

Infectious Diseases

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Fourth Edition

Edited by

Jonathan Cohen, MB, FRCP, FRCPE, FRCPath, FMedSci

Emeritus Professor of Infectious Diseases
Brighton and Sussex Medical School
Brighton, UK

William G. Powderly, MD, FRCPI

J. William Campbell Professor of Medicine
Larry J Shapiro Director, Institute for
Public Health
Co-director, Division of Infectious Diseases
Washington University in St Louis
St Louis, MO, USA

Steven M. Opal, MD

Professor of Medicine
Infectious Disease Division
Alpert Medical School of Brown University
Providence, RI, USA

Section Editors

Thierry Calandra, MD, PhD

Chairman, Department of Medicine
Head, Infectious Diseases Service
CHUV (Centre Hospitalier
Universitaire Vaudois)
Lausanne, Switzerland

Nathan Clumeck, MD, PhD

Professor of Infectious Diseases
Honorary Head, Department of
Infectious Diseases
Saint-Pierre University Hospital
Brussels, Belgium

Jeremy Day, MA, DTM&H, PhD, FRCP

Head, CNS-HIV Infections Research Group
Oxford University Clinical Research Unit
Wellcome Trust Major Overseas
Programme Vietnam
Ho Chi Minh City, Vietnam
Associate Professor
Centre for Tropical Medicine
Nuffield Department of Medicine
University of Oxford
Oxford, UK

Jeremy Farrar, FRS, FRCP, FMedSci, DPhil, OBE

Director, The Wellcome Trust
London, UK

Roy M. Gulick, MD, MPH

Rochelle Belfer Professor in Medicine
Chief, Division of Infectious Diseases
Department of Medicine
Weill Cornell Medical College
New York, NY, USA

Andy I.M. Hoepelman, MD, PhD

Professor in Medicine, Infectious
Diseases Specialist
Head, Department of Internal Medicine and
Infectious Diseases
University Medical Center
Utrecht, The Netherlands

Kieren A. Marr, MD

Professor of Medicine and Oncology
Director, Transplant and Oncology Infectious
Diseases Program
Johns Hopkins University School of Medicine
Baltimore, MD, USA

Jeanne Marrazzo, MD, MPH, FACP, FIDSA

Director, Division of Infectious Diseases
Professor of Medicine
University of Alabama at Birmingham
School of Medicine
Birmingham, AL, USA

Didier Raoult, MD, PhD

Professor, Faculté de Médecine, Director of
the Foundation Mediterranee Infection
Unité des Rickettsies
WHO Collaborative Center for Rickettsial
Reference and Research
Marseille, France

Robert T. Schooley, MD

Professor and Head
Division of Infectious Diseases
Academic Vice Chair
Department of Medicine
University of California San Diego
San Diego, CA, USA

Jos W.M. van der Meer, MD, PhD, FRCP, FRCP(Edin), FIDSA, MAE

Emeritus Professor of Medicine
Radboud University Medical Center
Nijmegen, The Netherlands

Richard J. Whitley, MD

Distinguished Professor
Loeb Chair in Pediatrics
Professor of Pediatrics, Microbiology,
Medicine and Neurosurgery
University of Alabama
Birmingham, AL, USA

Associate Editors (Educational Content)

Courtney D. Chrisler, MD

Instructor in Medicine
Division of Infectious Diseases
Washington University in St Louis
St Louis, MO, USA

Bethany Davies, MRCP, FRCPath

Specialist Registrar in Infectious Diseases and
Medical Microbiology
Brighton and Sussex University Hospitals
NHS Trust
Brighton, East Sussex, UK

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Content Development Specialist: Sharon Nash

Content Coordinator: Trinity Hutton

Project Manager: Joanna Souch

Design: Miles Hitchen

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†Deceased

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†Deceased

PREFACE TO THE FOURTH EDITION

We live in interesting times. The discipline of infectious diseases has rarely faced so much promise, and yet such peril. The possibility of an AIDS-free world within the next generation is now seriously contemplated, based on the intelligent use of combinations of antiretroviral agents and selected use of pre-exposure prophylaxis, and even without the benefit of a vaccine that induces sterilizing immunity against human immunodeficiency virus (HIV). This would not have seemed possible even 25 years ago. Similarly, the remarkable success story of possibly curing hepatitis C virus (HCV) with safe, oral, directly acting, antiviral agents is now well within our grasp. Only 30 years ago the cause of non-A non-B post-transfusion hepatitis was unknown and no serologic test was available to detect carriers and prevent transmission. Real progress in developing a multistage malaria vaccine has recently been made, and a vaccine for dengue is on the horizon. Promising and innovative vaccine strategies using reverse genetic approaches are now in development, targeting recalcitrant bacterial, fungal and parasitic pathogens. Rapid molecular diagnostics are finally making huge inroads in the clinical microbiology laboratory. Such advances are essential if we are to be able to make accurate diagnoses within hours and provide optimal care for our patients in this era of precision medicine.

Yet despite these advances, we are constantly reminded of just how fragile our dominion over the microbial world really is. The human population has swelled to over 7 billion inhabitants; most now reside in crowded cities, often without the benefits of adequate sanitation or reliable nutrition. As Paul Farmer has written, physicians 'need to think hard about poverty and inequality, which influence any population's morbidity and mortality', and this is no more so than in the case of infectious diseases. The global spread of antimicrobial resistance now poses the very real threat of infection for which there are no effective treatments. Novel resistance mechanisms in gram-negative bacteria have emerged and spread rapidly across the world, challenging the foundations of the modern era of medicine. Drug-resistant tuberculosis, including infection with organisms that are extensively resistant (XDR-TB), continues to challenge global efforts at control. Despite the extensive efforts to provide global access to antiretroviral therapy, new cases of HIV continue in epidemic numbers, and many continue to die from AIDS. The spread of vector-borne pathogens, especially dengue, chikungunya and Zika, continues and corona virus-related Middle Eastern respiratory syndrome has emerged as yet another unexpected challenge. Zika-induced microcephaly is hugely important and clearly demonstrates our continued vulnerability to new microbial

threats. However, nothing has demonstrated our collective vulnerability to pathogenic infection more than the West African outbreak of Ebola which showed the world the devastating effects of a lethal infection. Although ultimately controlled by effective infection prevention, this outbreak reminded us of the continued importance of understanding, preventing and treating infectious diseases.

It is against this background that we have prepared this fourth edition of *Infectious Diseases*. In doing this we have been conscious not only of the extraordinary developments in the science and practice of infection, but also in the evolving needs of our readers. Scientists and practitioners turn to books like this both for specific information on unfamiliar subjects but also as a source for further education and training. Mindful of this, we have introduced a variety of exciting new elements to the book. Alongside our widely acclaimed Practice Points offering pithy, practical advice on common management problems we have now added several new features designed to assist our readers. These include online mannequins providing a ready reference to pharmacokinetic data on antimicrobial agents, which are traditionally difficult to access in an easily useful form, and also a portfolio of online multiple choice questions, fully supported by reference material, as a resource for postgraduate education. We are grateful to our two new Associate Editors in Medical Education, Bethany Davies and Courtney Chrisler, for their help with this important new addition to the book. As ever, we are indebted to the extraordinary commitment and expertise of our Section Editor colleagues and to the very many expert contributors who have so graciously agreed to undertake comprehensive revision of their chapters from the previous edition, and, in many cases, write completely new chapters. We also wish to express our profound thanks to the team at Elsevier who have cajoled, supported and encouraged us to get this done, in particular Sharon Nash, Jo Souch and Belinda Kuhn, and last but by no means least, we thank the Section Editors from the previous edition, Jack Sobel, Roger Finch, Scott Hammer, Tim Kiehn and Keith McAdam, without whom we would never have been in a position to prepare this new edition of the book. We hope that you, the reader, will find what you are looking for and we welcome feedback on how we can continue to improve *Infectious Diseases*.

Jon Cohen
William Powderly
Steven Opal

LIST OF CONTRIBUTORS

The editors would like to acknowledge and offer grateful thanks for the input of all previous editions' contributors, without whom this new edition would not have been possible.

