b)(6) (b)((b)(6) DC; (b)(6) JtCIVtUSARMY (USA); (b)((b)(6) MD; Fantinato, Jessica (USDA.GOV); Martin, Greg (b)(6) (b)((b)(6) KAUSHIK, SANGEETA; (b)(6) (b)(6) (b)(6) (b)(6) (b)(6 (b)(6) (b ((b)(6) (b)(6) (b)(6) Larry G; Ignacio, Joselito; (b)(6 Hassell, (b)((Chris) (OS/ASPR/IO); (b) (b)(6) (b)(6) (b)(6) (b)(6) (b)(6)); (b)(6) (b)(6) (b)(6 (b)(6) (b)((b)(6) WILKINSON, THOMAS; WOLFE, HERBERT; (b)(6) Marinissen, Maria (HHS/OS/OGA); Sutter, (b)(6 (b)(6) (b)(6) (b)((b)((b) (b)(6 Krohmer, Jon (NHTSA); (b)(6) (b)(6) (APHMFP - Emergency Medicine); (b)(6) (b)(6) (b)(6) (b)((b)(6) (b)((b)(6) (b)((b)(6) (b)(6)
Subject: Re: Red Dawn Rhapsodizing Begin July 2, 2020

I had some discussion with the Germany science leader who advises Merkel (mostly I asked him a lot of questions about testing and contact-tracing Apps, and on-the-ground situations).

1. 90% of the people support the tight measure of the politicians who still listen to the scientists.

This percentage validates the optimized percentage of compliance that I obtained a few months ago for face masks and social distancing. We need everyone and at the minimum 90%.

2. There are a few local outbreaks: in slaughterhouses, senior homes, etc. but then the local regions come again under strict control (due to compliance of citizens) and the spread is stopped.

Universally across the world, factories with packed workers and also senior nursing homes remain high-risk and must be properly protected.

3. "Covid-19 testing is no problem in Germany. In fact, we have more capacity than needed and some test centers have already closed down." When some location becomes a sudden hotspot they are able to contact trace rapidly and “everybody around" is tested.

4. He is able to confirm “test response time”. According to the Websites of Corona test centers about the timing here are the data:
- testing takes 4-5 hours in the test lab
- the total time for obtaining results depends on the delivery time and possible queueing. The test centers guarantee an answer within 24 hours,
in urgent cases, almost immediately.

Recall Germany and Hong Kong co-designed the testing kits early on with results on Jan 17 and being adopted as WHO standard by aJan 24.
The first test was designed in Berlin on Jan 10 by a group of Professor Dr. Christian Drosten (who became very popular in Germany).

There are no patents on the tests. And this has resulted in a boom of local small to medium sized companies that produce test sets. (I asked him spefifically who the vendors are producing these testing kits and processing the labs).

5. An app for contact tracing has been introduced in Germany on June 16 and has become available in the beginning of July in all states of the European Union and some other countries. It is available in 20 different languages and can be downloaded for free from many app stores. The official "editor" of the app is the Robert Koch Institute in Berlin, but the app itself was developed by SAP and Deutsche Telekom with the support of 25 different companies, including Apple and Google because the interfaces of their operation systems had to be employed. It is impossible to figure out which type of person did what. The app is based on Bluetooth. Right now about 16 million Germans have downloaded the app.

As far as he knows, the app was not really successful, since the infection numbers are very low and the number of warnings are minimal. It would
be interesting to see the “reaction” of the app when there is a bigger outbreak or a second wave coming.

But still everybody believes that the app is an important additional tool in the toolbox for fighting the Corona virus. People are sure that it will help
in case of possible future outbreaks.

6. From my own experience, in Germany, all the buildings (business, hotels, obviously residential) have windows that can be opened. Naturally it is easy for them to have fresh air from outside. The school I work with has to renovate to have fresh air pumping in every 30 minutes. Open-air restaurant seatings are common practice also. Across the country, hygiene standards are high.

This is for Germany. Pretty ,much the same pattern for Italy, France, Spain, Switzerland, Denmark, (not Sweden).

Evaluation Only. Created with Aspose.HTML. Copyright 2013-2020 Aspose Pty Ltd.low is one for Israel.

On Mon, Jul 20, 2020 at 7:32 AM (b)(6) (b)(6) <cmecher@charter.net> wrote:

> Was curious and pulled the current COVID hospitalization rates for age groups from CDC. https://www.cdc.gov/coronavirus/2019-ncov/covid-data/covidview/index.html I then went back to the EIP data for flu hospitalizations and pulled the maximum recorded flu hospitalization rates for each age group. The 2017-18 season was the most severe overall and for ages ≥18; 2003-4 was most severe for ages 0-4 and 2009-10 most severe for ages 5-17. COVID hospitalizations reported by CDC (thru July 11) are added for comparison.

Age Category	Maximum Flu Hospitalization Rate per 100K	Season of Maximum	Current COVID Hospitalization Rate per 100K
0-4 yr	89.8	2003-04	10.6
5-17 yr	25.2	2009-10	5.3
18-49 yr	30	2017-18	72.4
50-64 yr	112.9	2017-18	171.8
65+ yr	437.4	2017-18	321.8
Overall	102.9	2017-18	113.6

> For context, the population distribution in the US by these age groups is provided below. The age group 18-64 has COVID hospitalization rates significantly higher than recorded maximum flu hospitalization rates. This demographic is also very large (200M).

Age Group	US Population 2019
0-4	19,576,683
5-17	53,461,244
18-49	137,050,390
50-64	62,906,022
65+	54,058,263
Total	327,052,602

But what is really striking in terms of hospitalization rates are the differences by race and ethnicity.

Here is a comparison of COVID hospitalizations per 100K by age group and flu hospitalization per 100K by age group for the 2017-18 season.

2017-18 flu season for comparison.
Sent from Mail for Windows 10

Sent from Mail for Windows 10

From: Dr. (b)(6)
Sent: Monday, July 20, 2020 4:57 AM
To: (b)(6)
Cc: (b)(6) MD; (b)(6) You, Edward H. (WMD) (FBI); Dr. (b)(6) (DSHS); Caneva, Duane; (b)(6) Keim, MD MBA; (b)(6) W; (b)(6) (HMFP - Emergency Medicine); (b)(6) BOURNE, ALEXANDRA; (b)(6) McDonald, Eric; (b)(6) V.,M.D.; (b)(6) S; (b)(6) McGinn, (b)(6) Kellermann; (b)(6) Eastman, (b)(6) LLogandakar; Walters, (b)(6) DC; (b)(6) JtCIVtUSARMY (USA); (b)(6) Desjardins, MD; Fantinato, Jessica (USDA.GOV); Martin, Greg (b)(6) KAUSHIK, SANGEETA; (b)(6) Larry G; Ignacio, Joselito; (b)(6) Hassell, (b)(6) (Chris) (OS/ASPR/IO); (b)(6)); (b)(6) WILKINSON, THOMAS; WOLFE, HERBERT; (b)(6) Marinissen, Maria (HHS/OS/OGA); Sutter, (b)(6) Krohmer, Jon (NHTSA); (b)(6) (APHMFP - Emergency Medicine); (b)(6)
Subject: Re: Red Dawn Rhapsodizing Begin July 2, 2020

I want to share with you some recent analysis on re-opening and case escalation. This relates to the April analysis I did to:

- Determine when to re-open
  - At which risk posture should a city/jurisdiction reopen
  - How to re-open (business, daily services, religion groups, schools)
- Determine optimal testing sampling size for disease containment
  - 1% to 5% (The optimal is 3%)
  - Testing accuracy
- Case isolation requirement
  - Use dorm/hotel rooms

- COVID-19 Hospital bed capacity

I want to overlay the current increase cases onto these curves for validation (3rd and 4th graph). This offers a means to validate and quantify the risk posture of each site at the time of re-opening.

Briefly, the first two graphs from April correspond to reopening while at various states of risk postures: high risk, medium risk, low risk, and within each, we have re-open all, maintain school closure, maintain school closure + 25% telework. The risk posture is defined based on the amount of community spread, current infection rate, and how far the epi curve is from the plateau.

This is for a city of a million: Different line types denote different levels of strategic sample testing and accuracy. The curve measures the infection escalation with respect to the date of re-opening.

When I sent around the counties that are ready to re-open (14 days 0-nadir)), they correspond to the low-risk posture group.

Below I first plot the current escalated cases with respect to the re-opening date for 11 cities (all normalized to per 1 million).

Next, I plot 10 States. We can see Arizona, Florida, Arkansas, California, Delaware, Georgia, all correspond to high-risk re-opening. DC is escalating somewhat. I hope Connecticut, Alaska, Colorado can follow the Red lines, that's medium risk with school closure.

It remains critical to look at city/county level to determine restrict-and-relax strategies, since they reflect the local situation better than looking at the entire state. E.g., Los Angeles vs San Diego / Santa Clara. However, always keep in mind the interdependencies and cascading effects: your neighbors are equally important.

As mentioned on May 13, it is very important we perform good biosurveillance as a way to inform decision/policy makers since decisive restriction MUST BE MADE in a timely manner as we start to relax. It is relax-and-restrict (strategic restriction at the earliest sign of potential community spread). If done right, and over time, it will be longer (period of) relax, shorter (period of) restrict for every single step. We see this in S. Korea, in Singapore, in Hong Kong. Mathematically, such a sequence will converge to a very nice result of the relaxation stage with not much restriction anymore.
I will send along a graph with all 50 States on.

On Sun, Jul 19, 2020 at 9:18 PM (b)(6) (b)(6) (b)(6) wrote:

Florida:

Sent from Mail for Windows 10

From: Dr. (b) (b)
Sent: Sunday, July 19, 2020 8:14 PM
To: (b) (b)(6) MD
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Subject: Re: Red Dawn Rhapsodizing Begin July 2, 2020

I apologize, spooked by bing's wrong statistics!! Too many sites and every one is different.

On Sun, Jul 19, 2020 at 7:57 PM Dr. (b) (b) (b)(6) wrote:

Total now iis 9,964... it was more than double within 24 hours from 4805 to 9964. As we have discussed, deaths are delayed (initially)....

On Sun, Jul 19, 2020 at 7:32 PM (b) (b)(6) MD (b)(6) wrote:

How many deaths in Florida?

Sent from my iPhone

Robert G. (b)(6) MD, FACEP
Founder, Chief Medical Officer
Patronus Medical
(b)(6)
(b)(6)

Mobile: (b)(6)
Fax: 703-738-7605

On Jul 19, 2020, at 19:13, Dr. (b) (b)
(b)(6) wrote:

1. Florida: Some serious news about mortality in Florida -5,159 cases of deaths for the last 24 hours.

2. School re-open has to be done by regions. There is no one-size-fit-all. We need to look at risk posture at each location to determine when and how to re-open. Brian and I have worked with one K12 school and it was opened successfully 2 weeks ago. So far so good. The school has done many things to renovate the environment to minimize disease transmission -- renovating the restroom (automate and handfree all process), circulating fresh air every 30 minutes, requiring face masks, keeping distance over 6 feet apart for each student indoors and outside, keeping class size to about 6-15 students, partnering with a hospital to handle health situations, implementing the screening tools for use by each student and staff. Of the 400 students, 104 chose to stay home for online learning. The kids are happy. We will see how long it sustains and I will report.

3. Some situations in other parts of the world that have been able to contain thus far, yet new situations regarding community spread:

Hong Kong has the first nursing home infection -- 1 single case and within 2 days, 80% of the nursing home residents became infected.

Hong Kong (1886 cases) and Japan (24,132 cases) are experiencing similar recent community spread.

In Hong Kong, that relates to a case from a bar, every similar to S. Korea's last case from a nightclub.

Japan (24,132 cases):
Hong Kong (1,885 cases): The first spike was from imported cases from Europe. This (current) is the first community spread they have experienced. Singapore's imported cases from Europe led to community spread (adding over 42,000 cases to Singapore).

Singapore (47,912 cases): The imported cases from Europe led to community spread and that led to over 45,000 cases. It is winding down.
4. Mexico is escalating, so is Texas.

