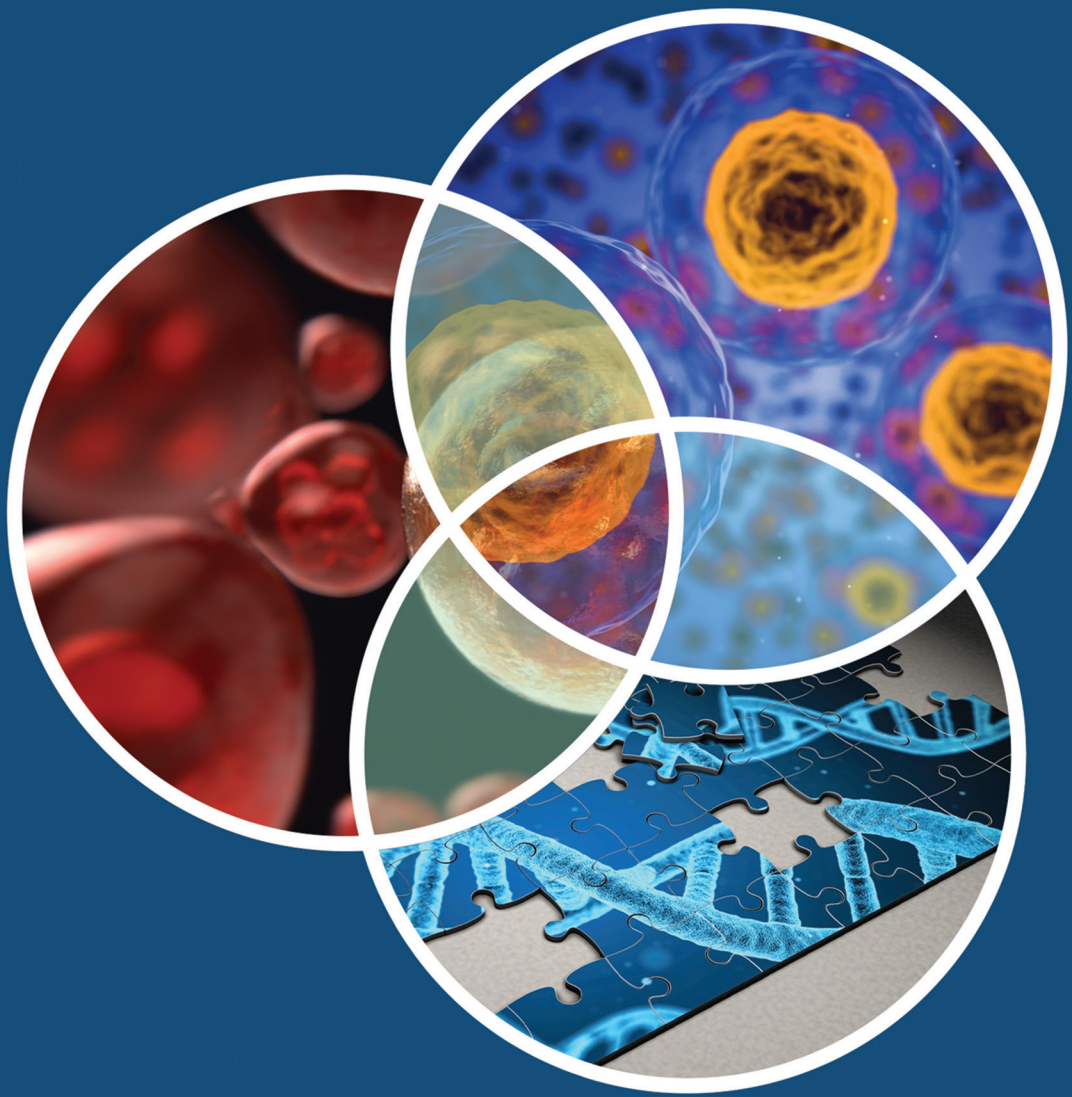
Current Issues in Medicine Vol. 1

ADVANCES IN MEDICAL BIOCHEMISTRY, GENOMICS, PHYSIOLOGY, AND PATHOLOGY

edited by

Raj Bawa | Esther H. Chang | Gerald F. Audette
Anil Diwan | Saadia A. Faiz



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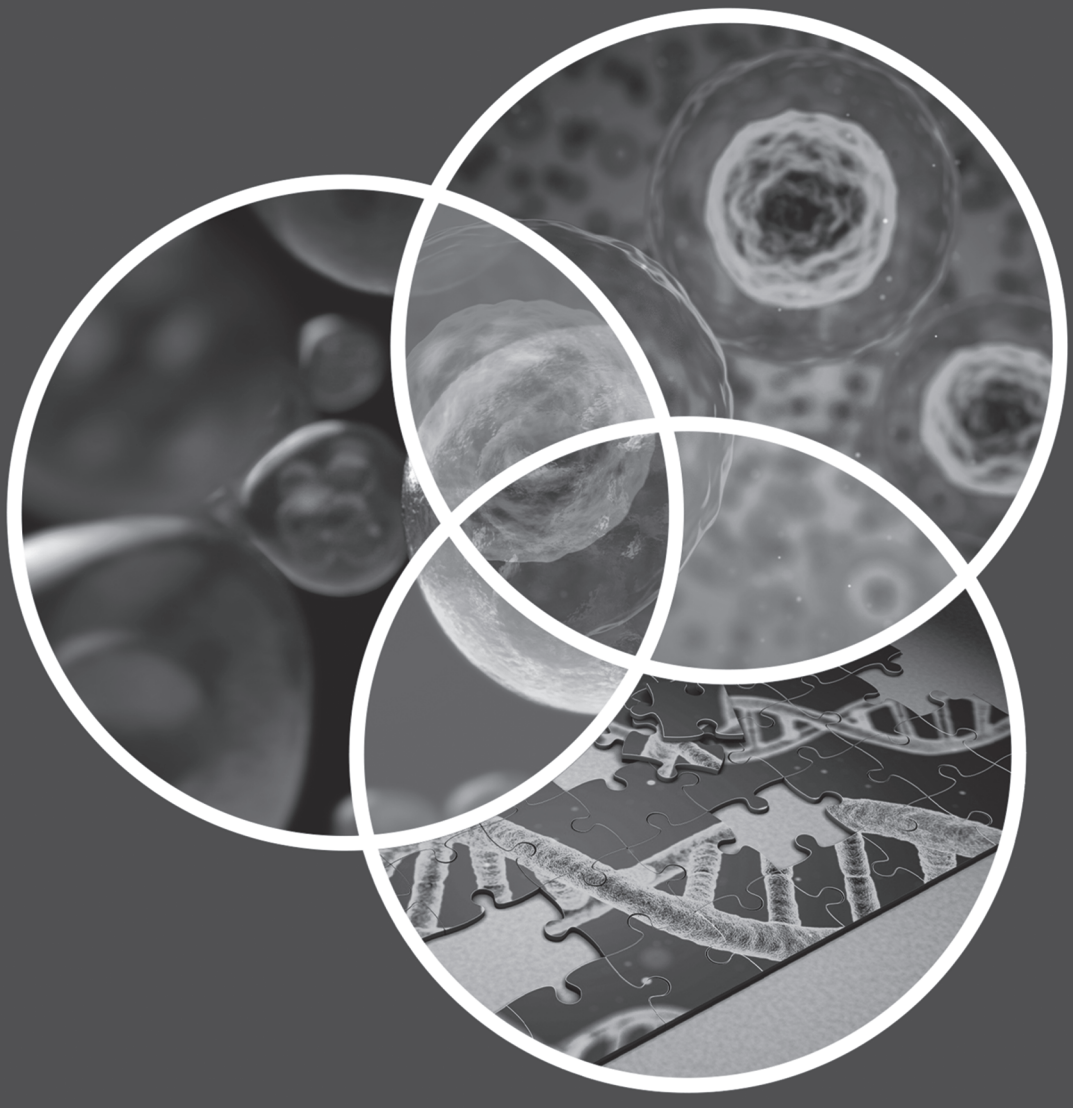

Current Issues in Medicine

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Raj Bawa

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2022
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Current Issues in Medicine Vol. 1

Advances in Medical Biochemistry, Genomics, Physiology, and Pathology

edited by

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Extensive efforts have been made to make the information provided herein as accurate and as up-to-date as possible. It is important to note that knowledge and best practices in the various fields represented in this book (medicine, pathology, biochemistry, genetics, drug delivery, nanomedicine, precision medicine, genomics, biologics, tissue engineering, patent law, FDA law, regulatory science, toxicology, pharmaceutical sciences, etc.) are constantly evolving. As new research and experience broaden our knowledge base, changes in medical care, diagnostics, therapy, research methods, assays, tools and techniques, medical formulations, and/or treatments may become necessary. Therefore, it is imperative that the reader does not solely rely on the information presented herein and always consults drug and device product labels, physician advice, warnings, and directions before using or consuming any drug product or using any device. For additional information about a product, please contact the appropriate medical professional, manufacturer, FDA, physician, pharmacist, or other licensed healthcare professional, as appropriate. Similarly, careful evaluation of any procedures, manufacturing steps, medical protocols, regulatory guidances, or assays described herein is warranted. To the fullest extent of the law, neither the publisher nor the editors or authors make any representations or warranties, express or implied, with respect to the information presented in this book, for its use or misuse, or interpretation thereof. In this regard, they assume no liability for any injury and/or damage to persons or property as a matter of product liability, negligence, or otherwise.

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Advances in Medical Biochemistry, Genomics, Physiology, and Pathology

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Dedication

In memory of my gentle mother, Mrs. Sudesh Bawa (1935–2020), who blessed me with immeasurable love and joy. She guided me to pursue my goals with integrity, inspired me with her perseverance, taught me to appreciate people for their inherent beauty, and instilled in me the desire to aid the helpless. It is these remarkable values that serve as the basis of newly formed *Sudesh Bawa Medical Foundation*. My memory is filled of images of her beautiful smile and steadfast support. She was my sunshine, my only sunshine...

All that I am or ever hope to be, I owe to my angel mother.
— Abraham Lincoln

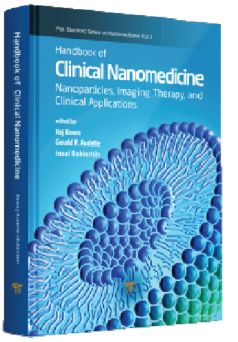
Youth fades, love droops, the leaves of friendship fall; a mother's secret hope outlives them all.
— Oliver Wendell Holmes

The loss of a mother is always keenly felt … She is the sweet rallying-point for affection, obedience, and a thousand tendernesses. Dreary the blank when she is withdrawn!
— Alphonse de Lamartine

Also Read

Handbook of Clinical Nanomedicine. Vol. 1. Nanoparticles, Imaging, Therapy, and Clinical Applications

Raj Bawa, MS, PhD, MD'22, Gerald F. Audette, PhD, and Israel Rubinstein, MD (Editors)



978-981-4669-20-7 (Hardcover), 978-981-4669-21-4 (eBook)
1662 pages

This handbook (55 chapters) provides a comprehensive roadmap of basic research in nanomedicine as well as clinical applications. However, unlike other texts in nanomedicine, it not only highlights current advances in diagnostics and therapeutics but also explores related issues like nomenclature, historical developments, regulatory aspects, nanosimilars and 3D nanofabrication. While bridging the gap between basic biomedical research, engineering, medicine and law, the handbook provides a thorough understanding of nano's potential to address (i) medical problems from both the patient and health provider's perspective, and (ii) current applications and their potential in a healthcare setting.

"Dr. Bawa and his team have meticulously gathered the distilled experience of world-class researchers, clinicians and business leaders addressing the most salient issues confronted in product concept development and translation."

Gregory Lanza, MD, PhD
Professor of Medicine and Oliver M. Langenberg Distinguished Professor
Washington University Medical School, USA

"This is an outstanding, comprehensive volume that crosscuts disciplines and topics fitting individuals from a variety of fields looking to become knowledgeable in medical nanotech research and its translation from the bench to the bedside."

Shaker A. Mousa, PhD, MBA
Vice Provost and Professor of Pharmacology
Albany College of Pharmacy and Health Sciences, USA

"Masterful! This handbook will have a welcome place in the hands of students, educators, clinicians and experienced scientists alike. In a rapidly evolving arena, the authors have harnessed the field and its future by highlighting both current and future needs in diagnosis and therapies. Bravo!"

Howard E. Gendelman, MD
Margaret R. Larson Professor and Chair
University of Nebraska Medical Center, USA

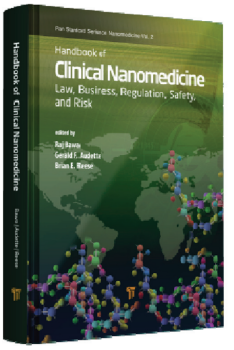
"It is refreshing to see a handbook that does not merely focus on preclinical aspects or exaggerated projections of nanomedicine. Unlike other books, this handbook not only highlights current advances in diagnostics and therapies but also addresses critical issues like terminology, regulatory aspects and personalized medicine."

Gert Storm, PhD
Professor of Pharmaceutics
Utrecht University, The Netherlands

Handbook of Clinical Nanomedicine. Vol. 2. Law, Business, Regulation, Safety, and Risk

Raj Bawa, MS, PhD, MD'22, (Editor), Gerald F. Audette, PhD, and Brian E. Reese, PhD, MBA, JD (Assistant Editors)

978-981-4669-22-1 (Hardcover), 978-981-4669-23-8 (eBook)
1448 pages



This unique handbook (60 chapters) examines the entire "product life cycle," from the creation of nanomedical products to their final market introduction. While focusing on critical issues relevant to nanoproduct development and translational activities, it tackles topics such as regulatory science, patent law, FDA law, ethics, personalized medicine, risk analysis, toxicology, nano-characterization and commercialization activities. A separate section provides fascinating perspectives and editorials from leading experts in this complex interdisciplinary field.

"The distinguished editors have secured contributions from the leading experts in nanomedicine law, business, regulation and policy. This handbook represents possibly the most comprehensive and advanced collections of materials on these critical topics. An invaluable standard resource."

Gregory N. Mandel, JD
Peter J. Liacouras Professor of Law and Associate Dean
Temple University Beasley School of Law, USA

"This is an outstanding volume for those looking to become familiar with nanotechnology research and its translation from the bench to market. Way ahead of the competition, a standard reference on any shelf."

Shaker A. Mousa, PhD, MBA
Vice Provost and Professor of Pharmacology
Albany College of Pharmacy, USA

"The editors have gathered the distilled experience of leaders addressing the most salient issues confronted in R&D and translation. Knowledge is power, particularly in nanotechnology translation, and this handbook is an essential guide that illustrates and clarifies our way to commercial success."

Gregory Lanza, MD, PhD
Professor of Medicine and Oliver M. Langenberg Distinguished Professor
Washington University Medical School, USA

"The title of the handbook reflects its broad-ranging contents. The intellectual property chapters alone are worthy of their own handbook. Dr. Bawa and his coeditors should be congratulated for gathering the important writings on nanotech law, business and commercialization."

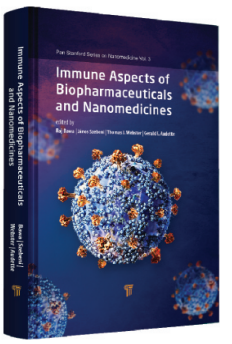
Richard J. Apley, JD
Chief Patent Officer
Litman Law Offices/Becker & Poliakoff, USA

"It is clear that this handbook will serve the interdisciplinary community involved in nanomedicine, pharma and biotech in a highly comprehensive way. It not only covers basic and clinical aspects but the often missing, yet critically important, topics of safety, risk, regulation, IP and licensing. The section titled 'Perspectives and Editorials' is superb."

Yechezkel (Chezy) Barenholz, PhD
Professor Emeritus of Biochemistry and Daniel Miller Professor of Cancer Research
Hebrew University-Hadassah Medical School, Israel

Immune Aspects of Biopharmaceuticals and Nanomedicines

Raj Bawa, MS, PhD, MD'22, János Szebeni, MD, PhD, DSc, Thomas J. Webster, MS, PhD, and Gerald F. Audette, PhD (Editors)



978-981-4774-52-9 (Hardback), 978-0-203-73153-6 (eBook)
1038 pages

The enormous advances in the immunologic aspects of biotherapeutics and nanomedicines in the past two decades has necessitated an authoritative and comprehensive reference source that can be relied upon by immunologists, biomedical researchers, clinicians, pharmaceutical companies, regulators, venture capitalists, and policy makers alike. This text provides a thorough understanding of immunology, therapeutic potential, clinical applications, adverse reactions, and approaches to overcoming immunotoxicity of biotherapeutics and nanomedicines. It also tackles critical, yet often overlooked topics such as immune aspects of nano-bio interactions, current FDA regulatory guidances, complement activation-related pseudoallergy (CARPA), advances in nanovaccines, and immunogenicity testing of protein therapeutics.

"This outstanding volume represents a review of the various effects of biopharmaceuticals and nanomedicines on the immune system: immunotherapy, vaccines, and drug delivery; challenges and overcoming translational barriers stemming from immunotoxicity; strategies to designing more immunologically friendly formulations."

África González-Fernández, PhD, MD
Professor of Immunology and President of the Spanish Society of Immunology,
University of Vigo, Spain

"For those who are specialists, and for those interested in a broader understanding of biologics and nanomedicines, this is a superb book, with internationally accomplished contributors. It serves both as a reference and as a practical guide to the newest advances in these important fields. Highly recommended!"

Carl R. Alving, MD
Emeritus Senior Scientist, Walter Reed Army Institute of Research, Silver Spring, Maryland, USA

"A skillfully produced book that addresses an often-missed topic: immune aspects of biologicals and nanoscale therapeutics, with an emphasis on clinical relevance and applications."

Rajiv R. Mohan, PhD
Professor and Ruth M. Kraeuchi Missouri Endowed Chair Professor,
University of Missouri, Columbia, USA

"An indispensable masterpiece! It represents a rich source of information on interactions of biologics and nanodrugs with the immune system—all critical for medical applications. Volume 3, once again, achieves the series' high standards."

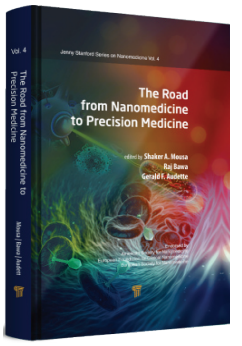
László Rosivall, MD, PhD, DSc Med, Med habil.
Széchenyi Prize Laureate and Professor, Faculty of Medicine, Semmelweis University,
Budapest, Hungary

"Hats off to Dr. Bawa for producing yet another impressive volume in terms of scope, timeliness, and relevance. With expert contributions from around the globe, this book addresses topics germane to researchers, clinicians, drug and biotherapeutic companies, regulators, policymakers, and patients."

Sara Brenner, MD, MPH
Associate Professor and Assistant Vice President, SUNY Polytechnic Institute, Albany,
New York, USA

The Road from Nanomedicine to Precision Medicine

Shaker A. Mousa, PhD, MBA, Raj Bawa, MS, PhD, MD'22, and Gerald F. Audette, PhD (Editors)



978-981-4800-59-4 (Hardback), 978-0-429-29501-0 (eBook)
1208 pages

The enormous advances in nanomedicine and precision medicine in the past two decades has necessitated a growing need for an authoritative and comprehensive reference source that can be relied upon by biomedical researchers, clinicians, pharmaceutical scientists, regulators, and lawyers alike. This stand-alone, full-color book provides a broad survey of various interconnected topics, all accomplished in a user-friendly format. Each chapter contains key words, tables, and figures in color, future projections, and an extensive list of references. It is intended to be a standalone reference volume that broadly surveys and highlights innovative technologies and advances pertaining to nanomedicine and precision medicine. In addition, it also addresses often-neglected yet key issues such as translational medicine, intellectual property law, FDA regulatory issues, nanomedicine nomenclature, and artificial nanomachines—all accomplished in a user-friendly, broad yet interconnected format. The book is essential reading for the novice and expert alike in diverse fields such as medicine, law, genomics, pharmaceutical sciences, biomedical sciences, ethics, and regulatory science. The book's multidisciplinary approach will attract a global audience. It will serve as a valuable reference resource for the industry, academia, and government.

"*The carefully selected range of topics in this masterpiece is perfect for academia, physicians, drug industry, healthcare systems, policymakers, regulatory bodies, and governments. In the coming decade, efforts in nanomedicine and precision medicine will be translated from the bench to the bedside, paving the way for more accurate diagnosis and more precise therapeutics. This volume is a standard reference for anyone involved in the coming healthcare revolution.*"

Tatiana K. Bronich, PhD
Parke-Davis Professor, University of Nebraska Medical Center, USA
Editor, *Nanomedicine* (Elsevier)

"*The first 3 volumes in this wonderful series have been inspirational. They form the most definitive and useful references about the clinical, technical, legal, and business aspects of nano. This fourth volume was awaited with great interest.*"

Peter J. Dobson, PhD, OBE
Academic Director, Begbroke Science Park, and Professor (retd), University of Oxford, UK

"*Ehrlich's vision of 'magic bullets' postulated in 1908 will be realized along the road from nanomedicine to precision medicine. The power unleashed by elucidation of the genome coupled with the elegance of site-specific drug delivery will revolutionize healthcare in the next century. In my 70-year career as a researcher and university professor, nothing has held greater potential to diagnose and treat diseases in a more customizable, targeted manner. This book reflects innovations, potential applications, and possible bottlenecks in these two interrelated fields.*"

S. R. Bawa, MSc, PhD
Founding Head and Professor of Biophysics (retd), Panjab University, India

"*Precision medicine and targeted nanomedicines are the 'Holy Grail' of medicine and drug delivery; this comprehensive volume highlights their salient features and interconnectivity. A team of distinguished editors and authors have done a superb job focusing on the critical and current issues, masterfully dissecting hype from reality.*"

János Szebeni, MD, PhD, DSc
Director, Nanomedicine Research & Education Center, Semmelweis University
CEO, SeroScience, Hungary

"*The growth, opportunity, and promise of nanomedicine have become breathtaking, which is why this book is my 'go to' reference. It puts cutting-edge nano-developments in context of precision medicine, and the lessons learned from applications in one clinical challenge may serve as a template for other challenges. Use this volume as a reference, but be sure to read it for inspiration.*"

Nicholas Borys, MD
Senior Vice President and Chief Medical Officer, Celsion Corporation, USA

Endorsed by

The American Society for Nanomedicine (ASNM) (https://www.nanomedus.org) is a nonprofit, professional medical organization based in Ashburn, Virginia, USA. It was founded in 2008 by Dr. Raj Bawa of Bawa Biotech LLC and Dr. Esther Chang of Georgetown Medical Center. The ASNM comprises members drawn from diverse fields, including medicine, law, nanotechnology, pharma, biotech, engineering, and biomedical sciences with the common goal of advancing nanomedicine research to benefit global health. These goals are achieved through an open forum of ideas and collaborative efforts as well as close cooperation with our partner organizations. Since its inception, the ASNM has organized and sponsored major international conferences.

Specifically, the vision of the ASNM includes

- promoting research related to all aspects of nanomedicine and providing a forum through scientific meetings for the presentation of basic, clinical, and population-based research;
- promoting and facilitating the formal training of physicians, basic medical scientists, engineers, molecular biologists, statisticians, and allied healthcare providers in nano-related medical research and education;
- encouraging preventive measures and nano-based technologies to reduce the incidences of various diseases;
- facilitating the establishment of programs and policies that can better serve early diagnosis.

The European Foundation for Clinical Nanomedicine (CLINAM) (https://www.clinam.org), founded in 2007 by Beat Löffler, MA, MD (Hon), and Patrick Hunziker, MD, is an organization based in Basel, Switzerland. Its primary mission is to advance medicine to the benefit of individuals and society through the application of nanoscience and targeted medicine. Aiming at prevention, diagnosis, and therapy, it supports clinically focused research and the interaction and information flow between clinicians, researchers, and the public. The major goal is to support the development and application of nanomedicine and targeted medicine and having in scope all nanomedicine-related fields. The foundation runs a lab, creates an annual summit for clinical nanomedicine, and established the *European Journal of Nanomedicine*. The CLINAM Summits held annually in Basel bring together over 500 participants from around the globe. CLINAM founded the European Society for Nanomedicine (ESNAM), which has more than 1,000 members today. ESNAM was the driving force for the formation of the International Society for Nanomedicine, (ISNM) which brings together members from Japan, Korea, USA, Canada, Europe, South America, Australia, Africa, and India. CLINAM organizes worldwide summer schools.