Fredrick M. Abrahamian, DO, FACEP, FIDSA

Clinical Professor of Medicine
David Geffen School of Medicine at UCLA
Los Angeles, CA, USA
Director of Education
Department of Emergency Medicine
Olive View-UCLA Medical Center
Sylmar, CA, USA

Michael J. Aldape, PhD

Research Investigator
Infectious Disease Section
Department of Research and Development
Veterans Affairs Medical Center
Boise, ID, USA

Edelweiss Aldasoro, MD

Medical Research Fellow
ISGlobal, Barcelona Ctr. Int. Health Res. (CRESIB), Hospital
Clínic-Universitat de Barcelona
Barcelona, Spain

Upton D. Allen, MBBS, MSc, FAAP, FRCPC, Hon FRCP(UK), FIDSA

Professor of Paediatrics
Division of Infectious Diseases
Department of Paediatrics
Hospital for Sick Children
University of Toronto
Toronto, ON, Canada

Hythem Al-Sum, MD

Clinical Fellow
Maternal-Fetal Medicine Division
Department of Obstetrics and Gynaecology
Mount Sinai Hospital-University of Toronto
Toronto, ON, Canada

Milan J. Anadkat, MD

Associate Professor of Medicine
Division of Dermatology
Washington University School of Medicine in St Louis
St Louis, MO, USA

Katherine Anders, MSc, PhD

Epidemiologist and Data Manager
Eliminate Dengue Program
Monash University
Melbourne, Australia

Emmanouil Angelakis, MD, PhD

Assistant Unité de Recherche sur les Maladies Infectieuses et
Tropicales Emergentes
Aix-Marseille Université
Marseille, France

Brian John Angus, MBChB, MD, DTM&H, FRCP

Associate Professor and Reader in Infectious Diseases
Nuffield Department of Medicine
University of Oxford
Oxford, UK

Anastasia Antoniadou, MD

Associate Professor of Medicine and Infectious Diseases
Fourth Department of Medicine
National and Kapodistrian University of Athens
Athens, Greece

Fabio Arena, MD

Senior Research Fellow in Clinical Microbiology
Department of Medical Biotechnologies
University of Siena
Siena, Italy

Joop E. Arends, MD, PhD

Infectious Diseases Physician
Internal Medicine and Infectious Diseases
University Medical Center Utrecht (UMCU)
Utrecht, The Netherlands

Jose R. Arribas, MD

Head, Infectious Diseases Unit, Internal Medicine
Hospital La Paz
Madrid, Spain

Andrew W. Artenstein, MD

Chair, Department of Medicine
Baystate Health
Tufts University School of Medicine Chair of Medicine at Baystate
Medical Center
Professor of Medicine
Tufts University School of Medicine
Springfield, MA, USA

John C. Atherton, MD, FRCP

Professor of Gastroenterology, Pro-Vice Chancellor and Dean of the
Faculty of Medicine and Health Sciences
NIHR Biomedical Research Unit in Gastrointestinal and Liver
Diseases
Nottingham University Hospitals NHS Trust
University of Nottingham, Queen's Medical Centre
Nottingham, UK

John N. Aucott, MD

Assistant Professor of Medicine
Division of Rheumatology
Johns Hopkins University School of Medicine
Baltimore, MD, USA

Tar-Ching Aw, MB, PhD, FRCPC, FFOM

Professor (EVP)
PAPRSB Institute of Health Sciences
Universiti Brunei Darussalam
Adjunct Professor
Herbert Wertheim College of Medicine
Florida International University
Miami, FL, USA

Hilary M. Babcock, MD, MPH

Medical Director
BJC Infection Prevention and Epidemiology Consortium
Medical Director of Occupational Health (Infectious Diseases)
Barnes-Jewish and St Louis Children's Hospitals
Associate Professor of Medicine
Infectious Disease Division
Department of Medicine
Washington University School of Medicine in St Louis
St Louis, MO, USA

Robin Bailey, BA, BM, FRCP, PhD, DTMH

Professor of Tropical Medicine
Department of Clinical Research
Faculty of Infectious and Tropical Diseases
London School of Hygiene and Tropical Medicine
London, UK

Thomas C. Bailey, MD

Professor of Medicine
Infectious Diseases Division
Department of Medicine
Washington University School of Medicine in St Louis
St Louis, MO, USA

Adam Z. Banks, MD

Resident, PGY-3
Department of Internal Medicine
Duke University Medical Center
Durham, NC, USA

David J. Barillo, MD, FACS, FCCM

Colonel (retired)
US Army Reserve
Disaster Response/Critical Care Consultants, LLC
Mount Pleasant, SC, USA

Ernie-Paul Barrette, MD, FACP

Associate Professor of Medicine
Department of Internal Medicine
Division of Infectious Diseases
Washington University School of Medicine in St Louis
St Louis, MO, USA

Martijn P. Bauer, MD, PhD

Senior Medical Specialist, Infectious Diseases
Center of Infectious Disease
Leiden University Medical Centre
Leiden, The Netherlands

Roger Bayston, MMedSci, MSc, PhD, FRCPath

Professor of Surgical Infection
School of Medicine
University of Nottingham
Nottingham, UK

C. Ben Beard, MS, PhD

Chief, Bacterial Diseases Branch
Division of Vector-Borne Diseases
US Centers for Disease Control and Prevention
Fort Collins, CO, USA

Justin Beardsley, MBChB

Senior Clinical Research Fellow
Nuffield Department of Medicine
Oxford University Clinical Research Unit
Ho Chi Minh City, Vietnam

Nick J. Beeching, MA, BMBCh, FRCP, FRACP, FFTM, RCPS(Glasg), DCH, DTM&H

Senior Clinical Lecturer
Department of Clinical Sciences and NIHR Health Protection
Research Unit in Emerging and Zoonotic Infections
Liverpool School of Tropical Medicine
Pembroke Place
Liverpool, UK

Rodolfo E. Bégué, MD

Professor of Pediatrics
Department of Pediatrics
Louisiana State University HSC School of Medicine
New Orleans, LA, USA

Guido Beldi, MD

Professor in Surgery
Department for Visceral Surgery and Medicine
Bern University Hospital
University of Bern
Bern, Switzerland

Constance A. Benson, MD, FACP, FIDSA

Professor of Medicine and Global Public Health
Infectious Diseases Training Program Director
Divisions of Infectious Diseases and Global Public Health
Department of Medicine
University of California, San Diego
San Diego, CA, USA

Elie F. Berbari, MD

Professor of Medicine
Division of Infectious Diseases
Section of Orthopedic Infectious Diseases
Mayo Clinic College of Medicine
Rochester, MN, USA

Jean-Michel Berenger, MD

Medical Entomologist
Aix-Marseille Université
URMITE
Marseille, France

Christoph Berger, MD

Associate Professor of Pediatrics and Pediatric Infectious Diseases
Division of Infectious Diseases and Hospital Epidemiology
University Children's Hospital
Zürich, Switzerland

Jose I. Bernardino, MD

Assistant Physician
HIV Unit, Department of Internal Medicine
Hospital Universitario La Paz, IdiPAZ
Madrid, Spain

Jacques Bille, MD

Honorary Professor of Medical Microbiology
Institute of Microbiology
Lausanne University Hospital Center and University of Lausanne
Lausanne, Switzerland

Alexander C. Billioux, MD, DPhil

Assistant Chief of Service, Thayer Firm
Department of Medicine
The Johns Hopkins Hospital
Baltimore, MD, USA

Ari Bitnun, MD, MSc

Associate Professor
Department of Pediatrics
Hospital for Sick Children
University of Toronto
Toronto, ON, Canada

Iain Blair, MBChir, MA, MFCM, MRCPG

Associate Professor
Institute of Public Health
College of Medicine and Health Sciences
United Arab Emirates University
Al Ain, Abu Dhabi, United Arab Emirates

Stéphane Blanche, MD

Professor of Pediatrics
Immunology and Hematology Unit
Hôpital Necker–Enfants Malades
University René Descartes
Paris, France

Thomas P. Bleck, MD

Professor of Neurological Sciences, Neurosurgery, Medicine, and
Anesthesiology
Rush University Medical Center
Chicago, IL, USA

Chantal P. Bleeker-Rovers, MD, PhD

Internist-Specialist in Infectious Diseases
Department of Internal Medicine
Division of Infectious Diseases
Radboud University Medical Center
Nijmegen, The Netherlands

Gijs Bleijenberg, PhD

Professor Emeritus
Expert Centre for Chronic Fatigue
Radboud University Medical Center
Nijmegen, The Netherlands

Karen C. Bloch, MD, MPH

Associate Professor
Departments of Medicine (Infectious Diseases) and Health Policy
Vanderbilt University School of Medicine
Nashville, TN, USA

Johannes Blum, MD

Professor
Department of Medical Services and Diagnostics
Swiss Tropical and Public Health Institute and University of Basel
Basel, Switzerland

Emily A. Blumberg, MD

Professor of Medicine, Director Transplant Infectious Diseases
Department of Medicine
Perelman School of Medicine at the University of Pennsylvania
Philadelphia, PA, USA

Robert A. Bonomo, MD

Chief, Medical Service
Louis Stokes Cleveland Department of Veterans Affairs Medical
Center
Professor of Medicine, Pharmacology, Biochemistry, Molecular
Biology and Microbiology
Case Western Reserve University School of Medicine
Cleveland, OH, USA

Marc J.M. Bonten, MD, PhD

Professor of Molecular Epidemiology of Infectious Diseases
Department of Medical Microbiology
Julius Center for Health Sciences and Primary Care
University Medical Center Utrecht
Utrecht, The Netherlands