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Sent Date:	2020/07/24 13:46:37
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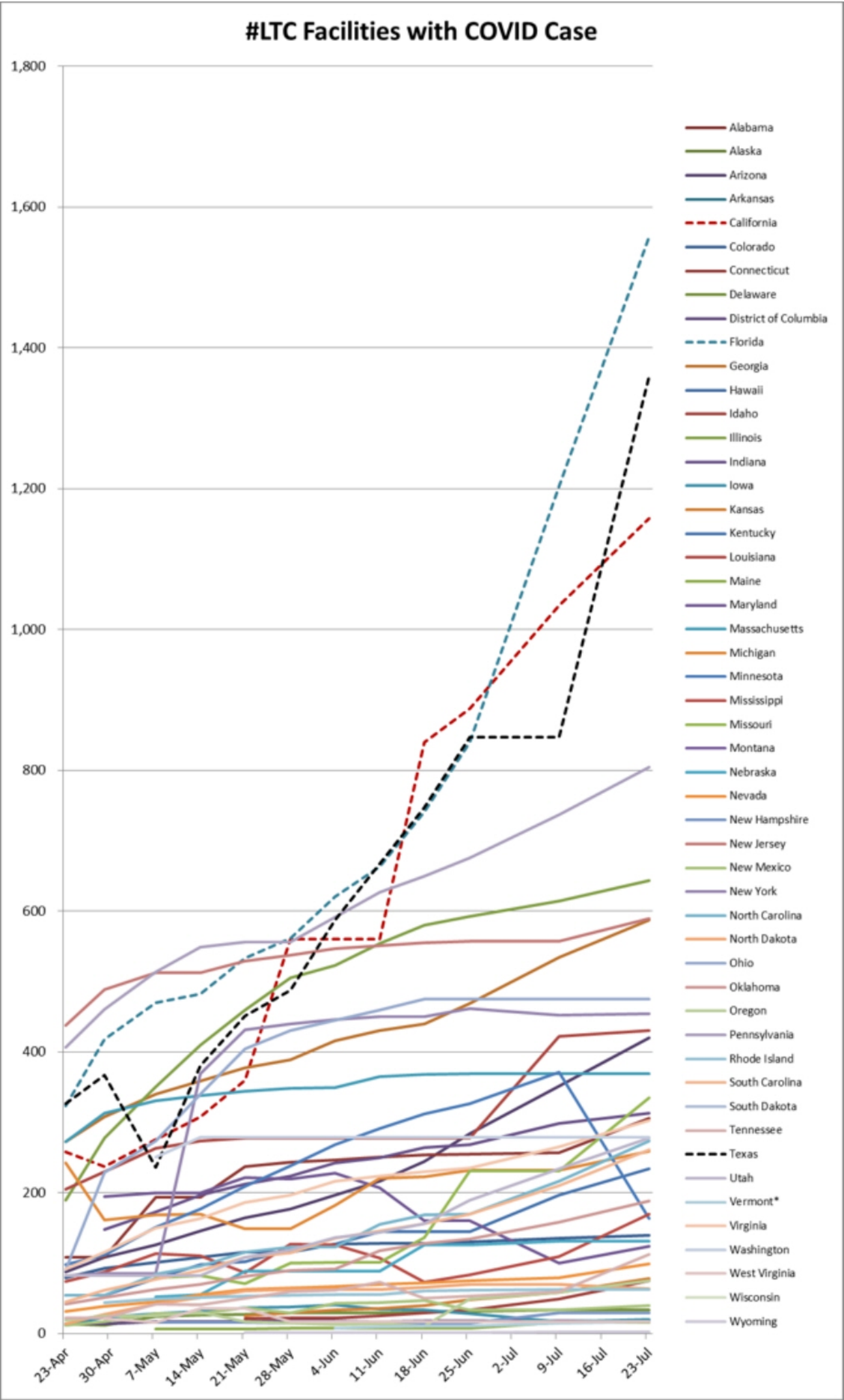
#LTC Facilities with COVID Case
1,800
1,600
1,400
1,200
1,000
800
600
400
200
0
23-Apr
30-Apr
7-May
14-May
21-May
28-May
4-Jun
11-Jun
18-Jun
25-Jun
2-Jul
9-Jul
16-Jul
23-Jul
Alabama
Alaska
Arizona
Arkansas
California
Colorado
Connecticut
Delaware
District of Columbia
Florida
Georgia
Hawaii
Idaho
Illinois
Indiana
Iowa
Kansas
Kentucky
Louisiana
Maine
Maryland
Massachusetts
Michigan
Minnesota
Mississippi
Missouri
Montana
Nebraska
Nevada
New Hampshire
New Jersey
New Mexico
New York
North Carolina
North Dakota
Ohio
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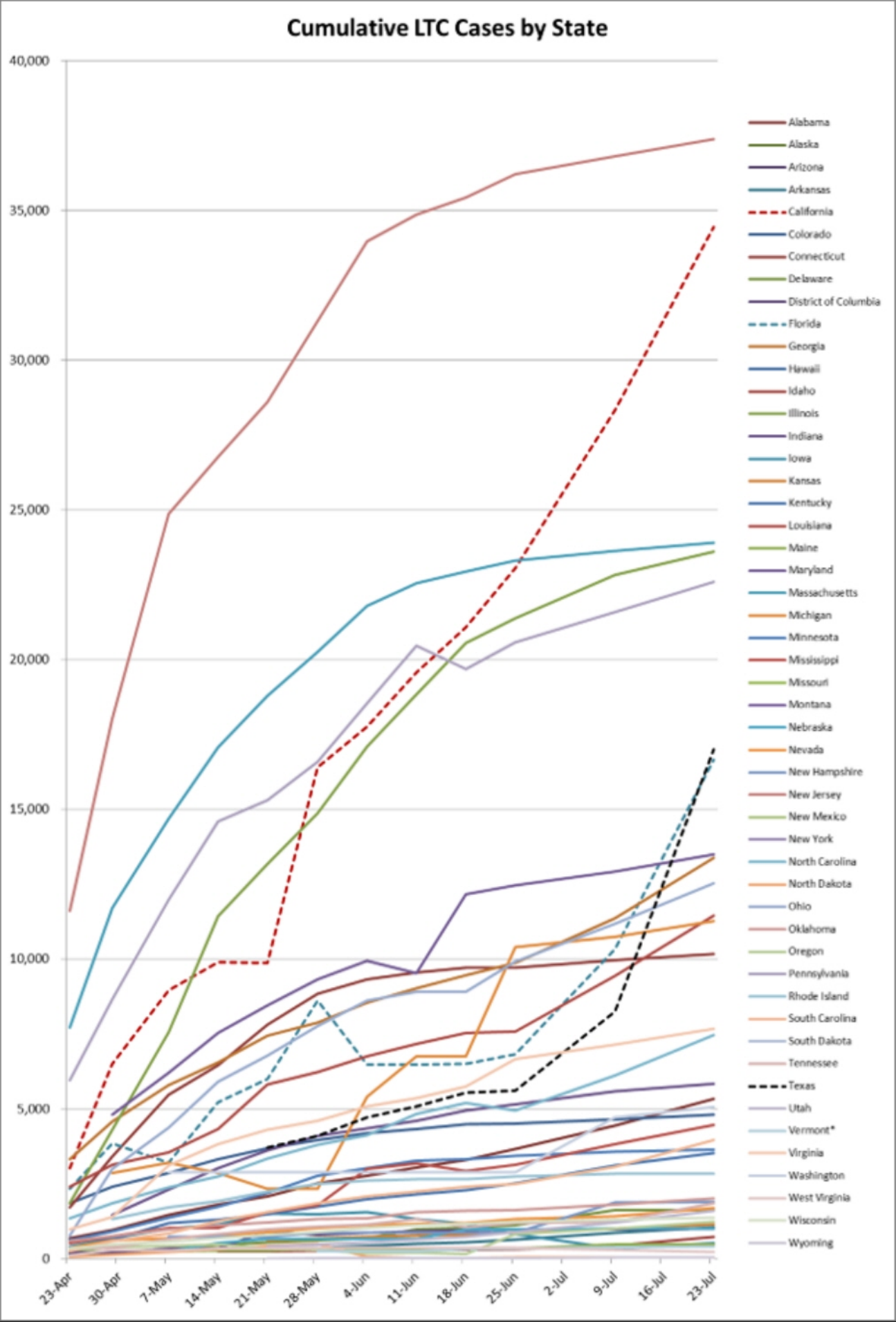
Washington
West Virginia
Wisconsin
Wyoming


Cumulative LTC Cases by State
40,000
35,000
30,000
25,000
20,000
15,000
10,000
5,000
0
23-Apr
30-Apr
7-May
14-May
21-May
28-May
4-Jun
11-Jun
18-Jun
25-Jun
2-Jul
9-Jul
16-Jul
23-Jul
Alabama
Alaska
Arizona
Arkansas
California
Colorado
Connecticut
Delaware
District of Columbia
Florida
Georgia
Hawaii
Idaho
Illinois
Indiana
Iowa
Kansas
Kentucky
Louisiana
Maine
Maryland
Massachusetts
Michigan
Minnesota
Mississippi
Missouri
Montana
Nebraska
Nevada
New Hampshire
New Jersey
New Mexico
New York
North Carolina
North Dakota
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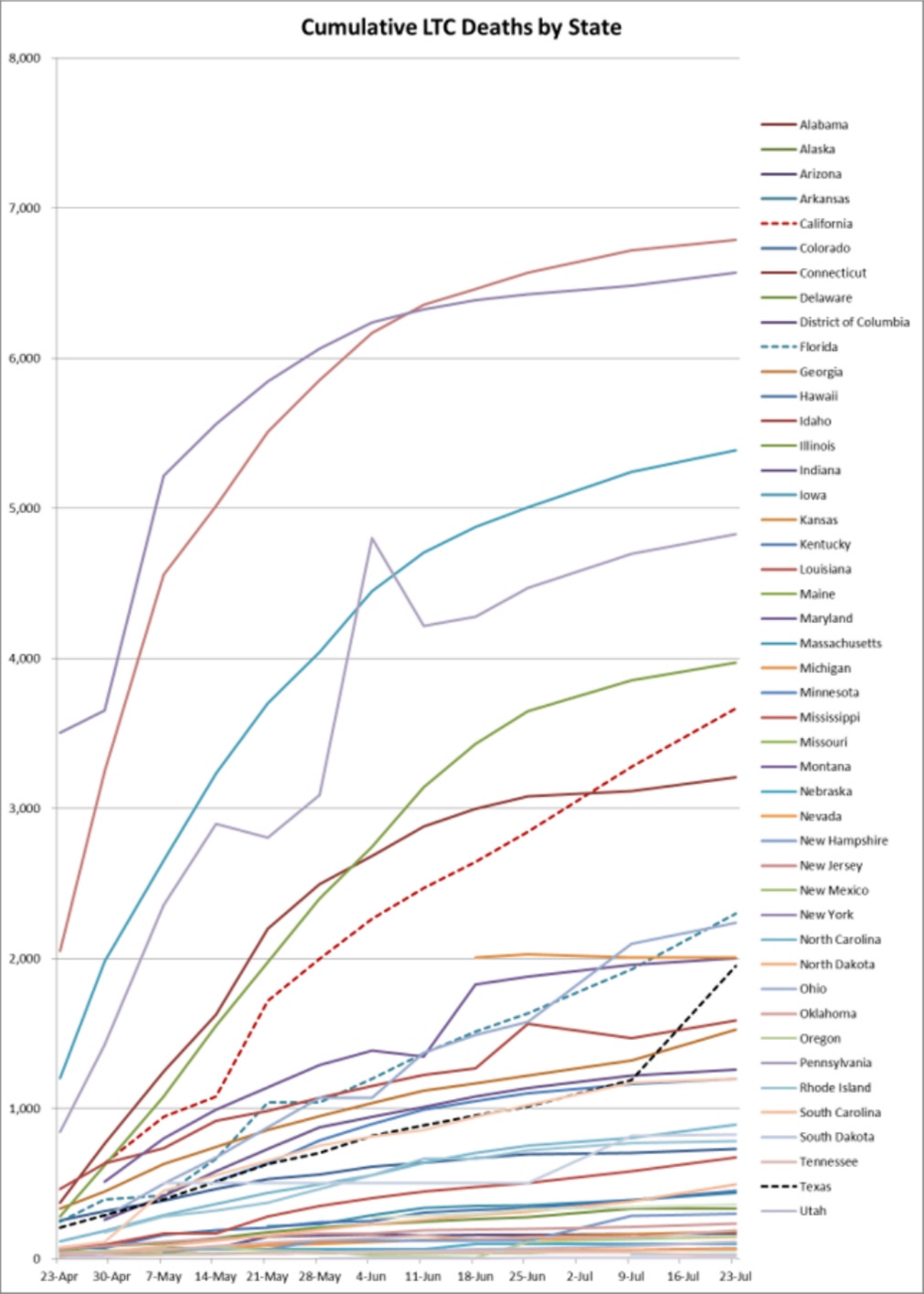
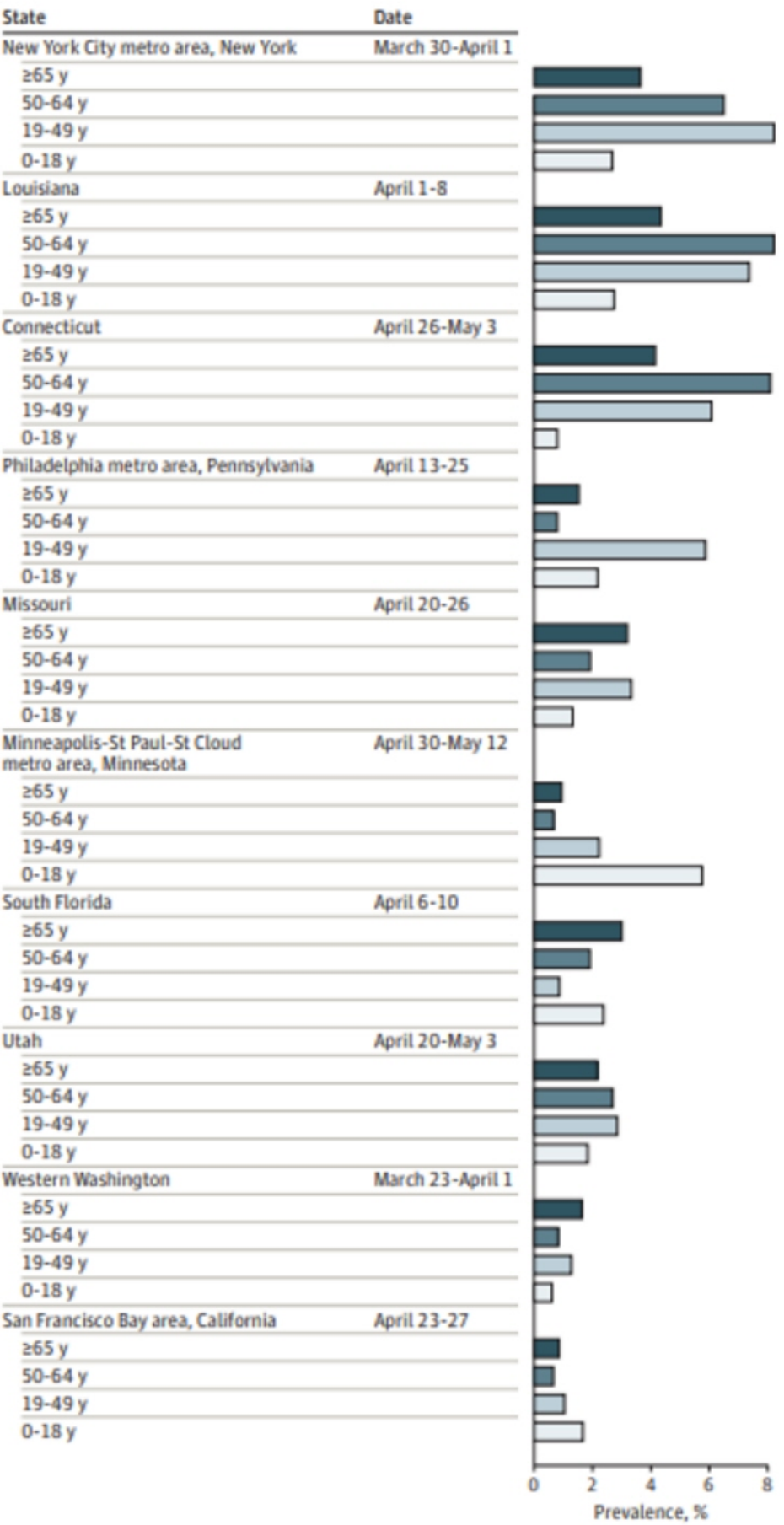
Washington
West Virginia
Wisconsin
Wyoming


Cumulative LTC Deaths by State
8,000
7,000
6,000
5,000
4,000
3,000
2,000
1,000
0
23-Apr
30-Apr
7-May
14-May
21-May
28-May
4-Jun
11-Jun
18-Jun
25-Jun
2-Jul
9-Jul
16-Jul
23-Jul
Alabama
Alaska
Arizona
Arkansas
California
Colorado
Connecticut
Delaware
District of Columbia
Florida
Georgia
Hawaii
Idaho
Illinois
Indiana
Iowa
Kansas
Kentucky
Louisiana
Maine
Maryland
Massachusetts
Michigan
Minnesota
Mississippi
Missouri
Montana
Nebraska
Nevada
New Hampshire
New Jersey
New Mexico
New York
North Carolina
North Dakota
Ohio
Oklahoma
Oregon
Pennsylvania
Rhode Island
South Carolina
South Dakota
Tennessee
Texas
Utah

B Estimates of seroprevalence by age group



DHS SCIENCE AND TECHNOLOGY

Master Question List for COVID-19 (caused by SARS-CoV-2)

Weekly Report

21 July 2020

For comments or questions related to the contents of this document, please contact the DHS S&T Hazard Awareness & Characterization Technology Center at (b)(6)

Homeland Security

Science and Technology

CLEARED FOR PUBLIC RELEASE

FOREWORD

The Department of Homeland Security (DHS) is paying close attention to the evolving Coronavirus Infectious Disease (COVID-19) situation in order to protect our nation. DHS is working very closely with the Centers for Disease Control and Prevention (CDC), other federal agencies, and public health officials to implement public health control measures related to travelers and materials crossing our borders from the affected regions.

Based on the response to a similar product generated in 2014 in response to the Ebolavirus outbreak in West Africa, the DHS Science and Technology Directorate (DHS S&T) developed the following "master question list" that quickly summarizes what is known, what additional information is needed, and who may be working to address such fundamental questions as, "What is the infectious dose?" and "How long does the virus persist in the environment?" The Master Question List (MQL) is intended to quickly present the current state of available information to government decision makers in the operational response to COVID-19 and allow structured and scientifically guided discussions across the federal government without burdening them with the need to review scientific reports, and to prevent duplication of efforts by highlighting and coordinating research.

The information contained in the following table has been assembled and evaluated by experts from publicly available sources to include reports and articles found in scientific and technical journals, selected sources on the internet, and various media reports. It is intended to serve as a "quick reference" tool and should not be regarded as comprehensive source of information, nor as necessarily representing the official policies, either expressed or implied, of the DHS or the U.S. Government. DHS does not endorse any products or commercial services mentioned in this document. All sources of the information provided are cited so that individual users of this document may independently evaluate the source of that information and its suitability for any particular use. This document is a "living document" that will be updated as needed when new information becomes available.