The Society for Brain Mapping and Therapeutics (SBMT) is a nonprofit society organized for the purpose of encouraging basic and clinical scientists who are interested in areas of brain mapping, engineering, stem cell, nanotechnology, imaging, and medical device to improve the diagnosis, treatment, and rehabilitation of patients afflicted with neurological disorders. This society promotes the public welfare and improves patient care through the translation of new technologies/ therapies into life-saving diagnostic and therapeutic procedures. The society is committed to excellence in education, and scientific discovery. The society achieves its mission through multidisciplinary collaborations with government agencies, patient advocacy groups, educational institutes, and industry, as well as philanthropic organization.

Brain Mapping Foundation (BMF) is a nonprofit, charitable organization, established for the purpose of facilitating multi-disciplinary brain and spinal cord research and expediting integration and translation of cutting-edge technologies into the field of neuroscience. BMF is focused on translating state-of-the-art technologies from space and defense industries into neuroscience in order to bring the most advanced medicine to wounded warriors as well as civilians.

The NCNBE mission is to establish collaborating research laboratories and network throughout the state of California and beyond in order to rapidly develop solutions for neurological disorders employing advances in nanotechnology, stem cell research, and medical devices (nanobioelectronics) while fostering biotech spinoffs for the purpose of job creation. NCNBE promotes the public welfare and improves patient care through the translation of new technologies into life-saving diagnostic and therapeutic procedures. The center is committed to excellence in education, and scientific discovery. The NCNBE achieves its mission through multidisciplinary collaborations/consortium with government agencies, patient advocacy groups, educational institutions, private sector, industry, and philanthropic organizations.

The Editors

Raj Bawa, MS, PhD, MD '22, is president of Bawa Biotech LLC (founded in 2002), a biotech/pharma consultancy and patent law firm based in Ashburn, Virginia, USA. Trained as a microbiologist and biochemist, he is an inventor, entrepreneur, professor, and registered patent agent (since 2002) licensed to practice before the US Patent & Trademark Office. He is currently a scientific advisor to Teva Pharmaceutical Industries Ltd. (Israel), a visiting research scholar at the Pharmaceutical Research Institute of Albany College of Pharmacy (Albany, NY), and vice president/chief IP officer at Guanine, Inc. (Rensselaer, NY). He is also a medical student and will receive the MD degree in 2022. He has served as a principal investigator of various research grants, most recently as a principal investigator of a CDC grant to develop an assay for carbapenemase-resistant bacteria. He was an adjunct professor at Rensselaer Polytechnic Institute (Troy, NY) from 1998 to 2018, where he received his doctoral degree in three years (biophysics/biochemistry). In the 1990s, Dr. Bawa held various positions at the US Patent & Trademark Office (Washington, DC), including primary examiner from 1996–2002. Presently, he is a life member of Sigma Xi, co-chair of the nanotech and precision medicine committees of the American Bar Association, and founding director of the American Society for Nanomedicine (founded in 2008). He has authored over 100 publications, co-edited 8 texts, and serves on the editorial boards of numerous peer-reviewed journals, including serving as an associate editor of *Nanomedicine* (Elsevier). Some of Dr. Bawa's awards include the Innovations Prize from the Institution of Mechanical Engineers, London, UK; Appreciation Award from the Undersecretary of Commerce, Washington, DC; Key Award from Rensselaer's Office of Alumni Relations; and Lifetime Achievement Award from the American Society for Nanomedicine.

Esther H. Chang, PhD, is a professor in the Department of Oncology at the Lombardi Comprehensive Cancer Center of Georgetown University Medical Center (Washington, DC). Before joining Georgetown University, she held positions in the National Cancer Institute as a cancer expert, in the Department of Surgery at Stanford University as a professor, and in the Department of Pathology at the Uniformed Services University of the Health Sciences as a professor. Currently, she is the president of the American Society for Nanomedicine and also an executive board member of the International Society for Nanomedicine in Basel. Dr. Chang is the founding scientist of, as well as a senior consultant for SynerGene Therapeutics, Inc.

Dr. Chang's research effort has focused primarily on the molecular mechanisms of carcinogenesis and in translating this basic information into clinical modalities in the form of novel nanomedicines. She was the first to identify human versions of a mouse viral oncogene and to demonstrate the role of these "*ras* oncogenes" in carcinogenesis. As determined by *Current Contents*, two of Dr. Chang's seminal papers on this topic were among the top 100 most-cited publications in life sciences (1982–84). Her research group also was one of the first two teams to demonstrate that a mutated p53 gene (one of the most frequently altered genes in human cancer) is the primary genetic defect in a cancer-prone family with Li-Fraumeni Syndrome. Dr. Chang's publication on this finding was among the top 10 most-cited publications in medicine (1991–92), according to Science Watch. More recently, her research group has been evaluating the combination of systemic, tumor-targeted molecular therapy and standard radiotherapy, chemotherapy, or immunotherapy for treatment of adult and pediatric cancers. Dr. Chang's nanotechnology-based therapeutic approaches have been shown to deliver the nanomedicine, homing specifically not only to the primary tumor but also to metastases after systemic administration. This nanodelivery system, carrying the human tumor suppressor gene p53 (in a product termed SGT-53), has successfully completed Phase I clinical trials as a single agent. SGT-53 has been shown to be safe and have anti-cancer activity. A Phase II trial with SGT-53 plus Abraxane® and gemcitabine for advanced, metastatic pancreatic cancer is being conducted at Mary Crowley Cancer Research Center, Dallas, Texas, and National Taiwan University Hospital, Taipei. In addition, a Phase I trial of SGT-53 in pediatric patients with recurrent brain tumors will soon be accruing at Children's National Medical Center, Washington, D.C. The same nanodelivery system carrying another tumor suppressor gene, RB94 (in a product termed SGT-94), has demonstrated safety and anticancer activity in a completed Phase I safety trial at the M.D. Anderson Cancer Center.

Dr. Chang has devoted a great deal of her recent efforts to developing the therapeutics capable of passing through the blood–brain barrier as countermeasures for nerve agents under a contract from the U.S. Department of Defense.

Dr. Chang has over 160 publications, is the inventor of over 140 issued patents, and has served as a member of a number of scientific advisory boards for the National Cancer Institute, NASA, the US Military Cancer Institute, and the Department of Energy. Her scientific findings have been published in prominent journals, including *Nature*, *Science*, *Cancer Research*, *Cell*, *Human Gene Therapy*, and *Molecular Therapy*, among others. She also has dedicated much time to the education of undergraduate, graduate, and medical students.

Gerald F. Audette, PhD, is associate dean in the Faculty of Science, professor of chemistry, and member of the Centre for Research on Biomolecular Interactions at York University (Toronto, Canada). His research focuses on the correlation between protein structure and biological activity of proteins involved in bacterial conjugation, in particular, the type 4 secretion system from the conjugative F-plasmid of *Escherichia coli*. In addition, his research targets the type IV pilins and associated assembly systems from several bacterial pathogens and is exploring the adaptation of these protein systems for applications in bionanotechnology and nanomedicine. Dr. Audette is the co-editor of volumes 1–4 of the *Jenny Stanford Series on Nanomedicine* and is a subject editor of structural chemistry and crystallography for the journal *FACETS*.

Anil Diwan, PhD, is president and chairman of NanoViricides, Inc. (Shelton, CT, USA), a publicly traded company (stock symbol: NNVC) dedicated to advancing antiviral applications of a novel nanomedicines platform. Dr. Diwan co-founded NanoViricides, Inc., in 2005 and played a key role in its listing on the NYSE exchange in 2013. Prior to that, he founded AllExcel, Inc., where he invented TheraCour®, a polymeric micelle zip-code-like targeting and encapsulating drug delivery platform. At AllExcel, he and colleagues also co-developed a novel cell therapy that promises to be a cure for Parkinson's Disease. Dr. Diwan is an inventor of various issued US patents and his PCT patent applications have matured into a number of patents worldwide. He has been instrumental in raising over $100 million at NanoViricides since founding it. He was also instrumental in the design and architecture of the new NanoViricides campus with discovery-to-cGMP-manufacture capabilities under one roof. Dr. Diwan was recognized as the "2014 Researcher of the Year" by BusinessNewHaven and NewHaven Register group, which provides annual recognitions for outstanding individuals in Connecticut. Dr. Diwan obtained a BTech in 1980 in chemical engineering from the Indian Institute of Technology, Bombay, India. Acceptance to the Indian Institute of Technology is based on the ultra-competitive exam, the Joint Entrance Examination (JEE), where he stood 9th. The qualification rate of the JEE in 2017 was ~0.92%. Following his undergraduate degree, he obtained his PhD in biochemical engineering in 1986 from Rice University in Houston, Texas, USA.

Saadia A. Faiz, MD, is a professor in the Department of Pulmonary Medicine at The University of Texas MD Anderson Cancer Center (Houston, Texas, USA). She currently practices as a pulmonary and sleep specialist in cancer medicine. She is board certified in internal medicine, critical care, pulmonary, and sleep medicine by the American Board of Internal Medicine. Dr. Faiz is an active member of professional societies, including the American College of Chest Physicians, the American Thoracic Society, the American Association for Bronchology and Interventional Pulmonology, and the Association of Pulmonary and Critical Care Medicine Program Directors. Her research interests include pulmonary manifestation of cancer, pleural disease in hematologic malignancies, pulmonary hypertension in cancer, and sleep and cancer. She also dedicates a significant amount of time to trainee education specifically using simulation for procedural education.

Contents

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Note from the Series Editor

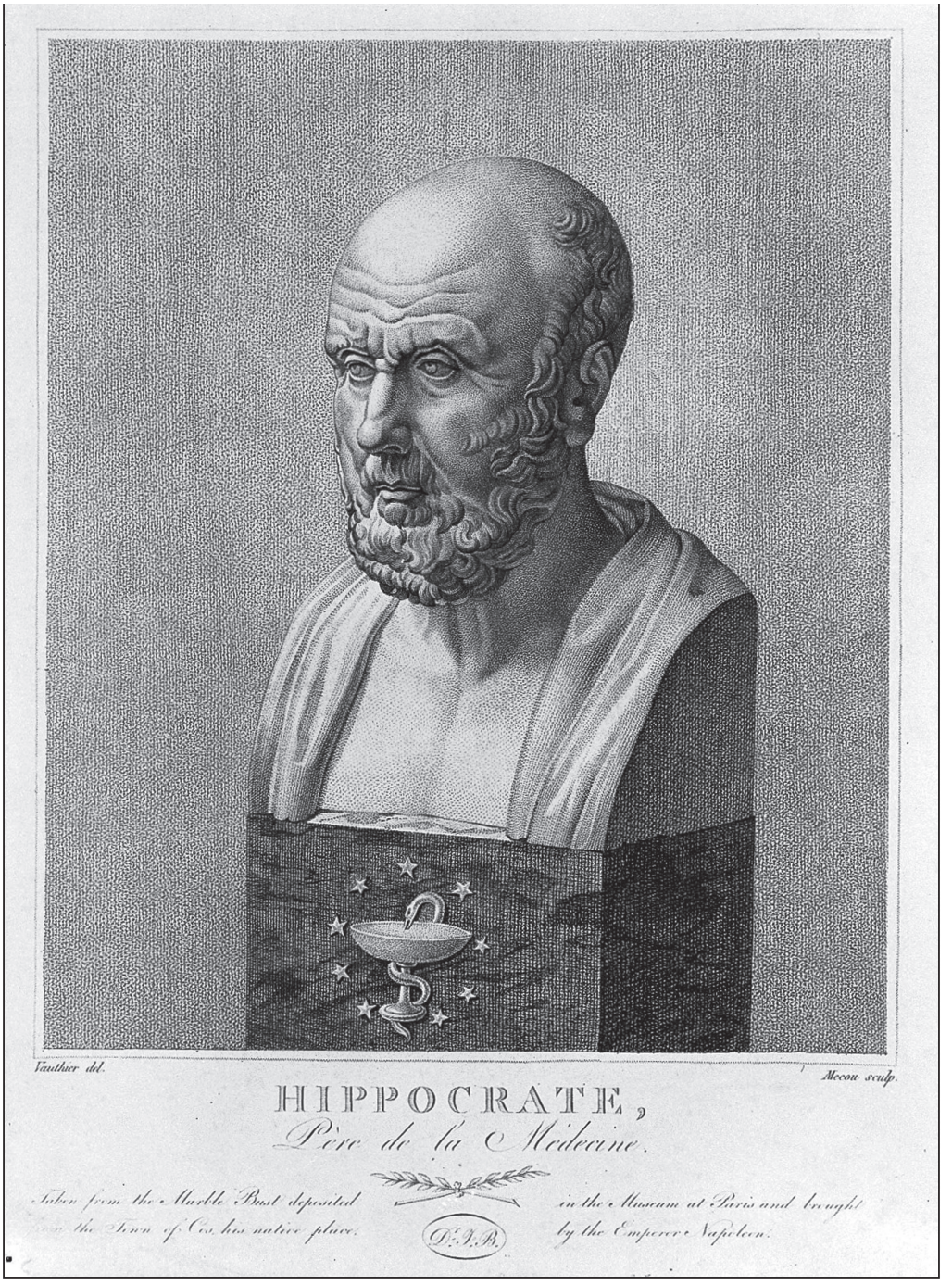
The incredible pace at which technology and medicine have advanced during the past two decades has revolutionized how we approach public health and deliver medical care. This has necessitated a growing need for a comprehensive reference series that highlights the current issues in medicine. This series does exactly that, all in a readily accessible, user-friendly format. Volume 1 in the *Current Issues in Medicine* series highlights current thinking, critical concepts, best practices, and perspectives in medical biochemistry, genomics, pathology, physiology, precision medicine, biologics, tissue engineering, patent and FDA law, regulatory science, and toxicology. These subjects are the underpinnings of medicine and part of most first-year medical school curricula. They are the basic and applied sciences that make the art of medicine possible. Specific chapters cover engineered proteins as therapeutics, aptamers, genetic markers in disease, biochemistry of neurodegenerative diseases, pharmacogenomics, cellular mechanisms of cardiovascular disease, diet microbiota, SARS-CoV-2 and COVID-19, genomic medicine, prion pathology, and physiological renormalization. This book is essential reading for physicians, medical students, nurses, fellows, residents, undergraduate and graduate students, educators, policymakers, and biomedical researchers. Undoubtedly, it will be a valuable reference for health facilities, medical institutions, industry, academia, and governments.

The range of topics covered in the *Current Issues in Medicine* series and the expertise of the contributing authors accurately reflect the rapidly evolving areas within medicine—from basic medical sciences to clinical specialties. Volumes 1 and 2 in this series are focused on the current issues in basic medical science, subjects that are fundamental to the practice of medicine. These subjects, traditionally taught in the first two years of medical school that precede clinical instruction, provide a core of basic knowledge critical to the success in clinical medicine during rotations, training, and medical practice. Obviously, knowledge gleaned from these subjects leads to better ways to predict, prevent, diagnose, and treat disease. Specifically, Volume 1 covers medical biochemistry, genomics, physiology, and pathology. Volume 2 discusses clinical immunology, medical microbiology, COVID-19, and big data. Surgical and clinical specialties are covered in Volume 3. Volume 4 is directed towards diagnosis and imaging techniques, Volume 5 focuses on drug delivery, and Volume 6 highlights novel therapies and clinical applications. Volume 7 is directed to critical editorials and perspectives pertaining to medicine and ancillary fields.

I am grateful to the authors, co-editors, and reviewers for meticulously ensuring the accuracy and completeness of information presented herein. I also thank Mr. Stanford Chong and Ms. Jenny Rompas of Jenny Stanford Publishing

for commissioning this outstanding series. Mr. Arvind Kanswal of Jenny Stanford Publishing and the staff at Bawa Biotech LLC are acknowledged for their valuable assistance with research, graphics, secretarial assistance, and publication coordination.

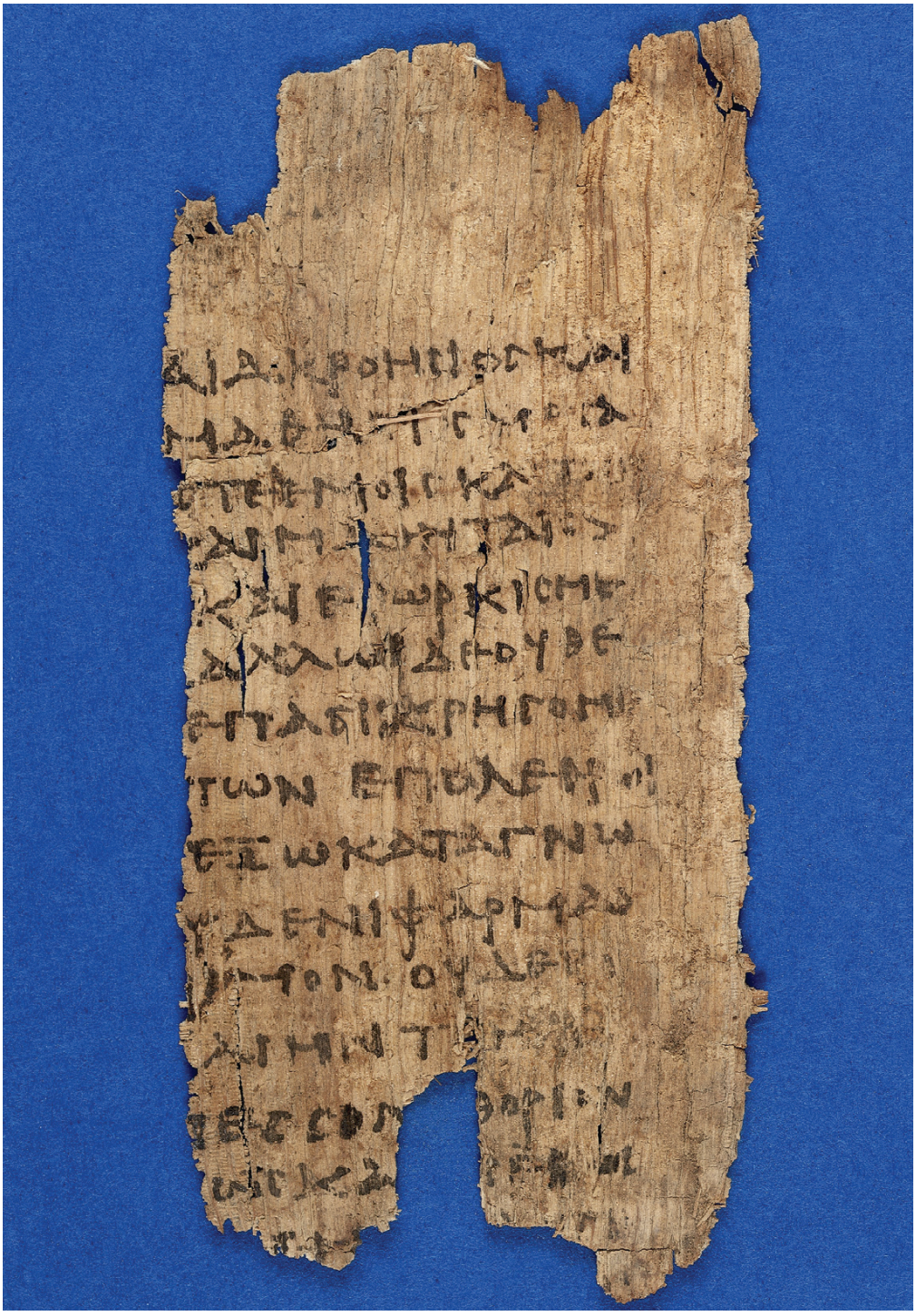
Dr. Raj Bawa
Series Editor



Engraving: marble bust of Hippocrates; by A. Mecou after Vauthier after a statue in the Louvre, n.d. Library reference no.: Burgess, Portraits, 1403.5. This bust is a typical portrayal of Hippocrates—as an experienced and wise old man. *Kindly provided by Wellcome Library, London.*

Hippocrates of Kos (Greek: Ἱπποκράτης ὁ Κῷος, translit. *Hippokrátēs ho Kôos*), also known as Hippocrates II, was a Greek physician of the Age of Pericles, who is considered one of the most outstanding figures in the history of medicine. Hippocrates (460–370 BC) is traditionally referred to as the "Father of Medicine" in recognition of his lasting contributions to the field, such as the use of prognosis and clinical observation and the systematic categorization of diseases. He was born in Kos—but apart from that, little is known of his life. Hippocrates is credited with being the first person to believe that diseases were caused naturally, not because of superstition and gods: "Science is the father of knowledge, but opinion breeds ignorance." He was the first to describe many diseases and also to set out standards of ethical behavior to which physicians were expected to adhere: "Cure sometimes, treat often, comfort always." He realized the vast amount of learning required to practice medicine—impossible for a person to learn even in a lifetime: "The life so short, the craft so long to learn." He emphasized that the purpose of medicine was to help nature apply its natural healing powers and to avoid doing harm: "Natural forces within us are the true healers of disease." He was the first to describe many signs and diseases—from clubbing to empyema. He classified diseases as acute or chronic and described the natural history of many diseases—from onset to convalescence. Some of his ideas and theories were proven to be incorrect.

—Dr. Raj Bawa



This torn papyrus text shows a fragment of the Hippocratic Oath. Library reference no.: External Reference Oxyrhynchus papyri no. 2547. *Kindly provided by Wellcome Library, London.*

The Hippocratic Oath is attributed to the Greek physician Hippocrates (460–370 BC). Ironically, it is not certain that Hippocrates actually wrote it. Most modern scholars believe that it originated after his death. The Hippocratic Oath is taken by physicians who promise to practice medicine to high ethical and professional standards. These include the principles of medical confidentiality and non-maleficence. It is often said that the exact phrase *First do no harm* (Latin: *Primum non nocere*) is a part of the original Hippocratic oath. Although the phrase does not appear in the AD 245 version of the oath, similar intentions are vowed by the phrase "I will abstain from all intentional wrong-doing and harm." The phrase *primum non nocere* is believed to date from the 17th century. There is no direct punishment for breaking the Hippocratic Oath, although a possible equivalent today is medical malpractice, which carries a wide range of punishments from legal action to civil penalties. In antiquity, the punishment for breaking the Hippocratic Oath could range from a penalty to losing the right to practice medicine. The Hippocratic Oath has been eclipsed as a document of professional ethics by regularly updated ethical codes issued by national medical associations, such as the American Medical Association Code of Medical Ethics (first adopted in 1847) and the British General Medical Council's Good Medical Practice. The modern version of the Hippocratic Oath, written in 1964 by Dr. Louis Lasagna, Dean of the School of Medicine at Tufts University, is shown below:

I swear to fulfill, to the best of my ability and judgment, this covenant:

I will respect the hard-won scientific gains of those physicians in whose steps I walk, and gladly share such knowledge as is mine with those who are to follow.

I will apply, for the benefit of the sick, all measures which are required, avoiding those twin traps of overtreatment and therapeutic nihilism.

I will remember that there is art to medicine as well as science, and that warmth, sympathy, and understanding may outweigh the surgeon's knife or the chemist's drug.

I will not be ashamed to say, "I know not," nor will I fail to call in my colleagues when the skills of another are needed for a patient's recovery.

I will respect the privacy of my patients, for their problems are not disclosed to me that the world may know. Most especially must I tread with care in matters of life and death. If it is given me to save a life, all thanks. But it may also be within my power to take a life; this awesome responsibility must be faced with great humbleness and awareness of my own frailty. Above all, I must not play at God.

I will remember that I do not treat a fever chart, a cancerous growth, but a sick human being, whose illness may affect the person's family and economic stability. My responsibility includes these related problems, if I am to care adequately for the sick.

I will prevent disease whenever I can, for prevention is preferable to cure.

I will remember that I remain a member of society, with special obligations to all my fellow human beings, those sound of mind and body as well as the infirm.

If I do not violate this oath, may I enjoy life and art, respected while I live and remembered with affection thereafter. May I always act so as to preserve the finest traditions of my calling and may I long experience the joy of healing those who seek my help.