Rafik Bourayou, MD

Hospital Practitioner
Department of Pediatrics
Bicêtre Hospital
Paris, France

Emilio Bouza, MD, PhD

Head, Clinical Microbiology and ID Division
Hospital Gregorio Marañón
Universidad Complutense de Madrid
Madrid, Spain

K. Ashley Brandt, DO

Resident Physician
Department of Obstetrics and Gynecology
Drexel University College of Medicine
Philadelphia, PA, USA

Florence Bretelle, MD, PhD

Professor of Obstetrics and Gynaecology
Department of Obstetrics and Gynaecology
University of Marseille
Marseille, France

Sylvain Brisse, PhD

Research Director
Microbial Evolutionary Genomics
Institut Pasteur
Paris, France

Warwick J. Britton, PhD, MBBS, FAAHMS, FRACP, FRCP, FRCPA

Bosch Professor of Medicine and Immunology
Centenary Institute and Discipline of Medicine
Sydney Medical School
University of Sydney
Sydney, Australia

Itzhak Brook, MD

Professor of Pediatrics
Georgetown University School of Medicine
Washington DC, USA

Matthijs C. Brouwer, MD, PhD

Neurologist
Department of Neurology
Academic Medical Center
University of Amsterdam
Amsterdam, The Netherlands

Sarah K. Browne, MD

Assistant Clinical Investigator
Division of Intramural Research
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Bethesda, MD, USA
Division of Vaccines and Related Product Applications
Center for Biologics Evaluation and Research, Food and Drug
Administration
Silver Spring, MD, USA

Amy E. Bryant, PhD

Research Career Scientist
Infectious Disease Section
Research and Development Service
Veterans Affairs Medical Center
Boise, ID, USA

Silja Bühler, MD, MSc

Research Scientist
Division of Infectious Diseases
Epidemiology, Biostatistics and Prevention Institute
University of Zurich
Zurich, Switzerland

Eileen M. Bulger, MD, FACS

Professor, Chief of Trauma
Department of Surgery
Harborview Medical Center, University of Washington
Seattle, WA, USA

R. Mark L. Buller, PhD

Professor of Molecular Microbiology and Immunology
Department of Molecular Microbiology and Immunology
Saint Louis University
St Louis, MO, USA

Leah A. Burke, MD

Instructor of Medicine
Department of Medicine
Division of Infectious Diseases
Weill Cornell Medical College
New York, NY, USA

Christian Burri, PhD, MPharm

Professor
Department of Medicines Research
Swiss Tropical and Public Health Institute
University of Basel
Basel, Switzerland

Marcus W. Butler, MD, MBBCh, FRCPI

Consultant Respiratory Physician
University College Dublin
School Of Medicine
St Vincent's Hospital
Dublin, Ireland

Thierry Calandra, MD, PhD

Chairman, Department of Medicine
Head, Infectious Diseases Service
CHUV (Centre Hospitalier Universitaire Vaudois)
Lausanne, Switzerland

David P. Calfee, MD, MS

Associate Professor
Departments of Medicine and Health Policy and Research
Weill Cornell Medical College
New York, NY, USA

Antonia Calvo-Cano, MD

Medical Research Fellow
ISGlobal, Barcelona Ctr. Int. Health Res. (CRESIB), Hospital
Clínic-Universitat de Barcelona
Barcelona, Spain

D. William Cameron, MD, FRCPC, FACP

Professor of Medicine
Divisions of Infectious Diseases and Respiriology
Senior Scientist
Clinical Epidemiology Program
University of Ottawa at The Ottawa Hospital Research Institute
Ottawa, ON, Canada

Joseph A. Carcillo, MD

Professor of Critical Care Medicine and Pediatrics
University of Pittsburgh
Pittsburgh, PA, USA

Gail Carson, MBChB, MRCP, DTM&H

Clinical Coordinator and Consultant in Infectious Diseases
International Severe Acute Respiratory and Emerging Infection
Consortium
Centre for Tropical Medicine and Global Health
Nuffield Department of Medicine
University of Oxford
Oxford, UK

Stephen T. Chambers, MBChB, MSc, MD, FRACP

Professor
Department of Pathology
University of Otago, Christchurch
Clinical Director
Department of Infectious Diseases
Christchurch Hospital
Christchurch, New Zealand

Remi N. Charrel, MD, PhD

Head, Emergence and Genomics of RNA Viruses
IRD French Institute of Research for Development, INSERM U1207
EHESP French School of Public Health,
EPV UMR190 "Emergence des Pathologies Virales"
IHU Méditerranée Infection, APHM Public Hospitals of Marseille
Aix Marseille Université
Marseille, France

Vinh Chau Van Nguyen, MD, PhD

Director of the Hospital for Tropical Diseases
Ho Chi Minh City, Vietnam
Deputy Head of Infectious Disease Division
University of Medicine and Pharmacy
Ho Chi Minh City, Vietnam

Stéphane Chevaliez, PharmD, PhD

Professor of Medicine
Department of Virology
Henri Mondor Hospital
University of Paris-Est & INSERM U955
Creteil, France

Tom M. Chiller, MD

Associate Director for Epidemiologic Science
Division of Foodborne, Waterborne and Environmental Diseases
National Center for Emerging and Zoonotic Infectious Diseases
Centers for Disease Control and Prevention
Atlanta, GA, USA

Eirini Christaki, MD

Infectious Diseases Consultant
Department of Medicine
AHEPA University Hospital
Thessaloniki, Greece
Research Associate in Medicine
Alpert Medical School of Brown University
Providence, RI, USA

Kevin K. Chung, MD, FCCM, FACP

Director of Research
US Army Institute of Surgical Research, Fort Sam
Houston, TX, USA

David B. Clifford, MD

Melba and Forest Seay Professor of
Clinical Neuropharmacology in Neurology
Washington University in St Louis
Saint Louis, MO, USA

Nathan Clumeck, MD, PhD

Professor of Infectious Diseases
Honorary Head, Department of Infectious Diseases
Saint-Pierre University Hospital
Brussels, Belgium

Jonathan Cohen, MB, FRCP, FRCPE, FRCPath, FMedSci

Emeritus Professor of Infectious Diseases
Brighton and Sussex Medical School
Brighton, UK

John Collinge, MRCP, MD, FRCPath

Professor of Neurology
Head of Department
Department of Neurodegenerative Diseases/Director
MRC Prion Unit
Institute of Neurology
University College London
London, UK

Christopher P. Conlon, MA, MD, FRCP, FRCPI

Professor of Infectious Diseases
Nuffield Department of Medicine
University of Oxford
Consultant Physician
Oxford University Hospitals NHS Foundation Trust
Oxford, UK

Curdin Conrad, MD, PD&MER

Head of the Psoriasis Center
Department of Dermatology
University Hospital of Lausanne, CHUV
Lausanne, Switzerland

Fiona J. Cooke, MA, PhD, MSc, MRCP, FRCPath, DTM&H

Consultant Medical Microbiologist
Clinical Microbiology and Public Health Laboratory
Cambridge University Hospitals NHS Foundation Trust
Cambridge, UK

Jennifer Rittenhouse Cope, MD, MPH

Medical Epidemiologist
National Center for Emerging and Zoonotic Infectious Diseases
Centers for Disease Control and Prevention
Atlanta, GA, USA

G. Ralph Corey, MD

Professor of Medicine and Pathology
Department of Medicine
Duke University Medical Center
Durham, NC, USA

The late John H. Cross, PhD

Professor
Tropical Public Health
Department of Preventive Medicine and Biometrics
Uniformed Services University of the Health Sciences
Bethesda, MD, USA

Burke A. Cunha, MD, MACP

Chief, Infectious Disease Division
Winthrop-University Hospital
Mineola, New York
Professor of Medicine
State University of New York School of Medicine
Stony Brook, NY, USA

Cheston B. Cunha, MD

Assistant Professor of Medicine
Medical Director, Antimicrobial Stewardship Program
Division of Infectious Disease
Brown University Alpert School of Medicine, Rhode Island Hospital
and Miriam Hospital
Providence, RI, USA

Benoit D'Journo, MD, PhD

Professor
Service de Chirurgie Thoracique
Assistance Publique-Hôpitaux de Marseille
Marseille, France

George L. Daikos, MD

Professor of Medicine and Infectious Diseases
First Department of Medicine
National and Kapodistrian University of Athens
Athens, Greece

Johannes M.A. Daniels, MD, PhD

Pulmonologist
Department of Pulmonary Diseases
VU University Medical Center
Amsterdam, The Netherlands

Robert N. Davidson, MD, FRCP, DTM&H

Consultant Physician
Department of Infectious Diseases and Tropical Medicine
Northwick Park Hospital
Harrow, UK

Nicholas P.J. Day, MA, BMBCh, DM, FRCP, FMedSci

Professor of Tropical Medicine
University of Oxford
Director, Mahidol-Oxford Tropical Medicine Research Unit
Faculty of Tropical Medicine
Mahidol University
Bangkok, Thailand

Kevin M. De Cock, MD, FRCP (UK), DTM&H

Director
Division of Global HIV/AIDS-Kenya
Centers for Disease Control and Prevention
Nairobi, Kenya