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Infectious Dose – How much agent will make a healthy individual ill? 3
The human infectious dose of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is unknown by all exposure routes. Studies from other animal models are used as surrogates for humans. Based on primate models, the inhalation median infectious dose (ID_{50}) in humans is likely less than 10,000 PFU, and possibly less than 1,000 PFU.
Identifying the infectious dose for humans by the various routes through which we become infected is critical to the effective development of computational models to predict risk, develop diagnostics and countermeasures, and effective decontamination strategies. Animal studies are a plausible surrogate.
Transmissibility – How does it spread from one host to another? How easily is it spread? 4
SARS-CoV-2 is passed easily between humans, likely through close contact with relatively large droplets and possibly through smaller aerosolized particles.
Individuals can transmit SARS-CoV-2 to others before they have symptoms.
Undetected cases play a major role in transmission, and most cases are not reported.[611]
Individuals who have recovered clinically, but test positive, appear unable to transmit COVID-19.
The relative contribution of different routes of transmission, such as close contact and droplet transmission versus aerosol transmission and contaminated objects and surfaces (fomites), is unknown and requires additional research.
Host Range – How many species does it infect? Can it transfer from species to species? 5
SARS-CoV-2 is closely related to other coronaviruses circulating in bats in Southeast Asia. Previous coronaviruses have passed through an intermediate mammal host before infecting humans, but the identity of the SARS-CoV-2 intermediate host is unknown.
SARS-CoV-2 uses the same receptor for cell entry as the SARS-CoV-1 coronavirus that circulated in 2002/2003.
To date, ferrets, mink, hamsters, cats, and primates have been shown to be susceptible to SARS-CoV-2 infection. It is unknown whether these animals can transmit infection to humans.
Several animal models have been developed to recreate human-like illness, though to date they have been infected with high dose exposures. Lower dose studies may better replicate human disease acquisition.
Incubation Period – How long after infection do symptoms appear? Are people infectious during this time? 6
The majority of individuals develop symptoms within 14 days of exposure. For most people, it takes at least 2 days to develop symptoms, and on average symptoms develop 5 days after exposure. Incubating individuals can transmit disease for several days before symptom onset. Some individuals never develop symptoms but can still transmit disease.
The incubation period is well-characterized. Patients may be infectious, however, for days before symptoms develop.
Clinical Presentation – What are the signs and symptoms of an infected person? 7
Approximately 40% of cases are asymptomatic.[397] Most symptomatic cases are mild, but severe disease can be found in any age group.[4] Older individuals and those with underlying medical conditions are at higher risk of serious illness and death.
The case fatality rate (CFR) varies substantially by patient age and underlying comorbidities.[570]
Additional studies on vulnerable subpopulations are required.
Children are susceptible to COVID-19,[142] though generally show milder[95, 332] or no symptoms.
The true case fatality rate is unknown, as the exact number of cases is uncertain. Testing priorities and case definitions vary by location. The proportion of asymptomatic infections is not known.
Protective Immunity – How long does the immune response provide protection from reinfection? 8
Infected patients show productive immune responses, but the duration of any protection is unknown. Initial evidence suggests that the neutralizing antibody response does not last more than a few months, though this varies by severity.
Currently, there is no evidence that recovered patients can be reinfected with SARS-CoV-2.
As the pandemic continues, long-term monitoring of immune activity and reinfection status is needed.
Clinical Diagnosis – Are there tools to diagnose infected individuals? When during infection are they effective? 9
Diagnosis relies on identifying the genetic signature of the virus in patient nose, throat, or sputum samples, or by identifying SARS-CoV-2 antibodies in individuals exposed to the virus. Confirmed cases are still underreported.
Validated serological (antibody) assays are being used to help determine who has been exposed to SARS-CoV-2. Serological evidence of exposure does not indicate immunity.

In general, PCR tests appear to be sensitive and specific, though confirmation of symptoms via chest CT is recommended.
The sensitivity and specificity of serological testing methods is variable, and additional work needs to be done to determine factors that affect test accuracy.
Medical Treatments – Are there effective treatments? **10**
Treatment for COVID-19 is primarily supportive care,[201, 351] and no single standard of care exists. Drug trials are ongoing.
Remdesivir shows promise for reducing symptom duration[41] and mortality[188] in humans.
Hydroxychloroquine is associated with risk of cardiac arrhythmias and provides limited to no clinical benefit at this time.
Dexamethasone may significantly reduce mortality in severely ill and ventilated patients.
Other pharmaceutical interventions are being investigated.
Additional information on treatment efficacy is required, particularly from large randomized clinical trials.
Vaccines – Are there effective vaccines? **11**
Work is ongoing to develop and produce a SARS-CoV-2 vaccine (e.g., Operation Warp Speed).[38, 206, 209-211, 386] Early results are being released, but evidence should be considered preliminary until larger trials are completed.
Published results from randomized clinical trials (Phase I – III) are needed.
Non-pharmaceutical Interventions – Are public health control measures effective at reducing spread? **12**
Broad-scale control measures such as stay-at-home orders are effective at reducing transmission.
Research is needed to help plan for easing of restrictions. Testing is critical, and synchronized interventions may help.
As different US states have implemented differing control measures at various times, a comprehensive analysis of social distancing efficacy has not yet been conducted.
Environmental Stability – How long does the agent live in the environment? **13**
SARS-CoV-2 can persist on surfaces for at least 3 days and on the surface of a surgical mask for up to 7 days depending on conditions. If aerosolized intentionally, SARS-CoV-2 is stable for at least several hours. The seasonality of COVID-19 transmission is unknown. SARS-CoV-2 on surfaces is inactivated rapidly with sunlight.
Additional testing on SARS-CoV-2, as opposed to surrogate viruses, is needed to support initial estimates of stability. Tests quantifying infectivity, rather than the presence of viral RNA, are needed.
Decontamination – What are effective methods to kill the agent in the environment? **14**
Soap and water, as well as common alcohol and chlorine-based cleaners, hand sanitizers, and disinfectants are effective at inactivating SARS-CoV-2 on hands and surfaces.
Additional decontamination studies, particularly with regard to PPE and other items in short supply, are needed.
PPE – What PPE is effective, and who should be using it? **15**
The effectiveness of PPE for SARS-CoV-2 is currently unknown, and data from other related coronaviruses are used for guidance. Healthcare workers are at high risk of acquiring COVID-19, even with recommended PPE.
Most PPE recommendations have not been made on SARS-CoV-2 data, and comparative efficacy of different PPE for different tasks (e.g., intubation) is unknown. Identification of efficacious PPE for healthcare workers is critical due to their high rates of infection.
Forensics – Natural vs intentional use? Tests to be used for attribution. **16**
All current evidence supports the natural emergence of SARS-CoV-2 via a bat and possible intermediate mammal species.
Identifying the intermediate species between bats and humans would aid in reducing potential spillover from a natural source. Wide sampling of bats, other wild animals, and humans is needed to address the origin of SARS-CoV-2.
Genomics – How does the disease agent compare to previous strains? **17**
Current evidence suggests that SARS-CoV-2 accumulates substitutions and mutations at a similar rate as other coronaviruses. Mutations and deletions in specific portions of the SARS-CoV-2 genome have not been linked to any changes in transmission or disease severity, though modeling work is attempting to identify possible changes.
Research linking genetic changes to differences in phenotype (e.g., transmissibility, virulence, progression in patients) is needed.
Forecasting – What forecasting models and methods exist? **18**
Forecasts differ in how they handle public health interventions such as shelter-in-place orders and tracking how methods change in the near future will be important for understanding limitations going forward.

Infectious Dose – How much agent will make a healthy individual ill?

What do we know?

The human infectious dose of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is unknown by all exposure routes. Studies from other animal models are used as surrogates for humans. Based on primate models, the inhalation median infectious dose (ID_{50}) in humans is likely less than 10,000 PFU, and possibly less than 1,000 PFU.

Non-human primates

- A total dose of approximately 700,000 plaque-forming units (PFU) of the novel coronavirus SARS-CoV-2 infected cynomolgus macaques via combination intranasal and intratracheal exposure (10^6 $TCID_{50}$ total dose).[452] Macaques did not exhibit clinical symptoms, but shed virus from the nose and throat.[452]
- Rhesus and cynomolgus macaques showed mild to moderate clinical infections at doses of $4.75x10^6$ PFU (SARS-CoV-2 delivered through several routes), while common marmosets developed mild infections when exposed to $1.0x10^6$ PFU intranasally.[331]
- Rhesus macaques are effectively infected with SARS-CoV-2 via the ocular conjunctival and intratracheal route at a dose of approximately 700,000 PFU (10^6 $TCID_{50}$).[135] Rhesus macaques infected with 2,600,000 $TCID_{50}$ of SARS-CoV-2 by the intranasal, intratracheal, oral and ocular routes combined recapitulate moderate human disease.[380]
- African green monkeys replicate aspects of human disease, including severe pathological symptoms (exposed to 500,000 PFU via intranasal and intratracheal routes),[577] mild clinical symptoms (aerosol exposures between 5,000 and 16,000 PFU),[213] and acute respiratory distress syndrome (ARDS), with small particle aerosol exposure doses as low as 2,000 PFU.[51]
- Aerosol exposure of three primate species (African green monkeys, cynomolgus macaques, and rhesus macaques) via a Collison nebulizer resulted in mild clinical disease in all animals with doses between 28,700 and 48,600 PFU.[251]

Rodents

- Golden Syrian hamsters exposed to 80,000 $TCID_{50}$ (~56,000 PFU) via the intranasal route developed clinical symptoms reminiscent of mild human infections (all hamsters infected).[489] In a separate study, immunosuppressed Golden Syrian hamsters showed severe clinical symptoms (including death) after exposure to 100-10,000 PFU via intranasal challenge.[59]
- Golden Syrian hamsters infected with 100,000 PFU intranasally exhibited mild clinical symptoms and developed neutralizing antibodies,[91] and were also capable of infecting individuals in separate cages. In another study, older hamsters had more severe symptoms and developed fewer neutralizing antibodies than younger hamsters.[399]
- Mice genetically modified to express the human ACE2 receptor (transgenic hACE2 mice) were inoculated intranasally with 100,000 $TCID_{50}$ (~70,000 PFU), and all mice developed pathological symptoms consistent with COVID-19.[34]
- Transgenic (hACE2) mice became infected after timed aerosol exposure (36 $TCID_{50}$/minute) to between 900 and 1080 $TCID_{50}$ (~630-756 PFU). All mice (4/4) exposed for 25-30 minutes became infected, while no mice (0/8) became infected after exposure for 0-20 minutes (up to 720 $TCID_{50}$, ~504 PFU).[35] Key methodological details (e.g., particle size, quantification of actual aerosol dose) are missing from the study's report.
- Transgenic (hACE2) mice exposed intranasally to 400,000 PFU of SARS-CoV-2 develop clinical and pathological symptoms seen in humans.[507]

Other animal models

- Ferrets infected with 316,000 $TCID_{50}$[263] or 600,000 $TCID_{50}$[443] of SARS-CoV-2 by the intranasal route show similar symptoms to human disease.[263, 443] Uninfected ferrets in direct contact with infected ferrets test positive and show disease as early as 2 days post-contact.[263] In one study, direct contact was required to transfer infection between ferrets,[263] however, transmission without direct contact was found in another study.[443]
- In a ferret study, 1 in 6 individuals exposed to 10^2 PFU via the intranasal route became infected, while 12 out of 12 individuals exposed to $>10^4$ PFU became infected.[462]
- Domestic cats exposed to 100,000 PFU of SARS-CoV-2 via the intranasal route developed severe pathological symptoms including lesions in the nose, throat, and lungs.[487] In a separate study, infected cats showed no clinical signs, but were able to shed virus and transmit to other cats.[54]

Related Coronaviruses

- The infectious dose for severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1) in mice is estimated to be between 67-540 PFU (average 240 PFU, intranasal route).[130, 132]
- Genetically modified mice expressing DPP4 exposed intranasally to doses of Middle East respiratory syndrome coronavirus (MERS-CoV) between 100 and 500,000 PFU show signs of infection. Infection with higher doses result in severe syndromes.[13, 113, 301, 620]

What do we need to know?

Identifying the infectious dose for humans by the various routes through which we become infected is critical to the effective development of computational models to predict risk, develop diagnostics and countermeasures, and effective decontamination strategies. Animal studies are a plausible surrogate.

- Human infectious dose by aerosol, surface contact (fomite), fecal-oral routes, and other potential routes of exposure
- Most appropriate animal model(s) to estimate the human infectious dose for SARS-CoV-2

Transmissibility – How does it spread from one host to another? How easily is it spread?

What do we know?

SARS-CoV-2 is passed easily between humans, likely through close contact with relatively large droplets and possibly through smaller aerosolized particles.

- As of 7/21/2020, pandemic COVID-19 has caused 14,730,716 infections and 610,587 deaths[244] in 188 countries and territories.[80, 478, 566] There are 3,831,450 confirmed COVID-19 cases across all 50 US states, with 140,909 deaths.[244]
- Initial high-quality estimates of human transmissibility (R_0) range from 2.2 to 3.1,[346, 408, 447, 585, 619] though recent estimates suggest that early transmission rates were higher.[467] Transmission rates can vary substantially among neighboring populations.[191, 547] The majority of new infections come from relatively few infectious individuals.[10, 152]
- SARS-CoV-2 is believed to spread through close contact and droplet transmission,[85] with fomite transmission[247] and close-contact aerosol transmission likely.[20, 60, 200, 375] On 7/9/2020, the WHO acknowledged that aerosol transmission is plausible, and could not be ruled out in all cases.[568]
- SARS-CoV-2 replicates in the upper respiratory tract,[222] and infectious virus is detectable in throat and lung tissue for at least 8 days.[572] Respiratory fluids from severely ill patients contained higher viral RNA loads than respiratory fluids from mildly ill patients,[623] but similar viral RNA loads have been found in asymptomatic and symptomatic individuals.[290]
- Contamination of patient rooms with aerosolized SARS-CoV-2 in the human respirable range (0.25-2.5 µm) indicates the potential for airborne transmission.[324] Viral RNA was detected up to 4 meters from ICU patient beds.[203] To date infectious virus has not been isolated from aerosol samples.[469]
- SARS-CoV-2 may be spread by conversation and exhalation.[7, 299, 469, 499] A preliminary study in China detailing a restaurant-associated outbreak supports transmission via aerosol.[309] Contact tracing in Japan has identified clusters associated with large gatherings in bars, restaurants, music festivals, and other social activities involving close contact.[606] Clusters of COVID-19 cases tend to come from indoor locations such as bars[292] and offices.[409]
- Experimentally infected ferrets were able to transmit SARS-CoV-2 to other ferrets through the air (ferrets in an adjacent enclosure, separated by 10 cm).[442] Similar results have been documented in transgenic mice.[35]
- At least one case of vertical transmission has been confirmed from mother to infant prior to birth,[533] though most evidence suggests this is rare.[97, 102, 105, 476, 515, 597, 602]
- SARS-CoV-2 RNA has been found in semen from both clinically symptomatic and recovered cases,[300] but the potential for sexual transmission is unknown. Infectious SARS-CoV-2 has been cultured from patient feces[590] and urine.[505]
- Older children (>10 years old) appear to transmit SARS-CoV-2 as frequently as adults, while younger children (<10 years old) appear to transmit infection less often.[410] These estimates, however, were generated during school closures, and may underestimate the risk of infection from school-age children.

Individuals can transmit SARS-CoV-2 to others before they have symptoms.