—Dr. Raj Bawa

This image shows a reconstruction of the facade of the temple of Asclepius at Epidaurus, Greece. Today, only the foundation of the temple is preserved. However, the original temple has had a long-lasting influence on the architecture of buildings associated with medicine. Watercolour. From: Epidaure, restauration & description des principaux monuments du sanctuaire d'Asclépios. By: Defrasse, Alphonse and Lechat, Henri. Published: Librairies-Imprimeries Reunies Paris 1895. Plate III. *Kindly provided by Wellcome Library, London.*

Asclepius (Greek: Ἀσκληπιός *Asklēpiós* [asklɛːpiós]; Latin: *Aesculapius*), or Hepius, is a hero and god of medicine in ancient Greek religion and mythology. The temple of Asclepius at Epidaurus was built in the 4th century BC. Medicine and medical education have been intertwined with religion for centuries. For example, the witch-doctor (with his psychosomatic associations), the priests of ancient times (with access to the gods of health), first treatments for diseases (with their religious prayers, dances or ceremonies), and religious shamans (with their magical cures) tended to underline the importance of medicine as an art or mystique rather than as a science with its application of techniques (and now technology). Over the millennia, medicine has slowly shed its religious origins. However, few remnants persist. Latin continues to have a strong influence over the language of both religion and medicine.

—Dr. Raj Bawa

Chapter 1

The Age of COVID-19: Medical Facts and Fiction

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I dedicate this chapter to my late mother, Mrs. Sudesh Bawa (1935–2020), in whose memory I have established the *Sudesh Bawa Medical Foundation*. This section is based, in part, on discussions I have had with my 92-year-old father, Dr. S. R. Bawa, an anatomist and a retired university professor/chair. My parents were married in 1954 and exemplified how a lifelong relationship of love, dedication and perseverance gives meaning to life.

Keywords: acute respiratory distress syndrome, angiotensin converting enzyme 2, antibody test, antigen presentation, antigen-based tests, *Aspergillus fumigatus,* asymptomatic hosts, B cells, biosafety level-4, *Candida auris,* cellular immunity, Centers for Disease Control and Prevention, *Coccidioides immitis,* common cold virus, contact-tracing, controlled trial, convalescent plasma, coronavirus, coronavirus 2, Coronavirus disease 2019, COVID-19, cross-reactive antibody, cytokine storm, cytotoxic T cells, killer T cells, damage-associated molecular patterns, dendritic cells, diagnostic test, direct-to-consumer, emergency use authorization, epizootic, exocytosis, genetically engineered, Golgi intermediate, herd immunity, heterologous prime-boost, humoral immunity, hyperinflammatory immune response, immunity passports, immunization information system, immunosurveillance, interferon, interleukin, long COVID, Long Haulers, lymphocytes, major histocompatibility complexes, Middle East Respiratory Syndrome, multiple organ dysfunction syndrome, N antigen, nasal mucosa, neutralization capacity, NF-κB, nucleic acid amplification test, nucleocapsid, Operation Warp Speed, over-the-counter, pandemic, panzootic, passive immunotherapy, patents, pathogenicity, pattern recognition receptors, point-of-care, polymerase chain reaction, post COVID syndrome, prion, reactive oxygen species, regulatory T cells, RNA viruses, RT-PCR test, SARS-CoV, SARS-CoV-2, scanning electron micrograph, sensitivity, serology tests, seroprevalence, Severe Acute Respiratory Syndrome, single-stranded RNA genome, Spanish Flu, specificity, T cell immunity, T cells, T helper cells, transmissibility, transmission electron micrograph, tumor necrosis factor, US Department of State, US Food and Drug Administration, vaccination, variants of concern, viral surveillance, virulence, World Health Organization, Wuhan Institute of Virology, zoonosis, zoonotic, zoonotic reservoirs, zoonotic spillover

1.1 Emerging Pathogens: A Clear and Present Danger

Messieurs, c'est les microbes qui auront le dernier mot.
(Gentlemen, it is the microbes who will have the last word.)

—Louis Pasteur

Epidemics on the other side of the world are a threat to us all. No epidemic is just local.

—Peter Piot

Infectious diseases are a familiar enemy. Throughout history, viruses, bacteria, and parasites have killed more humans than wars and natural disasters. Viral diseases were recorded ever since humans began living together in communities with smallpox being the first reported around 10,000 BC. Smallpox was the deadliest human disease to ever exist, with a devastating 20–60% mortality rate, killing an estimated 300 million people in the 20th century alone.[1] I would add to this list, deadly human fungi that kill at least 1.6 million people globally.[2] In the past century, we have faced five pandemic respiratory diseases caused by different subtypes of influenza virus. In 1918, the H1N1 Spanish Flu, infected one-third of the world's population and killed an estimated 50–100 million people. The causative agent for this influenza pandemic was a mystery because the structure and function of viruses was unknown.[3] Other influenza pandemics include the 1957 H2N2 (Asian Flu) that originated in China and killed around 4 million people worldwide, the 1968 H3N2 (Hong Kong Flu) that killed 1 million people worldwide, the 2005 H5N1 (Bird Flu)[4] which caused a few deaths, and the 2009 H1N1 (Swine flu) which caused 18,000 deaths.

In addition to influenza pandemics, coronaviruses have also caused regional epidemics prior to the current pandemic. Coronaviruses are divided into four

[1]S. Riedel. (2005). Edward Jenner and the history of smallpox and vaccination. *Proc. Bayl. Univ. Med. Cent.* **18**:21–25.

[2]In our frantic attempts to save COVID-19 patients consigned to intensive care units on intravenous anti-infective and immunosuppressive drugs, they could be susceptible to pathogenic fungi like *Candida auris, Coccidioides immitis, Aspergillus fumigatus*, etc. In fact, there are reports that deadly fungi are gaining a foothold in COVID-19 patients as broad-spectrum antibiotics also wipe off beneficial bacteria that keep invading microbes in check. I fail to understand why medical students are not taught more medical mycology during the first year of medical school given that there are 300+ fungal species (out of a total of 5 million+) that cause human diseases.

[3]Unlike bacteria or fungi, viruses cannot be seen under a light microscope. The electron microscope was invented in the 1940s and this sophisticated instrument can resolve viruses. During the 1918 pandemic, a viral etiology could only be identified indirectly via an ultrafiltrate from a diseased subject to induce disease in a susceptible plant or animal host, or by detecting the presence of antibodies against the disease in survivors.

[4]Various H5N1 strains have evolved since 2005 and they are significantly different at the genome level. H5N1 is a fast-mutating, highly pathogenic avian influenza virus (HPIV) found in multiple bird species. It is both epizootic (an epidemic in non-humans) and panzootic (a disease affecting animals of many species).

genera, namely, alpha (α), beta (β), gamma (γ), and delta (δ), with pathology ranging from upper respiratory symptoms typical of the common cold to life-threatening lower respiratory disease. The common cold-causing coronaviruses, 229E and OC43, were first isolated in the mid-1960s, with two additional coronaviruses, NL63 and HKU1, identified in 2004 and 2005, respectively. It is well established that all are ubiquitous human pathogens. Two beta coronaviruses of zoonotic[5] origin have caused large-scale cluster outbreaks of severe respiratory disease. They were the Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) epidemic in 2003 in mainland China, and the Middle East Respiratory Syndrome Coronavirus (MERS-CoV) epidemic in 2012 in Saudi Arabia and in 2015 in South Korea. SARS-CoV spread to 26 countries before the outbreak was contained with over 8,000 people infected and a case fatality rate of approximately 10%. Regarding MERS-CoV, infections are still occurring and have been reported in almost 30 countries. While human-to-human transmission for MERS-CoV is rare, some studies show the case fatality rate to be greater than 30%.

Development of vaccines, antibiotics, and dramatically improved sanitation has greatly reduced morbidity and mortality from pathogenic microbes. As a result, we have become more complacent about the potential threat posed by our tiny, yet mighty, adversaries. In fact, world health bodies and politicians' response to global infectious disease threats has been poor as other priorities have generally taken precedence. Sadly, that same pattern initially unfolded and was on full display at the onset of the coronavirus disease 2019 (COVID-19) crisis. Except, this time around, governments, politicians, and health organizations were eventually forced to act.

The year 2020 will forever be marked by the presence of the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) and the associated COVID-19 pandemic. COVID-19 has had a catastrophic effect on the world's demographics resulting in ~3.76 million deaths. After the first cases of this predominantly respiratory viral illness were first "officially" reported by the Chinese government in late December 2019, SARS-CoV-2 rapidly circumvented the globe in a matter of weeks, compelling the World Health Organization (WHO) to declare it as a global pandemic on March 11, 2020. As of June 8, 2021, globally, there have been 174,591,505 coronavirus cases and 3,757,419 deaths, and 157,941,391 patients have recovered from COVID-19[6] (Fig. 1.1). Virtually overnight, this pandemic profoundly altered the world as it struggled to contain SARS-CoV-2 while mitigating its health, economic, and social impact. *For a global pandemic to occur, the following requirements are needed: emergence of a new human microbe; reduced or minimal population immunity to that microbe; and a relatively simple mode of*

[5]See, https://en.wikipedia.org/wiki/Zoonosis: "A zoonosis (plural zoonoses, or zoonotic diseases) is an infectious disease caused by a pathogen (an infectious agent, such as a bacterium, virus, parasite, or prion) that has jumped from an animal (usually a vertebrate) to a human. Typically, the first infected human transmits the infectious agent to at least one other human, who, in turn, infects others."

[6]Worldometer. COVID-19 outbreak live update. Available at: https://www.worldometers.info/coronavirus (accessed on June 8, 2021). Another authoritative source is the Johns Hopkins Coronavirus Resource Center: https://coronavirus.jhu.edu/.

transmission from one person to another. The SARS-CoV-2 virus fulfills all three of these criteria.

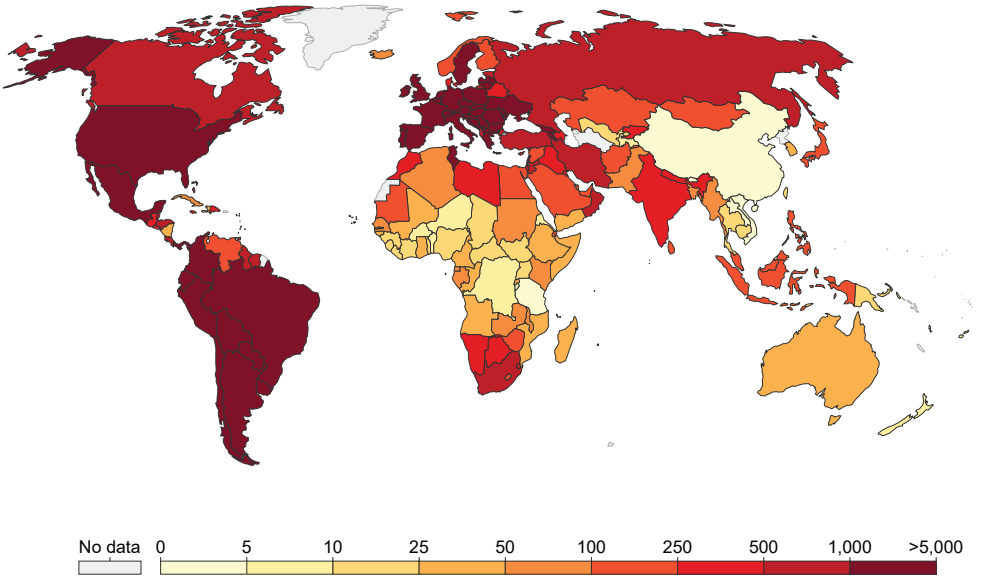


Figure 1.1 World map of total confirmed COVID-19 cases per million people. The confirmed counts shown here are lower than the total counts. The main reason for this is limited testing and challenges in the attribution of the cause of death. *Source*: Our World In Data (CC BY 4.0).

For the past three decades, infectious viruses have emerged to pose great threats to human health and society (Fig. 1.2). In this regard, hemorrhagic fever viruses (Lassa, Ebola), novel coronaviruses and highly pathogenic influenza are the prime culprits. Viral emergence from a zoonotic reservoir is common, and coronaviruses (CoVs) are no exception. CoVs infect a wide range of species and have been isolated from dogs, cats, horses, cattle, swine, chickens, turkeys, and humans with clinical signs of disease (and coronaviruses have frequently expanded their host range). Most human coronaviruses are thought to have originated from bats. Coronavirus strains that infect humans generally cause mild symptoms though animal coronaviruses have caused outbreaks of severe respiratory disease in humans, including SARS, MERS, and now, COVID-19. SARS-CoV spread rapidly prior to being controlled. The MERS-CoV outbreak is still circulating in the human population. Scientists are still trying to understand how the SARS-CoV-2 virus relates to SARS-CoV at the genome level, transcriptomic level, structurally, and biochemically. Most importantly, we need to know how these impact virulence, transmissibility, and the potential to generate variants.

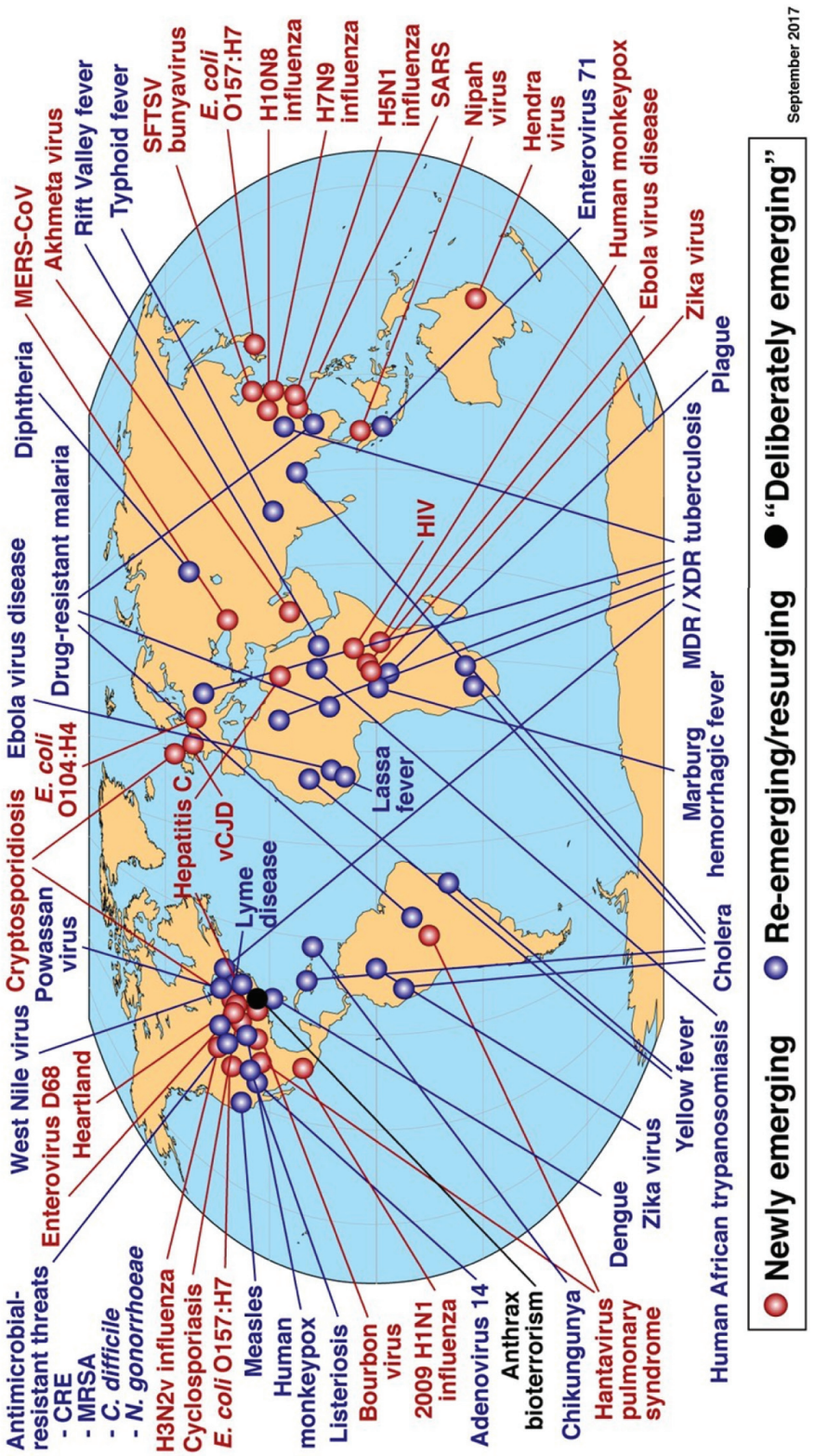


Figure 1.2 Global examples of emerging and reemerging infections. *Courtesy of Dr. Anthony S. Fauci and NIH.*

According to a National Academies report[7]: "The convergence of any number of factors can create an environment in which infectious diseases can emerge and become rooted in society. A model was developed to illustrate how the convergence of factors in four domains impacts on the human-microbe interaction and results in infectious disease (Fig. 1.3). Ultimately, the emergence of a microbial threat derives from the convergence of (1) genetic and biological factors; (2) physical environmental factors; (3) ecological factors; and (4) social, political, and economic factors. As individual factors are examined, each can be envisioned as belonging to one or more of these four domains."

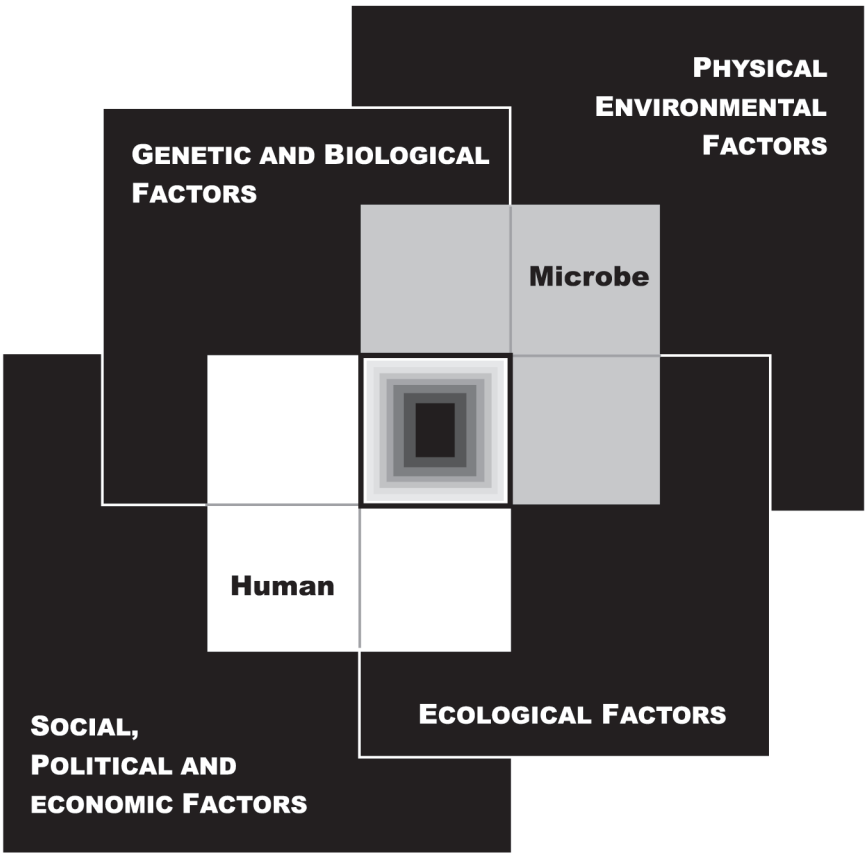


Figure 1.3 The convergence model. At the center of the model is a box representing the convergence of factors leading to the emergence of an infectious disease. The interior of the box is a gradient flowing from white to black; the white outer edges represent what is known about the factors in emergence, and the black center represents the unknown (similar to the theoretical construct of the "black box" with its unknown constituents and means of operation). Interlocking with the center box are the two focal players in a microbial threat to health—the human and the microbe. The microbe-host interaction is influenced by the interlocking domains of the determinants of the emergence of infection: genetic and biological factors; physical environmental factors; ecological factors; and social, political, and economic factors. *Courtesy of the National Academy of Sciences*.

[7]M. S. Smolinski, M. A. Hamburg, and J. Lederberg. (2003). *Microbial Threats to Health: Emergence, Detection, and Response.* National Academies Press, Washington, DC.

As a microbiologist, I am fully aware that our world is a playground for microbes. As an adjunct professor at Rensselaer Polytechnic Institute in Troy, NY, I designed and taught a course for over a decade titled "Biodefense: A clear and present danger." It included lectures on emerging and re-emerging infectious diseases, including the potential of coronaviruses to cause pandemics. A few lectures covered microbial bioweapons and biodefenses against them. The inspiration for the course was based on a half-day meeting at the Center for Biodefense at George Mason University in Virginia with its director, Dr. Kenneth "Ken" Alibek (Col. Kanatzhan "Kanat" Alibekov). He was the First Deputy Director of Biopreparat from 1988–1992, the offensive biological weapons program of the Soviet Union, a gigantic biowarfare project that, at its height, had 50,000+ employees. There he oversaw projects that included weaponizing microbes that cause glanders, smallpox, plague, tularemia, Ebola, and Marburg, and the creation of a new "battle strain" of anthrax. The size and scope of the Soviet Union's bioweapon's efforts were truly staggering. They stockpiled tons of anthrax bacilli and smallpox virus, some for use in intercontinental ballistic missiles. Dr. Alibek gifted me his superb book, titled "Biohazard,"[8] excerpts of which I have continued to use in the classroom for the past 15 years. The subtitle for the book, "The chilling true story of the largest covert biological weapons program in the world—Told from the inside by the man who ran it," is an appropriate summary of the book's contents. It is a must-read for any medical student, microbiologist, policy-maker, or health-care professional. *The book highlights that (i) in spite of international conventions banning bioweapon development, secrecy regarding genetic manipulation of microbes to enhance their pathogenicity and virulence is a reality at state-run labs of numerous countries; and (ii) the potential that the world's most dangerous pathogens can escape from biosafety labs, including the controversial biosafety level-4 (BSL-4) labs, is typically guarded as a state secret.* Given this backdrop, it is possible that the Wuhan Institute of Virology (WIV) in China created the SARS-CoV-2 virus via genetic engineering and it accidently leaked out resulting in the current COVID-19 pandemic. If this did happen, it also points to the wider concern many experts have had that microbial leaks, even at BSL-4 labs like the one at WIV, present serious public health concerns. In fact, such concerns were raised back in 2017 during the certification of the lab at WIV as meeting the standards and criteria of BSL-4: "Some scientists outside China worry about pathogens escaping, and the addition of a biological dimension to geopolitical tensions between China and other nations ... The SARS virus has escaped from high-level containment facilities in Beijing multiple times."[9] Such worries are real with documented

[8]K. Alibek and S. Handelman. (1999). *Biohazard.* Random House, New York, NY.
[9]D. Cyranoski. (2017). Inside China's pathogen lab. *Nature* **554**:339–340.

leaks provided as evidence. Elaborate coverups, which possibly are also underway at WIV are typical of dictatorships like China and Russia.[10] Tighter security is needed at BSL-4 labs to prevent theft, accidents, or terrorism.

Pandemics can be triggered by unavoidable or uncontrollable natural processes like genetic variations and climate change. They can also arise from risks generated by human activities or practices like antibiotic overuse or misuse, destruction of forest habitats of microbe-carrying animals and an increase in the ease and speed of global transportation that spreads disease-causing pathogens. By some estimates, of the 1,461 diseases now recognized in humans, approximately 60% are due to multi-host pathogens characterized by their movement across species lines.[11] Other reports conclude that over the past three decades, about 75% of new emerging human infectious diseases have a zoonotic origin.[12] Clearly, human-animal interactions and interdependence is likely the most critical risk factor to our health with regard to infectious diseases. Obviously, to gauge a "spillover event," enormous scientific resources must be directed towards predicting where the deadliest viruses reside, their life cycles, susceptibilities, and ability to cross species barriers. Emerging pathogens pose a clear and present danger and pandemic preparedness is essential.

1.2 SARS-CoV-2: Structure and Pathogenesis

[It is] really hard for the human brain to grasp the exponential growth of an existential threat.