Thushan I. de Silva, BSc, MBChB, MRCP, FRCPath, DTM&H, PhD

NIHR Academic Clinical Lecturer in Infectious Diseases and
Microbiology
Department of Infection and Tropical Medicine
Royal Hallamshire Hospital
Sheffield, UK

Henry J.C. de Vries, MD, PhD

Dermatologist
Department of Dermatology
Academic Medical Center (AMC)
University of Amsterdam
Amsterdam, The Netherlands
Center for Infection and Immunology Amsterdam (CINIMA)
Academic Medical Center (AMC)
University of Amsterdam
Amsterdam, The Netherlands
STI Outpatient Clinic
Public Health Service of Amsterdam (GGD Amsterdam)
Amsterdam, The Netherlands

Stéphane de Wit, MD, PhD

Head of Department
Infectious Diseases
Saint-Pierre University Hospital
Brussels, Belgium

Julie Delaloye, MD, PhD

Infectious Disease Specialist
Centre Hospitalier Universitaire Vaudois
Lausanne, Switzerland

David W. Denning, FRCP, FRCPath, FMedSci

Professor of Infectious Diseases in Global Health
The University of Manchester
Director
National Aspergillosis Centre
University Hospital of South Manchester
Manchester, UK

David T. Dennis, MD, MPH

Medical Epidemiologist
Centers for Disease Control and Prevention (Ret.)
Fort Collins, CO, USA

Shireesha Dhanireddy, MD

Associate Professor
Division of Infectious Diseases, Department of Medicine
University of Washington
Seattle, WA, USA

Elodi J. Dielubanza, MD

Housestaff Physician
Department of Urology
Feinberg School of Medicine Northwestern University
Chicago, IL, USA

David J. Diemert, MD, FRCP(C)

Associate Professor
Department of Microbiology
Immunology and Tropical Medicine
George Washington University School of Medicine and Health
Sciences
Washington, DC, USA

Mehmet Doganay, MD

Professor of Infectious Diseases
Department of Infectious Diseases
Faculty of Medicine, Erciyes University
Kayseri, Turkey

Tom Doherty, MD, FRCP, DTM&H

Consultant Physician
Hospital for Tropical Diseases
University College London Hospitals
London, UK

Christiane Dolecek, MD, PhD, FRCP

University Research Lecturer
Centre for Tropical Medicine and Global Health
Nuffield Department of Medicine
Spatial Ecology and Epidemiology Group
Department of Zoology
University of Oxford
Oxford, UK

Arjen M. Dondorp, MD, PhD

Professor of Tropical Medicine
University of Oxford
Oxford, UK

Abby Douglas, MBBS(Hons), BMedSci

Infectious Diseases Registrar
Department of Infectious Diseases
St Vincent's Hospital Melbourne
Melbourne, Australia

Michel Drancourt, MD, PhD

Professor
Unité de Recherches sur les Maladies Infectieuses et Tropicales
Emergentes
Aix-Marseille Université
Marseille, France

Grégory Dubourg, PharmD

University Hospital Assistant
Unité de Recherche sur les Maladies Infectieuses et Tropicales
Emergentes
Aix-Marseille University
Marseille, France

Michael N. Dudley, PharmD, FIDSA

Senior Vice President and Chief Scientific Officer (Rempex)
Health Sciences Lead
Infectious Diseases Global Innovation Group
The Medicines Company
San Diego, CA, USA

Guillaume Durand, MD

Medicine Resident
Unité de Recherche sur les Maladies Infectieuses et Tropicales
Emergentes
University of Marseille
Marseille, France

Benjamin J. Eckhardt, MD

Infectious Diseases Fellow
Division of Infectious Diseases
Weill Cornell Medical College
New York, NY, USA

Androulla Efstratiou, PhD

Director
WHO Collaborating Centre for Reference and Research on
Diphtheria and Streptococcal Infections
Reference Microbiology Division
Public Health England (PHE)
London, UK

Miquel B. Ekkelenkamp, MD, PhD

Clinical Microbiologist
Department of Medical Microbiology
University Medical Center Utrecht
Utrecht, The Netherlands

Ambika Eranki, MD, MPH

Assistant Professor
Division of Infectious Disease
Department of Medicine
State University of New York/Upstate Medical Center
Syracuse, NY, USA

Hakan Erdem, MD

Professor of Infectious Diseases and Clinical Microbiology
Gulhane Medical Academy and Infectious Diseases Department
GATA Hospital
Etlik, Ankara, Turkey

Gerome V. Escota, MD

Clinical Instructor of Medicine
Division of Infectious Disease
Washington University School of Medicine in Saint Louis
Saint Louis, MO, USA

Heather L. Evans, MD, MS, FACS

Associate Professor of Surgery
Department of Surgery
University of Washington
Seattle, WA, USA

Alice Chijioke Eziefula, MA, MBBS, MRCP, FRCPath

Specialist Registrar in Infectious Diseases and Medical Microbiology
Department of Infection
Brighton and Sussex University Hospitals NHS Trust
Brighton, UK

Florence Fenollar, MD, PhD

Professor
Institut Hospitalo-Universitaire Méditerranée-Infection
Aix-Marseille Université
Marseille, France

Alan Fenwick, PhD

Professor of Tropical Parasitology
Department of Infectious Disease Epidemiology
Imperial College London
London, UK

Joshua Fierer, MD

Chief, Infectious Disease
VA San Diego Healthcare System
Professor of Medicine and Pathology
University of California San Diego
San Diego, CA, USA

Roger G. Finch, MBBS, FRCP, FRCPath, FRCPEd, FFPM

Professor of Infectious Diseases
School of Molecular Medical Science
Division of Microbiology and Infectious Disease
Nottingham University Hospitals NHS Trust
Nottingham, UK

James M. Fleckenstein, MD

Associate Professor of Medicine and Molecular Microbiology
Department of Medicine, Division of Infectious Diseases
Washington University School of Medicine in St Louis
St Louis, MO, USA

Christina Forstner, MD

Assistant Professor
Specialist for Internal Medicine
Department of Medicine I
Division of Infectious Diseases and Tropical Medicine
Medical University of Vienna
Vienna, Austria

Federico Foschi, MD

Resident Physician
Department of Internal Medicine I
Division of Infectious Diseases
Tübingen University Hospital
Tübingen, Germany

Pierre-Edouard Fournier, MD, PhD

Professor of Clinical Microbiology
Institut Hospitalo-Universitaire Méditerranée-Infection
Aix-Marseille Université
Marseille, France

Martyn A. French, MB ChB, MD, FRCPath, FRCP, FRACP

Professor in Clinical Immunology
School of Pathology and Laboratory Medicine
University of Western Australia
Perth, Australia

Kenneth L. Gage, PhD

Chief, Entomology and Ecology Activity
Bacterial Diseases Branch
Division of Vector-Borne Diseases
Centers for Disease Control and Prevention
Fort Collins, CO, USA

Lynne S. Garcia, MS, CLS, FAAM

Director
LSG & Associates
Santa Monica, CA, USA

Joaquim Gascon, MD, PhD

Research Professor
ISGlobal, Barcelona Ctr. Int. Health Res. (CRESIB), Hospital
Clínic-Universitat de Barcelona
Barcelona, Spain

Arturo S. Gastañaduy, MD

Associate Professor of Pediatrics
Department of Pediatrics
Louisiana State University HSC School of Medicine
New Orleans, LA, USA

Philippe Gautret, MD, PhD, MSc, DTM&H

Director of Travel Clinic
University Hospital Institute for Infectious Diseases and Tropical
Medicine, Méditerranée Infection
Aix-Marseille University
Marseille, France

William M. Geisler, MD, MPH

Professor
Department of Medicine, Division of Infectious Diseases
The University of Alabama at Birmingham
Birmingham, AL, USA

Khalil G. Ghanem, MD, PhD

Associate Professor of Medicine
Division of Infectious Diseases
Johns Hopkins University School of Medicine
Baltimore, MD, USA

Tommaso Gianni, PhD

Assistant Professor
Department of Medical Biotechnologies
University of Siena
Siena, Italy

Maddalena Giannella, MD, PhD

ID Consultant
Infectious Diseases Unit, Department of Medical and Surgical
Sciences
Sant'Orsola Hospital, University of Bologna
Bologna, Italy

Bruce L. Gilliam, MD

Associate Professor of Medicine
Institute of Human Virology
University of Maryland School of Medicine
Baltimore, MD, USA

Michel Gilliet, MS

Chief of Service
Dermatology
Department of Medicine
Centre Hospitalier Universitaire Vaudois
Lausanne, Switzerland

Carol A. Glaser, DVM, MD

Associate Clinical Professor of Pediatrics
Division of Pediatric Infectious Diseases
University of California, San Francisco
San Francisco, CA, USA