- Individuals may be infectious for 1-3 days prior to symptom onset,[553] and culturable virus has been found up to 6 days prior to symptom onset.[26] Pre-symptomatic[52, 270, 498, 504, 594, 622] or asymptomatic[33, 227, 336] patients can transmit SARS-CoV-2, and asymptomatic individuals shed virus for as long as mildly symptomatic individuals.[327] At least 12% of all cases are estimated to be due to asymptomatic transmission.[145] It has been estimated that 23-56% of infections may be caused by pre-symptomatic transmission.[76, 216, 321] Individuals are most infectious before symptoms begin and within 5 days of symptom onset,[104] and pre-symptomatic individuals contribute to environmental contamination.[245]
- Attack rates of the virus are higher among household members than casual contacts.[64, 484] The attack rate ranges from 11%,[46] 16%,[305] and 38%[454] of household members, with rates increasing with age.[454] The attack rate for children is low in households with an adult COVID-19 case (6.1% overall), and is lowest for children <5 years old (1.3%).[607] Individuals transmit infection to household members before they exhibit symptoms at least as often as they do after symptoms develop.[248] Transmission rates are high in confined areas such as prisons.[465]

Undetected cases play a major role in transmission, and most cases are not reported.[611]

- Models suggest up to 86% of early COVID-19 cases in China were undetected, and these infections were the source for 79% of reported cases.[304] Models estimate that the true number of cases may be approximately 11 times greater than the reported number of cases in the UK,[599] and 5 to 10 times greater than the reported number of cases in the US.[249, 461, 490]

Individuals who have recovered clinically, but test positive, appear unable to transmit COVID-19.

- Individuals who have clinically recovered from COVID-19, but later show PCR positive tests, are likely not infectious.[260]

What do we need to know?

The relative contribution of different routes of transmission, such as close contact and droplet transmission versus aerosol transmission and contaminated objects and surfaces (fomites), is unknown and requires additional research.

- Capability of SARS-CoV-2 to be transmitted by contact with fomites (phones, doorknobs, surfaces, clothing, etc.)
- Is sexual transmission possible?
- Is it possible to determine the route by which someone became infected by the clinical presentation or progression of disease?

Host Range – How many species does it infect? Can it transfer from species to species?

What do we know?

SARS-CoV-2 is closely related to other coronaviruses circulating in bats in Southeast Asia. Previous coronaviruses have passed through an intermediate mammal host before infecting humans, but the identity of the SARS-CoV-2 intermediate host is unknown.

- Early genomic analysis indicates similarity to SARS-CoV-1,[627] with a suggested bat origin.[114, 627]
- Positive samples from the South China Seafood Market strongly suggests a wildlife source,[87] though it is possible that the virus was circulating in humans before the disease was associated with the seafood market.[39, 115, 592, 603]
- Analysis of SARS-CoV-2 genomes suggests that a non-bat intermediate species is responsible for the beginning of the outbreak.[451] The identity of the intermediate host remains unknown.[308, 315, 317]
- Viruses similar to SARS-CoV-2 were present in pangolin samples collected several years ago,[283] and pangolins positive for coronaviruses related to SARS-CoV-2 exhibited clinical symptoms such as cough and shortness of breath.[307] Additionally, there is evidence of vertical transmission in pangolins, suggesting circulation in natural populations.[307]
- However, a survey of 334 pangolins did not identify coronavirus nucleic acid in 'upstream' market chain samples, suggesting that positive samples from pangolins may be the result of exposure to infected humans, wildlife or other animals within the wildlife trade network. These data suggest that pangolins are incidental hosts of coronaviruses.[293] Additional research is needed to identify whether pangolins are a natural host of SARS-COV-2-related coronaviruses.

SARS-CoV-2 uses the same receptor for cell entry as the SARS-CoV-1 coronavirus that circulated in 2002/2003.

- Experiments show that SARS-CoV-2 Spike (S) receptor-binding domain binds the human cell receptor (ACE2) stronger than SARS-CoV-1,[580] potentially explaining its high transmissibility. The same work suggests that differences between SARS-CoV-2 and SARS-CoV-1 Spike proteins may limit the therapeutic ability of SARS antibody treatments.[580]
- Modeling of SARS-CoV-2 Spike and ACE2 proteins suggests that SARS-CoV-2 can bind and infect human, bat, civet, monkey and swine cells.[537] Host range predictions based on structural modeling, however, are difficult,[177] and additional animal studies are needed to better define the host range.
- In vitro experiments suggest a broad host range for SARS-CoV-2, with more than 44 potential animal hosts, based on viral binding to species-specific ACE2 orthologs.[322] The host range is predicted to be limited primarily to mammals.
- Genetic and protein analysis of primates suggests that African and Asian primates are likely more susceptible to SARS-CoV-2, while South and Central American primates are likely less susceptible.[361] Identifying the SARS-CoV-2 host range is important for identifying animal reservoirs.
- Changes in proteolytic cleavage of the Spike protein can also affect cell entry and animal host range, in addition to receptor binding.[362]

To date, ferrets, mink, hamsters, cats, and primates have been shown to be susceptible to SARS-CoV-2 infection. It is unknown whether these animals can transmit infection to humans.

- Animal model studies suggest that Golden Syrian hamsters, primates, and ferrets may be susceptible to infection.[91, 263] In the Netherlands, farmed mink developed breathing and gastrointestinal issues, which was diagnosed as SARS-CoV-2 infection.[1] It is thought that an infected mink has transmitted SARS-CoV-2 to a human.[278] Golden Syrian hamsters are able to infect other hamsters via direct contact and close quarters aerosol transmission.[489]
- Domestic cats are susceptible to infection with SARS-CoV-2 (100,000-520,000 PFU via the intranasal route[487] or a combination of routes[205]), and can transmit the virus to other cats via droplet or short-distance aerosol.[487] Dogs exposed to SARS-CoV-2 produced anti-SARS-CoV-2 antibodies[54] but exhibited no clinical symptoms.[487, 494]
- Wild cats (tigers)[552] can be infected with SARS-CoV-2, although their ability to spread to humans is unknown.[347, 616] Two cases have been confirmed of pet domestic cats infected with SARS-CoV-2.[79]
- Ducks, chickens, and pigs remained uninfected after experimental SARS-CoV-2 exposure (30,000 CFU for ducks and chickens, 100,000 PFU for pigs, all via intranasal route).[487] There is currently no evidence that SARS-CoV-2 infects livestock.[233]
- Pigs and chickens were not susceptible to SARS-CoV-2 infection when exposed to an intranasal dose of 10^5 $TCID_{50}$ (~70,000 PFU), confirmed by lack of positive swab and tissue samples.[473] Fruit bats and ferrets were susceptible to this same exposure.[473]
- Chicken, turkey, duck, quail, and geese were not susceptible to SARS-CoV-2 after experimental exposures.[503]

What do we need to know?

Several animal models have been developed to recreate human-like illness, though to date they have been infected with high dose exposures. Lower dose studies may better replicate human disease acquisition.

- What is the intermediate host(s)?
- Can infected animals transmit to humans (e.g., pet cats to humans)?
- Can SARS-CoV-2 circulate in animal reservoir populations, potentially leading to future spillover events?

Incubation Period – How long after infection do symptoms appear? Are people infectious during this time?

What do we know?

The majority of individuals develop symptoms within 14 days of exposure. For most people, it takes at least 2 days to develop symptoms, and on average symptoms develop 5 days after exposure. Incubating individuals can transmit disease for several days before symptom onset. Some individuals never develop symptoms but can still transmit disease.

- The incubation period of COVID-19 is between 5[289] and 6[554] days.[598] Fewer than 2.5% of infected individuals show symptoms sooner than 2 days after exposure.[289]
- There is evidence that younger and older individuals have longer COVID-19 incubation periods, creating a U-shaped relationship between incubation period length and patient age.[271]
- Individuals can test positive for COVID-19 even if they lack clinical symptoms.[33, 90, 201, 514, 622]
- Individuals can be infectious while asymptomatic,[85, 456, 514, 622] and asymptomatic and pre-symptomatic individuals have similar amounts of virus in the nose and throat compared to symptomatic patients.[26, 262, 630]
- Peak infectiousness may be during the incubation period, one day before symptoms develop.[216] Infectious virus has been cultured in patients up to 6 days before the development of symptoms.[26]
- Infectious period is unknown, but possibly up to 10-14 days.[5, 304, 478]
- Asymptomatic individuals are estimated to be infectious for a median of 9.5 days.[225]
- On average, there are approximately 4[145] to 7.5[303] days between symptom onset in successive cases of a single transmission chain (i.e., the serial interval). Based on data from 339 transmission chains in China, the mean serial interval is between 4.6[598] and 5.29 days.[144]
- Children are estimated to shed virus for 15 days on average, with asymptomatic individuals shedding virus for less time (11 days) than symptomatic individuals (17 days).[333]
- Most hospitalized individuals are admitted within 8-14 days of symptom onset.[625]
- Asymptomatic and mildly ill patients who test positive for SARS-CoV-2 presence take less time to test negative than severely ill patients.[295]
- Patients infected by asymptomatic or young (<20 years old) individuals may take longer to develop symptoms than those infected by other groups of individuals.[554]
- Viral RNA loads in the upper respiratory tract tend to peak within a few days of symptom onset and become undetectable approximately two weeks after symptoms begin.[535] The duration of the infectious period is unknown,[535] though patients can test positive for SARS-CoV-2 viral RNA for extended periods of time, particularly in stool samples.

What do we need to know?

The incubation period is well-characterized. Patients may be infectious, however, for days before symptoms develop.

- What is the average infectious period during which individuals can transmit the disease?
- How infectious are asymptomatic and pre-symptomatic individuals compared to mildly, moderately, or severely ill patients?

Clinical Presentation – What are the signs and symptoms of an infected person?

What do we know?

Approximately 40% of cases are asymptomatic.[397] Most symptomatic cases are mild, but severe disease can be found in any age group.[4] Older individuals and those with underlying medical conditions are at higher risk of serious illness and death.

- Between 16% and 58% of patients are asymptomatic throughout the course of their infection.[66, 290, 295, 371, 388, 509, 519]
- Most symptomatic COVID-19 cases are mild (81%, n=44,000 cases).[514, 569] Initial COVID-19 symptoms include fever (87.9% overall, but only 44-52% present with fever initially),[24, 201] cough (67.7%),[201] fatigue, shortness of breath, headache, and reduced lymphocyte count.[86, 93, 226] Chills, muscle pain, headache, sore throat, and loss of taste or smell[415, 596] are also possible COVID-19 symptoms.[86] GI symptoms are present in approximately 9% of patients,[453] but may be more common in severe cases.[257] Neurological symptoms such as agitation,[217] loss of coordination,[348] and stroke[529] may present with COVID-19,[413] may be more common in severe cases,[122] and neurological involvement (e.g., encephalitis) can be seen in brain tissue on autopsy.[534] Ocular issues[587] and skin lesions[178] may also be symptoms of COVID-19.[55] There are concerns that COVID-19 can lead to new-onset diabetes.[458]
- COVID-19 symptoms, especially fatigue and shortness of breath, commonly persist for several months after initial onset.[74]
- Complications include acute respiratory distress syndrome (ARDS, 17-29% of hospitalized patients, leading to death in 4-15% of cases),[101, 226, 540] pneumonia,[404] cardiac injury (20%),[488] secondary infection, kidney damage,[25, 501] arrhythmia, sepsis, stroke (1.6% of hospitalized patients),[365] and shock.[201, 226, 540, 625] Most deaths are caused by respiratory failure or respiratory failure combined with heart damage.[457] Half of hospitalized COVID-19 patients show abnormal heart scans.[147]
- Clinically, COVID-19 appears to present as three different phenotypes, including ARDS.[450]
- Approximately 15% of hospitalized patients are classified as severe,[201, 514] and approximately 5% of patients are admitted to the ICU.[201, 514] Patient deterioration can be rapid.[196] The survival rate of patients requiring mechanical ventilation varies widely (e.g., 35%,[232] 70%,[28] 75.5%[444]). Higher SARS-CoV-2 viral RNA load on admission (measured by RT-PCR cycle threshold values) have been associated with greater risk of intubation and death.[341]
- Recent evidence suggests that SARS-CoV-2 may attack blood vessels in the lung, leading to clotting complications and ARDS.[9, 530] Clotting may be associated with severely ill COVID-19 patients[265] and those with ARDS,[122] and affects multiple human organ systems.[435] COVID-19 patients should be monitored for possible thrombosis.[298] In autopsies of several COVID-19 patients, there was evidence of diffuse alveolar damage (DAD)[471] and increased blood clotting.[472]
- COVID-19 patients undergoing unrelated surgical procedures have high levels of postoperative complications and death.[384]

The case fatality rate(CFR) varies substantially by patient age and underlying comorbidities.[570]

- Cardiovascular disease, obesity,[11, 421] hypertension,[614] diabetes, and respiratory conditions all increase the CFR.[514, 625] Hypertension and obesity are common in the US[180] and contribute to mortality.[25, 406]
- Individuals >60 are at higher risk of death, and the CFR for individuals >85 is between 10 and 27%.[514, 625] In a small study, men exhibited more severe symptoms and died at higher rates than women.[246] The effect of comorbidities on the likelihood of severe symptoms is higher for men.[363]

Additional studies on vulnerable subpopulations are required.

- Black, Asian, and Minority Ethnic (BAME) populations acquire SARS-CoV-2 infection at higher rates than other groups[403] and are disproportionately represented in hospitalized populations.[180, 426] African American communities contribute disproportionately to the number of deaths in the US.[219, 369] Hospitalization rates in Native American, Hispanic, and Black populations are 4-5 times higher than those in non-Hispanic white populations.[82] In the US, Hispanic and Black patients tend to die at younger ages than white patients.[579]
- Pregnant women appear to develop severe symptoms at the same rate as the general population[100, 255, 609] or at a slightly elevated rate.[150] Severe symptoms in pregnant women may be associated with underlying conditions such as obesity.[325] There is some evidence that rates of stillbirth and preterm delivery have increased during the COVID-19 pandemic, though these instances have not been conclusively linked to maternal COVID-19 infection.[261] More work is needed.

Children are susceptible to COVID-19,[142] though generally show milder[95, 332] or no symptoms.

- Between 21-28% of children may be asymptomatic.[332, 411, 428] Most symptomatic children present with mild or moderate symptoms,[195, 411] with few exhibiting severe or clinical illness.[584]
- Severe symptoms in children are possible[320] and more likely in those with complex medical histories[482] or underlying conditions such as obesity.[608] Infant deaths have been recorded.[62, 332]
- The WHO[565] and US CDC[243] have issued case definitions for a rare condition in children (termed Pediatric Multi-System Inflammatory Syndrome)[190] linked to COVID-19 infection.[448]

What do we need to know?

The true case fatality rate is unknown, as the exact number of cases is uncertain. Testing priorities and case definitions vary by location. The proportion of asymptomatic infections is not known.

- How long does it take for infected individuals to recover outside of a healthcare setting?
- What proportion of infected individuals are asymptomatic? Does this vary by age, location, or comorbidities?

Protective Immunity – How long does the immune response provide protection from reinfection?

What do we know?

Infected patients show productive immune responses, but the duration of any protection is unknown. Initial evidence suggests that the neutralizing antibody response does not last more than a few months, though this varies by severity.