—Charity Dean on 60 Minutes, 2021

SARS-CoV-2 (Boxes 1.1 and 1.2) genome is comprised of ~30,000 nucleotides. It encodes four structural proteins: **N**ucleocapsid (N) protein, **M**embrane (M) protein, **S**pike (S) protein, **E**nvelop (E) protein, and several **n**on-**s**tructural **p**roteins (nsp).

A delicate dance between a virus (the invading pathogen) and the immune system (host defense mechanisms) unfolds each time the virus infects the host (Figs. 1.4–1.8). Host immune cells and antibodies are in constant battle with virus invaders, with one just barely keeping the other in check. One of the most confusing and fundamental questions around viruses is why they are severely pathogenic to some hosts and asymptomatic in others. This is observed not only with SARS-CoV-2 but a host of others, including, SARS, MERS, influenza, Ebola, dengue, yellow fever, chikungunya, West Nile, Lassa, Japanese encephalitis,

[10]See, F. Frischknecht. (2003). The history of biological warfare. *EMBO Reports* **4**:S47–S52: "In 1979, the Soviet secret police orchestrated a large cover-up to explain an outbreak of anthrax in Sverdlovsk, now Ekaterinburg, Russia, with poisoned meat from anthrax-contaminated animals sold on the black market. It was eventually revealed to have been due to an accident in a bioweapons factory, where a clogged air filter was removed but not replaced between shifts."

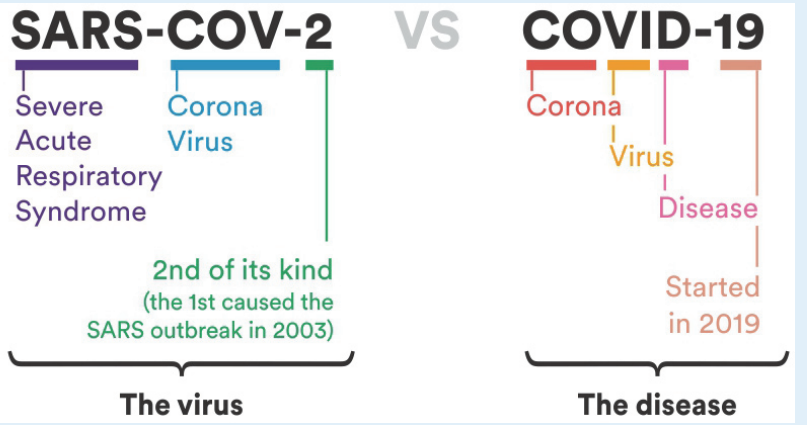
[11]E. F. Torrey and R. H. Yolken. (2005). *Beasts of the Earth*. Rutgers University Press, New Brunswick, NJ.

[12]L. H. Taylor, S. M. Latham, and M. E. Woolhouse (2001). Risk factors for human disease emergence. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* **356**:983–989.

Epstein-Barr, polio, etc. Today, there are numerous qualitative and quantitative assays, imaging tools, mathematical models, and genetic tools to identify and isolate viruses that shine a light on current or past infection, even in asymptomatic hosts. After all, it is in the virus's best interest, from an evolutionary perspective, to co-exist in the host in a chronic asymptomatic state without causing major damage. Smart viruses maintain a carrier state, a sort of equilibrium with the host's immune cells in an asymptomatic fashion.

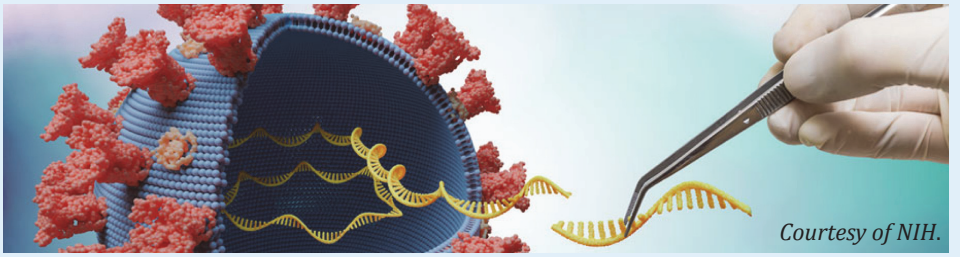
Box 1.1 What's in a name? Importance of nomenclature

It is important to distinguish the SARS-CoV-2 virus from the disease it causes, namely, COVID-19. The disease is caused by a coronavirus, the same class of virus that causes the common cold. During the initial outbreak various names were used for the virus, including, the "coronavirus," "Wuhan coronavirus," or "the Chinese virus." In February 2020, the International Committee on Taxonomy of Viruses adopted the official name "Severe Acute Respiratory Syndrome Coronavirus 2" (SARS-CoV-2). This name comes from the disease it causes, namely, **s**evere **a**cute **r**espiratory **s**yndrome; CoV stands for **co**rona**v**irus, and the number **2** was added because it is the second coronavirus that causes a serious respiratory disease (in 2019). Some publications and articles in the media refer to SARS-CoV-2 as "the COVID-19 virus" or "HCoV-19 virus."



A virus is an entity that infects living organisms/cells and requires a host for survival and multiplication. The term "pandemic," on the other hand, refers to the outbreak, occurrence, and spread of a particular disease. In that sense, it has a much more prominent social connotation. The layperson often calls both the virus and the disease it causes, "coronavirus," often omitting the numerical designation at the end. As a microbiologist, I will not use the two terms SARS-CoV-2 (the virus) and COVID-19 (the disease) interchangeably because they are distinct. In this chapter, I will use the terms SARS-CoV-2 virus, CoV-2 virus, and coronavirus 2 interchangeably to refer to the virus that causes COVID-19.

Box 1.2 Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)



Courtesy of NIH.

The first coronavirus, avian infectious bronchitis virus, was discovered in 1937. Forty years later when electron microscopy was performed on specimens from cultures of viruses known to cause colds in humans, the particles were and identified as avian infectious bronchitis virus. The term "coronavirus," is from the Latin word, *corona* ("crown") because the glycoprotein spikes of these viruses create an image similar to a solar corona (Box 1.1, the figure on the next page, and also Figs. 1.4a,b and 1.5). Coronaviruses belong to the Coronaviridae family in the Nidovirales order and are in the nanoparticle size range (65–125 nm in diameter) and contain a single-stranded RNA as a nucleic material, ranging from 26 to 32kbs in length. The subgroups of coronaviruses family are alpha (α), beta (β), gamma (γ), and delta (δ) coronavirus. SARS-CoV, H5N1 influenza A, H1N1 2009, and MERS-CoV cause acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) which leads to pulmonary failure and result in fatality.

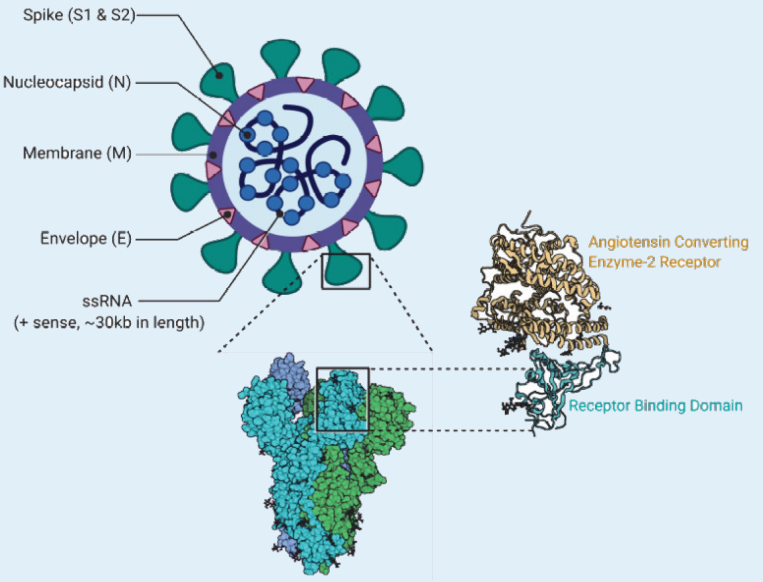
The Chinese government informed the WHO in December 2019 that SARS-CoV-2 originated in Wuhan. However, circumstantial evidence now (in May 2021) points to its emergence months earlier in 2019, with the finger pointing to a possible lab leak (see Section 1.3). The WHO declared it as Public Health Emergency of International Concern (PHEIC) in January 2020, and finally a pandemic in March 2020. According to one study, of the individuals infected by the virus, about 80% had mild to moderate disease and among those with severe disease, 5% develop critical illness (*JAMA* 2020; **323**:1239–1242). Those infected with SARS-CoV-2 virus generally develop symptoms 4–5 days postexposure and include fever, throat pain, cough, muscle or body aches, loss of taste or smell, and diarrhea. Recovery from mild infection commonly resolves within 7–10 days after the onset of symptoms but can take 3–6 weeks in severe/critical illness (Report of the WHO-China joint mission on coronavirus disease 2019). However, continued follow-up of patients who recovered from COVID-19 showed that one or more symptoms persist in a substantial percentage of people, even weeks or months after COVID-19. Coronavirus can also cause forgetfulness, psychosis, mania, or a stutter (*Scientific American Health & Medicine* 2021; **3(2)**:15–18). Along with the pneumonia, blood clots, and other serious health concerns

(*Continued*)

Box 1.2 (*Continued*)

caused by SARS-CoV-2, some studies have now also identified another troubling connection: the virus can target and impair cells in the pancreas causing Type 1 diabetes (*Cell Metab* 2021; S1550–4131(21)00232-1; *Cell Metab*. 2021; S1550–4131(21)00230-8.). A few of those who recovered from COVID-19 develop persistent or new symptoms lasting weeks or months; this is referred to as "long COVID," "Long Haulers," or "Post COVID syndrome." Long COVID can be continuous or relapsing and remitting in nature (*BMJ* (2020). **370**:m3489, http://dx.doi.org/10.1136/bmj.m3489). Majority of patients with post-COVID syndrome are polymerase chain reaction (PCR) negative.

Genomic analysis revealed that SARS-CoV-2 is phylogenetically related to SARS-like bat viruses, leading to the theory that this novel virus is also of bat origin with a currently unknown animal species potentially acting as an intermediate host between bats and humans. The highly infectious virus mainly targets pulmonary epithelial cells via its spike protein that binds to the host's angiotensin converting enzyme 2 (ACE2) receptor. There is data to show that besides human ACE2 (hACE2), SARS-CoV-2 also recognizes ACE2 from pig, ferret, rhesus monkey, civet, cat, pangolin, rabbit, and dog. An important conclusion of this broad receptor usage of SARS-CoV-2 implies that it may have a wide host range, and the varied efficiency of ACE2 usage in different animals may indicate their different susceptibilities to SARS-CoV-2 infection. I am certain that studies will confirm this.



SARS-CoV 2 Structure. *Courtesy of Dr. R. B. Singh.*

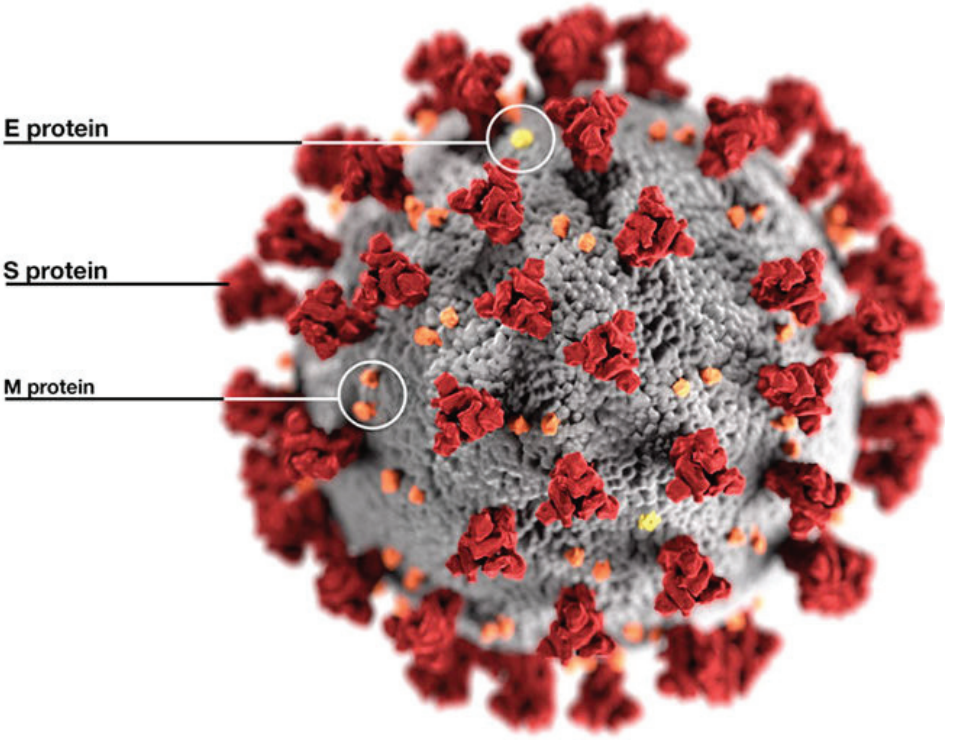


Figure 1.4a The peplomers of a SARS-CoV-2. This illustration reveals the surface morphology/topography of the virus nanoparticle. Note the spikes that adorn the outer surface of the virus, which impart the look of a corona surrounding it, when viewed electron microscopically. A peplomer (Greek: *peplos*, 'robe', '[woman's] dress' + *meros*, 'part') is one of the knoblike spike structures (red, orange, yellow), generally composed of glycoproteins (spike protein) and projecting from the lipid bilayer of the surface envelope of an enveloped virus. Peplomers play important roles in the infection process. *Courtesy of the CDC*.

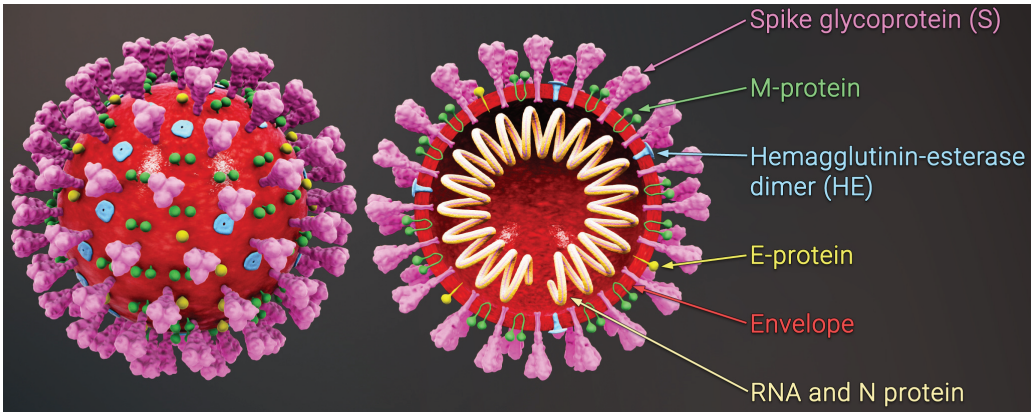


Figure 1.4b Structural view of a coronavirus. *Source*: https://commons.wikimedia.org/wiki/File:3D_medical_animation_coronavirus_structure.jpg (CC BY-SA 4.0).

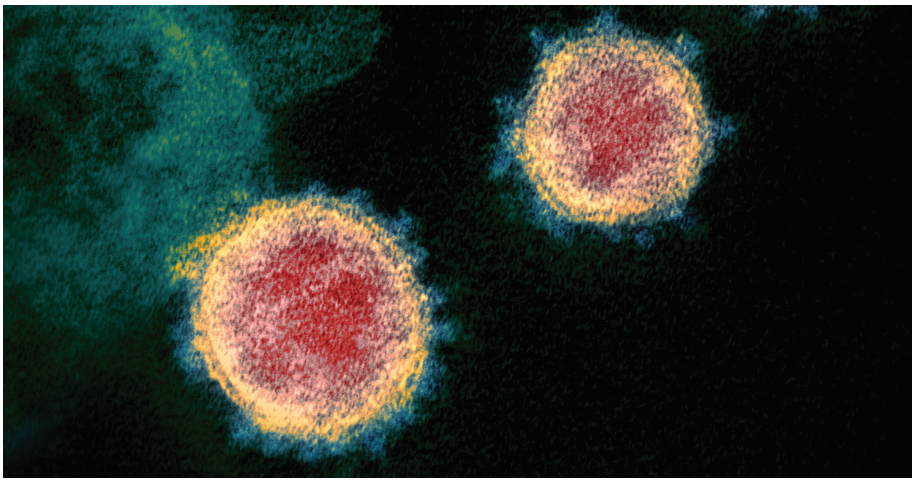


Figure 1.5 Digitally colorized transmission electron micrograph of SARS-CoV-2 virions. Virion nanoparticles, isolated from a patient in the US, are shown emerging from the surface of cells cultured in the lab. The coronae (bluish) are visible on the surface of the virus (yellow-red). *Courtesy of NIH.*

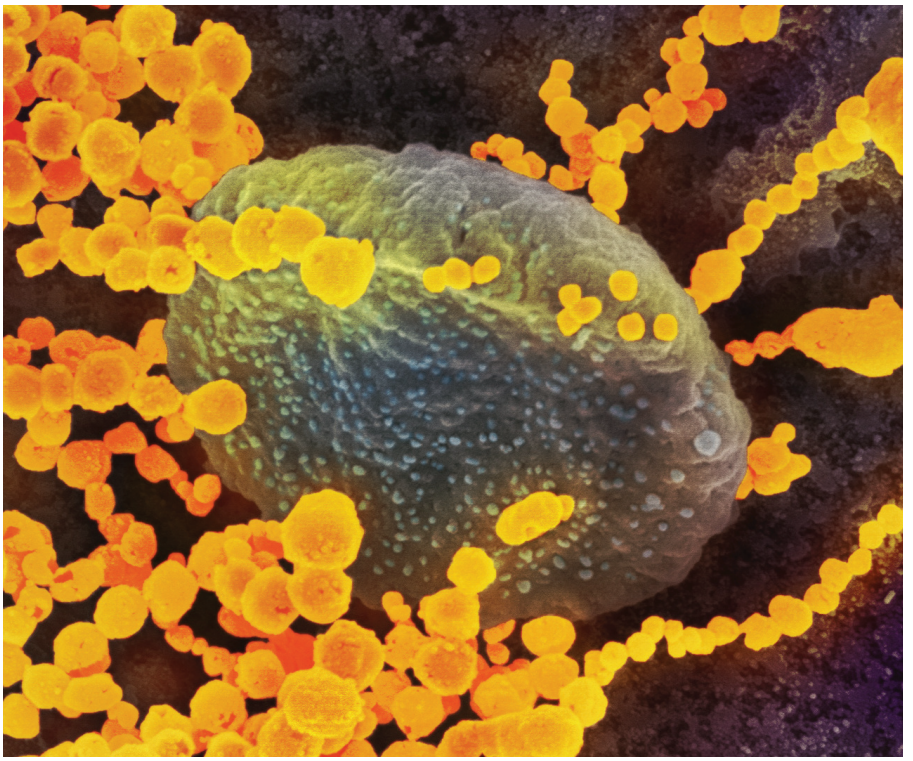


Figure 1.6 Digitally colorized scanning electron micrograph of SARS-CoV-2 virions. Virion nanoparticles (yellow), isolated from a patient in the US, are shown emerging from the surface of cells cultured in a lab. *Courtesy of NIH.*

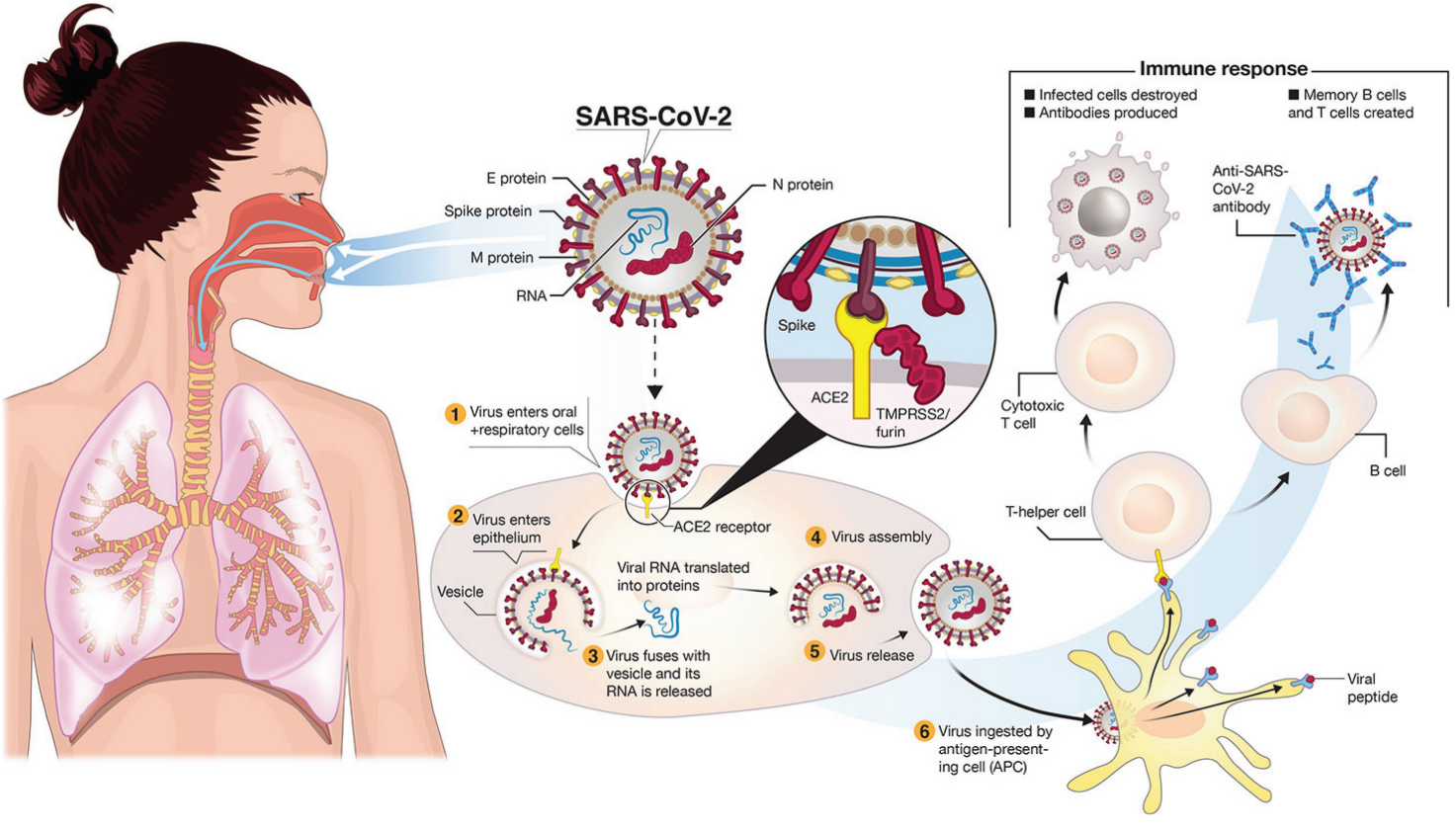


Figure 1.7 Transmission and life-cycle of SARS-CoV-2 causing COVID-19. SARS-CoV-2 is transmitted via infected respiratory droplets to oral and respiratory mucosal cells. The virus, possessing a single-stranded RNA genome wrapped in nucleocapsid (N) protein and three major surface proteins: membrane (M), envelope (E), and spike (S), replicates and passes to the lower airways potentially leading to severe pneumonia. The gateway to host cell entry (magnified view) is via Spike-converting enzyme 2 (ACE2) interaction with cleavage of spike in the prefusion state via proteases TMPRSS-2/furin. A simplified depiction of the life cycle of the virus is shown along with potential immune responses elicited. *Source*: C. D. Funk, C. Laferrière, and A. Ardakani (2020). A snapshot of the global race for vaccines targeting SARS-CoV-2 and the COVID-19 pandemic. *Front. Pharmacol.* **11**:937.