Youri Glupczynski, MD, PhD

Professor and Head of Clinical Microbiology
Microbiology Laboratory and National Reference Laboratory for
Monitoring of Antimicrobial Resistance in Gram-Negative
Bacteria
CHU Dinant-Godinne, UCL Namur
Yvoir, Belgium

John W. Gnann, Jr, MD

Professor of Medicine
Department of Medicine, Division of Infectious Diseases
Medical University of South Carolina
Charleston, SC, USA

Ellie J.C. Goldstein, MD, FSHEA, FIDSA

Clinical Professor of Medicine
David Geffen School of Medicine at UCLA
Los Angeles, CA, USA
Director, R.M. Alden Research Laboratory
Santa Monica, CA, USA

Bruno Gottstein, PhD, AssEVPC

Full Professor of Medical and Veterinary Parasitology
Institute of Parasitology
Department of Infectious Diseases and Pathobiology
University of Bern
Bern, Switzerland

Frederique Gouriet, MD, PhD

Physician
Research Unit of Emerging Infectious and Tropical Diseases
Faculty of Medicine
Aix-Marseille University
Marseille, France

Patti E. Gravitt, PhD, MS

Professor
Department of Pathology
University of New Mexico Health Sciences Center
Albuquerque, NM, USA

Michael D. Green, MD, MPH

Professor of Pediatrics, Surgery and Clinical and Translational
Science
University of Pittsburgh School of Medicine
Attending Physician
Division of Infectious Diseases
Children's Hospital of Pittsburgh of UPMC
Pittsburgh, PA, USA

Stephen T. Green, MD, BSc, MBChB, FRCP(Lond & Glas), FFTM, DTM&H

Honorary Professor of International Health at Sheffield Hallam
University
Consultant Physician in Infectious Diseases and Tropical Medicine
Department of Infection and Tropical Medicine
Royal Hallamshire Hospital
Sheffield, UK

Andreas H. Groll, MD

Professor of Pediatrics
Center for Bone Marrow Transplantation and Department of
Pediatric Hematology/Oncology
University Children's Hospital Münster
Münster, Germany

Roy M. Gulick, MD, MPH

Rochelle Belfer Professor in Medicine
Chief, Division of Infectious Diseases
Department of Medicine
Weill Cornell Medical College
New York, NY, USA

Arjun Gupta, MBBS

Internal Medicine PGY1
University of Texas Southwestern Medical Center
Dallas, TX, USA

Gilbert Habib, MD

Cardiologist
Department of Cardiology
La Timone Hospital
Marseille, France

Stephan Harbarth, MD, MS

Associate Professor of Medicine
Infection Control Programme
Department of Medicine
Geneva University Hospitals and Faculty of Medicine
Geneva, Switzerland

Marianne Harris, MD

Clinical Assistant Professor, Department of Family Practice
Associate Member, Division of AIDS
Faculty of Medicine
University of British Columbia
Vancouver, BC, Canada

Frederick G. Hayden, MD

Stuart S. Richardson Professor of Clinical Virology and Professor of
Medicine
Department of Medicine
Division of Infectious Diseases and International Health
University of Virginia
Charlottesville, VA, USA

David J. Hetem, MD, PhD

Clinical Microbiologist
Department of Medical Microbiology
University Medical Center Utrecht
Utrecht, The Netherlands

Philip C. Hill, BHB, MBChB, MPH, MD, FranceCP, FAFPHM

McAuley Professor of International Health
Centre for International Health
University of Otago,
Dunedin, New Zealand

Bernard Hirschel, MD

Professor Emeritus
Division of Infectious Disease
Geneva University Hospitals
Geneva, Switzerland

Aimee C. Hodowanec, MD

Assistant Professor
Section of Infectious Diseases
Department of Medicine
Rush University Medical Center
Chicago, IL, USA

Louis Hoffart, MD

Service d'Ophtalmologie
Hôpital de la Timone
Marseille, France

Christian Hoffmann, MD, PhD

Associate Professor
University of Schleswig Holstein
Campus Kiel Hemato-oncologist Infektionsmedizinisches Centrum
Hamburg (ICH) ICH Study Center Hamburg
Hamburg, Germany

Steven M. Holland, MD

Chief
Laboratory of Clinical Infectious Diseases
National Institute of Allergy and Infectious Diseases, NIH,
Bethesda, MD, USA

Peter W. Horby, MBBS, FRCP, PhD

Associate Professor
Centre for Tropical Medicine and Global Health
University of Oxford
Oxford, UK

David J. Horne, MD, MPH

Assistant Professor of Medicine
Division of Pulmonary and Critical Care Medicine, Department of
Medicine
Harborview Medical Center, University of Washington
Seattle, WA, USA

Sami Hraiech, MD, PhD

Assistance Publique-Hôpitaux de Marseille
Hôpital Nord
Réanimation des Détresses Respiratoires et des Infections Sévères
Aix-Marseille Université
Marseille, France

Mark W. Hull, MD, MHS

Clinical Associate Professor
Division of AIDS
Department of Medicine
University of British Columbia
Vancouver, BC, Canada

Angela Huttner, MD

Instructor
Infection Control Programme
Geneva University Hospitals and Faculty of Medicine
Geneva, Switzerland

Richard J.M. Ingram, BMedSci, BMBS(Hons), MRCP

Clinical Research Fellow in Gastroenterology
NIHR Biomedical Research Unit in Gastrointestinal and Liver
Diseases
Nottingham University Hospitals NHS Trust
University of Nottingham, Queen's Medical Centre
Nottingham, UK

Jasmin Islam, MBBS, PhD, MRCP

Specialist Registrar Infectious Diseases and Medical Microbiology
Department of Infection and Microbiology
Brighton and Sussex University Hospital
Brighton, UK

Michael G. Ison, MD, MS, FIDSA, FAST

Associate Professor
Divisions of Infectious Diseases and Organ Transplantation
Northwestern University Feinberg School of Medicine
Chicago, IL, USA

Scott H. James, MD

Assistant Professor of Pediatrics
Department of Pediatrics
Division of Infectious Diseases
University of Alabama at Birmingham School of Medicine
Birmingham, AL, USA

Claire Jenkins, PhD

Head of E. coli, Shigella, Yersinia & Vibrio Reference Services
Gastrointestinal Bacteria Reference Unit
Public Health England
London, UK

Stephen G. Jenkins, PhD

Adjunct Professor of Pathology and Laboratory Medicine
Adjunct Professor of Pathology in Medicine
Weill Cornell Medical College
New York, NY, USA

Jørgen Skov Jensen, MD, PhD, DMedSci

Consultant Physician
Microbiology and Infection Control
Statens Serum Institut
Copenhagen, Denmark

Christine Johnston, MD, MPH

Assistant Professor of Medicine
Division of Infectious Diseases, Department of Medicine
University of Washington
Seattle, WA, USA

Theodore B. Jones, MD, FACOG

Residency Program Director
Obstetrics and Gynecology
Department of Obstetrics and Gynecology
Beaumont Oakwood
Associate Professor
Wayne State University School of Medicine
Dearborn, MI, USA

Stephen J. Jordan, MD, PhD

Clinical Fellow
Department of Medicine, Division of Infectious Diseases
The University of Alabama at Birmingham
Birmingham, AL, USA

Kathleen G. Julian, MD

Associate Professor of Medicine
Department of Medicine
Division of Infectious Diseases
Penn State Hershey Medical Center
Hershey, PA, USA

Yasuyuki Kato, MD, MPH, DTM

Chief, Division of Preparedness and Emerging Infections
Disease Control and Prevention Centre
National Centre for Global Health and Medicine
Tokyo, Japan

Carol A. Kauffman, MD

Chief, Infectious Diseases Section
Veterans Affairs Ann Arbor Healthcare System
Professor of Internal Medicine
University of Michigan Medical School
Ann Arbor, MI, USA

Keith S. Kaye, MD, MPH

Professor of Medicine
Corporate Vice President of Quality and Patient Safety
Corporate Medical Director, Infection Prevention, Epidemiology and
Antimicrobial Stewardship
Detroit Medical Center and Wayne State University
University Health Center
Detroit, MI, USA

Michael P. Keane, MD FRCPI

Professor of Medicine
University College Dublin
School of Medicine
St Vincent's Hospital
Dublin, Ireland

James Keeney, MD

Chief, Adult Hip and Knee Reconstructions Service
Associate Professor, Department of Orthopaedic Surgery
University of Missouri
Columbia, MO, USA

Paul Kelly, MD, FRCP

Professor of Tropical Gastroenterology
Blizard Institute
Barts & The London School of Medicine
Queen Mary University of London
London, UK

Stephen J. Kent, MBBS, MD, FRACP

Professor of Microbiology and Immunology
Department of Microbiology and Immunology
University of Melbourne
Melbourne, Australia

Winfried V. Kern, MD

Professor of Internal Medicine and Infectious Diseases
Division of Infectious Diseases
University Hospital and Medical Center
Freiburg, Germany