- In a small comparison series (n=74), both asymptomatic and mildly symptomatic individuals showed reductions in IgG antibody levels 8 weeks after infection.[327] The correlation to long-term immunity is unknown.
- In a larger study (n=175), most patients developed neutralizing antibodies within 10-15 days after disease onset. Elderly patients had significantly higher neutralizing antibody titers than younger patients.[582] In a separate study, elderly patients also showed higher viral loads than younger patients.[518] Approximately half of infected individuals on an aircraft carrier developed detectable neutralizing antibody responses to SARS-CoV-2.[415]
- In a study of 285 COVID-19 patients, 100% developed antiviral immunoglobulin-G within 19 days of symptom onset.[326] The neutralizing ability of these antibodies was not tested.[326] In a smaller in vitro study (n=23 patients), levels of antibodies (immunoglobulins M and G) were positively correlated with SARS-CoV-2 neutralizing ability.[518] In a smaller study of 44 patients, plasma from 91% demonstrated SARS-CoV-2 neutralizing ability, appearing ~8 days after symptom onset.[508]
- In a small study (n=26 mild cases), researchers found prolonged persistence of SARS-CoV-2 antibodies and SARS-CoV-2 RNA for up to 50 days.[539]
- A small subset of COVID-19 patients in China (8%) did not develop a serological response to infection, though the potential for reinfection in these patients is unknown.[582] Similarly, between 16.7% (for IgG) and 51.7% (for IgM) of patients in a separate study did not exhibit any immune response, in terms of production of those two types of antibodies.[511]
- In a study of 221 COVID-19 patients, levels of two types of antibodies (IgM and IgG) were not associated with the severity of symptoms.[224] However, in a smaller study, patients with severe disease showed stronger antibody responses than those with non-severe symptoms.[518]
- Severely ill individuals develop higher levels of neutralizing antibodies[314] and greater T-cell response frequencies[479] than mildly symptomatic or asymptomatic individuals.
- The early recovery phase of COVID-19 patients is characterized by inflammatory immune response,[556] suggesting the potential for adverse reactions after clinical improvement.
- Two studies identified key components of the adaptive immune system ($CD4^+$ T cells) in the majority of recovered COVID-19 patients, and these cells reacted to SARS-CoV-2 Spike protein.[57, 198] These studies also identified Spike protein responses in $CD4^+$ T cells of ~30-40% of unexposed patients,[198] suggesting some cross-reactivity between other circulating human coronaviruses and SARS-CoV-2.[57, 198] Long-lasting T-cell responses have been seen in SARS-CoV-1 patients, and T-cell cross-reactivity between other coronaviruses and SARS-CoV-2 suggest additional immune protection.[291] The strength and duration of any T-cell derived protection is currently unknown.

Currently, there is no evidence that recovered patients can be reinfected with SARS-CoV-2.

- Two studies suggest limited reinfection potential in macaques. In the first, two experimentally infected macaques were not capable of being reinfected 28 days after their primary infection resolved.[136] In the second, rhesus macaques exposed to different doses of SARS-CoV-2 via the intranasal and intratracheal routes (10^4 – 10^6 PFU) developed pathological infection and were protected upon secondary challenge 35 days after initial exposure.[92]
- Ferrets infected with 10^2-10^4 PFU were protected from acute lung injury following secondary challenge with SARS-CoV-2 28 days after initial exposure, but they did exhibit clinical symptoms such as lethargy and ruffled fur.[462] Cats exposed to SARS-CoV-2 after initial recovery did not shed virus, suggesting some protective effect of primary infection.[54]
- According to the WHO, there is no evidence of re-infection with SARS-CoV-2 after recovery.[288]
- Patients can test positive via PCR for up to 37 days after symptoms appear,[625] and after recovery and hospital discharge.[284]
- **The strength and duration of any immunity after initial COVID-19 infection is unknown.[16, 562]**
- In a small study (n=65), 95% of patients developed neutralizing antibodies within 8 days of symptom onset,[480] but neutralizing antibody titers declined substantially when assayed after 60 days.[480] Individuals with more severe infections developed higher neutralizing antibody levels that persisted longer than those with asymptomatic or mild infections.[480] Protective antibody immunity may depend on the severity of initial infection, and may not persist for more than a few months, which is consistent with observations in other human coronaviruses.
- In a 35-year study of 10 men, immunity to seasonal coronaviruses waned after one year.[148] Reinfection was observed between one and three years after initial infection.[148]
- Previous studies on coronavirus immunity suggest that neutralizing antibodies may wane after several years.[69, 586]

What do we need to know?

As the pandemic continues, long-term monitoring of immune activity and reinfection status is needed.

- How long does the immune response last? Is there evidence of waning immunity?
- Can humans become reinfected, or are reports of reinfection vestiges from initial infection?
- How do different components of the immune response contribute to long-term protection?

Clinical Diagnosis – Are there tools to diagnose infected individuals? When during infection are they effective?

What do we know?

Diagnosis relies on identifying the genetic signature of the virus in patient nose, throat, or sputum samples, or by identifying SARS-CoV-2 antibodies in individuals exposed to the virus. Confirmed cases are still underreported.

- The US CDC has expanded testing criteria to include symptomatic patients at clinician discretion.[37]
- PCR protocols and primers have been widely shared internationally.[77, 117, 303, 486, 561, 567] PCR-based diagnostic assays are unable to differentiate between active and inactive virus.
- A combination of pharyngeal (throat) RT-PCR and chest tomography is recommended,[440] particularly when results from one test are inconclusive.[274] A single throat swab detects 78.2% of infections, and duplicate tests identify 86.2% of infections.[440] PCR tests using saliva are at least as effective as those using nasopharyngeal swabs.[98, 589] Evaluation of seven RT-PCR diagnostic test kits in China showed high overall accuracy, but some variability among test kits.[538]
- Nasal and pharyngeal swabs may be less effective as diagnostic specimens than sputum and bronchoalveolar lavage fluid,[545] although evidence is mixed.[572] Combination RT-PCR and serology (antibody) testing may increase the ability to diagnose patients with mild symptoms, or identify patients at higher risk of severe disease.[621] Assays targeting antibodies against the nucleocapsid protein (N) instead of the Spike protein (S) of SARS-CoV-2 may improve detection.[63]
- The timing of diagnostic PCR tests impacts results. The false-negative rate for RT PCR tests is lowest between 7 and 9 days after exposure, and PCR tests are more likely to give false-negative results before symptoms begin (within 4 days of exposure) and more than 14 days after exposure.[281]
- The FDA issued an Emergency Use Authorization for an antigen-based diagnostic assay, limited to use in certified laboratories (clinical laboratory improvement amendments, CLIA).[157]
- The FDA released an Emergency Use Authorization enabling laboratories to develop and use tests in-house for patient diagnosis.[162] Tests from the US CDC are available to states.[77, 85] Rapid test kits have been produced by universities and industry.[44, 49, 125, 160, 532] Home tests are being developed, though they cannot be used for diagnosis and have not been approved by the FDA.[381-382, 407] The US CDC is developing serological tests to assess SARS-CoV-2 exposure prevalence.[253]
- Artificial intelligence algorithms were able to improve the ability of radiologists to distinguish COVID-19 pneumonia from non-COVID-19 pneumonia on chest CT scans.[32]
- The CRISPR-Cas12a system is being used to develop fluorescence-based COVID-19 diagnostic tests.[229]
- Deaths due to COVID-19 are underreported. In New York City, up to 5,293 (22%) of period-specific excess deaths are unexplained and could be related to the pandemic.[395] COVID-19 related deaths in the US were likely underestimated by up to 35% in March through late April.[576] More work is needed.
- Immunological indicators[30, 151, 215, 228, 423, 506, 541] and fasting blood glucose levels[544] may help differentiate between severe and non-severe cases, and decision-support tools for diagnosing severe infections have been developed.[583]
- Individuals who test positive again after hospital discharge were more likely to have had short hospital stays, be younger than 18, and have had mild or moderate COVID-19 symptoms.[605] Such "re-positive" patients had the same levels of antibodies as those testing negative after discharge and experienced no additional clinical symptoms.[605]

Validated serological (antibody) assays are being used to help determine who has been exposed to SARS-CoV-2. Serological evidence of exposure does not indicate immunity.

- Repeated serological testing is necessary to identify asymptomatic[425] and other undetected patients at locations like skilled nursing facilities.[468] Exclusively testing symptomatic healthcare workers is likely to exclude a large fraction of COVID-19 positive personnel.[500]
- Research has shown high variability in the ability of tests (ELISA[394]and lateral flow assays) by different manufacturers to accurately detect positive and negative cases (sensitivity and specificity, respectively).[287, 557] The FDA has recommended against the use of several dozen serological diagnostic assays based on failure to conform to updated regulatory requirements.[159] Researchers have designed a standardized ELISA procedure for SARS-CoV-2 serology samples.[266]
- Meta-analysis suggests that lateral flow assays (LFIA) are less accurate than ELISA or chemiluminescent methods (CLIA), but that the target of serological studies (e.g., IgG or IgM) does not affect accuracy.[311] Additionally, most reported serological studies suffer from bias related to selected patients, limiting their applicability to general populations.[311]
- The false positive rate of serological assays may account for a substantial portion of reported exposures,[42] particularly if the true proportion of positive patients is low.

What do we need to know?

In general, PCR tests appear to be sensitive and specific, though confirmation of symptoms via chest CT is recommended. The sensitivity and specificity of serological testing methods is variable, and additional work needs to be done to determine factors that affect test accuracy.

- How many serological tests need to be done to obtain an accurate picture of underlying exposure?
- What fraction of exposed individuals fail to develop antibody responses that are the target of serological assays?

Medical Treatments – Are there effective treatments?

What do we know?

Treatment for COVID-19 is primarily supportive care,[201, 351] and no single standard of care exists. Drug trials are ongoing. Remdesivir shows promise for reducing symptom duration[41] and mortality[188] in humans.

- Remdesivir can reduce the duration of symptoms in infected individuals, from 15 days to 11 days on average (compared to controls).[41] Remdesivir received an Emergency Use Authorization from FDA[387] and is recommended for use in the EU.[571]
- A press release reports that remdesivir reduced 14-day mortality in COVID-19 patients across racial and ethnic groups when compared to standard of care alone, though concerns exist regarding the appropriate control group.[188]
- A randomized clinical trial of remdesivir found no significant clinical benefits (n=237 patients), though the trial ended early and there were differences in the treatment vs. placebo patient populations.[549] In a separate clinical trial of severe COVID-19 patients, the effects of remdesivir were inconclusive due to a limitation in the study sample size.[550]

Hydroxychloroquine is associated with risk of cardiac arrhythmias and provides limited to no clinical benefit at this time.

- Two new studies, including a randomized trial of non-hospitalized patients, found no clinical benefits to hydroxychloroquine.[221, 496] Several large clinical trials have stopped administering hydroxychloroquine due to lack of efficacy.[212, 220, 383] Other existing studies have found no benefit of hydroxychloroquine (with or without azithromycin)[17, 94, 99, 183, 268, 340, 342, 512] as well as cardiac side effects[43, 110, 186, 241, 343, 364] and elevated risk of mortality.[340] Individuals taking hydroxychloroquine for autoimmune disorders were not protected from COVID-19,[184] though sample sizes were limited. Patients given hydroxychloroquine after exposure to COVID-19 were not protected from disease.[56] The FDA revoked its EUA for hydroxychloroquine on 6/15/20.[156]
- Initial results purporting benefits of hydroxychloroquine and azithromycin[182] have been called into question. One small clinical trial (n=62) suggests that hydroxychloroquine can reduce recovery time compared to control group,[103] but lacks key methodological details.[103] A small retrospective study (n=48) found benefits to hydroxychloroquine, though details on patient study population selection were limited.[601] A larger retrospective study (n=2,541) found that hydroxychloroquine reduced mortality.[27] However, concerns still exist over the patient selection protocol and the time-course of the study.[294]

Dexamethasone may significantly reduce mortality in severely ill and ventilated patients.

- A press release from the RECOVERY trial (n=2,104) indicates substantial reductions in mortality for ventilated patients given the steroid dexamethasone, and smaller reductions in mortality for patients receiving supplemental oxygen.[2] Dexamethasone did not reduce mortality in patients who did not need oxygen or mechanical ventilation.[2]

Other pharmaceutical interventions are being investigated.

- Several studies of methylprednisolone suggest clinical benefits in severely ill patients (e.g., reduction in ventilator use, mortality), but have not been tested separately from other standard-of-care treatments.[118, 345, 466, 470] Providing anti-inflammatory treatments in the first few days of hospital admission may be beneficial.[368]
- There is evidence for efficacy of several interferon-based treatments, including interferon beta-1b,[231] interferon beta-1a,[129] and interferon alpha-2b.[418] In these studies, interferons were generally administered with other treatments. A press release suggests that an inhaled interferon beta reduced the need for mechanical ventilation.[424]
- Small, observational studies have found benefits of tocilizumab[167, 214, 455, 497, 593] in severe COVID-19 patients, and Phase II trial results show limited reductions in mortality.[420] Tocilizumab efficacy may depend on C-reactive protein levels[175, 350] and may be more beneficial when administered early.[194, 377] Tocilizumab has been associated with reduced risk of severe illness[23, 267] and death,[377] but also an increased risk of secondary (non-COVID-19) (b)(6) Other trials have found benefits of itolizumab[48] but no consistent benefits from sarilumab.[437]
- Limited, preliminary evidence from clinical trials supports the efficacy of favipiravir,[96] intravenous immunoglobulin,[72] baricitinib,[70] ivermectin,[432] and pidotimod.[521] Lenzilumab, a monoclonal antibody, showed benefits to oxygenation levels in severely ill patients (n=12).[513] There is no clinical benefit from combination ritonavir/lopinavir.[71, 197, 310] Phase II clinical trial results for the kinase inhibitor ruxolitinib showed few severe side effects and suggested benefits in terms of symptom duration and mortality.[73] High doses of chloroquine diphosphate were associated with lethality in severely ill patients.[53]
- The anticoagulant heparin is being used to mitigate risks of pulmonary embolism.[151] Systemic anticoagulant use was associated with reduced mortality rates in severely ill patients.[405]
- Passive antibody therapy (convalescent serum)[75] is being given to patients,[161] appears safe,[254] and several small trials (<50 patients) suggest benefits from convalescent patient plasma for infected patients.[153, 319, 339, 349, 464, 483, 485] Clinical trial results (n=103) showed no significant benefits of plasma therapy, though the sample size was low.[302] Another randomized trial with convalescent plasma was halted due to similar neutralizing antibody levels in enrolled recipients and donors.[187]

What do we need to know?

Additional information on treatment efficacy is required, particularly from large randomized clinical trials.

- Do monoclonal antibodies exhibit any efficacy in human trials?
- Are there treatments that reduce the development of severe symptoms when administered early?
- Do androgen levels in males alter disease severity?[193, 374, 536]

Vaccines – Are there effective vaccines?

What do we know?

Work is ongoing to develop and produce a SARS-CoV-2 vaccine (e.g., Operation Warp Speed).[38, 206, 209-211, 386] Early results are being released, but evidence should be considered preliminary until larger trials are completed.