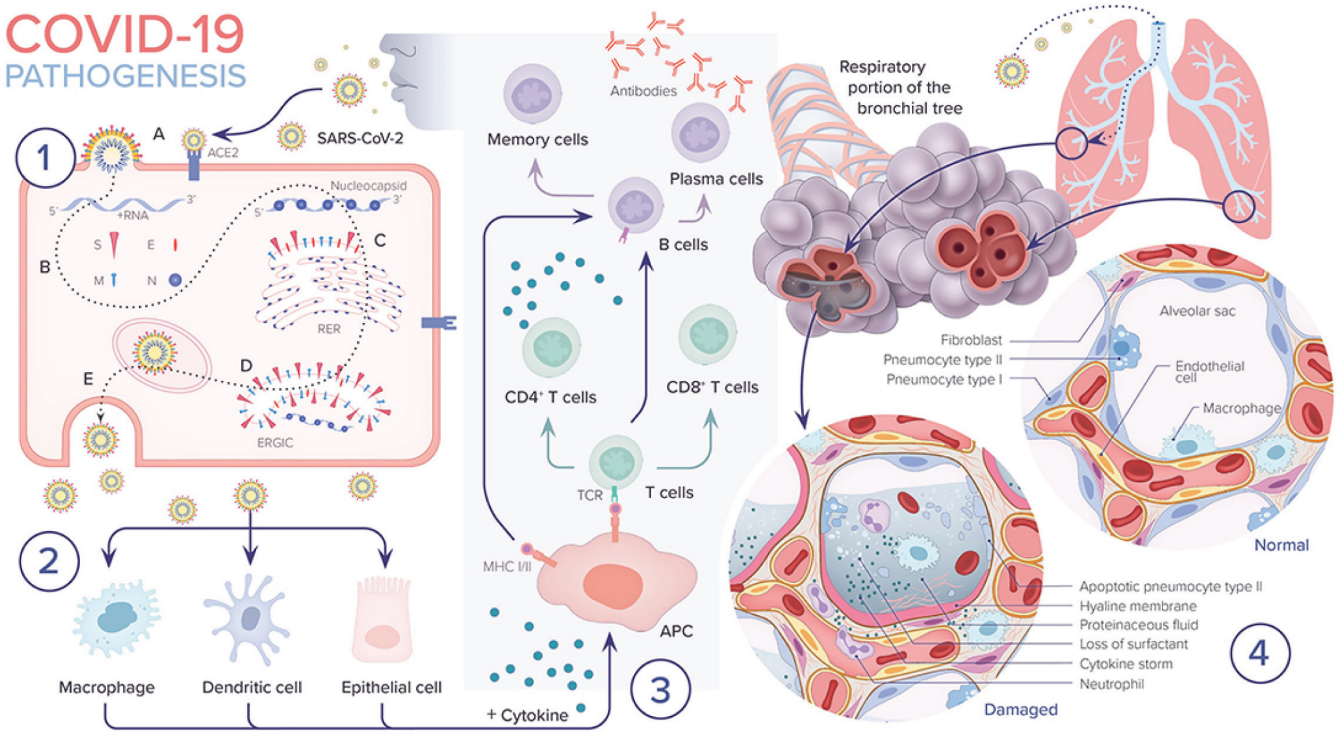


Figure 1.8 COVID-19 pathogenesis. 1. A. SARS-CoV-2 enters the epithelial cell either via endocytosis or by membrane fusion through binding to ACE2 receptor and releasing its RNA into the cytoplasm. B. Viral RNA uses the cell's machinery to translate its viral non-structural and structural proteins and replicate its RNA. C. Viral structural proteins S, E, and M assemble in the rough endoplasmic reticulum (RER). D. Viral structures and nucleocapsid subsequently assemble in the endoplasmic reticulum Golgi intermediate (ERGIC). E. New virion packed in Golgi vesicles fuse with the plasma membrane and get released via exocytosis. 2. SARS-CoV-2 infection induces inflammatory factors that lead to activation of macrophages and dendritic cells. 3. Antigen presentation of SARS-CoV-2 via major histocompatibility complexes I and II (MHC I and II) stimulates humoral and cellular immunity resulting in cytokine and antibody production. 4. In severe COVID-19 cases, the virus reaches the lower respiratory tract and infects type II pneumocytes leading to apoptosis and loss of surfactant. The influx of macrophages and neutrophils induces a cytokine storm. Leaky capillaries lead to alveolar edema. Hyaline membrane is formed. All of these pathological changes result in alveolar damage and collapse, impairing gas exchange. *Source*: N. Chams, et al. (2020). COVID-19: A multidisciplinary review. *Front. Public Health* **8**:383.

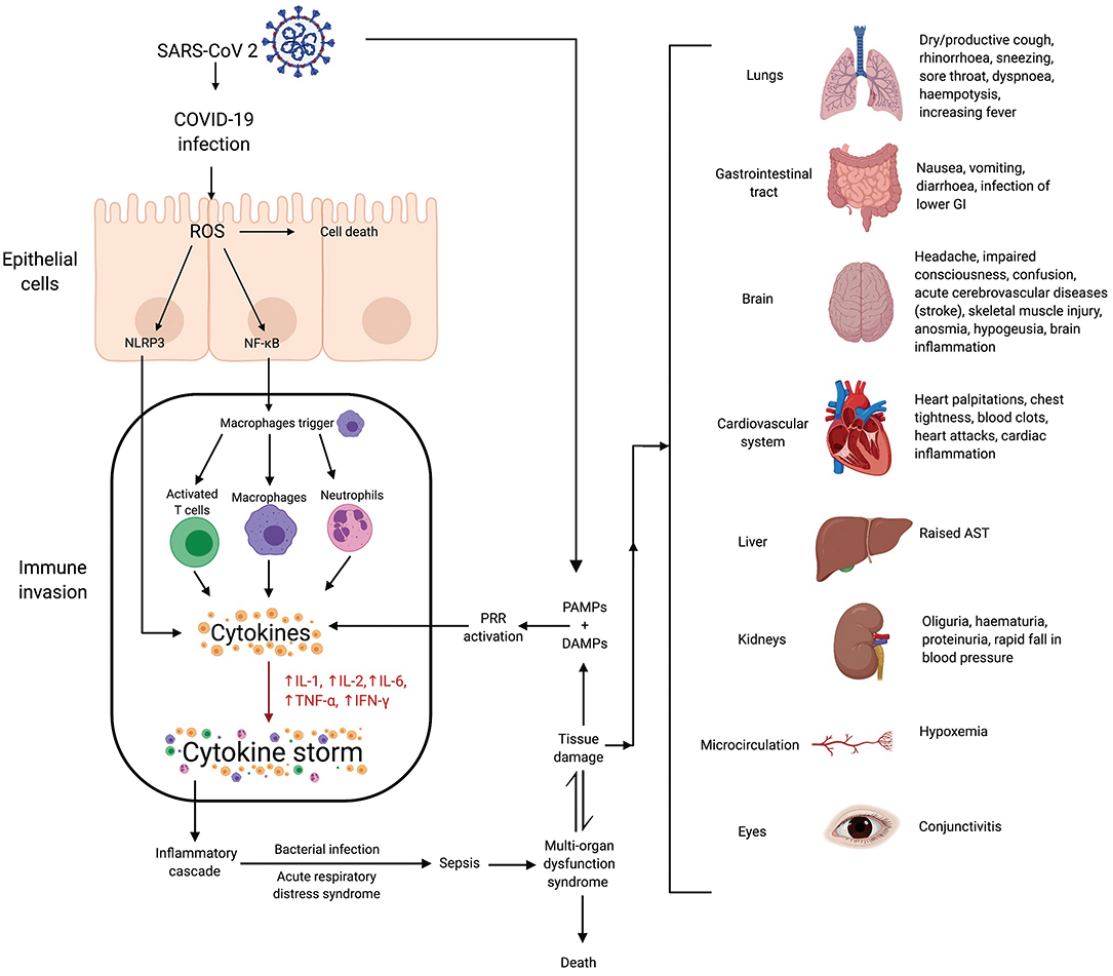


Figure 1.9 Mechanisms of SARS-CoV-2 associated cytokine storm and associated damage. Infection with SARS-CoV 2 can stimulate a hyperinflammatory immune response wherein epithelial-cell-mediated production of reactive oxygen species (ROS) can cause cell death. ROS can also stimulate the synthesis of NLRP3 and NF-κB which contribute to increased cytokine levels, and thus, the cytokine storm. This essentially causes immune invasion which can lead to clinically relevant conditions such as ARDS, sepsis, MODS, and potentially even death. The organs affected as a result of MODS, and their associated symptoms, have been shown. Lower gastrointestinal (GI) is rich in ACE2 receptors and hence at higher risk of infection due to COVID-19. Twenty percent of COVID-19 patients have diarrhea as symptoms. SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; COVID-19, coronavirus disease 2019; ROS, reactive oxygen species; NLRP3, (NOD)-like receptor protein 3 inflammasome; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; IL, interleukin; TNF, tumor necrosis factor; IFN, interferon; PAMPs, pathogen-associated molecular patterns; DAMPs, damage-associated molecular patterns; PRR, pattern recognition receptors; AST, aspartate aminotransferase; MODS, multiple organ dysfunction syndrome. *Source*: S. Bhaskar, et al. (2020). Cytokine storm in COVID-19—immunopathological mechanisms, clinical considerations, and therapeutic approaches: The REPROGRAM Consortium position paper. *Front. Immunol.* **11**:1648.

1.3 Origin of SARS-CoV-2: A Chinese Lab Leak?

Life on Earth is at the ever-increasing risk of being wiped out by a disaster, such as sudden global nuclear war, a genetically engineered virus or other dangers we have not yet thought of.

—Stephen Hawking

Is it possible that SARS-CoV-2 began when an animal virus found its way unaided into humans, i.e., a zoonotic spillover? Is it more likely that the virus began in a Chinese government laboratory? Was it genetically engineered in this lab to enhance its virulence and infectivity? Did it accidentally leak from the lab? Is it a man-made bioweapon? We do not know the precise answer to these questions at the moment. But, strong circumstantial evidence is building that points towards a lab leak and Chinese cover-up.

China's response to the COVID-19 outbreak has been scrutinized since the virus was first detected in its Wuhan province. In response, China has responded with questionable tactics. This has led to calls for an open investigation into the possibility that the coronavirus leaked from a lab. Even if SARS-CoV-2 originated naturally, from animal-human contact, it does not preclude the possibility that the virus was the result of an accidental leak from the China's Wuhan Institute of Virology (WIV), where coronavirus research was being conducted on bats. In an effort to deflect blame for a potential leak, the Chinese government has promoted unsubstantiated theories that the virus may have entered China via frozen food.

The WHO does not have the regulatory authority to force governments to disclose information and it has been particularly weak dealing with China on the COVID-19 pandemic. China did recently invite a small team of disease experts to "investigate" the outbreak but its findings were of limited value since the team's constraints reveal how little power it had to conduct a fair probe. To me, this visit was akin to a "student field trip" but where the final conclusions were redetermined and scientifically fraudulent. No wonder, the WHO was broadly criticized by many governments over its limited access to "complete, original data and samples" and overly deferential treatment of China throughout the course of this study. Moreover, this study was co-authored by 17 Chinese scientists, several of them from state-run institutions—a clear conflict of interest.

A US State Department fact sheet from January 2021 highlights reports of sick lab researchers at the WIV in the fall of 2019. It also points to research with virulent coronavirus strains and indicates secret Chinese military activity at the lab (Box 1.3). Now, in May 2021, strong evidence from a previously undisclosed US intelligence report is available that details three researchers from this institute becoming ill enough to seek hospital care in the autumn of 2019.[13] The intelligence in this report go beyond the original State

[13]M. R. Gordon, W. P. Strobel, and D. Hinshaw (2021). Intelligence on sick staff at Wuhan lab fuels debate on Covid-19 origin. *Wall Street J.*, May 23 issue. Among the first 27 documented hospitalized patients, most cases were epidemiologically linked to Huanan Seafood Wholesale Market, a wet market that sold animals, including wildlife. On December 31, 2019, the Wuhan Municipal Health Commission notified the public of a pneumonia outbreak of unidentified cause and also informed the WHO.

Department fact sheet reproduced below as Box 1.3. Clearly, more rigorous investigations are required to establish the original source of this pandemic, with or without China's assistance. I predict that the Chinese government will continue to stonewall any efforts to determine the true origins of SARS-CoV-2. As a side note, the question has also arisen whether plaintiffs from other countries can sue China for COVID-19 and hold it legally accountable in their respective courts. In fact, the first lawsuits against the government of China and the Chinese Communist Party (CCP) were filed in 2020 with a heavy emphasis on mass torts and class actions.[14] However, a major obstacle to these lawsuits is the bedrock doctrine of sovereign immunity which protects a nation from being sued in another nation.

Box 1.3 Fact sheet: activity at the Chinese Wuhan Institute of Virology

For more than a year, the Chinese Communist Party (CCP) has systematically prevented a transparent and thorough investigation of the COVID-19 pandemic's origin, choosing instead to devote enormous resources to deceit and disinformation. Nearly two** million people have died. Their families deserve to know the truth. Only through transparency can we learn what caused this pandemic and how to prevent the next one.
**As of June 8, 2021, this number is ~3.76 million.

The U.S. government does not know exactly where, when, or how the COVID-19 virus—known as SARS-CoV-2—was transmitted initially to humans. We have not determined whether the outbreak began through contact with infected animals or was the result of an accident at a laboratory in Wuhan, China.

The virus could have emerged naturally from human contact with infected animals, spreading in a pattern consistent with a natural epidemic. Alternatively, a laboratory accident could resemble a natural outbreak if the initial exposure included only a few individuals and was compounded by asymptomatic

(*Continued*)

[14]D. Ricker. (2020). Suing China for COVID-19. *ABA J.,* August/September issue, page 17.

Box 1.3 (*Continued*)

infection. Scientists in China have researched animal-derived coronaviruses under conditions that increased the risk for accidental and potentially unwitting exposure.

The CCP's deadly obsession with secrecy and control comes at the expense of public health in China and around the world. The previously undisclosed information in this fact sheet, combined with open-source reporting, highlights three elements about COVID-19's origin that deserve greater scrutiny:

1. Illnesses inside the Wuhan Institute of Virology (WIV):
    - The U.S. government has reason to believe that several researchers inside the WIV became sick in autumn 2019, before the first identified case of the outbreak, with symptoms consistent with both COVID-19 and common seasonal illnesses. This raises questions about the credibility of WIV senior researcher Shi Zhengli's public claim that there was "zero infection" among the WIV's staff and students of SARS-CoV-2 or SARS-related viruses.
    - Accidental infections in labs have caused several previous virus outbreaks in China and elsewhere, including a 2004 SARS outbreak in Beijing that infected nine people, killing one.
    - The CCP has prevented independent journalists, investigators, and global health authorities from interviewing researchers at the WIV, including those who were ill in the fall of 2019. Any credible inquiry into the origin of the virus must include interviews with these researchers and a full accounting of their previously unreported illness.
2. Research at the WIV:
    - Starting in at least 2016—and with no indication of a stop prior to the COVID-19 outbreak—WIV researchers conducted experiments involving RaTG13, the bat coronavirus identified by the WIV in January 2020 as its closest sample to SARS-CoV-2 (96.2% similar). The WIV became a focal point for international coronavirus research after the 2003 SARS outbreak and has since studied animals including mice, bats, and pangolins.
    - The WIV has a published record of conducting "gain-of-function" research to engineer chimeric viruses. But the WIV has not been transparent or consistent about its record of studying viruses most similar to the COVID-19 virus, including "RaTG13," which it sampled from a cave in Yunnan Province in 2013 after several miners died of SARS-like illness.

- WHO investigators must have access to the records of the WIV's work on bat and other coronaviruses before the COVID-19 outbreak. As part of a thorough inquiry, they must have a full accounting of why the WIV altered and then removed online records of its work with RaTG13 and other viruses.

3. Secret military activity at the WIV:
    - Secrecy and non-disclosure are standard practice for Beijing. For many years the United States has publicly raised concerns about China's past biological weapons work, which Beijing has neither documented nor demonstrably eliminated, despite its clear obligations under the Biological Weapons Convention.
    - Despite the WIV presenting itself as a civilian institution, the United States has determined that the WIV has collaborated on publications and secret projects with China's military. The WIV has engaged in classified research, including laboratory animal experiments, on behalf of the Chinese military since at least 2017.
    - The United States and other donors who funded or collaborated on civilian research at the WIV have a right and obligation to determine whether any of our research funding was diverted to secret Chinese military projects at the WIV.

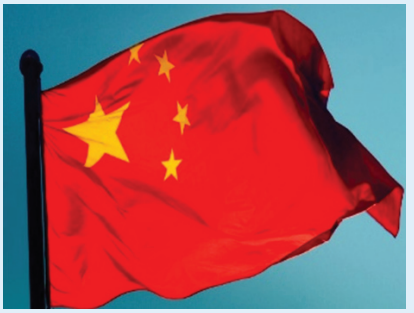
Today's revelations just scratch the surface of what is still hidden about COVID-19's origin in China. Any credible investigation into the origin of COVID-19 demands complete, transparent access to the research labs in Wuhan, including their facilities, samples, personnel, and records.

As the world continues to battle this pandemic—and as WHO investigators begin their work, after more than a year of delays—the virus's origin remains uncertain. The United States will continue to do everything it can to support a credible and thorough investigation, including by continuing to demand transparency on the part of Chinese authorities.

Courtesy of the US Department of State, Office of the Spokesperson, January 15, 2021.

Meanwhile, the largest biotech company in the world, a Chinese company, the BGI Group, offered to build COVID labs in at least six US states (Box 1.4). Clearly, the Chinese government is trying to control the world's biodata. This can lead to complete control over health care: if a person's current or future medical condition is known through DNA and other data, the entity that knows this can gain a monopoly over the therapy or drugs to treat the person.

Box 1.4 China's push to control Americans' health-care future



For all the polarization that grips Washington, here's a source of rare consensus: the emerging threat of China's push to acquire our health-care data, including the DNA of American citizens. US officials tell us the communist regime's aggressive collection of our most personal information presents a danger both to national security and our economy. As alarm bells ring across agencies, parties, and presidential administrations, different branches of government have taken action over the past year to stem the tide of our medical data flowing to China. The quest to control our biodata—and, in turn, control health care's future—has become the new space race, with more than national pride in the balance. Our investigation begins with an unsolicited and surprising proposal that came from overseas at the onset of the COVID crisis … It's not just China that's recognized what a valuable commodity your DNA can be. As you'll hear: some of the fastest-growing US tech companies are in this space, as well. In fact, you may have already surrendered your DNA by spitting in a tube.

Questions regarding relationships between US firms and foreign entities can be directed to the National Counterintelligence and Security Center (NCSC) and the Office of the Director of National Intelligence (ODNI).

Courtesy of CBS News, January 31, 2021.

1.4 Vaccines, Herd Immunity, Transmissibility, and SARS-CoV-2 Variants

I hope that someday the practice of producing cowpox in human beings will spread over the world—when that day comes, there will be no more smallpox.

—Edward Jenner

Without equity, pandemic battles will fail. Viruses will simply recirculate, and perhaps undergo mutations or changes that render vaccines useless, passing through the unprotected populations of the planet.

—Laurie Garrett, discussing Warner Brothers film "Contagion" in 2011

Vaccines and immunizations are among the most effective public health interventions of the last century. They represent great strides in taming or conquering microbial diseases. By some estimates, 2.5 million child deaths around the world are prevented each year by immunization. According to recent Centers for Disease Control and Prevention (CDC) data, routine childhood vaccinations prevented 732,000 early deaths from 1994 to 2013.

Thankfully, there was positive news in early 2021 in the battle against SARS-CoV-2, though the war is far from won. Here in the US, the massive $10 billion investment of the Trump administration in Operation Warp Speed to fast-track the development of SARS-CoV-2 vaccines within one year has paid dividends and resulted in a dozen or more potential vaccine candidates. Importantly, a few SARS-CoV-2 vaccines have been approved and made available in the US, *albeit* the rollout has been nothing but disastrous. The picture on the therapeutic, diagnostic, and vaccine delivery fronts is discouraging and complex. Regular reports on advances relating to "full" clinical trials drive expectations. Then, viral mutants of greater pathogenicity and infectivity fuel concerns over the ineffectiveness of marketed vaccines to combat them. Currently, there are six approved vaccines authorized for use in select countries: mRNA-1273 (Moderna/NIAID), BNT162b2 (Pfizer-BioNTech), Ad26.COV2.S (Johnson & Johnson/Janssen), ChAdOx1 nCoV-19 (University of Oxford/AstraZeneca), Gam-COVID-Vac/Sputnik V (Gamaleya Research Institute of Epidemiology and Microbiology, Russia), and BBIBP-CorV (Sinopharm/Beijing Institute of Biological Products, China). Based on published clinical trial data, their efficacies range from 65.5% to 94.6% in preventing symptomatic COVID-19. The overall efficacies of the three US Food and Drug Administration (FDA)-authorized vaccines currently marketed in the US[15] (e.g., Pfizer-BioNTech, Moderna, Johnson & Johnson/Janssen)[16] tested prior to the emergence of deadlier variant varieties are in the 90%+ range. I am not sure how effective any of these first generation vaccines will be upon encountering deadlier variants of SARS-CoV-2 in the near future.

Preliminary data reported in May 2021 from a trial of more than 600 people are the first to show the benefits of combining different vaccines (heterologous prime-boost). Such mix-and-match COVID-19 vaccination strategies may

[15]Traditional vaccines contain ingredients to generate an immune response, usually protein fragments (active agents) of the microbe that causes the disease along with preservations and excipients (inactive agents). In the case of the COVID-19 vaccine, instead of using the whole virus to generate an immune response, vaccines formulations comprise RNA sequences correspond to the coronavirus's outer spike proteins, which are what antibodies use to recognize the virus. In other words, the genetic code used by the virus to synthesize the spike proteins is the active agent in the vaccine formulation. The RNA is protected by a lipid coating. When injected into a patient, the RNA enters healthy cells where it helps orchestrate the production of coronavirus spike proteins, kickstarting the immune system and producing antibodies.

[16]Two vaccines not (yet) available in the US are Oxford-AstraZeneca and Novavax. For an excellent comparison of all vaccines, see: Comparing the COVID-19 vaccines: How are they different? Available at: https://www.yalemedicine.org/news/covid-19-vaccine-comparison (accessed on May 28, 2021). Also see: COVID-19 vaccine & therapeutics tracker. Available at: https://biorender.com/covid-vaccine-tracker (accessed on May 28, 2021).

trigger stronger, more robust immune responses than will two doses of a single vaccine, while simplifying immunization efforts where vaccine supplies are less reliable. I wonder what the long-term safety data of such an approach will be given that RNA vaccines (in contrast to traditional vaccines) tend to trigger stronger side effects with added doses.

It is important to note that for other coronaviruses, such as the common cold virus (SARS-CoV) and the MERS virus, immunity declines over time. But, at this stage, it is uncertain as to how long antibodies and immunity lasts for those vaccinated, or even those exposed to the virus. In my assessment, we will require regular booster shots for the virus as novel variants continue to emerge, as COVID-19 morphs into a chronic multisystemic viral disease. More effective vaccines of broader scope, preferably single-shot, are urgently needed.[17]

As countries roll out vaccines against the SARS-CoV-2 virus (Fig. 1.10), studies are under way to determine whether shots can also stop viral transmission as this could be critical to bringing the pandemic under control but only if enough people are vaccinated. Some studies suggest that some vaccines are likely to have a transmission-blocking effect. However, this is not easy to establish because a drop in infections can be due to other factors, such as lockdowns and personal behavior.

Another important point is whether asymptomatic individuals can serve as viral carriers. Early data indicate that vaccines will likely help prevent asymptomatic transmission, although most of it is not peer-reviewed. Still it is worth mentioning. For example, data from the Israeli Health Ministry and Pfizer demonstrated an 89% reduction in both symptomatic and asymptomatic infections following vaccination while a vaccine trial by Johnson & Johnson found that its vaccines prevented asymptomatic infection in 74% of recipients. Even based on this incomplete picture regarding asymptomatic viral spread, I cannot underscore enough the need for universal vaccination.