Yoav Keynan, MD, PhD

Assistant Professor
Department of Internal Medicine
Medical Microbiology and Community Health Sciences
University of Manitoba
Winnipeg, Canada

Andrea A. Kim, PhD, MPH

Chief, Surveillance and Epidemiology Branch
Division of Global HIV/AIDS—Kenya
Centers for Disease Control and Prevention
Nairobi, Kenya

Isabelle Koné-Paut, MD

Professor of Medicine
Department of Pediatrics
University of Paris Sud
Paris, France

Chris Kosmidis, MD, PhD

Consultant in Infectious Diseases
National Aspergillosis Centre
University Hospital of South Manchester
Hon. Senior Lecturer
The University of Manchester
Manchester, UK

Aloys C.M. Kroes, MD, PhD

Professor of Medical Microbiology and Clinical Virology
Department of Medical Microbiology
Leiden University Medical Center
Leiden, The Netherlands

Frank P. Kroon, MD PhD

Internist-Specialist in Infectious Diseases
Department of Infectious Diseases
Leiden University Medical Center
Leiden, The Netherlands

Thomas G. Ksiazek, DVM, PhD

Professor
Sealy Center for Vaccine Development
University of Texas Medical Branch
Galveston, TX, USA

F. Matthew Kuhlmann, MD

Instructor in Medicine
 Division of Infectious Diseases, Department of Medicine
 Washington University School of Medicine in St Louis
 St Louis, MO, USA

Ed J. Kuijper, MD, PhD

Professor of Medical Microbiology
 Department of Medical Microbiology
 Center of Infectious Disease
 Leiden University Medical Centre
 Leiden, The Netherlands

Jennie H. Kwon, DO

Senior Clinical Research Fellow
 Division of Infectious Diseases
 Department of Internal Medicine
 Washington University School of Medicine in St Louis
 St Louis, MO, USA

George B. Kyei, MBChB, PhD

Assistant Professor of Medicine
 Department of Medicine
 Washington University School of Medicine in St Louis
 Saint Louis, MO, USA

Karine Lacombe, MD, PhD

Associate Professor
 Infectious Diseases Department
 Hôpital St Antoine
 Paris, France

Philippe Lagacé-Wiens, MD, FRCPC, DTM&H

Professor
 Department of Medical Microbiology and Infectious Diseases
 University of Manitoba College of Medicine
 Winnipeg, Manitoba, Canada

Jean-Christophe Lagier, MD, PhD

Associate Professor of Medicine
 Institut Hospitalo-Universitaire Méditerranée-Infection
 Aix-Marseille Université
 Marseille, France

Theresa Lamagni, MSc, PhD

Senior Epidemiologist
 Healthcare-Associated Infections and Antimicrobial Resistance
 Department
 Public Health England
 London, UK

Luce Landraud, MD, PhD

Medical Doctor
 Microbiology Department
 Archet II-Hospital
 Microbial Toxins in Host Pathogen
 Interactions
 Sophia Antipolis University
 Nice, France

Fanny Lanternier, MD

Researcher Université Paris–Descartes
 Hôpital Necker–Enfants Malades
 Service des Maladies Infectieuses et Tropicales
 Institut Imagine, APHP, Centre d'Infectiologie Necker–Pasteur
 Paris, France

Kerry L. LaPlante, PharmD, FCCP

Professor of Pharmacy
 Department of Pharmacy Practice
 University of Rhode Island
 Kingston, RI, USA
 Adjunct Clinical Associate Professor of Medicine
 Alpert Medical School of Brown University
 Providence, RI, USA
 Director of the Rhode Island Infectious Diseases Research Program
 (RIID) and Infectious Diseases Pharmacotherapy Specialist
 Veterans Affairs Medical Center
 Providence, RI, USA

Stephen D. Lawn, BMedSci MB BS, MD, FRCP, DTM&H, DiP HIV MED

Professor of Infectious Diseases
 Department of Clinical Research
 Faculty of Infectious and Tropical Diseases
 London School of Hygiene & Tropical Medicine
 London, UK

Steven J. Lawrence, MD, MSc

Assistant Professor of Medicine
 Department of Medicine
 Washington University School of Medicine in St Louis
 St Louis, MO, USA

Hakan Leblebicioglu, MD

Head of Department of Infectious Diseases & Clinical Microbiology
 Coordinator of ESCMID Study Group for Infections in Travelers
 and Migrants (ESGITM)
 Ondokuz Mayıs University
 Samsun, Turkey

Nelson Lee, MD

Professor of Infectious Medicine and Therapeutics
 The Chinese University of Hong Kong
 Hong Kong, People's Republic of China

James E. Leggett, MD

Associate Professor, Department of Internal Medicine, Oregon
 Health and Sciences University
 Infectious Diseases, Department of Medical Education, Providence
 Portland Medical Center
 Portland, OR, USA

Philippe Lehours, PharmD, PhD

Assistant Professor in Microbiology
 Department of Bacteriology
 University of Bordeaux
 Bordeaux, France

Pierre-Yves Levy, MD

Associate Professor of Microbiology
 Institut Hospitalier Universitaire Méditerranée Infection
 Marseille, France

Rainer G. Leyh, MD, PhD

Professor, Director and Chairman
 Department of Thoracic and Cardiovascular Surgery
 Universitätsklinikum Würzburg
 Würzburg, Germany

Rebecca A. Lillis, MD

Associate Professor of Medicine
Department of Medicine, Section of Infectious Diseases
Louisiana State University School of Medicine
New Orleans, LA, USA

Direk Limmathurotsakul, MD, MSc, PhD

Assistant Professor of Epidemiology
Department of Tropical Hygiene and
Mahidol-Oxford Tropical Medicine Research Unit
Faculty of Tropical Medicine
Mahidol University
Bangkok, Thailand

Jennifer Lin, MD

Chief, Division of HIV/AIDS Medicine
Santa Clara Valley Medical Center
San Jose, CA, USA
Clinical Instructor, Affiliated
Division of Infectious Diseases
Stanford University
Stanford, CA, USA

H.D. Alan Lindquist, PhD

Biologist
Senior Advisor
Water Supply and Water Resources Division
National Risk Management Research Laboratory
Office of Research and Development
U.S. Environmental Protection Agency
Cincinnati, OH, USA

Benjamin A. Lipsky, MD, FACP, FIDSA, FRCP

Emeritus Professor
Department of Medicine
University of Washington
Visiting Professor
Department of Medicine (Infectious Diseases)
Geneva University Hospitals and Faculty of Medicine
Teaching Associate
Green Templeton College
Division of Medical Sciences
University of Oxford
Oxford, UK

Christina Liscynsky, MD

Assistant Professor of Internal Medicine
Division of Infectious Disease
The Ohio State University College of Medicine
Associate Medical Director
Clinical Epidemiology at the Ohio State University Wexner Medical
Center
Columbus, OH, USA

David Looney, MD

Staff Physician Infectious Disease
VA San Diego Healthcare System
Associate Professor of Medicine
University of California San Diego
San Diego, CA, USA

Olivier Lortholary, MD, PhD

Professor of Infectious Diseases and Tropical Medicine
Centre d'Infectiologie Necker-Pasteur
Hospital Necker Enfants Malades
Institut Pasteur
National Reference Center for Invasive Mycoses and Antifungals
Paris, France

Franklin D. Lowy, MD

Professor of Medicine and Pathology and Cell Biology
Department of Medicine
Columbia University
College of Physicians and Surgeons
New York, NY, USA

Benjamin J. Luft, MD

Edmund D. Pellegrino Professor
Department of Medicine
State University of New York at Stony Brook
Stony Brook, NY, USA

Philip A. Mackowiak, MD, MBA, MACP

Emeritus Professor of Medicine
Carolyn Frenkil and Selvin Passen History of Medicine
Scholar-in-Residence
University of Maryland School of Medicine
Baltimore, MD, USA

Paul A. MacPherson, PhD, MD, FRCPC

Associate Professor of Medicine
Division of Infectious Diseases
The Ottawa Hospital
Ottawa, ON, Canada

Valérie Maghraoui-Slim, MD

Hospital Practitioner
Department of Pediatrics
Bicêtre Hospital
Paris, France

Patrick W. Mallon, MBBCh, FRACP, PhD

Associate Dean for Research Innovation and Impact
School of Medicine and Medical Science
University College Dublin
Dublin, Ireland

Julie E. Mangino, MD, FSHEA

Professor of Medicine
Division of Infectious Diseases
The Ohio State University College of Medicine
Medical Director
Clinical Epidemiology at the Ohio State University Wexner Medical
Center
Columbus, OH, USA

Oriol Manuel, MD

Associate Physician
Infectious Diseases Service and Transplantation Center
University Hospital and University of Lausanne
Lausanne, Switzerland

Oscar Marchetti, MD

Associate Professor
Infectious Diseases Service
Department of Medicine
Lausanne University Hospital (CHUV)
Lausanne, Switzerland