Phase III Trials (testing for efficacy):

- Moderna has registered for Phase III trials of its COVID-19 vaccine, which will target 30,000 participants.[373]
- University of Oxford's ChAdOx1 candidate (now called AZD1222) has begun Phase II/III human trials.[401]
- Sinovac will begin Phase III trials of its CoronaVac candidate in healthcare professionals.[491]
- Sinopharm will begin Phase III trials of its inactivated SARS-CoV-2 vaccine candidate.[36]

Phase II Trials (initial testing for efficacy, continued testing for safety):

- CanSino's Ad5-nCoV adenovirus vaccine candidate has advanced to Phase II human trials.[312] China has given approval to vaccinate members of its military with the product.[318]
- Moderna has begun its Phase II trial of mRNA-1273 with 600 participants.[353]
- Sinovac reported no severe adverse events among 600 Phase II participants given their CoronaVac candidate (inactivated virus), and 90% of patients developed neutralizing antibodies 14 days after administration.[493]
- Sinopharm (with the Wuhan Institute of Biological Products) reported neutralizing antibody development in all 1,120 participants given its inactivated virus vaccine (two times, 14 days apart) with no severe adverse events.[313]
- Inovio has registered for a Phase II trial of their INO-4800 DNA vaccine candidate.[237]

Phase I Trials (initial testing for safety):

- mRNA vaccines developed by several groups are currently being tested in Phase I trials, including CureVac (candidate is CVnCoV),[123] the Chinese Academy of Military Sciences (ARCoV),[134] BioNTech and Pfizer (BNT162 program),[422] and Moderna (mRNA-1273).[372] Data from a Phase I trial of Moderna's mRNA-1273 candidate suggest that the vaccine is well-tolerated by human subjects, and induces an antibody response against SARS-CoV-2.[240] Preliminary Phase I/II results for BioNTech's BNT162b1 mRNA candidate show mild side effects in low dose groups, and patients generated neutralizing antibodies at 21 days post vaccination.[379]
- Adenovirus-based vaccines from several groups are being tested in Phase I trials, including CanSino (Ad5-nCoV),[628] Johnson and Johnson (Ad.26-COV2-S),[250] the University of Oxford (ChAdOx1, now called AZD1222),[527] and Gamaleya Research Institute of Epidemiology and Microbiology (Gam-COVID-Vac Lyo).[564] Phase I trial results for the CanSino vaccine (Ad5-nCoV) showed few severe adverse reactions in humans within 28 days of follow-up (side effects included fever [sometimes severe], fatigue, headache, and muscle pain).[628] Immune responses were found in most patients, peaking at 14 days for T-cells and 28 days for antibodies.[628] In Phase I/II trials, the ChAdOx-1 COVID-19 (AZD1222) vaccine showed a tolerable safety profile and most recipients developed positive T-cell and neutralizing antibody responses.[174]
- Several groups have developed heat-inactivated vaccine candidates, including the Chinese Academy of Medical Sciences,[477] the Beijing Institute of Biological Products,[427] the Wuhan Institute of Biological Products,[588] Immunitor LLC (V-Sars),[360] and Sinovac Biotech (CoronaVac).[492] Sinovac Biotech has reported that their inactivated virus vaccine (CoronaVac) shows protective effects in rhesus macaques, particularly at high vaccine doses.[179]
- Several groups are developing recombinant subunit vaccines, including Vaxine Pty (Covax-19),[531] Clover Biopharmaceuticals (SCB-2019),[359] Novavax (NVX-CoV2373),[355] and the Chinese Academy of Sciences (RBD-Dimer).[328] The University of Queensland has started Phase I trials of its UQ vaccine candidate, which uses Spike protein subunits.[429]
- Several groups are testing DNA vaccines in Phase I trials, including Inovio (INO-4800),[236] Genexine (GX-19)[185] and AnGes (AG0301-COVID19).[22] Results from Inovio's INO-4800 show no serious adverse side effects and high immunogenicity.[236]
- Imperial College London is beginning Phase I/II trials of their RNA vaccine candidate, LNP-nCoVsnRNA.[392]
- Shenzhen Geno-Immune Medical Institute is testing its aAPC[358] and lentiviral (LV-SMENP-DC)[356] vaccines.
- Symvivo Corporation (Canada) will begin a Phase I trial of its oral bacTRL-Spike vaccine candidate.[354]
- Aivita will begin a Phase Ib/II clinical trial of its DC-ATA candidate, comprised of dendritic cells and SARS-CoV-2 antigens.[357]
- Medicago will begin the Phase I trials of their vaccine, a plant-derived virus-like-particle candidate.[352]
- Phase I/II trials are beginning for vaccine candidates from Zydus Cadila (ZyCoV-D, DNA plasmid)[631] and Baharat (Covaxin, inactivated rabies virus used as carrier for SARS-CoV-2 proteins).[155]

Non-target vaccines

- The potential benefits of non-SARS-CoV-2 vaccines, such as *Bacillus* Calmette-Guerin (BCG), are under investigation.[154, 481]

What do we need to know?

Published results from randomized clinical trials (Phase I – III) are needed.

- Safety of candidate vaccines in humans and animals
- Efficacy of candidate vaccines in humans and animals
- Length of any vaccine-derived immunity
- Evidence for vaccine-derived enhancement (immunopotentiation)

Non-pharmaceutical Interventions – Are public health control measures effective at reducing spread?

What do we know?

Broad-scale control measures such as stay-at-home orders are effective at reducing transmission.

- Social distancing and other policies are estimated to have reduced COVID-19 spread by 44% in Hong Kong[121] and reduced spread throughout China,[276, 280, 282, 329, 344, 543] Europe,[181, 259] and the US.[275] Restrictive lockdowns in China are estimated to have reduced disease transmission within only a few days[629] by reducing contacts.[612] In China, modeling suggests that a one-day delay in implementing control measures increased the time needed to curtail an outbreak by 2.4 days.[143] In the US, each day of delay in emergency declarations and school closures was associated with a 5-6% increase in mortality.[600]
- Modeling demonstrates that multifaceted restrictions and quarantines in China reduced the R_0 of SARS-CoV-2 from greater than 3 to less than 1 between January 23 and February 5.[402] Additionally, movement restrictions and other control measures helped limit the amount of time where community transmission was possible (i.e., $R_0 > 1$).[613]
- A US county-level model found that shelter in place orders (SIPOs) and restaurant and bar closures were associated with large reductions in exponential growth rate of cases.[119] School closures and cancellation of large gatherings had smaller effects.[119] Similarly, researchers found that a larger number of public health interventions in place was strongly associated with lower COVID-19 growth rates in the next week.[256] Individual behaviors such as wearing face coverings and practicing social distancing have been associated with reduced risk of COVID-19 infection.[415]
- Mobility[171, 286] and physical contact rates[242] decline after public health control measures are implemented. Mobility reductions in the US have been associated with significant reductions in COVID-19 case growth.[31] Modeling suggests that on their own, travel restrictions delay peak prevalence by only a few days but do not limit epidemic size.[15]
- Models indicate that a combination of school closures, work restrictions, and other measures are required to effectively limit transmission.[166, 272] School closures alone appear insufficient.[239, 282]
- Non-pharmaceutical interventions in China did not reduce transmission equally across all groups.[402]
- Two modeling studies identified large reductions in transmission due to country lockdowns[173] and other social distancing measures,[223] with substantial variation in the efficacy of particular policies in different countries.[173, 223]
- Contact tracing to identify infected individuals reduces the amount of time infectious individuals can transmit disease in a population and increases the time between successive cases.[46] Robust contact tracing and case finding may be needed to control COVID-19 in the US, but requires additional resources.[551] In South Korea, early implementation of rapid contact tracing, testing, and quarantine of confirmed and suspected cases was able to reduce the transmission rate of COVID-19.[504] Modeling studies suggest that contact tracing combined with high levels of testing may limit COVID-19 resurgence once initial social distancing policies are relaxed.[14, 168] Contact tracing is likely to be more effective when conducted in combination with other control measures such as expanded testing and physical distancing.[279]

Research is needed to help plan for easing of restrictions. Testing is critical, and synchronized interventions may help.

- Relaxing public health interventions is projected to increase cases and deaths.[126, 524] As of 7/21/2020, 41 US states are experiencing increases in the average daily rate of new confirmed cases, and 26 US states are experiencing increases in the average daily rate of new COVID-19 deaths (for the prior 14 days).[391]
- Modeling suggests that optimal control policies involve quickly quarantining infected individuals, and that periods of social distancing or lock-down may be effective in reducing overall exposure from asymptomatic or unconfirmed cases.[520] Testing is critical to balancing public health and economic costs.[520] Rolling interventions, whereby social distancing measures are put into place every few weeks, may keep healthcare demand below a critical point.[599] Undetected cases can lead to elevated risk of re-emergence after restrictions are lifted, highlighting the need for robust testing strategies.[207]
- Synchronizing public health interventions and lockdowns across US state lines may reduce the total number of interventions necessary to eliminate transmission as COVID-19 cases continue to resurge.[459]
- Modeling indicates that COVID-19 is likely to become endemic in the US population, with regular, periodic outbreaks, and that additional social or physical distancing measures may be required for several years to keep cases below critical care capacity in absence of a vaccine or effective therapeutic.[264] Results depend on the duration of immunity after exposure.[264]
- Balancing control measures to maintain R_0 below 1 may be more efficient than allowing R_0 to increase above 1.[296]
- The WHO has released guidelines on public health strategy,[560] and Johns Hopkins released a report outlining how to re-open certain categories of activities (e.g., schools, restaurants, events) while reducing COVID-19 risk.[449]
- Surveys indicate that the majority of Americans were complying with non-pharmaceutical interventions.[124] In the US, mask use increased after recommendations from the White House Task force and CDC.[170]

What do we need to know?

As different US states have implemented differing control measures at various times, a comprehensive analysis of social distancing efficacy has not yet been conducted.

- What are plausible options for relaxing social distancing and other intervention measures without resulting in a resurgence of COVID-19 cases?
- How is COVID-19 incidence changing in states that have begun easing movement and activity restrictions?

Environmental Stability – How long does the agent live in the environment?

What do we know?

SARS-CoV-2 can persist on surfaces for at least 3 days and on the surface of a surgical mask for up to 7 days depending on conditions. If aerosolized intentionally, SARS-CoV-2 is stable for at least several hours. The seasonality of COVID-19 transmission is unknown. SARS-CoV-2 on surfaces is inactivated rapidly with sunlight.

SARS-CoV-2 Data

- In simulated saliva on stainless steel surfaces, SARS-CoV-2 exhibits negligible decay over 60 minutes in darkness, but loses 90% of infectivity every 6.8-12.8 minutes, depending on the intensity of simulated UVB radiation levels.[436]
- The Department of Homeland Security (DHS) developed a data-based model for SARS-CoV-2 decay on inert surfaces (stainless steel, ABS plastic and nitrile rubber) at varying temperature and relative humidity. This model estimates virus decay in the absence of exposure to direct sunlight.[140]
- SARS-CoV-2 can persist on plastic and metal surfaces between 3 days (21-23°C, 40% RH)[526] and 7 days (22°C, 65% RH). Infectious virus can be recovered from a surgical mask after 7 days (22°C, 65% RH).[109]
- At room temperature (22°C), SARS-CoV-2 remains detectable (via plaque assay) on paper currency for up to 24 hours, on clothing for up to 4 hours, and on skin for up to 96 hours.[208] Persistence is reduced with warmer temperatures (37°C), and enhanced at colder temperatures (4°C).[208]
- SARS-CoV-2 persists for less than 3 days within the pages of library books, and for less than 1 day on the exterior of book and DVD covers.[3]
- Both temperature and humidity contribute to SARS-CoV-2 survival on nonporous surfaces, with cooler, less humid environments facilitating survival (stainless steel, ABS plastic, and nitrile rubber; indoors only; simulated saliva matrix).[50]
- Experimental studies using SARS-CoV-2 aerosols (1.78-1.96 µm mass median aerodynamic diameter in artificial saliva matrix) found that simulated sunlight rapidly inactivates the virus, with 90% reductions in infectious concentration after 6 minutes in high-intensity sunlight (similar to mid-June) and 19 minutes in low-intensity sunlight (similar to early March or October).[475] In dark conditions, the half-life of aerosolized SARS-CoV-2 is approximately 86 minutes in simulated saliva matrix.[475] Humidity had no significant impact on aerosolized virus survival.[475]
- DHS developed a tool for estimating the decay of airborne SARS-CoV-2 in different environmental conditions.[139]
- SARS-CoV-2 has an aerosol half-life of 2.7 hours (particles <5 µm, tested at 21-23°C and 65% RH).[526]
- Research suggests SARS-CoV-2 retains infectivity as an aerosol for up to 16 hours in appropriate conditions (23°C, 53% RH, no sunlight).[164]
- SARS-CoV-2 is susceptible to heat treatment (70°C) but can persist for at least two weeks at refrigerated temperatures (4°C).[109, 434]
- SARS-CoV-2 genetic material (RNA) was detected in symptomatic and asymptomatic cruise ship passenger rooms up to 17 days after cabins were vacated. The infectiousness of this material is not known.[376]
- In a preliminary study, SARS-CoV-2 stability was enhanced when present with bovine serum albumin, which is commonly used to represent sources of protein found in human sputum.[412]
- No strong evidence exists showing a reduction in transmission with seasonal increase in temperature and humidity.[335] Modeling suggests that even accounting for potential reductions in transmission due to weather and behavioral changes, public health interventions will still need to be in effect to limit COVID-19 transmission.[366]
- A recent study determined that approximately 0.1-1% of initial SARS-CoV-2 inoculated on plastic, stainless steel, glass, ceramics, wood, latex gloves, cotton, paper, and surgical masks remained after 48 hours.[323] Approximately 0.1% of SARS-CoV-2 remains in fecal matter after 6 hours.[323] Approximately 0.1% of SARS-CoV-2 in human urine persists after 4-5 days.[323]
- RNA in clinical samples collected in viral transport medium is stable at 18-25°C or 2-8°C for up to 21 days without impacting real-time RT-PCR results.[495] RNA in clinical samples is also stable at 4°C for up for 4 weeks with regard to quantitative RT-PCR testing (given that the sample contains 5,000 copies/mL). Separately, storage of RNA in PBS at room-temperature (18-25°C) resulted in unstable sample concentrations.[417]
- SARS-CoV-2 was detectable on wooden chopsticks used by symptomatic and asymptomatic COVID-19 patients, though sample sizes were small and no efforts were made to isolate infectious virus.[334]

What do we need to know?

Additional testing on SARS-CoV-2, as opposed to surrogate viruses, is needed to support initial estimates of stability. Tests quantifying infectivity, rather than the presence of viral RNA, are needed.

- Duration of SARS-CoV-2 infectivity via fomites and surfaces (contact hazard)
- Stability of SARS-CoV-2 on PPE (e.g., Tyvek)
- Stability of SARS-CoV-2 in food (to date, no known infections from contaminated food).[558]

Decontamination – What are effective methods to kill the agent in the environment?

What do we know?

Soap and water, as well as common alcohol and chlorine-based cleaners, hand sanitizers, and disinfectants are effective at inactivating SARS-CoV-2 on hands and surfaces.