Over time, viruses are also prone to mutations of their genomes which arise from random genomic changes as they replicate in an infected person. This results in variants that may have different characteristics than their ancestral strains. Variants pose different concerns of differing degrees. These relate to their: (i) transmissibility (propensity to spread); (ii) virulence (severity of illness); (iii) neutralization capacity (likelihood they will infect people who have recovered from a previous bout of COVID-19), and (iv) potential impact on vaccination

[17]In May 2021, the UK's Medicines and Healthcare products Regulatory Agency (MHRA) announced that it had approved a single-shot coronavirus vaccine developed by Johnson & Johnson/Janssen. However, it is 67% effective overall at preventing moderate to severe covid-19, with studies suggesting that it also offers complete protection from admission to hospital and death. According to Johnson & Johnson, the vaccine works across multiple variants of coronavirus. Clinical trial data published earlier in 2021, showed that the level of protection against moderate to severe COVID-19 infection was found to be 72% in the US arm of the trial. It was 66% in the Latin American arm of the trial, and 57% in South Africa, where a different variant of the virus has been dominating. Hence, the overall efficacy from these trials combined was 67%.

through their ability to evade immunosurveillance. Obviously, SARS-CoV-2 variants[18] that are more virulent or infectious—or both —are of particular concern. From a genomic standpoint, according to a few studies, the coronavirus shares approximately 50–79% of its genetic sequence (Fig. 1.11) with the MERS-CoV and the first coronavirus, SARS-CoV. Also, interestingly, SARS-CoV-2 shares the receptor-binding domain structure with SARS-CoV.

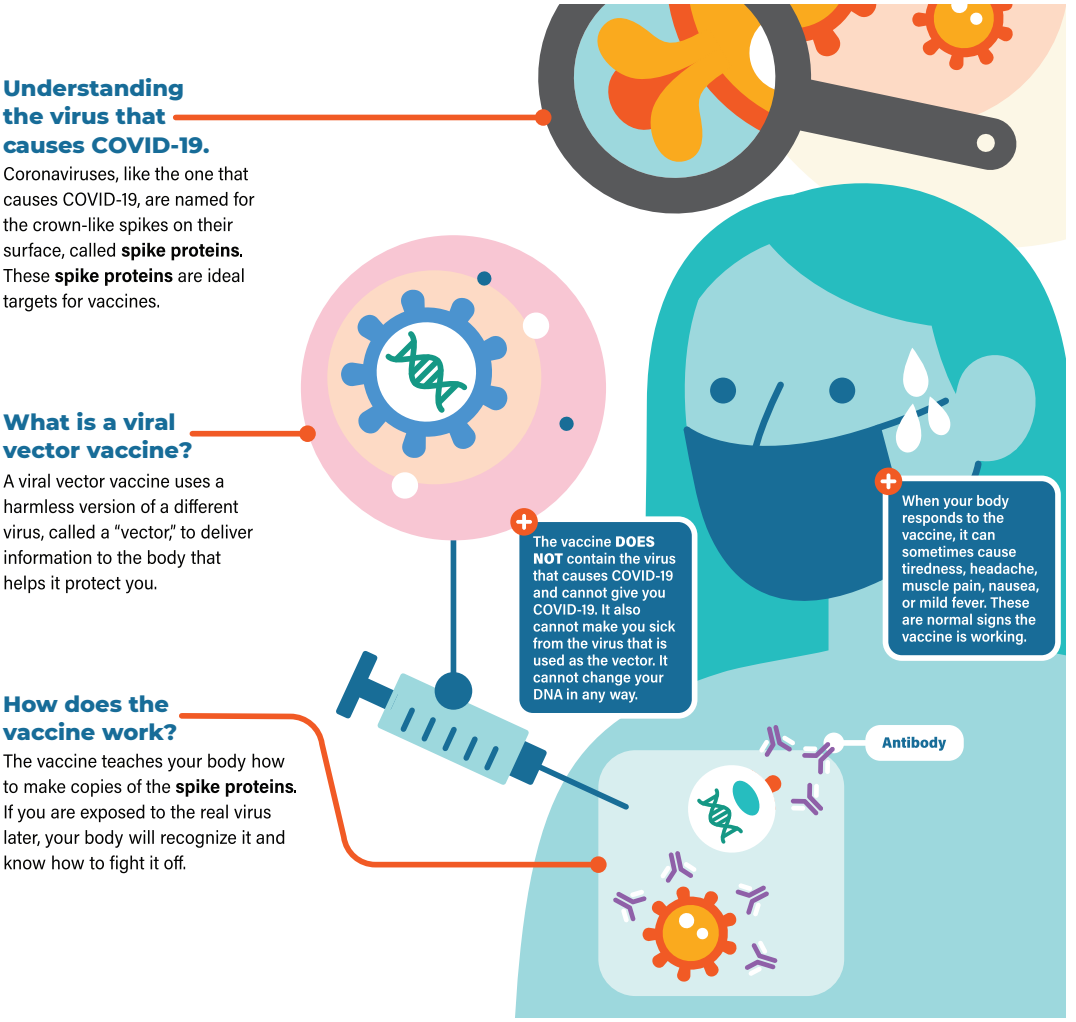


Figure 1.10 How viral vector COVID-19 vaccines work. *Courtesy of the CDC.*

[18]During replication, a virus often undergoes genetic mutations that may create what are called variants (sometimes referred to as strains). Some mutations weaken the virus while others may yield some advantage that enables the variants to proliferate. A variant that deviates significantly from its viral ancestors may be identified as a new lineage, or branch on the evolutionary tree.

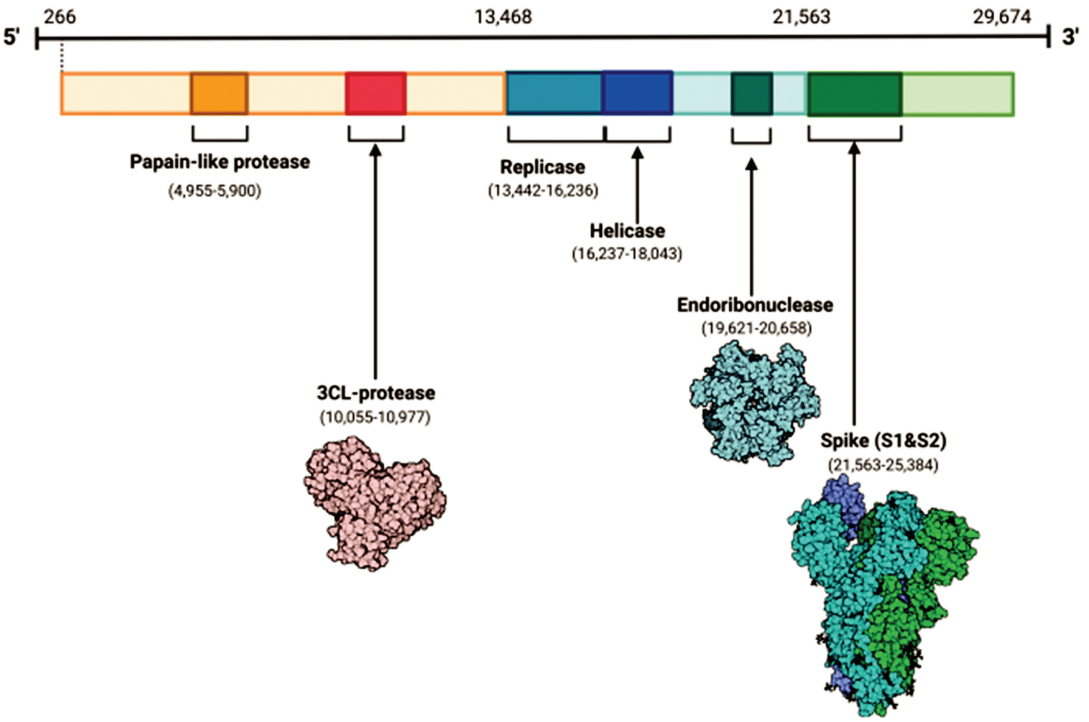


Figure 1.11 Single stranded genome of SARS-Cov-2 (~30kb length). *Courtesy of Dr. R. B. Singh.*

Monitoring the coronavirus for key mutation(s) in important genomic regions is critical. Most mutations may not affect the virus's virulence or transmissibility because they do not alter the major proteins involved in infection. These are eventually outcompeted by variants with mutations that are more beneficial to the coronavirus. Since the genome sequence of SARS-CoV-2 was first reported in January 2020, thousands of variants have been reported. Most of the genetic and antigenic variations are innocuous and do not contribute to enhanced virulence or infectivity. However, the emergence of a few variants, referred to as variants of concern (VOCs), have caused considerable consternation (Fig. 1.12). The B.1.1.7 lineage (or VOC 202012) variant was the first VOC described in the UK in late December 2020 (Fig. 1.13). This variant is considerably more contagious than the original virus and recent evidence indicates that infection with this B.1.1.7 variant also comes with an increased risk of severe illness and death. A second variant, the B.1.351 lineage (or 501Y.V2) was reported in South Africa in late 2020. A third VOC, B.1.1.248/B1.1.28/P1 (or 501Y.V3), was reported in Brazil in early January 2021. As of May 2021, all three variants have been found in the US. A fourth variant, the 20A.EU1 variant, first identified in Spain, contains a mutation called A222V on the viral spike protein. According to the WHO, another VOC, labeled the B.1.617 variant, has become the dominant strain across India. Evidence is growing that this variant might be more transmissible and slightly better at evading immunity than the existing variants.

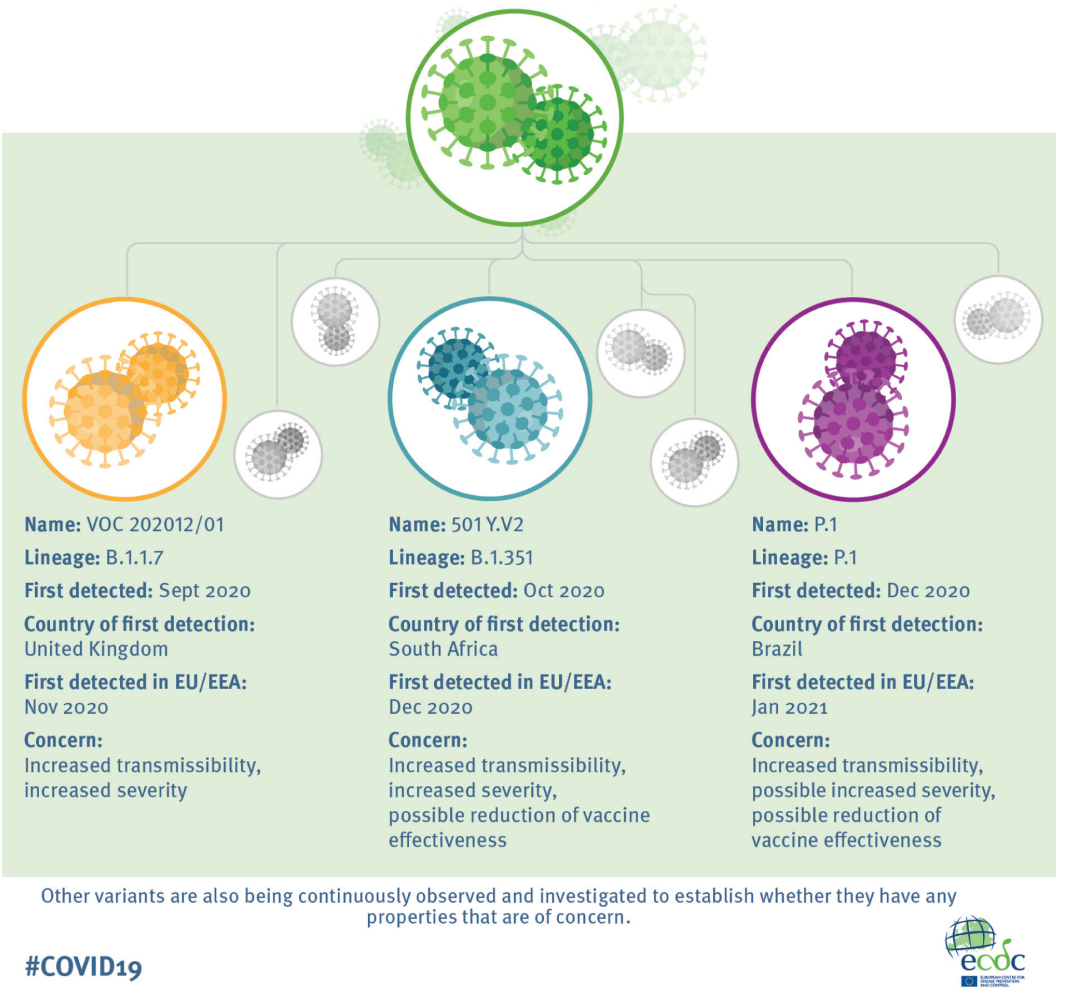


Figure 1.12 Mutation of SARS-CoV-2: Variants of concern as of April 2021.

I am skeptical if vaccine companies can develop new vaccine versions promptly prior to the emergence of deadlier second and third generation variant waves. In my view, genomic surveillance is key here as it serves as an early warning system that can detect threatening mutations before they become more widespread. Furthermore, genetic variations in a virus can render diagnostic tests ineffective.[19] What makes the future of this virus so hard to predict is that it is not just the individual mutations that matter, but also the order and combinations in which they occur. *Will SARS-CoV-2 retain its ability to cause enhanced infection and virulence as it mutates further and more people gain immunity through infections or vaccines?*

[19]For molecular tests, their sensitivity and specificity depends on the number and location of genes that the test targets. Most antigen-based tests should continue to work as most are targeting the N antigen of the virus, a region that has so far remained conserved in the variants. But this can change in the near future.

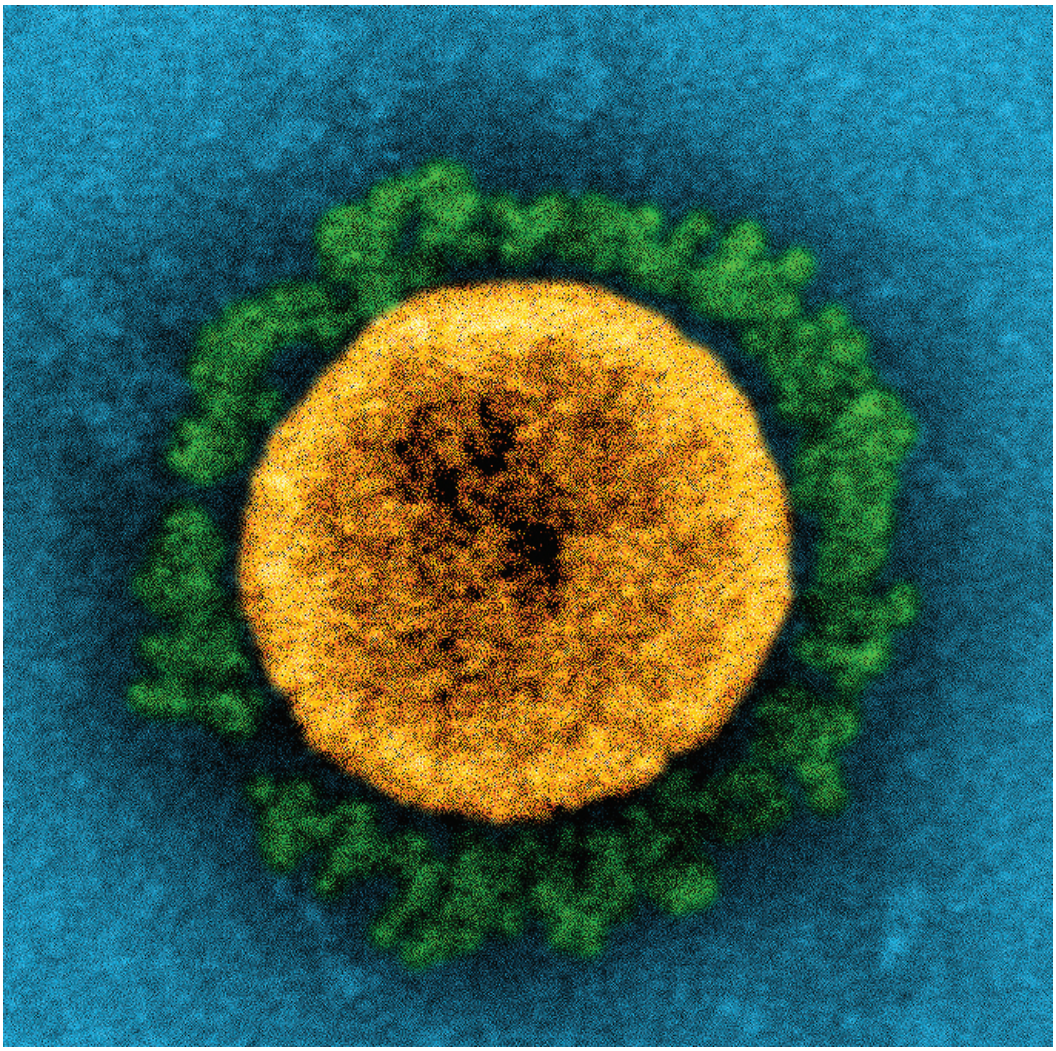


Figure 1.13 False-color transmission electron micrograph of the UK B.1.1.7 variant coronavirus. The variant's increased transmissibility is believed to be due to changes in the structure of the spike proteins, shown here in green. The prominent projections (green) seen on the outside of the virus particle (yellow) are spike proteins. This fringe of proteins enables the virus to attach to and infect host cells and then replicate. Image captured at the NIAID Integrated Research Facility in Fort Detrick, Maryland. *Courtesy of NIH.*

Objectivity and fairness in journalism has been supplanted by "opinion news," exemplified by CNN, Fox News and others. Inaccurate reporting of the pandemic has been costly with lives lost here at home and throughout the world. The misinformation pandemic continues. Another casualty has been mass vaccination efforts as governments and heath organizations like the WHO, the CDC, and even the FDA lose credibility. In fact, a massive PR failure to convince everyone to come on board

and get vaccinated means that the pandemic will linger and variants will continue to evolve. Obviously, this will be tragic if we fail to stamp out the virus simply because large swaths of the population refuse to be vaccinated. Achieving herd immunity (Box 1.5; Figs. 1.14 and 1.15) requires vaccination (or natural infection). According to few estimates and my own calculations, given the various variants of SARS-CoV-2, we may need a vaccination rate of 80–90% if some degree of normalcy is desired. A tremendous effort will be required to achieve such high vaccination rates. This would mean that all adults and adolescents in the US will have to be fully vaccinated to approach 80% vaccination—a high bar indeed. Is it possible? I am not sure if herd immunity threshold will ever be attainable. Daily vaccination rates are slipping, viral variants are emerging fast, poor infectious disease management policies are reappearing, and some pandemic restrictions are being relaxed prematurely.

Global distribution of the COVID-19 vaccine has been lopsided. So far, in May 2021, major populations like India have only fully vaccinated 3%+ of their populations while here in the US the vaccination rate currently stands ~45%. BBC reports that as of March 2021, 80% of the vaccines have been administered to the developed nations while only 20% have gone to the developing nations. According to data collected by Bloomberg, as of May 29, 2021, countries/regions with the highest incomes are getting vaccinated more than 30 times faster than those with the lowest. In fact, data shows that more than 1.84 billion doses have been administered around the world—enough to only fully vaccinate 12% of the global population. As discussed above, this is a far cry from what will be needed for herd immunity and to minimize emergence of virulent novel variants. A failure to vaccinate much of the developing world will leave a large reservoir of circulating virus, giving it the chance to mutate and spill over to developed countries. *Why is it so hard for us to grasp that we are all in this together?*

Another important point to remember is that it is hard to achieve our goal of universal vaccination or herd immunity in the absence of vaccinations to infants and young people. By focusing solely on adult vaccination R&D, we have left out the vulnerable, immunologically naïve ~25% of the population that still have no available shots: kids. In my view, a pediatric vaccine for the disease is an urgent global health priority and the time for that to happen is now. This is especially true since we have substantial safety data from adult vaccine R&D, clinical trials, and field use. Vaccines given to kids will not only help curb the spread of SARS-CoV-2 but also protect young people who are at high risk. Big pharma is finally turning its attention towards this important demographic and clinical trials in adolescents or young children[20] are underway.

[20]There is some evidence that coronaviruses that cause common colds in children may offer some protection from COVID-19 (i) due to cross-reactive immunity (T cell immunity and cross-reactive antibodies) between the common coronaviruses and SARS-CoV-2; and (ii) due to fewer angiotensin-converting enzyme (ACE)-2 receptors in nasal mucosa of children.

Box 1.5 What is herd immunity?

Herd immunity, sometimes called community immunity, is the indirect protection from an infectious disease that occurs when a high percentage of population is immune either through vaccination and/or immunity developed through previous infection. Theoretically, this makes the spread of the infectious disease from person to person unlikely. Herd immunity protects the most vulnerable members of the population (babies who have not received vaccinations, pregnant women, and the immunocompromised). Unlike the unethical and rash approach of Sweden, herd immunity against COVID-19 should be achieved through vaccination, not by exposing the population to the virus. Achieving herd immunity via vaccines makes diseases rarer and saves lives. On the contrary, letting COVID-19 spread through populations, of any age or health status, will lead to unnecessary infections, suffering, and death. To safely achieve herd immunity, a substantial proportion of a population would need to be vaccinated, lowering the overall amount of virus able to spread in the whole population. Although the proportion of the population that must be vaccinated against SARS-CoV-2 to begin inducing herd immunity is unknown, I believe that it could be as high as 85–90%. This means that about 85–90% of a population will need to be vaccinated while the remaining 10–15% will be protected by the fact that COVID-19 will not spread among those who are not vaccinated.

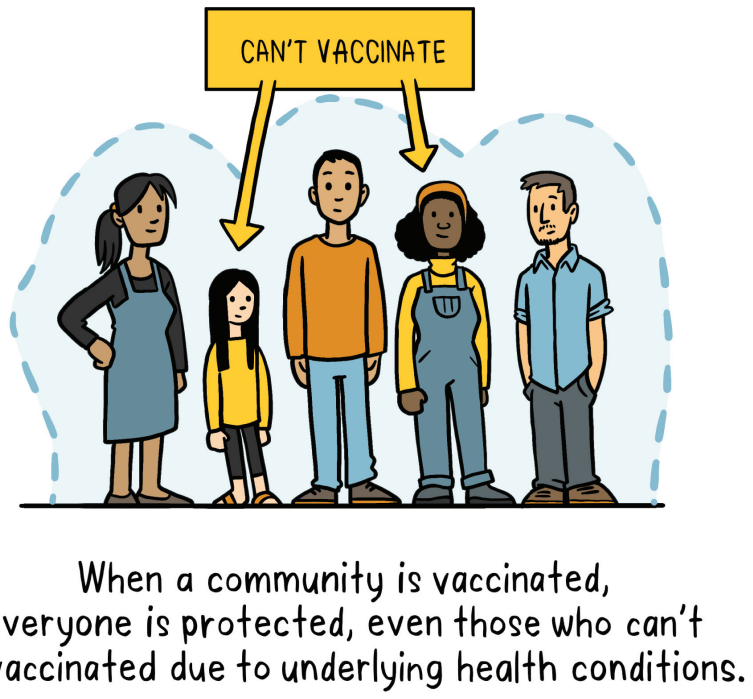


Figure 1.14 Herd immunity protects vulnerable communities. *Courtesy of WHO, CC BY-SA 3.0 IGO, CC BY-SA 3.0 IGO, via Wikimedia Commons.*

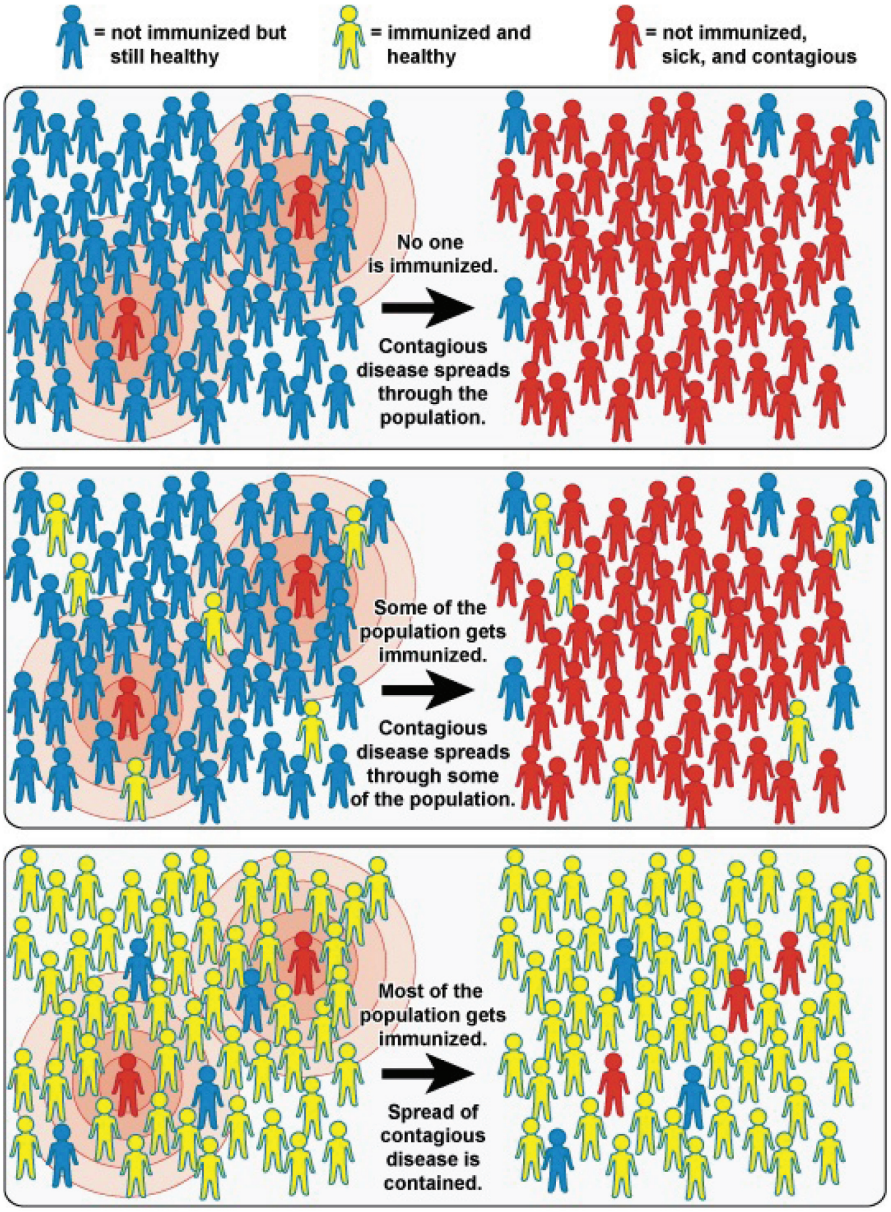


Figure 1.15 Building the herd: The concept of herd immunity. When a critical portion of a community is immunized against a contagious disease, most members of the community are protected against that disease. The principle of community immunity applies to control of a variety of contagious diseases, including influenza, measles, mumps, rotavirus, and pneumococcal disease. The top box depicts a community in which no one is immunized and an outbreak occurs. In the middle box, some of the population is immunized but not enough to confer community immunity. In the bottom box, a critical portion of the population is immunized, protecting most community members. *Legend*: not immunized, healthy immunized, healthy not immunized, sick, and contagious. *Courtesy of Tkarcher, CC BY-SA 4.0 via Wikimedia Commons*.