Kristen M. Marks, MD, MS

Assistant Professor of Medicine
Weill Cornell Medical College
New York, NY, USA

Kieren A. Marr, MD

Professor of Medicine and Oncology
 Director, Transplant and Oncology Infectious
 Diseases Program
 Johns Hopkins University School of Medicine
 Baltimore, MD, USA

Jeanne Marrazzo, MD, MPH, FACP, FIDSA

Director, Division of Infectious Diseases
 Professor of Medicine
 University of Alabama at Birmingham School of Medicine
 Birmingham, AL, USA

Jonas Marschall, MD, MSc

Director of Infection Prevention
 Department of Infectious Diseases
 Bern University Hospital
 Bern, Switzerland
 Adjunct Assistant Professor
 Division of Infectious Diseases
 Washington University School of Medicine in St Louis
 St Louis, MO, USA

David H. Martin, MD

Harry E. Dascomb Professor of Medicine and Professor of
 Microbiology
 Chief, Section of Infectious Diseases
 Department of Internal Medicine
 Louisiana State University Health Sciences Center
 New Orleans, LA, USA

Frédéric Matonti, MD

Ophthalmology Department
 Aix-Marseille Université
 APHM, Hôpital Nord
 Marseille, France

Richard S. Matulewicz, MS, MD

Resident Physician
 Department of Urology
 Northwestern University Feinberg School of Medicine
 Chicago, IL, USA

Kenneth H. Mayer, MD

Professor of Medicine and Community Health
 Brown University
 Director of Brown University
 Infectious Diseases Division
 The Miriam Hospital
 Providence, RI, USA

Russell J. McCulloh, MD

Assistant Professor, Infectious Diseases
 Department of Pediatrics
 Department of Internal Medicine
 University of Missouri-Kansas City School of Medicine
 Kansas City, MO, USA

Rose McGready, MBBS, PhD

Professor of Tropical Maternal and Child Health
 Maternal and Child Health
 Shoklo Malaria Research Unit
 Mae Sot, Tak, Thailand

Rennatus Mdodo, DrPH, MS, MPhil

Epidemiologist
 Surveillance and Epidemiology Branch
 Division of Global HIV/AIDS-Kenya
 Centers for Disease Control and Prevention
 Nairobi, Kenya

Simon Mead, MD

Honorary Consultant Neurologist and Professor of Neurology
 MRC Prion Unit
 Institute of Neurology
 University College London
 London, UK

Francis Mégraud, MD

Professor of Bacteriology
 University of Bordeaux
 Bordeaux, France

Graeme Meintjes, MBChB, FRCP(UK), FCP(SA), MPH, PhD

Associate Professor of Medicine
 Department of Medicine
 University of Cape Town
 Cape Town, South Africa

Sarah C. Metcalf, MBChB, FRACP, DTM&H

Consultant Infectious Diseases Physician
 Department of Infectious Diseases
 Christchurch Hospital
 Christchurch, New Zealand

Marian G. Michaels, MD, MPH

Professor of Pediatrics and Surgery
 Pediatric Infectious Diseases
 Children's Hospital of Pittsburgh of UPMC University of Pittsburgh
 School of Medicine
 Pittsburgh, PA, USA

Giovanni Battista Migliori, MD, FRCP(Lond), FERS

Director, WHO Collaborating Center for Tuberculosis and Lung
 Diseases
 Fondazione Salvatore Maugeri, Care and Research Institute
 Tradate, Italy

Michael A. Miles, MSc, PhD, DSc, FRCPath

Professor of Medical Protozoology
 Department of Pathogen Molecular Biology
 Faculty of Infectious and Tropical Diseases
 London School of Hygiene and Tropical Medicine
 London, UK

Alastair Miller, MA, FRCP, FRCP(Edin), DTM&H

Honorary Senior Lecturer
 Institute of Infection and Global Health
 University of Liverpool
 Liverpool, UK
 Deputy Medical Director
 Joint Royal College of Physicians Training Board
 London, UK

Matthew J. Mimiaga, ScD, MPH

Professor of Epidemiology and Behavioral & Social Health Sciences
(tenured)
Director, Institute for Community Health Promotion (ICHP)
Brown University, School of Public Health
Adjunct Professor of Epidemiology, Harvard School of Public Health
Senior Research Scientist and Director, Epidemiology and Global
Health Research, The Fenway Institute
Harvard Medical School
Boston, MA, USA

Marie-Paule Mingeot-Leclercq, MSc, PharmD, PhD

Professor
Pharmacologie Cellulaire et Moléculaire
Louvain Drug Research Institute
Université Catholique de Louvain
Brussels, Belgium

Elizabeth Ann Misch, MD

Clinical Assistant Professor
Division of Allergy and Infectious Diseases
Department of Medicine
University of Washington
Seattle, WA, USA

Makedonka Mitreva, PhD

Assistant Professor of Medicine Infectious Diseases Division
Assistant Director
The Genome Institute
Washington University School of Medicine in St Louis
St Louis, MO, USA

Julio S.G. Montaner, MD, DSc

Professor of Medicine
Faculty of Medicine
University of British Columbia
Vancouver, BC, Canada

Caroline B. Moore, MSc, PhD, MRSB

Principal Clinical Mycologist
Mycology Reference Centre
University Hospital of South Manchester
University of Manchester
Manchester, UK

Patricia Muñoz, MD, PhD

Clinical Microbiology and Infectious Diseases Department
Hospital General Universitario Gregorio Marañón
Instituto de Investigación Sanitaria del Hospital Gregorio Marañón
CIBER Enfermedades Respiratorias-CIBERES
Medicine Department
School of Medicine
Universidad Complutense de Madrid
Madrid, Spain

Jose Muñoz, MD, PhD

Assistant Research Professor
ISGlobal, Barcelona Ctr. Int. Health Res. (CRESIB), Hospital
Clínic-Universitat de Barcelona
Barcelona, Spain

Clinton K. Murray, MD

Colonel, Medical Corps
Professor of Medicine
Uniformed Service University Corps Specific Branch Proponent
Officer, Medical Corps
Army Medical Department Center and School
Houston, TX, USA

Didier Musso, MD

Laboratory Director
Unit of Emerging Infectious Diseases
Institut Louis Malardé
Tahiti, French Polynesia

Mable Mutengo, MSc

Chief Biomedical Scientist
Department of Pathology and Microbiology
University Teaching Hospital
Lusaka, Zambia

Misha M. Mutizwa, MD

Assistant Professor, Dermatology
Director, HIV Dermatology
Temple University Hospital
Philadelphia, PA, USA

Kurt G. Naber, MD, PhD

Associate Professor of Urology
Department of Urology
Technical University of Munich
Munich, Germany

Pavithra Natarajan, BMedSci, BMBS, MCRCP, DTM&H (Hons)

Specialist Registrar in Infectious Diseases and Tropical Medicine
Tropical and Infectious Diseases Unit
Royal Liverpool Hospital
Liverpool, UK

Santiago Neme, MD, MPH

Medical Director
Infection Prevention and Employee Health Services
Northwest Hospital/UW Medicine
Clinical Instructor and Attending Physician
Division of Allergy and Infectious Diseases
Department of Medicine
University of Washington
Seattle, WA, USA

Paul N. Newton, DPhil, MRCP

Professor of Tropical Medicine, University of Oxford
Lao-Oxford-Mahosot Hospital-Wellcome Trust Research Unit
(LOMWRU)
Microbiology Laboratory
Mahosot Hospital
Vientiane
Lao PDR

Ronald A. Nichols, MD, MPH FACOG

Associate Program Director
Obstetrics and Gynecology
Department of Obstetrics and Gynecology
Beaumont Oakwood
Assistant Clinical Professor
Wayne State University School of Medicine
Dearborn, MI, USA

Lindsay E. Nicolle, MD, FRCPC

Professor
Departments of Internal Medicine and Medical Microbiology
University of Manitoba
Winnipeg, Manitoba, Canada

François Nosten, MD, PhD

Professor of Tropical Medicine
Shoklo Malaria Research Unit
Mahidol–Oxford University Research Unit
Mae Sot, Thailand

Luigi D. Notarangelo, MD

Prince Turki bin Abdul Aziz al-Saud Professor of Pediatrics
Harvard Medical School
Division of Immunology
Boston Children's Hospital
Boston, MA, USA

Thomas B. Nutman, MD

Head, Helminth Immunology Section
Head, Clinical Parasitology Section
Laboratory of Parasitic Diseases
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Bethesda, MD, USA

Paul Nyirjesy, MD

Professor of Obstetrics and Gynecology and of Medicine
Drexel University College of Medicine
Philadelphia, PA, USA

P. Ronan O'Connell, MD, FRCSI, FRCS (Glas), FRCS (Edin)

Professor of Surgery
Head, Section of Surgery and Surgical Specialties
School of Medicine and Medical Sciences
University College Dublin
Consultant Surgeon
St Vincent's University Hospital
Dublin, Ireland