SARS-CoV-2

- Alcohol-based hand rubs are effective at inactivating SARS-CoV-2.[277]
- Chlorine bleach (1%, 2%), 70% ethanol and 0.05% chlorhexidine are effective against live virus in lab tests.[108]
- Twice-daily cleaning with sodium dichloroisocyanurate decontaminated surfaces in COVID-19 patient hospital rooms.[396]
- EPA has released a list of SARS-CoV-2 disinfectants, but most solutions were not tested on SARS-CoV-2.[12] Several solutions have been tested against SARS-CoV-2 and found to be effective, including those based on para-chloro-meta-xylenol, salicylic acid, and quaternary ammonium compounds.[235] Two of these products, Lysol Disinfectant Spray (EPA Reg No. 777-99) and Lysol Disinfectant Max Cover Mist (EPA Reg No. 777-127) have specifically been approved for SARS-CoV-2 decontamination.[337]
- Oral antiseptic rinses used in pre-procedural rinses for dentistry containing povidone-iodine (PVP-I) are effective decontaminants of SARS-CoV-2, with 15-sec and 30-sec contact times completely inactivating SARS-CoV-2 at concentrations above 0.5% in lab tests.[47]
- Holder pasteurization of donor breast milk spiked with SARS-CoV-2 rendered the virus inactive, demonstrating that standard decontamination procedures are effective at reducing risk of COVID-19 risk in infants via donor breast milk.[523]
- Efforts are ongoing to create paint-on surfaces that can rapidly inactivate SARS-CoV-2.[40]
- Researchers have identified four methods capable of decontaminating N95 respirators while maintaining physical integrity (fit factor): UV radiation, heating to 70°C, and vaporized hydrogen peroxide (VHP).[169] Ethanol (70%) was associated with loss of physical integrity.[169]
- Hydrogen peroxide vapor (VHP) can repeatedly decontaminate N95 respirators.[445] Devices capable of decontaminating 80,000 masks per day have been granted Emergency Use Authorization from the FDA.[157]
- The FDA has issued an Emergency Use Authorization for a system capable of decontaminating ten N95 masks at a time using devices already present in many US hospitals.[58]
- Respirator decontamination methods such as VHP appear to maintain filtration efficiency after repeated decontamination cycles.[416] Several decontamination methods, including VHP, moist heat, and UVC, are capable of decontaminating N95 respirators for 10-20 cycles without loss of fit or filtration efficiency.[6]

Other Coronaviruses

- Chlorine-based[564] and ethanol-based[116] solutions are recommended.
- Heat treatment (56°C) is sufficient to kill coronaviruses,[431, 624] though effectiveness depends partly on protein in the sample.[431]
- 70% ethanol, 50% isopropanol, sodium hypochlorite (0.02% bleach), and UV radiation can inactivate several coronaviruses (MHV and CCV).[463]
- Ethanol-based biocides effectively disinfect coronaviruses dried on surfaces, including ethanol containing gels similar to hand sanitizer.[230, 573]
- Surface spray disinfectants such as Mikrobac, Dismozon, and Korsolex are effective at reducing infectivity of the closely related SARS-CoV-1 after 30 minutes of contact.[430]
- Coronaviruses may be resistant to heat inactivation for up to 7 days when stabilized in stool.[516-517]
- Coronaviruses are more stable in matrixes such as respiratory sputum.[146]

What do we need to know?

Additional decontamination studies, particularly with regard to PPE and other items in short supply, are needed.

- What is the minimal contact time for disinfectants?
- Does contamination with human fluids/waste alter disinfectant efficacy profiles?
- How effective is air filtration at reducing transmission in healthcare, airplanes, and public spaces?
- Are landfills and wastewater treatment plants effective at inactivating SARS-CoV-2?
- Is heat or UV decontamination effective to clean N95 masks, respirators and other types of PPE for multi-use?

PPE – What PPE is effective, and who should be using it?

What do we know?

The effectiveness of PPE for SARS-CoV-2 is currently unknown, and data from other related coronaviruses are used for guidance. Healthcare workers are at high risk of acquiring COVID-19, even with recommended PPE.

- Healthcare worker illnesses[514] demonstrates human-to-human transmission despite isolation, PPE, and infection control.[474] Risk of transmission to healthcare workers is high, with up to 20% of healthcare workers in Lombardy, Italy becoming infected.[439] Over 50% of US healthcare workers infected with COVID-19 report work in a healthcare setting as their single source of exposure.[65] Hospital-acquired infection rates fell after introduction of comprehensive infection control measures, including expanded testing and use of PPE for all patient contacts.[446] Universal masking policies also reduced the rate of new healthcare worker infections.[546]
- A modeling study suggests that healthcare workers are primarily at risk from droplet and inhalation exposure (compared to contact with fomites), with greater risk while in closer proximity to patients.[252]
- "Healthcare personnel entering the room [of SARS-CoV-2 patients] should use standard precautions, contact precautions, airborne precautions, and use eye protection (e.g., goggles or a face shield)."[83] WHO indicates healthcare workers should wear clean long-sleeve gowns as well as gloves.[563] PPE that covers all skin may reduce exposure to pathogens.[165, 555]
- Respirators (NIOSH-certified N95, EUFFP2 or equivalent) are recommended for those dealing with possible aerosols.[564] Additional protection, such as a Powered Air Purifying Respirator (PAPR) with a full hood, should be considered for high-risk procedures (i.e., intubation, ventilation).[61]
- KN95 respirators are, under certain conditions, approved for use under FDA Emergency Use Authorization.[158] On May 7, the FDA rescinded a number of KN95 models that no longer meet the EUA criteria and are no longer authorized.[163]
- A study suggests that P100 respirators with removable filter cartridges have similar filtration efficiency compared to N95 respirators and could plausibly be used if N95 respirators were in short supply. The study used an experimental setup with aerosolized simulant, not human testing.[414]
- Particular care should be taken with "duckbill" N95 respirators, which may fail fit tests after repeated doffing.[133] Dome-shaped N95 respirators also failed fit tests after extended use.[133]

Masks may be effective at slowing transmission.

- On 4/3/2020, the US CDC recommended wearing cloth face masks in public where social distancing measures are difficult to maintain.[84] The WHO recommends that the general population wear non-medical masks when in public settings and when physical distancing is difficult, and that vulnerable populations (e.g., elderly) wear medical masks when close contact is likely.[559] Infected individuals wearing facemasks in the home before the onset of symptoms was associated with a reduction in household transmission.[548]
- Modeling suggests that widespread use of facemasks is effective at reducing transmission.[385]
- A meta-analysis of SARS-CoV-1, MERS, and COVID-19 transmission events found evidence that wearing face masks and eye protection were each associated with lower risk of transmission.[111] N95 respirators were associated with a larger reduction in transmission risk compared to surgical face masks.[111] Physical distance (>1 or 2 meters) was also associated with lower transmission risk.[111] In a separate meta-analysis, N95 respirators were found to be beneficial for reducing the occurrence of respiratory illness in health care professionals including influenza, though surgical masks were similarly effective for influenza.[393] N95 respirators were associated with large reductions (up to 80%) in SARS-CoV-1 infections.[393]
- Surgical face masks, respirators and homemade face masks may prevent transmission of coronaviruses from infectious individuals (with or without symptoms) to other individuals.[128, 297, 525] Surgical masks were associated with a significant reduction in the amount of seasonal coronavirus (not SARS-CoV-2) expressed as aerosol particles (<5 µm).[297]
- The efficacy of homemade PPE, made with T-shirts, bandanas, or similar materials, is less than standard PPE, but may offer some protection if no other options are available.[112, 127, 441] The filtering efficiency of homemade mask materials is variable. Some non-standard materials (e.g., cotton, cotton hybrids) may be able to filter out >90% of simulant particles >0.3µm,[269] while other materials (e.g., T-shirt, vacuum cleaner bag, towels) appear to have lower filtration efficacy (~35-62%).[542] Of 42 homemade materials tested, the three with the greatest filtration efficiencies were layered cotton with raised visible fibers,[610] though homemade materials were not as effective as surgical or N95 masks.

What do we need to know?

Most PPE recommendations have not been made on SARS-CoV-2 data, and comparative efficacy of different PPE for different tasks (e.g., intubation) is unknown. Identification of efficacious PPE for healthcare workers is critical due to their high rates of infection.

- What is the importance of aerosol transmission (particles <5µm)? What is the effective distance of spread via droplet or aerosol?
- How effective are barriers such as N95 respirators or surgical masks for SARS-CoV-2?
- What is the appropriate PPE for first responders? Airport screeners?
- What are proper procedures for reducing spread and transmission rates in medical facilities?
- How effective are homemade masks at reducing SARS-CoV-2 transmission?

Forensics – Natural vs intentional use? Tests to be used for attribution.

What do we know?

All current evidence supports the natural emergence of SARS-CoV-2 via a bat and possible intermediate mammal species.

- Genomic analysis places SARS-CoV-2 into the beta-coronavirus clade, with close relationship to bat coronaviruses. The SARS-CoV-2 virus is distinct from SARS-CoV-1 and MERS viruses.[141]
- Genomic analysis suggests that SARS-CoV-2 is a natural variant and is unlikely to be human-derived or otherwise created by "recombination" with other circulating strains of coronavirus.[18, 627]
- Comparing genomes of multiple coronaviruses using machine-learning has identified key genomic signatures shared among high case fatality rate coronaviruses (SARS-CoV-1, SARS-CoV-2, MERS) and animal counterparts.[204] These data further suggest that SARS-CoV-2 emergence is the result of natural emergence and that there is a potential for future zoonotic transmission of additional pathogenic strains to humans.[204]
- Deletion mutants were identified at low levels in human clinical samples, suggesting that the PRRA furin cleavage site alone is not fully responsible for human infection, but does confer a fitness advantage in the human host.[575] Additional whole-genome sequencing in humans would help to confirm this finding.
- Genomic data support at least two plausible origins of SARS-CoV-2: "(i) natural selection in a non-human animal host prior to zoonotic transfer, and (ii) natural selection in humans following zoonotic transfer."[18] Both scenarios are consistent with the observed genetic changes found in all known SARS-CoV-2 isolates.
- Some SARS-CoV-2 genomic evidence indicates a close relationship with pangolin coronaviruses,[574] and data suggest that pangolins may be a natural host for beta-coronaviruses.[315, 317] Genomic evidence suggests a plausible recombination event between a circulating coronavirus in pangolins and bats could be the source of SARS-CoV-2.[306, 591] Emerging studies are showing that bats are not the only reservoir of SARS-like coronaviruses.[617] Additional research is needed.
- There are multiple studies showing that the SARS-CoV-2 S protein receptor binding domain, the portion of the protein responsible for binding the human receptor ACE2, was acquired through recombination between coronaviruses from pangolins and bats.[19, 306, 316, 617] These studies suggest that pangolins may have played an intermediate role in the adaptation of SARS-CoV-2 to be able to bind to the human ACE2 receptor. Additional research is needed.
- A novel bat coronavirus (RmYN02) has been identified in China with an insertion in the viral furin cleavage site. While distinct from the insertion in SARS-CoV-2, this evidence shows that such insertions can occur naturally.[626]
- Additionally, "[…] SARS-CoV-2 is not derived from any previously used virus backbone," reducing the likelihood of laboratory origination,[18] and "[…] genomic evidence does not support the idea that SARS-CoV-2 is a laboratory construct, [though] it is currently impossible to prove or disprove the other theories of its origin."[18]
- Work with other coronaviruses has indicated that heparan sulfate dependence can be an indicator of prior cell passage, due to a mutation in the previous furin enzyme recognition motif.[131]

What do we need to know?

Identifying the intermediate species between bats and humans would aid in reducing potential spillover from a natural source. Wide sampling of bats, other wild animals, and humans is needed to address the origin of SARS-CoV-2.

- What tests for attribution exist for coronavirus emergence?
- What is the identity of the intermediate species?
- Are there closely related circulating coronaviruses in bats or other animals with the novel PRRA cleavage site found in SARS-CoV-2?

Genomics – How does the disease agent compare to previous strains?

What do we know?

Current evidence suggests that SARS-CoV-2 accumulates substitutions and mutations at a similar rate as other coronaviruses. Mutations and deletions in specific portions of the SARS-CoV-2 genome have not been linked to any changes in transmission or disease severity, though modeling work is attempting to identify possible changes.

- There have been no documented cases of SARS-CoV-2 prior to December 2019. Preliminary genomic analyses, however, suggest that the first human cases of SARS-CoV-2 emerged between 10/19/2019 – 12/17/2019.[21, 39, 433]
- Analysis of more than 7,000 SARS-CoV-2 genome samples provides an estimated mutation rate of $6x10^{-4}$ nucleotides per genome per year.[528] The same analysis estimates the emergence of SARS-CoV-2 in humans between October and December 2019.[528] This aligns with the first known human cases in China in early December 2019, in Europe in late December 2019,[138] circulation in the US (Washington State) in February 2020,[578] and circulation in Mexico in March, 2020.[510] In both California[137] and New York City,[192] phylogenetic evidence supports multiple introductions of SARS-CoV-2 from both inside and outside the US.
- Despite evidence of variation in the genome[89] and areas under positive selection,[68] there are no known associations between particular mutations and changes in transmission or virulence.[67] Thus, there is currently no evidence of distinct SARS-CoV-2 phenotypes at this time.[338, 528] Research attempting to define clades or subgroups of SARS-CoV-2 based solely on genomic features has suffered from limited data[604] and sampling bias.[176] In 94 COVID-19 patients, there was no association between viral genotype and clinical severity.[618]
- Phylogenetic and clinical analysis suggests the D614G mutation in the Spike protein is associated with higher rates of SARS-CoV-2 transmission, but no change in clinical severity in infected patients.[273] However, it is difficult to determine whether this mutation is overrepresented due to founder effects, or whether it truly spreads more rapidly than other isolates. Preliminary experimental evidence suggests that this mutation increases infectivity in cell lines, but additional animal model work is needed to confirm the effect of this mutation on transmission.[615]
- Recent analysis of >16,000 genomes of SARS-CoV-2 suggests two major introductions in the US, one associated with the West coast and one with the Eastern portion of the US.[378]
- A genome-wide association study in humans identified two loci corresponding to higher risk of severe COVID-19 (3p.21.31 and 9q34.2), including one associated with blood type.[149] Individuals with type-O blood showed reduced risk of severe disease, while individuals with type-A blood showed an increased risk.[149]
- SARS-CoV-2 is acquiring nucleotide changes at a rate that suggests the virus is undergoing purifying selection (that the genome is stabilizing toward a common genome).[581] Low genetic diversity early in the epidemic suggests that SARS-CoV-2 was capable of jumping to human and other mammalian hosts,[581] and that additional jumps into humans from reservoir species may occur.
- Phylogenetics suggest that SARS-CoV-2 is of bat origin, but is closely related to coronaviruses found in pangolins.[315, 317]
- The SARS-CoV-2 Spike protein, which mediates entry into host cells and is the major determinant of host range, is very similar to the SARS-CoV-1 Spike protein.[330] The rest of the genome is more closely related to two separate bat[330] and coronaviruses found in pangolins.[317]
- An analysis of SARS-CoV-2 sequences from Singapore has identified a large nucleotide (382 bp) deletion in ORF-8.[502] In Arizona, researchers identified an 81-base pair deletion (removing 27 amino acids) in the ORF-7a protein, indicating that mutations can be detected by routine sentinel surveillance. The function of these deletions are unknown at this time.[218]
- A recent report of virus mutations within patients needs more research.[258] Additional analysis of data suggests the results may be due to experimental methods.[189, 595]
- Structural modeling suggests that observed changes in the genetic sequence of the SARS-CoV-2 Spike protein may enhance binding of the virus to human ACE2 receptors.[398] More specifically, changes to two residues (Q493 and N501) are linked with improving the stability of the virus-receptor binding complex.[398] Additionally, structural modeling identified several existing mutations that may enhance the stability of the receptor binding domain, potentially increasing binding efficacy.[400] Infectivity assays are needed to validate the genotypic changes and possible phenotypic results identified in these studies.
- A key difference between SARS-CoV-2 and other beta-coronaviruses is the presence of a polybasic furin cleavage site in the Spike protein (insertion of a PRRA amino acid sequence between S1 and S2).[120]
- The US CDC is launching a national genomics consortium to assess SARS-CoV-2 genomic changes over time.[78]

What do we need to know?

Research linking genetic changes to differences in phenotype (e.g., transmissibility, virulence, progression in patients) is needed.

- Are there similar genomic differences in the progression of coronavirus strains from bat to intermediate species to human?
- Are there different strains or clades of circulating virus? If so, do they differ in virulence?
- What are the mutations in SARS-CoV-2 that allowed human infection and transmission?

Forecasting – What forecasting models and methods exist?

What do we know?

There are many groups focused on forecasting cases, hospitalizations, or fatalities due to COVID-19. Each model has its own methods and goals, summarized in this section. An evaluation of model performance is beyond the scope of this document. Assumptions and limitations of each model are detailed at the linked reference.