There is also enormous confusion, disagreement, lack of scientific knowledge, and conflicting information pertaining to the delivery, use, and safety of COVID-19 vaccines. For instance, confusion continues regarding vaccination of pregnant women as expectant couples fret over vaccine safety for themselves and their babies (Box 1.6). According to the latest official guidance from the CDC, pregnant women who are health-care personnel or essential workers "may choose to be vaccinated." The major problem is that there is hardly any data available on COVID-19 vaccine safety with respect to pregnant women, given that they were excluded from clinical trials as has historically been the case. Two recent research studies[21] (not clinical trials) show that the two COVID-19 mRNA vaccines currently available in the US appear to be safe and effective in pregnancy, with the potential to benefit both mother and baby. In my view, more data derived from robust clinical trials is warranted.

Box 1.6 Should pregnant women get vaccinated?

Guidance from public health officials about whether pregnant women should get the COVID-19 vaccine has been conflicted and cautious to the point of being noncommittal. For instance, the World Health Organization initially advised that only pregnant women at high risk of COVID-19 exposure or with a separate underlying condition should get the vaccine; then the WHO revised the guidance to reflect the higher risk pregnant women face of getting severe COVID and the increased risk of pre-term birth. But it added a qualification: the available data was "insufficient to assess vaccine efficacy or vaccine-associated risks in pregnancy," even though "animal studies showed no harmful effects in pregnancy." An independent advisory committee of the U.S. Centers for Disease Control and Prevention suggested that pregnant women consider getting the shots "after consulting with their physician." It's no wonder pregnant women are confused about the COVID-19 vaccines.

Source: A. Piore. (2021). Should pregnant women get vaccinated? *Newsweek*, March issue, 28–34.

Waiving vaccine patents in an effort to evenly manufacture and distribute COIVD-19 vaccines (and other therapeutics) around the world was a hotly debated topic in June 2021. This gained increased traction following the explosion of cases and deaths in India in May 2021. The easing of patent protections is essential in a pandemic. The campaign was initiated by India and South Africa, and is being backed by more than 100 countries, the WHO, UNAIDS, etc. The US has joined in and supports a waiver on intellectual property for COVID vaccines (Box 1.7), even though big pharma and most developed countries do not support it. I consider this a historic move. As a patent agent for the past two

[21] A. Y. Collier, et al. (2021). Immunogenicity of COVID-19 mRNA vaccines in pregnant and lactating women. *JAMA* e217563. doi: 10.1001/jama.2021.7563; E. D. Shanes, et al. (2021). Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccination in pregnancy: Measures of immunity and placental histopathology. *Obstet Gynecol.* doi: 10.1097/AOG.0000000000004457.

Box 1.7 Waiving patents on COVID vaccines

Office of the United States Trade Representative

FOR IMMEDIATE RELEASE:
May 5, 2021

CONTACT: media@ustr.eop.gov

STATEMENT FROM AMBASSADOR KATHERINE TAI ON THE COVID-19 TRIPS WAIVER

WASHINGTON – United States Trade Representative Katherine Tai today released a statement announcing the Biden-Harris Administration's support for waiving intellectual property protections for COVID-19 vaccines.

"This is a global health crisis, and the extraordinary circumstances of the COVID-19 pandemic call for extraordinary measures. The Administration believes strongly in intellectual property protections, but in service of ending this pandemic, supports the waiver of those protections for COVID-19 vaccines. We will actively participate in text-based negotiations at the World Trade Organization (WTO) needed to make that happen. Those negotiations will take time given the consensus-based nature of the institution and the complexity of the issues involved.

"The Administration's aim is to get as many safe and effective vaccines to as many people as fast as possible. As our vaccine supply for the American people is secured, the Administration will continue to ramp up its efforts—working with the private sector and all possible partners—to expand vaccine manufacturing and distribution. It will also work to increase the raw materials needed to produce those vaccines."

Courtesy of Office of the United States Trade Representative.

decades, I prefer compulsory licensing over outright patent waivers. However, the scope of the current pandemic makes waivers appropriate. In addition

to waivers, patent pooling is also an excellent mechanism to pool our global intellectual property resources and is suggested by many[22]: "We call on pharmaceutical companies to contribute to a pool of patents set up by the World Health Organization (WHO). That will speed up the manufacture of generic, affordable COVID-19 vaccines and treatments while protecting firms' incentives to invest in future research. The WHO's COVID-19 Technology Access Pool has so far received no contributions from industry. Asking governments in rich nations to donate vaccines to lower-income countries will not hasten manufacture. India and South Africa have proposed suspending patents related to COVID-19 products, but companies contend that this could dent drug development. The practice of pooling patented technologies for the production of medicines already occurs for HIV, hepatitis C, and tuberculosis treatments. Fees are typically lower when licences are negotiated as a bundle with generics producers, implying increased volume. Yet firms can anticipate extra revenue from participation in a voluntary pool, and thus be more willing to maintain innovation and share know-how than with compulsory licensing."

1.5 Vaccine Passports: A Bad Government Idea

They that can give up essential liberty to obtain a little temporary safety deserve neither liberty nor safety.

—Benjamin Franklin, *Historical Review of Pennsylvania*, 1759

No culture can live if it attempts to be exclusive.

—Mahatma Gandhi

Jurisdictions in the US and around the world are handling the current pandemic in variety of ways. Some are enforcing mask mandates while others are passing laws where masks[23] cannot be forced upon a person. Some are using contact-tracing applications (Box 1.14 in Section 1.8) and systems to conduct "viral surveillance" while others are passing laws that grant citizens complete freedom to decide if they should participate in such programs. Some issue stringent requirements for social distancing while others forbid such actions. Some are passing regulations about self-isolation and quarantines while others are not. The list goes on and on. In essence, we have a maze of confusing policies, along

[22]E. B. de Villemeur, et al. (2021). Pool patents to get COVID-19 vaccines and drugs to all. *Nature* **591**:529.

[23]There has been a major culture change when it comes to basic public health hygiene. Data has always confirmed that mask wearing is extremely effective in stopping the spread of all kinds of pathogenic respiratory microbes. For example, flu cases have been at record lows so far in 2021 in the US (less than a thousand so far in 2021 compared to ~24,000 flu deaths during the 2019–2020). Although other factors (lockdowns, school closures, and decreased travel) have contributed to low flu rates, masking has most likely played a significant role.

with protests, dissent, shut-downs, riots, and fear. The COVID-19 crisis points out that we have to balance competing medical, legal, ethical, privacy, and moral principles. Easier said than done. In this backdrop, I discuss below the concept of "vaccine or immunity passports," and why they are a bad idea.

Immune response to SARS-CoV-2 is a complex topic. For instance, an immune response to the live virus is different from the response to a single viral protein introduced via a vaccine. And then there are those who have been vaccinated following Covid-19. Our knowledge regarding the humoral immune response to SARS-CoV-2 has been rapid, though areas of uncertainty persist. We are a long way from understanding the characteristics of the antibody response, its dynamics over time, its determinants, and the immunity it confers to different age groups and disease. On the other hand, relatively less is known about cell-mediated immunity to SARS-CoV-2 (Box 1.8). We are slowly learning more. For example, a recent report[24] demonstrated that blood levels of antibodies fall sharply following acute infection while memory B cells remain quiescent in the bone marrow ready to take action as needed.

Box 1.8 Cellular immune responses to COVID-19

Protective and enduring immune responses to viral infections or vaccines usually arise from the combined actions of lymphocytes: B cells (responsible for humoral antibody immunity) and T cells (responsible for cellular immunity and helping B cell responses). B cells produce detectable antibodies in classes IgM, IgG, and IgA along with lesser amounts of IgD and IgE. For SARS-CoV-2, the causative agent of COVID-19, the focus is mainly on IgM, IgG, and IgA antibodies that can neutralize the virus by binding to the spike and other membrane proteins and thus preventing infection. Understanding the lesser known roles of T cells and cellular immunity will deepen our insights into COVID-19 pathogenesis and help inform both vaccine development and pandemic containment strategies. An effective immune response to SARS-CoV-2 involves four types or subsets of T cells: T helper cells (CD4) are responsible for cellular immunity and for helping B cells to produce neutralizing antibodies; cytotoxic or killer T cells (CD8) directly kill infected cells—aided by helper T cells; other T cells (including T-17 (Th17) cells) drive the inflammatory responses that help to control infections; and regulatory T cells (T regs) help to contain the immune response, to prevent over-reaction and damage to tissues.

Source: H. Sewell, et al. (2020). Cellular immune responses to covid-19. *Br. Med. J*. **370**:m3018.

[24]J. S. Turner, et al. (2021). SARS-CoV-2 infection induces long-lived bone marrow plasma cells in humans. *Nature*, https://doi.org/10.1038/s41586-021-03647-4.

In any case, clinical, policy, and economic implications will be greatly driven by our knowledge of the immunology of SARS-CoV-2. These include the proposed use of an "immunity passport" or a "risk-free certificate,"[25] (Box 1.9) a form of certification for individuals with positive detection of antibodies that can enable them to avoid quarantine and allow them to travel or to return to work. The assumption is that they are protected against reinfection. But, what about reinfection from variants that are undetectable via current tests? What about reinfection from asymptomatic carriers?

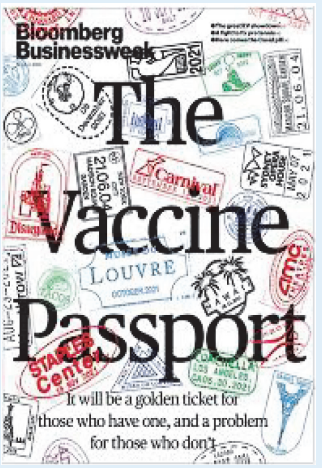
The idea is being floated in Germany, the United Kingdom, and other nations. Australia, Denmark, and Sweden have committed to implementation; and Israel is already issuing "green passes" to vaccinated residents. Hungary has introduced a policy allowing people to enter the country if they can provide evidence that they have already recovered from COVID-19. Iceland is planning on introducing a similar policy that will allow people who have already had COVID-19 to be exempt from the nationwide mask mandate. The European Union plans a "Digital Green Certificate" enabling free travel within the bloc. Although travel eligibility has been the primary focus here, some use these certificates to regulate access to social events, recreational activities, sporting arenas, theatrical performances, and more. New York's "Excelsior Pass" permits attendance at theaters, arenas, event venues, and large weddings. Airlines could soon introduce "vaccine passports" to facilitate international travel. On the other hand, some US states like Florida and Texas have banned businesses from requiring vaccination certificates.

Currently, in this evolving pandemic, the issue of immunity passports is a poor proposal given the uncertainties relating to COVID-19 immunity. There is simply not enough evidence about the effectiveness of antibody-mediated immunity to guarantee such certification.[26] As discussed earlier, the data is incomplete on asymptomatic spread in vaccinated individuals. Such certificates falsely assume that a second infection will not occur if a person has recovered from COVID-19, has had a positive COVID-19 test, or has been vaccinated. Immunity passports also raise ethical, legal, and practicality issues, doubtful economic benefits, privacy concerns, and the risk of discrimination. In fact, they may lull individuals into a false sense of security, leading them to ignore public health advice and increasing the risks of continued viral spread. Even if immunity passports were limited to health-care personnel, the number of tests required would be unfeasible. Many respectable health organizations, medical societies, religious leaders, and medical editors have opposed vaccine passports (Box 1.9).

[25]Technically, any documentation that proves a full dose of COVID-19 vaccination can be considered a vaccine passport. Presently, yellow fever is the only disease indicated in the International Health Regulations for which nations may require vaccination proof as a condition for entry. Obviously, WHO can recommend (via advisories) that countries require vaccination proofs.

[26]As of the June 2021, there is no conclusive data that establishes with certainty that the presence of antibodies to SARS-CoV-2 confers immunity to subsequent infections. I strongly believe that we will require booster shots periodically.

Box 1.9 Say "no" to mandating vaccine passports



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An immunity passport is an official document that certifies "an individual has been infected and is purportedly immune to SARS-CoV-2." In principle, this can then give an individual more freedom to travel and socialize, allowing people to enter a country if they can provide evidence that they have already recovered from COVID-19. The theory is that by providing proof of a positive and then a negative test, the person will have had the disease and is expected to have developed antibodies or other forms of immune memory to protect them from getting ill again … This raises difficult questions as some people with underlying health conditions, including autism, panic disorders, and breathing difficulties, are already exempt from wearing a mask but have not necessarily recovered from infection or have any immunity to it.

Source: Gavi, the international global vaccine alliance (https://www.gavi.org/).

At the present time, it is WHO's position that national authorities and conveyance operators should not introduce requirements of proof of COVID-19 vaccination for international travel as a condition for departure or entry, given that there are still critical unknowns regarding the efficacy of vaccination in reducing transmission. In addition, considering that there is limited availability of vaccines, preferential vaccination of travellers could result in inadequate supplies of vaccines for priority populations considered at high risk of severe COVID-19 disease. WHO also recommends that people who are vaccinated should not be exempt from complying with other travel risk-reduction measures. These Temporary Recommendations are in accordance with the advice that the International Health Regulations Emergency Committee on COVID-19 pandemic formulated at its 6th meeting on January 14, 2021.

Source: WHO, May 2021 (https://www.who.int/).

Digital health passes (DHPs) involve considerable scientific and technical challenges, including variable effectiveness by vaccine type, effectiveness in preventing transmission, durability of immunity, and emergence of variant strains … Digital health passes also involve technical challenges, including authentication of vaccine status. Unlike most high income countries, the US has no national immunization information system (IIS), a confidential, secure, population based digital data base that records all vaccine doses … Government DHPs must navigate constitutional and civil rights constraints. While the Supreme Court grants public health agencies wide discretion, it is more protective of First Amendment freedoms, including religion, speech, and assembly.

Source: *JAMA.* (2021). **325**(19):1933–1934.

1.6 COVID-19 Testing

You're paying billions of dollars in this very inequitable way to get the most worthless test results of any country in the world. No other country has this testing insanity.

—Bill Gates

In February 2020, the FDA began authorizing tests to diagnose active COVID-19 infections. During an emergency, the FDA can grant an emergency use authorization (EUA)[27] for medical products using a lowered approval standard rather than the full approval based upon more extensive evidence. According to the FDA: "The EUA process is different than FDA approval, clearance, or licensing because the EUA standard requires less evidence than the full approval, clearance, or licensing standard. Under an EUA, the data must show that a product may be effective and that the known and potential benefits outweigh the known and potential risks. This enables the FDA to authorize the emergency use of medical products that meet the criteria within days or weeks rather than months to years. The FDA has prioritized review of EUA requests for tests where authorization would increase testing accessibility (such as point-of-care (POC) tests, home collection tests, and at-home tests) or would significantly increase testing capacity (such as tests that reduce reliance on test supplies and high-throughput, widely distributed tests)."

Serology tests (i.e., antibody testing) are critically important for virus outbreaks. However, it is essential that national and international regulatory agencies like the FDA and EMA not permit substandard serology tests to be marketed or unauthorized products to appear in the marketplace. Unfortunately, this did happen and made viral testing confusing and unreliable. This reflected the broader problem with governments who were ill equipped to handle a pandemic. Clearly, they lacked a coordinated preparedness plan and there was over reliance on their antiquated regulatory system or they approved COVID-19 tests under extreme political and public pressure. Maybe, it would be helpful to be proactive and evaluate test performance prior to global microbial outbreaks. *A common approach to validating test design and performance is urgently needed and federal governmental agencies need to step up their game in this regard. Independent assessment of molecular diagnostic, antigen, and serology test accuracy is needed. Along with this, test developers and biomedical researchers should receive robust and coordinated assistance from national and international mechanisms in obtaining patient specimens or other clinical samples to validate their tests.*

[27] In certain emergencies, the FDA can issue an EUA to provide more timely access to critical medical products (including medicines and tests) when there are no adequate, approved, and available alternative options.

No test can ever be 100% accurate. Any COVID-19 test's performance will vary and is based on disease prevalence in the tested population. In fact, diagnostic tests may be less accurate in populations with a low prevalence of disease and in asymptomatic individuals, individuals who shed little virus, or individuals who are early or late in the course of illness. We all know that tests are rated on their sensitivity and specificity. In simple terms, sensitivity of a test is defined as the fraction of positive cases that the test correctly identifies as positive, and specificity of a test is defined as the fraction of negative cases that the test correctly identifies as negative. A highly sensitive test will generally have a low false negative rate but will run a risk of false positives if the test's specificity is low. A highly specific test will generally have a low false positive rate but will run a risk of false negatives if the test's sensitivity is low. To reduce the risk of false negative results, it is important to perform the test in accordance with its authorization and as described in the authorized labeling. To mitigate the false results, most COVID-19 tests are ordered by clinicians and are prescription-only so that the results can be interpreted for patients. Any tests authorized for non-prescription use (i.e., direct-to-consumer (DTC) or over-the-counter" (OTC) use) direct patients to consult their health-care provider for result interpretation. There are two different types of tests—diagnostic tests and antibody tests, as discussed in Table 1.1 and Fig. 1.16.

The latest guidance for antigen testing for SARS-CoV-2 is available on the CDC's website (https://www.cdc.gov/coronavirus/2019-ncov/lab/resources/antigen-tests-guidelines.html) as of June 13, 2021. They are based on the following points:

- new published studies on antigen test performance;
- clarification about which nucleic acid amplification tests (NAATs) should be used for confirmatory testing;
- considerations for people who have had previous SARS-CoV-2 infections and those who have been fully vaccinated;
- two new antigen testing algorithms, one for congregate living settings, and one for community settings; and
- updates to testing suggestions for fully vaccinated, asymptomatic people.

One of the most important aspects of COVID-19 testing centers around interpretation of results. In fact, there are problems with interpretation of serology test results to inform patient care. These problems continue to this day and I provide excerpts from a May 2021 article from *New York* that highlights this critical issue (Box 1.10). Again, the role of federal agencies is paramount here as well. The misuse of serology tests for diagnosis; the potential for false positive results when a single test is used in populations with a low rate of infection; and the perception of immunity can all result in a skewed picture of the pandemic. This leads not only to misdiagnosis but also imposition of improper quarantine and other restrictive measures.

Table 1.1 Coronavirus disease 2019 testing basics: comparing the diagnostic and antibody tests. *Courtesy of the FDA.*

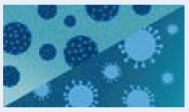
There are two different types of tests – diagnostic tests and antibody tests.

Diagnostic tests can show if you have an active Covid-19 infection and need to take steps to quarantine or isolate yourself from others. **Molecular** and **antigen tests** are types of diagnostic tests than can detect if you have an active COVID-19 infection. Samples for diagnostic tests are typically collected with a nasal or throat swab, or saliva collected by spitting into a tube.

Antibody tests look for antibodies in your immune system produced in response to SARS-CoV-2, the virus that causes COVID-19. **Antibody tests should not be used to diagnose an active COVID-19 infection.** Antibodies can take several days or weeks to develop after you have an infection and may stay in your blood for several weeks or more after recovery. Samples for antibody tests are typically blood from a finger stick, or blood drawn by your doctor or other medical personnel.

	MOLECULAR TEST	ANTIGEN TEST	ANTIBODY TEST
Also known as...	Diagnostic test, viral test, molecular test, nucleic acid amplification test (NAAT), RT-PCR test, LAMP test	Diagnostic test, viral test, rapid test	Serological test, serology, blood test, serology test
How the sample is taken...	Nasal swabs, either shallow or deep (most tests). Saliva (some tests)	Nasal or nasopharyngeal swab (most tests)	Blood from a fingerstick or vein
How long it takes to get results...	Less than an hour (at-home tests and some point-of-care locations), same day (some point-of-care locations) or 1-3 days (tests sent to a lab for processing). Some tests may take longer in some locations, depending on testing capacity.	Some may be very fast (15–30 minutes), depending on the test	Same day (some point-of-care locations) or 1-3 days (tests sent to a laboratory for processing)
Is another test needed...	Not usually. This type of test is typically highly accurate andmusually does not need to be repeated. Some may indicate the need to re-test in certain circumstances.	Maybe. Positive results are usually highly accurate, but false positives can happen, especially in areas where very few people have the virus. Negative results may need to be confirmed with a molecular test.	Sometimes a second antibody test is needed for accurate results.
What it shows...	Diagnoses active COVID-19 infection. (Some tests may also diagnose influenza or other respiratory viruses)	Diagnoses active COVID-19 infection. (Some tests may also diagnose influenza or other respiratory viruses)	Shows if you've been infected by the virus that causes COVID-19 in the past
What it can't do...	It cannot show if you ever had COVID-19 or were infected with the virus that causes COVID-19 in the past	It may not detect an early COVID-19 infection. Your health care provider may order a molecular test if your antigen test shows a negative result, but you have symptoms of COVID-19. It also cannot show if you ever had COVID-19 or were	It cannot diagnose COVID-19 at the time of the test or show that you do not have COVID-19

- **Rapid, point-of-care** diagnostic tests use a mucus sample from the nose or throat but can be analyzed at the doctor's office or clinic where the sample is collected and results may be available in minutes. These may be molecular or antigen tests.



- **Combination tests** can test for the flu and the coronavirus at the same time. Some can test for many different types of respiratory viruses, including the one that causes COVID-19.