US CDC forecasting

The US CDC is hosting an ongoing forecasting initiative, and provides ensemble forecasts based on the arithmetic mean of participating groups.[81]

- Columbia University Model: Spatially-explicit SEIR model incorporating contact rate reductions due to social distancing. Estimates total cases and risk of healthcare overrun.[460]
- Imperial College London: Week-ahead forecasts of cases, deaths, and transmissibility (R_0) at the country-level. Transmissibility estimates used to forecast incidence based on Poisson renewal process.[45]
- Institute of Health Metrics and Evaluation (IHME): Mechanistic SEIR model combined with curve-fitting techniques to forecast cases, hospital resource use, and deaths at the state and country level.[234]
- Los Alamos National Laboratory: Forecasts of state-level cases and deaths based on statistical growth model fit to reported data. Implicitly accounts for effects of social distancing and other control measures.[285]
- Massachusetts Institute of Technology: Mechanistic SEIR model that forecasts cases, hospitalizations, and deaths. Also includes estimates of intervention measures, allows users to project based on different intervention scenarios (e.g., social distancing lasting for 3 vs. 4 weeks).[370]
- Northeastern University: Spatially explicit, agent-based epidemic model used to forecast fatalities, hospital resource use, and the cumulative attack rate (proportion of the population infected) for unmitigated and mitigated scenarios.[389]
- Notre Dame University: Agent-based model forecasting cases and deaths for Midwest states. Includes effectiveness of control measures like social distancing.[419]
- University of California, Los Angeles: Mechanistic SIR model with statistical optimization to find best-fitting parameter values. Estimates confirmed and active cases, fatalities, and transmission rates at the national and state levels.[522]
- University of Chicago: Age-structured SEIR model that accounts for asymptomatic individuals and the effectiveness of social distancing policies. Forecasts only for Illinois.[107]
- University of Geneva: Country-level forecasts of cases, deaths, and transmissibility (R_0). Uses statistical models fit to reported data, not mechanistic models.[172]
- University of Massachusetts, Amherst: Aggregation of state and national forecasts to create ensemble model.[438]
- University of Texas, Austin: Machine learning model aimed at identifying links between social distancing measures and changes in death rates. Forecasts fatalities at the state, metropolitan area, and national level. Cannot be used to make projections beyond initial infection wave.[367]
- Youyang Gu: Mechanistic SEIR model coupled with machine learning algorithms to minimize error between predicted and observed values. Forecasts deaths and infections at the state and national level, including 60 non-US countries. Includes effects of public health control efforts.[199]
- Auquan: SEIR model used to forecast deaths and illnesses at the country and state level.[29]
- CovidSim: SEIR model allowing users to simulate the effects of future intervention policies at the state and national level (US only).[106]

Other forecasting efforts:

- University of Georgia: Statistical models used to estimate the current number of symptomatic and incubating individuals, beyond what is reported (e.g., "nowcasts"). Available at the state and national level for the US.[88]
- Hospital IQ has a dashboard that forecasts hospital and ICU admissions for each county in the US. Relies in part on IHME forecasts.[238]
- COVID Act Now: State and county-level dashboard focused on re-opening strategies, showing trends in four metrics related to COVID-19 risk (change in cases, total testing capacity, fraction of positive tests, and availability of ICU beds). Fundamentally uses an SEIR model fit to observed data.[390]
- Researchers use a rolling window analysis incorporating uncertainty in the generation time distribution to estimate time-varying transmission rates in US states (the effective reproduction number, R_{eff} or R_t).[8]

What do we need to know?

Forecasts differ in how they handle public health interventions such as shelter-in-place orders and tracking how methods change in the near future will be important for understanding limitations going forward.

Table 1. Definitions of commonly-used acronyms

Acronym/Term	Definition	Description
ACE2	Angiotensin-converting enzyme 2	Acts as a receptor for SARS-CoV and SARS-CoV-2, allowing entry into human cells
Airborne transmission	Aerosolization of infectious particles	Aerosolized particles can spread for long distances (e.g., between hospital rooms via HVAC systems). Particles generally <5 µm.
ARDS	Acute respiratory distress syndrome	Leakage of fluid into the lungs which inhibits respiration and leads to death
Attack rate	Proportion of "at-risk" individuals who develop infection	Defined in terms of "at-risk" population such as schools or households, defines the proportion of individuals in those populations who become infected after contact with an infectious individual
CCV	Canine coronavirus	Canine coronavirus
CFR	Case Fatality Rate	Number of deaths divided by confirmed patients
CoV	Coronavirus	Virus typified by crown-like structures when viewed under electron microscope
COVID-19	Coronavirus disease 19	Official name for the disease caused by the SARS-CoV-2 virus.
Droplet transmission	Sneezing, coughing	Transmission via droplets requires relatively close contact (e.g., within 6 feet)
ELISA	Enzyme-linked immunosorbent assay	Method for serological testing of antibodies
Fomite	Inanimate vector of disease	Surfaces such as hospital beds, doorknobs, healthcare worker gowns, faucets, etc.
HCW	Healthcare worker	Doctors, nurses, technicians dealing with patients or samples
Incubation period	Time between infection and symptom onset	Time between infection and onset of symptoms typically establishes guidelines for isolating patients before transmission is possible
Infectious period	Length of time an individual can transmit infection to others	Reducing the infectious period is a key method of reducing overall transmission; hospitalization, isolation, and quarantine are all effective methods
Intranasal	Agent deposited into external nares of subject	Simulates inhalation exposure by depositing liquid solution of pathogen/virus into the nose of a test animal, where it is then taken up by the respiratory system.
MERS	Middle-East Respiratory Syndrome	Coronavirus with over 2,000 cases in regional outbreak since 2012
MHV	Mouse hepatitis virus	Coronavirus surrogate
Nosocomial	Healthcare- or hospital-associated infections	Characteristic of SARS and MERS outbreaks, lead to refinement of infection control procedures
PCR	Polymerase chain reaction	PCR (or real-time [RT] or quantitative [Q] PCR) is a method of increasing the amount of genetic material in a sample, which is then used for diagnostic testing to confirm the presence of SARS-CoV-2
PFU	Plaque forming unit	Measurement of the number of infectious virus particles as determined by plaque forming assay. A measurement of sample infectivity.
PPE	Personal protective equipment	Gowns, masks, gloves, and any other measures used to prevent spread between individuals
R_0	Basic reproduction number	A measure of transmissibility. Specifically, the average number of new infections caused by a typical infectious individual in a wholly susceptible population.

Acronym/Term	Definition	Description
SARS	Severe Acute Respiratory Syndrome	Coronavirus with over 8,000 cases in global 2002-2003 outbreak
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2	Official name for the virus previously known as 2019-nCoV.
SEIR	Susceptible (S), exposed (E), infected (I), and resistant (R)	A type of modeling that incorporates the flow of people between the following states: susceptible (S), exposed (E), infected (I), and resistant (R), and is being used for SARS-CoV-2 forecasting
Serial interval	Length of time between symptom onset of successive cases in a transmission chain	The serial interval can be used to estimate R_0, and is useful for estimating the rate of outbreak spread
SIR	Susceptible (S), infected (I), and resistant (R)	A type of modeling that incorporates the flow of people between the following states: susceptible (S), infected (I), and resistant (R), and is being used for SARS-CoV-2 forecasting
$TCID_{50}$	50% Tissue Culture Infectious Dose	The number of infectious units which will infect 50% of tissue culture monolayers. A measurement of sample infectivity.
Transgenic	Genetically modified	In this case, animal models modified to be more susceptible to MERS and/or SARS by adding proteins or receptors necessary for infection

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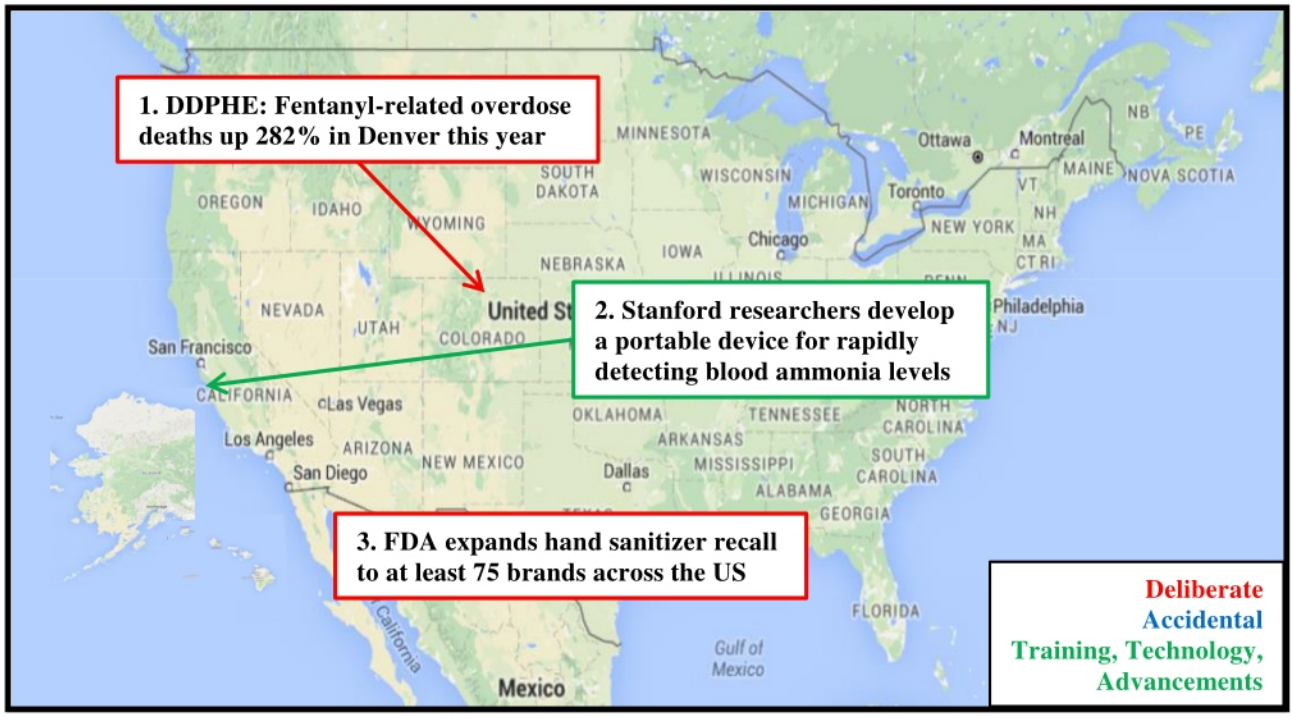

1. DDPHE: Fentanyl-related overdose deaths up 282% in Denver this year. July 22, 2020 (The Denver News Channel). Fentanyl-related overdose deaths are up a staggering 282% in Denver from January of this year to May, compared to the same time period in 2019, according to new data released Wednesday from the Denver Department of Public Health & Environment (DDPHE). The data shows 48 people have died from fentanyl overdose as of Friday, July 17 of this year. That's compared to a total of 58 deaths related to the drug for the entire year of 2019, a 341% increase from the previous year (2018). The majority of drug overdose deaths in Denver involve multiple substances found in the deceased's system. In 2020 so far 62% of deaths involved 3 or more drugs in the deceased's system: 19% of deaths involved 5 or more drugs in the deceased's system. The overwhelming majority of probable overdose deaths — 83% — occurred in populations outside the homeless community, according to the Denver Office of the Medical Examiner. https://www.thedenverchannel.com/news/local-news/ddphe-fentanyl-related-overdose-deaths-up-282-in-denver-this-year

2. Stanford researchers develop a portable device for rapidly detecting blood ammonia levels. July 21, 2020 (news-medical.net). Ammonia is a natural product of digestion that is usually processed into urea by the liver and passed out of the body in urine. Too much ammonia in the blood can cause mental and physical dysfunction and is a concern for people with liver disease or genetic conditions that hinder ammonia metabolism. The new device could be especially beneficial for newborns with these metabolic diseases. In this population, brain damage can occur within hours of elevated ammonia levels and, for treatment, some families must drive long distances to obtain adequate testing. While the sensor inside the

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device is very similar to existing ammonia sensors, the test strips are made from scratch. Blood applied to a small hole at one end of the strip zips through a microscopic channel and sinks into a paper-lined well at the opposite end, which is coated with an inexpensive chemical that liberates the ammonia from the sample. Inside the device, this well sits directly under the ammonia sensor. https://www.news-medical.net/news/20200721/Stanford-researchers-develop-a-portable-device-for-rapidly-detecting-blood-ammonia-levels.aspx

Understanding ammonia sensors and their applications. http://goodforgas.com/wp-content/uploads/2013/12/AP1002_understanding-_ammonia_sensors_and_their_applications_2_25_13.pdf

3. FDA expands hand sanitizer recall to at least 75 brands across the US. July 22, 2020 (NBC News). The recalled products contain methanol which can be harmful if absorbed through the skin or fatal if ingested. The FDA said that there has been an increase in hand sanitizers that are labeled to contain ethyl alcohol, or ethanol, but have tested positive for methanol, or wood alcohol. If methanol is absorbed through the skin, it can cause blindness and hospitalizations, or death if ingested. The demand for hand sanitizer has surged and questionable new brands have made their way to store shelves across the United States, most imported from Mexico. It's unclear how the products are landing in U.S. stores, but there may be scores of new hand sanitizer brands since the beginning of the pandemic. Visit FDAs searchable list to help you identify whether a firms' hand sanitizer product is being recalled or has potential or confirmed methanol contamination: https://t.co/GeUwr33Y6W pic.twitter.com/iqn8Lop6hD https://www.nbcnews.com/health/health-news/fda-expands-hand-sanitizer-recall-least-75-brands-across-u-n1234246

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4. Japan bets on ammonia as the fuel of the future. July 22, 2020 (Yahoo Finance). By the year 2030 it should provide more than 1 per cent of Japan's total electricity supply, according to a consortium of leading players in the industry. The push to use ammonia highlights Japan's ambitious plans to import renewable energy from other countries after the 2011 Fukushima disaster led to the shutdown of many nuclear reactors. If successful, it could lead to important changes to global energy markets, with shipments of ammonia replacing coal or natural gas. "For decarbonisation we need to use renewable energy as much as possible on a global basis," Mr. Muraki says. But densely populated, mountainous Japan has limited potential to produce sustainable energy of its own, so the country is looking for ways to import. In practice this means fixing energy in some kind of hydrogen-containing compound that can be transported by sea as a liquid. "We've been looking at liquid hydrogen, organic hydrides and ammonia," Mr. Muraki says. The conclusion is that ammonia — a compound comprising three atoms of hydrogen to one of nitrogen — is the "most viable option." Though ammonia contains no carbon, it is only emission-free if no carbon is used to produce it. https://finance.yahoo.com/news/japan-bets-ammonia-fuel-future-000000956.html

5. 2.4kg GBL found after SUV's near-miss with police car at Newtown. July 23, 2020 (Mirage). NSW, Australia - A man is due in court today charged after 2.4kg of the date rape drug gamma butyrolactone (GBL) was seized when his car was stopped in the Inner West overnight. Officers attached to the Inner West Proactive Crime Team were conducting high-visibility patrols of King Street, Newtown, about 7.15pm (Wednesday 22 July 2020), when they stopped an SUV after the driver almost hit a fully-marked police car. After speaking with the 33-year-old driver, police searched the vehicle and seized almost 2.4kg of GBL and $6750 cash. The drugs have an estimated potential street value of $7500. The driver was arrested and taken to Newtown Police Station where he was charged with suppling a commercial quantity of an illegal drug. https://www.miragenews.com/24kg-gbl-found-after-suv-s-near-miss-with-police-car-at-newtown/

DHS S&T CSAC provides a robust and reliable 24/7 science-based technical assistance capability, addressing traditional warfare agents and emerging chemical threats. CSAC will also extend to the accidental or intentional release of chemicals. Contact information for CSAC is below.

Technical Assistance Contact Information

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