- **Home Collection Test:** sample is collected at home but analyzed in a laboratory
- **Direct to Consumer (DTC) Test:** home collection tests available without a prescription, but the sample is analyzed in a laboratory
- **At-home Testing:** consumer completes sample collection and testing at home
- **Over the Counter (OTC) Test:** consumer completes sample collection and testing at home, without a prescription

- **Saliva tests** allow a patient to spit into a tube rather than get their nose or throat swabbed. Saliva tests may be more comfortable for some people and may be safer for health care workers who can be farther away during the sample collection.

Ordering a Test

Many tests, including some home collection and at-home tests, require a prescription or order from a health care provider.

Prescription Tests – Health care providers can determine whether you need a test, and ensure you get the most appropriate test and that you know what the results mean. For example, certain tests are authorized only for people suspected of having COVID-19 or for people with COVID-19 symptoms that started within a certain number of days. A health care provider can help determine which test is best for your situation. Prescription-only home collection and at-home tests may require you to answer some questions online so that a health care provider can determine whether to prescribe or order a specific test.

Non-Prescription Tests – Some tests are available without a prescription. Home collection and at-home tests available without a prescription may be called "direct-to-consumer" (DTC) or "over-the-counter" (OTC). DTC and OTC tests may be available to purchase at a pharmacy or online, but they may not be available everywhere.

Figure 1.16 Diagnostic tests with alternative options. *Courtesy of the FDA.*

Box 1.10 What really happened with that weird Yankees COVID outbreak

Does that mean you think that a lot of the cases throughout the pandemic maybe shouldn't have been treated as true positives—by which I mean, infections actually likely to cause illness and transmission? That's correct. We should have been much more discerning about how we used and interpreted the PCR results. I published on the need to interpret the PCR Ct values in a paper at the very beginning of this pandemic and suggested that many if not most PCR positive people no longer need to be in isolation—we missed the boat on those people. Most people only made it in to get the PCR test or only eventually got the results after their period of transmission was good and done. In fact, when PCR tests were taking 10 days to return, then if you got a positive result then the understanding of that should have been: I'm done with my isolation window of time. Unfortunately, I may have spread the virus already, but now I no longer need to isolate.

(*Continued*)

Box 1.10 (*Continued*)

It seems somewhat related to the matter of super spreader dynamics, where a vast majority of cases are produced by a sliver of infections. Yeah, I would say that's exactly right. But what we see is the variation of viral load within a person is much, much greater than the variance of viral load across people. A paper came out recently that showed 90 percent of the viral particles in a population were held by just 2 percent of the people. Well, that's true, but what really has to be taken into account is that those people change daily. Most people who get an infection, they'll probably go through a period of time where they can contribute to that 2% of people holding 90% of the viral particles and be a super spreader, but that time period is so short. You might be infected for three or four or five weeks, but if you walk into a bar in a certain three day window, you might not just be a transmitter but a super spreader. But if you were to walk into that same bar, five days later, with same infection, you're still PCR positive, but you might not transmit to anyone because your viral load will be a million or a billion times lower than it was just a few days earlier.

Which does emphasize the need for rapid testing—the faster the viral dynamics change the faster you need your diagnostic tools to work. The only way you're ever going to stop transmission is if you find people who are about to hit that really high viral load or are already in the middle of it and isolate those people, even for just three or four days until they pass peak infectiousness. If you're not doing frequent testing, you're very unlikely to just happen to stick a swab into somebody's nose in the day or two before they hit those really peak numbers. Most of the rest of the time, if you get a positive reading you're getting it when you are no longer infectious.

Which means, I guess, that using PCR testing to guide isolation or quarantine is a really crude approach, which is going to lead to many times more people being isolated for much longer than is necessary. It's almost an argument against using PCR tests at all, and just using antigen tests instead. The whole thing with needing to get a PCR test within three days of getting on a plane, for instance, that's so incredibly dangerous compared to a rapid test, because you could be negative one day and then, two or three days later, you could be at your absolute peak viral titers—like trillions of viral titers. Whereas if you were to use an antigen test right before that event, even if the antigen tests a thousand times less sensitive, you would absolutely find the people who are transmitting, and would have almost no risk of somebody walking in who's a super spreader. It's a remarkable lack of insight into the viral load kinetics by our policymakers to push for three days earlier PCR testing instead of a rapid test immediately before.

Which means there's no motivation for it to evolve, right? Right. And so, if you already have an antibody response—because you've been vaccinated or you've been previously infected—in that case maybe the virus is only able to grow to a million titers instead of a billion ... Well, those million viral particles per ml are each bumping into your already-existing antibodies, so there is

actually something for them to try to learn how to evade. That's when, theoretically, you would see the most likely scenario for immune evasion and mutation that would improve the virus's fitness against immunity—specifically in those people who have already been vaccinated or infected and who are getting re-exposed and reinfected. That's the theoretical piece. But you have to layer on top of its community transmission. And if through vaccination you can drop everyone's viral loads and transmissibility by 90 percent, then overall you should expect at a community level to have just many fewer infections. And so that should hopefully balance out that potential increase of evolutionary capacity. In other words, they're really competing forces—do you want no immunity, and to just keep having viruses transmit unabated, or do you want to have immunity, giving the virus something to learn from, but overall have it happened in many, many fewer people? We don't really know which exact way it balances out.

Source: D. Wallace-Wells. (2021). What really happened with that weird Yankees COVID outbreak. *New York*, May 21 issue.

1.7 Convalescent Plasma

I need hardly add that the fight against cattle tuberculosis only marks a stage on the road which leads finally to the effective protection of human beings against the disease.

—Emil Adolf von Behring, Nobel Lecture, 1901

Intravenous human immunoglobulin delivery for prophylaxis and treatment is well known for numerous microbial diseases. Passive immunotherapy[28] has been used since the late 19th century. In fact, the first Nobel Prize to von Behring in 1901 was awarded for passive serum therapy (immune serum containing neutralizing antibodies) for patients with diphtheria. During the Spanish Flu of 1918, serum from convalescent (recovered) patients was used. Similarly, its use is advocated for the treatment of patients with COVID-19. The idea is to give convalescent plasma to an infected patient (i.e., that person is getting antiviral antibodies) because it may take weeks to produce his/her own antibodies while the virus can continue replicating unchecked. Convalescent plasma can be used for prophylaxis of high-risk people before they get infected or for treatment of patients who are *already* infected but are not fighting the virus well. Plasma harvested from convalescent COVID-19 patients, containing antibodies against SARS-CoV-2, can be used in two ways (Fig. 1.17). I wish to point out that in spite of what the FDA says, use of convalescent plasma therapy against SARS-CoV-2 is not a simple or straightforward issue (Box 1.11). In my view, antibody cocktails in test tubes can never be equated to vaccines for a variety of reasons, including the effectiveness of the latter in priming humoral and cellular arms of the immune system. Also, there is data that antibody cocktails, such as those currently being tested by Regeneron and Eli Lilly, may be less effective against mutations present in the B.1.351 variant of SARS-CoV-2.

[28]On the other hand, vaccination therapy is a form of active immunotherapy.

Box 1.11 (A little) Clarity on convalescent plasma for COVID-19

"Considering the number of SARS-CoV-2 infections, the paucity of treatment options, and the enthusiasm for and controversy about convalescent plasma, a high-quality, multicenter, randomized, controlled trial is most welcome ... Uncontrolled compassionate use of convalescent plasma in patients other than those with an early infection that is likely to progress to more severe illness should be discouraged, even though clinicians recognize how difficult it can be to "just stand there" at the bedside of a patient in the ICU. Constraints on therapies for COVID-19 that are effective for limited patient populations are a powerful argument for continued consistent adherence to recommended nonpharmaceutical interventions and the rapid deployment and uptake of effective vaccines."

Source: L. M. Katz. (2021). (A little) clarity on convalescent plasma for COVID-19. *N. Engl. J. Med.* **384**(7):666–668.

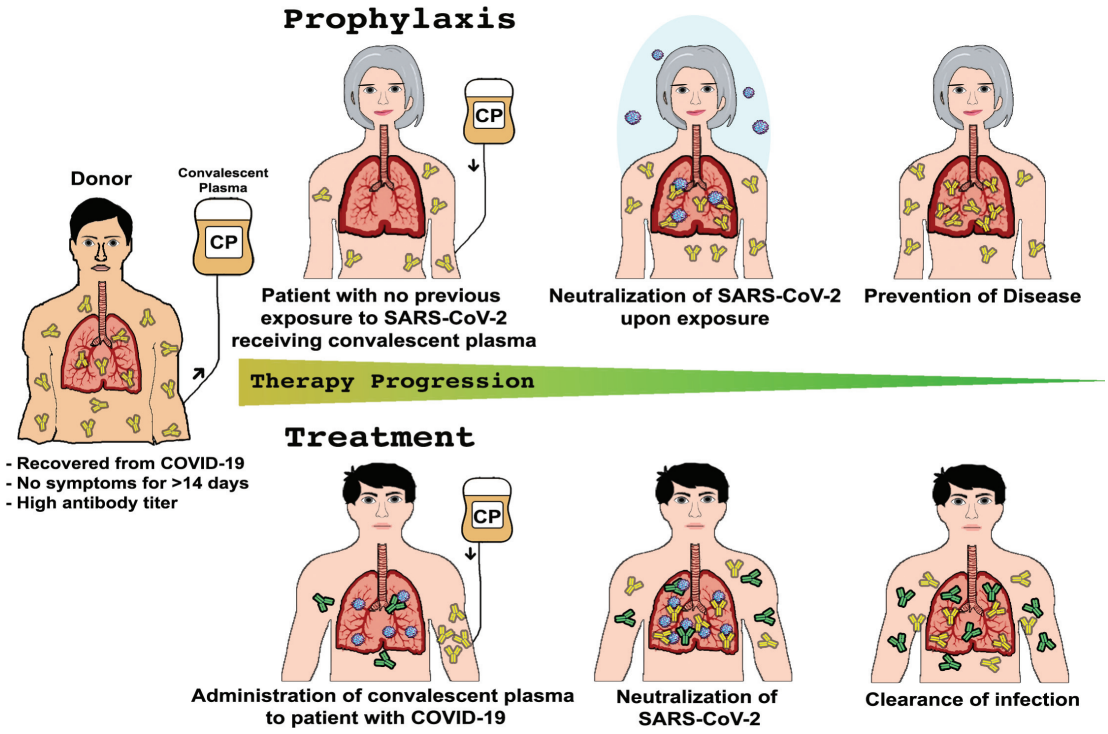


Figure 1.17 Overview of the use and applications of convalescent plasma therapy. Virus-neutralizing antibodies in the plasma of a patient who recovered from COVID-19 can be administered prophylactically to prevent infection in vulnerable individuals and those with known exposure to the virus (prophylaxis). Convalescent plasma can also be administered to infected individuals to improve the clinical outcome (treatment). *Source*: D. Montelongo-Jauregui, et al. (2020). Convalescent serum therapy for COVID-19: A 19th century remedy for a 21st century disease. *PLoS Pathog*. **16**(8):e1008735.

1.8 Looking Back and Moving Forward: Will We Win?

[H]ave the infectious diseases that we observe today always existed? Or have some of them appeared in the course of history? Can we assume that new ones will appear? Can we assume that some of these diseases will disappear? Have some of them already disappeared? Finally, what will become of humanity and domestic animals if, as a result of more and more frequent contacts between people, the number of infectious diseases continues to increase?

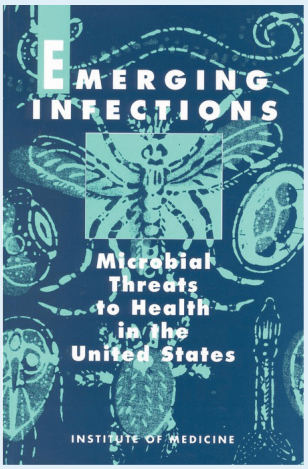
—Charles Nicolle, *Destin des maladies infectieuses,* 1933

Alone we can do so little; together we can do so much.

—Helen Keller

The final trajectory of the pandemic is impossible to predict. Wuhan, China was ground zero for SARS-CoV-2 but now we are in this together and in order to survive we will need a concerted effort. Our track record for eliminating viruses has been a poor one. Classic examples that highlight this glaring fact are smallpox and polio. Obviously, this does not bode well for the current pandemic. Disease spread is inevitable in our interconnected world. In fact, for decades experts have warned us of impending danger, recommended setting up surveillance programs to recognize emerging/reemerging microbes and proposed methods of intervention (Box 1.12).

Box 1.12 Emerging and reemerging diseases: warning signs



A well-designed, well-implemented surveillance program can detect unusual clusters of disease, document the geographic and demographic spread of an outbreak, and estimate the magnitude of the problem. It can also help to describe the natural history of a disease, identify factors responsible for emergence, facilitate laboratory and epidemiological research, and assess the success of specific intervention efforts.

Source: J. Lederberg, R. E. Shope, and S. C. Oaks, Jr. (1992). *Emerging Infections: Microbial Threats to Health in the United States.* National Academies Press, Washington, DC.

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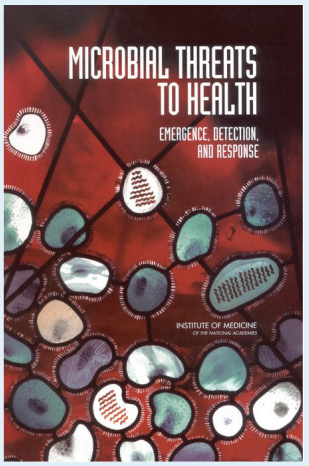
Box 1.12 (*Continued*)



As we enter the twenty-first century, infectious diseases continue to burden populations around the world. Both naturally occurring and intentionally introduced biological threats hold increasing potential to cause disease, disability, and death. And beyond disease itself, the ability of infectious agents to destabilize populations, economies, and governments is fast becoming a sad fact of life. The prevention and control of infectious diseases are fundamental to individual, national, and global health and security; failure to recognize—and act on—this essential truth will surely lead to disaster. Over the past decade, the United States has taken important steps to strengthen its capacity to address the threats posed by these diseases. However, we must do more to improve our ability to detect, prevent, and control emerging and resurging diseases if we are to be better prepared for future microbial threats to health…we must continue to trumpet the message of urgency and concern, but our more demanding task is to take stock of existing preventive and remedial measures, and to consider what further investments of fiscal and political capital are needed if we are to keep pace with our microbial competitors. We need no longer limit our concern to the United States as the venue for microbial threats to health, as it is now widely understood that our borders offer trivial impediment to such threats. Nor need we have an exclusive focus on emerging diseases when we have so far to go in dealing globally with tuberculosis, malaria, and HIV/AIDS, which emerge and reemerge with violent fluctuations of intensity in different parts of the world.

Source: M. S. Smolinski, M. A. Hamburg, and J. Lederberg. (2003). *Microbial Threats to Health: Emergence, Detection, and Response.* National Academies Press, Washington, DC.

This terrible global risk/benefit calculus means viruses may now swiftly enter every region of the world, but the protective gear, treatments, and vaccines necessary to save lives remain primarily available to lucky residents of the United States, Canada, Western Europe, Japan, and a handful of other countries. There is no governing structure for a pandemic, and little more than vague political pressure to ensure limited access to life-sparing tools and medicines for more than half the world population … A man lucky enough to receive an effective vaccine against a new viral threat in Los Angeles may be re-exposed a year later to a mutated

version of that germ that circulated among unimmunized populations in poor countries, only to slam North America in a second wave. That is what happened with influenza in 1918, which spread across Europe in a mild form, returning months later in its terrifying virulence and killing more than 50 million people (by recently adjusted estimates perhaps 100 million people).

Courtesy of Laurie Garret, discussing the Warner Brothers film "Contagion" on CNN in 2011.

Ending, or at least stabilizing, the current pandemic and addressing future public health emergencies should be the focus. How people and health systems respond to the current pandemic will be key, not only to planning for and protecting from emerging microbes of the future, but for maintaining economic and political stability for the 2020s and beyond. Public health infrastructures, big pharma, a wealth of drugs, hospitals, health-care providers, and scientists, all have fared poorly to contain this pandemic. The volatile mix of politics (Box 1.13), globalization, national rivalries, inept health organizations, misinformation, arrogance, and ignorance all fueled the development and spread of COVID-19. In the critical early phases, nations failed to implement basic infectious disease control management measures such as data gathering, testing, contact tracing (Box 1.14), and distribution of critical medical supplies to health-care providers.

Box 1.13 COVID-19 and politics: disarray, blame, and mismanagement

The most terrifying words in the English language are: I'm from the government and I'm here to help.

—Ronald Reagan

The highly politicized response to the pandemic added fuel to the fire. Politicians certainly share a major portion of blame for the pandemic and its perpetuation. Political leaders either failed to follow established basic pandemic-response plans, or never fully and reliably funded existing pandemic plans. The haphazard and disjointed approach of political leaders and health-care organizations shows how miserably they have failed in addressing the seriousness that this microbe poses with respect to its impact on society, political stability, and the economy. We have so much talent and brilliance on this planet, yet it is stifled by politicians, religious leaders, and fanatics. Societal divisiveness and political upheaval continues to cause us to stumble as we struggle to convince citizens to get vaccinated or follow the latest guidelines. This dangerous trajectory is likely to continue for years. Coordinated preparation and action was critical. Instead, government leaders, healthcare organizations, and society failed to provide an effective response. Demands for freedom pushed aside commonsense approaches crucial to tackling a serious infectious microbe.

(*Continued*)

Box 1.13 (*Continued*)

Many political leaders from Britain to Brazil to India ignored advice of their own health advisors. They found political gain more expedient. They continued to hold vast rallies at super spreader events. They even belittled those who were seriously ill with COVID-19. Some of them spun the pandemic to shine a spotlight on themselves and highlight their own perceived achievements. Authoritarians and politicians always seize the megaphone for themselves. A classic example is that of "Dr." Andrew M. Cuomo, the now disgraced governor of New York state, who gave daily briefings and PowerPoint presentations on TV. He authoritatively ticked through the latest statistics on infections, hospitalizations, nursing homes patients, and deaths—all sprinkled with medical errors and politics (photo below). It was especially painful and disgusting for me to watch this arrogance on display while my helpless 85-year old mother languished in a private nursing home in New York state, whose health department had lost control over the pandemic along with nursing home data. It was clear that this corrupt politician only cared about his ratings and image.

Health-care agencies tasked with springing into action during a pandemic have also been in disarray and not fared much better than the politicians that controlled them. The WHO correctly received poor marks and harsh criticism for its passivity in the face of the pandemic. Since the Centers for Disease Control and Prevention failed miserably in the early phase of the pandemic and played a side role, some labeled it the "Centers for Disease Observation." The FDA was a mess as well with the rollout of its COVID-19 testing. It became clear that a large proportion of COVID-19 negative results were inaccurate ("false negatives") because of an issue inherent in the tests' design resulting from inadequate regulatory reviews.

Handling a pandemic in a decentralized manner where local politicians dictate events is not an ideal approach. However, this is the flaw that we must endure in a democracy where government power is not concentrated and there is a patchwork of decentralized mechanisms to address pandemics. Microbes do not recognize boundaries, timelines, politics, or policies but rather feed on chaos, global conflicts, confusion, arrogance, and divisiveness.

Box 1.14 Power of digital contact tracing for COVID-19

There's been much interest in using digital technology to help contain the spread of COVID-19 in our communities. The idea is to make available opt-in smart phone apps that create a log of other apps operating on the phones of nearby participants. If a participant tests positive for COVID-19 and enters the result, the app will then send automatic alerts to those phones—and participants—who recently came into close proximity with them. In theory, digital tracing would be much faster and more efficient than the challenging detective work involved in traditional contract tracing. But many have wondered how well such an opt-in system would work in practice.

A recent paper (*Nature* 2021 May 12. doi: 10.1038/s41586-021-03606-z) shows that a COVID-19 digital tracing app worked quite well in the United Kingdom. The research comes from Christophe Fraser, Oxford University, and his colleagues in the UK. The team studied the NHS COVID-19 app, the National Health Service's digital tracing smart phone app for England and Wales. Launched in September 2020, the app has been downloaded onto 21 million devices and used regularly by about half of eligible smart phone users, ages 16 and older. That's 16.5 million of 33.7 million people, or more than a quarter of the total population of England and Wales. From the end of September through December 2020, the app sent about 1.7 million exposure notifications. That's 4.4 on average for every person with COVID-19 who opted-in to the digital tracing app. The researchers estimate that around 6 percent of app users who received notifications of close contact with a positive case went on to test positive themselves. That's similar to what's been observed in traditional contact tracing. Next, they used two different approaches to construct mathematical and statistical models to determine how likely it was that a notified contact, if infected, would quarantine in a timely manner. Though

(*Continued*)

Box 1.14 (*Continued*)

the two approaches arrived at somewhat different answers, their combined outputs suggest that the app may have stopped anywhere from 200,000 to 900,000 infections in just three months. This means that roughly one case was averted for each COVID-19 case that consented to having their contacts notified through the app. Of course, these apps are only as good as the total number of people who download and use them faithfully. They estimate that for every 1 percent increase in app users, the number of COVID-19 cases could be reduced by another 1 or 2 percent. While those numbers might sound small, they can be quite significant when one considers the devastating impact that COVID-19 continues to have on the lives and livelihoods of people all around the world.

Courtesy of Dr. Francis S. Collins and NIH.

The disastrous start with inaccurate and chaotic testing has continued with vaccination rates far below what would be considered as potentially rendering herd immunity. Due to globalization, the risk of pandemics is shared by the entire planet, but vaccines, testing, and therapeutics remain prioritized to exclusive, usually wealthy nations. Obviously, while it may make us feel safer here in the US, variants from the developed world will evolve further and infect the globe. This is likely to reduce efficacy or render useless the current generation of vaccines here.

So, have we learnt any lessons? One is the need for integration between science and policy. Another is that accurate dissemination of information to the public is essential. Trust is the primary currency of good crisis communication and political leaders quickly lost trust with inaccurate, untimely, inconsistent policies, and information. In a foreshadowing of COVID-19 outbreaks all over the world, health-care systems and facilities were completely overwhelmed. Unfortunately, this vicious cycle continues to play out as the pandemic roars on from one epicenter to another. A flattening of the curve in one region will lead to a spike elsewhere. Today we may rejoice lowered infections here in the US only to repent a spike in the months to follow. Next time, the attack may be with more virulent variants. An epidemic in one spot may morph into a pandemic in another area. Hopefully, we will not become complacent as we feel secure and consider this someone else's problem. Our track record is poor as after each disease threat faded, so did urgency and governmental funding. Flexible adaptation is key to managing pandemics. What is a great approach today may need to be tweaked or discarded for policies that are more sensible tomorrow. A reasonable leeway for balancing protection of public health with a return to pre-pandemic life is essential, though I am doubtful that we will ever return to pre-pandemic normalcy. In my view, here and abroad, we will continue to face a patchwork of ineffective policies, poor contact tracing efforts and inequitable vaccination rates, as novel variants evolve.

Let us not lose sight of the fact that while we may be far from others in distance and perspective, we are brought nearer in our common conflict with this deadly nanoparticle, the SARS-CoV-2. This is a story of humanity, of fear and resignation, of compassion and dilemma, of persistence and hope. As global citizens, it has made painfully real our interconnectedness while also strengthening it with the many acts of kindness and compassion that should continue to serve as a uniting thread.

The solutions for pandemic control are well-known based on lessons from the past. They include adequately investing in a public health systems to detect early signs of a microbial outbreak; ensuring that public and private labs collaborate on testing, tracing, and quarantining people exposed to an infection; ensuring an adequate supply of facilities (hospital beds, personal protective equipment, drugs, health-care staff, and medical supplies); and investing in an efficient R&D infrastructure to develop, scale-up, and distribute vaccines and therapeutics.

Declaring hollow victories, issuing vaccine passports, ignoring contact tracing, or hoarding vaccines and therapeutics will not ensure global safety, slow down viral transmission, or prevent virulent mutants from evolving. In fact, all of these poor approaches will have the exact opposite effect. A viral wave elsewhere today will arrive as a spike here tomorrow. I am certain that virulent microbes will continue to evolve from their zoonotic reservoirs and jump to humans. This reality must spur everyone—lawmakers, big pharma, citizens, regulatory agencies, global health organizations, biomedical researchers, physicians—to examine what went wrong and create a more workable plan for future outbreaks.

After all, alone we can do so little, but together we can do so much. And we are all in this together.

Disclosures and Conflict of Interest

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About the Series Editor

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