Steven M. Opal, MD

Professor of Medicine
Infectious Disease Division
Alpert Medical School of Brown University
Providence, RI, USA

L. Peter Ormerod, BSc, MBChB(Hons), MD, DSc(Med), FRCP

Professor of Medicine
Chest Clinic
Blackburn Royal Infirmary
Blackburn, UK

Douglas R. Osmon, MD

Consultant
Division of Infectious Diseases
Mayo Clinic
Rochester, MN, USA

Marie Boulze Pankert, MD

Maisonneuve-Rosemont Hospital Research Center
Montreal, Québec, Canada
Département d'ophtalmologie
Université d'Aix-Marseille
Marseille, France

Giuseppe Pantaleo, MD

Chief of Service
Immunology and Allergy
Department of Medicine
Centre Hospitalier Universitaire Vaudois
Lausanne, Switzerland

Laurent Papazian, MD, PhD

Assistance Publique–Hôpitaux de Marseille
Hôpital Nord
Réanimation des Détresses Respiratoires et des Infections Sévères
Aix–Marseille Université
Marseille, France

Diane M. Parente, PharmD

Clinical Pharmacist Specialist, Infectious Diseases
The Miriam Hospital
Providence, RI, USA
Adjunct Assistant Professor
Department of Pharmacy Practice
University of Rhode Island College of Pharmacy
Kingston, RI, USA

Philippe Parola, MD, PhD

Professor of Medicine
Chief of the Acute infectious Diseases Unit
University Hospital Institute For Infectious Diseases and Tropical
Medicine, Méditerranée Infection
Aix-Marseille University
Marseille, France

Shadi Parsaei, DO

Instructor
Division of Infectious Diseases
Washington University School of Medicine in St Louis
St Louis, MO, USA

Manuel A. Pascual, MD

Chief and Professor
Transplantation Center
Medicine and Surgery
University Hospital of Lausanne (CHUV)
Lausanne, Switzerland

Rupa Patel, MD, MPH

Instructor
Department of Medicine
Washington University School of Medicine in St Louis
St Louis, MO, USA

Eleni Patrozou, MD

Research Associate
Department of Medicine
Alpert Medical School of Brown University
Providence, RI, USA

Jean-Michel Pawlotsky, MD, PhD

Professor of Medicine
Department of Virology
Henri Mondor Hospital, University of Paris-Est & INSERM U955
Créteil, France

Sharon J. Peacock, BM, FRCP, FRCPath, PhD

Professor of Clinical Microbiology
Department of Medicine
University of Cambridge
Cambridge, UK

The late Jean-Claude Pechère

Department of Microbiology and Molecular Medicine
University of Geneva
Geneva, Switzerland

Ivan Pelegrin, MD

Infectious Diseases Research Fellow
Infectious Diseases Department
Hospital Universitari de Bellvitge
Barcelona, Spain

Barry S. Peters, MBBS, MD, FRCP

Reader in Infectious Diseases
Department of Infectious Diseases
Kings College London
London, UK

Edgar J.G. Peters, MD, PhD

Internist-Specialist in Infectious Diseases and Acute Medicine
VU University Medical Center
Department of Internal Medicine
Amsterdam, The Netherlands

Jeannine M. Petersen, PhD

Research Microbiologist
Division of Vector-Borne Diseases
Centers for Disease Control and Prevention
Fort Collins, CO, USA

Lyle R. Petersen, MD, MPH

Director
Division of Vector-Borne Diseases
Centers for Disease Control and Prevention
Fort Collins, CO, USA

Vidmantas Petraitis, MD

Senior Research Associate
Transplantation-Oncology Infectious Diseases Program
Weill Cornell Medicine of Cornell University
New York, NY, USA

Luu-Ly Pham, MD

Former Senior Registrar
Hospital Practitioner
Department of Pediatrics
Bicêtre Hospital
University of Paris Sud
Paris, France

Albert Picado, DVM, MSc, PhD

Assistant Research Professor
ISGlobal, Barcelona Ctr. Int. Health Res. (CRESIB), Hospital
Clínic-Universitat de Barcelona
Barcelona, Spain

Adrian Pilatz, MD

Consultant Urologist
Department of Urology, Pediatric Urology and Andrology
Justus Liebig University, Giessen
Giessen, Germany

Benoit Pilmis, MD

Hospital Practitioner
Equipe Mobile d'Infectiologie
Service de Maladies Infectieuses et Tropicales
Hôpital Necker-Enfants Malades
Paris, France

María-Jesús Pinazo, MD

Medical Doctor
International Health
ISGlobal, Barcelona Ctr. Int. Health Res. (CRESIB), Hospital
Clínic-Universitat de Barcelona
Barcelona, Spain

Mathias W. Pletz, MD

Full Professor for Infectious Diseases
Center for Infectious Diseases and Infection Control
Jena University Hospital
Jena, Germany

Jason M. Pogue, PharmD

Clinical Pharmacist, Infectious Diseases
Department of Pharmacy Services
Sinai-Grace Hospital; Detroit Medical Center
Detroit, MI, USA

Evelyn L. Polgreen, MS

Environmental Science Consultant
Oxford, UK

Philip M. Polgreen, MD MPH

Associate Professor
Department of Internal Medicine
University of Iowa
Iowa City, IA, USA

Klara M. Posfay-Barbe, MD, MS

Professor and Head of Pediatric Infectious Diseases Unit
Department of Pediatrics
Children's Hospital of Geneva, University Hospitals of Geneva
Geneva, Switzerland

William G. Powderly, MD, FRCPI

J. William Campbell Professor of Medicine
Larry J Shapiro Director, Institute for Public Health
Co-director, Division of Infectious Diseases
Washington University in St Louis
St Louis, MO, USA

Rachel Presti, MD, PhD

Assistant Professor of Medicine
Division of Infectious Disease, Department of Medicine
Washington University School of Medicine in St Louis
St Louis, MO, USA

Guy Prod'hom, MD

Head of Bacteriology Unit
Institute of Microbiology
Lausanne University Hospital Center and University of Lausanne
Lausanne, Switzerland

Mirja Puolakkainen, MD, PhD

Adjunct Professor in Medical Microbiology
Department of Virology
University of Helsinki
Helsinki, Finland

Thomas C. Quinn, MD, MSc

Professor of Medicine and Pathology
Division of Infectious Diseases
Johns Hopkins School of Medicine
Baltimore, MD, USA

Didier Raoult, MD, PhD

Professor, Faculté de Médecine, Director of the Foundation
Mediterranean Infection Unit des Rickettsies
WHO Collaborative Center for Rickettsial Reference and Research
Marseille, France

Raymund R. Razonable, MD, FIDSA, FAST

Professor of Medicine
 Chair, Transplant Infectious Diseases
 Division of Infectious Diseases
 Department of Medicine
 William J von Liebig Center for Transplantation and Clinical
 Regeneration
 Mayo Clinic
 Rochester, MN, USA

Robert C. Read, MD, FRCP, FIDSA

Professor of Infectious Diseases
 University of Southampton Medical School
 Southampton, UK

Robert R. Redfield, MD

Professor of Medicine
 Institute of Human Virology
 University of Maryland School of Medicine
 Baltimore, MD, USA

Rob J. Rentenaar, MD, PhD

Clinical Microbiologist
 Department of Medical Microbiology
 University Medical Centre Utrecht
 Utrecht, The Netherlands

Steven J. Reynolds, MD, MPH, FRCP(C)

Senior Clinician
 National Institute of Allergy and Infectious Diseases
 National Institutes of Health
 Bethesda, MD, USA
 Associate Professor of Medicine and Epidemiology
 Division of Infectious Diseases
 Johns Hopkins University
 School of Medicine
 Baltimore, MD, USA

Camillo Ribi, MD

Associated Physician
 Department of Immunology and Allergy
 CHUV University Hospital Lausanne
 Lausanne, Switzerland

Malcolm D. Richardson, PhD, FSB, FRCPPath

Professor and Director
 Mycology Reference Centre
 University Hospital of South Manchester
 University of Manchester
 Manchester, UK

Michele L. Ritter, MD

Associate Clinical Professor of Medicine
 Division of Infectious Diseases
 Department of Medicine
 University of California
 San Diego, CA, USA

Antoine Roch, MD, PhD

Professor of Medicine
 Assistance Publique–Hôpitaux de Marseille
 Hôpital Nord
 Réanimation des Détresses Respiratoires et des Infections Sévères
 Aix–Marseille Université
 Marseille, France

Jürgen Kurt Rockstroh, MD, JKR

Professor of Medicine
 Department of Medicine I
 Bonn University Hospital
 University of Bonn
 Bonn, Germany

Amanda Rojek, BAppSci(Hons), MBBS, MSc

Medical Doctor
 Doctor of Philosophy Candidate
 Epidemic Diseases Research Group, Centre for Tropical Medicine
 and Global Health
 University of Oxford
 Oxford, UK

José R. Romero, MD, FAAP

Professor of Pediatrics
 Horace C. Cabe Endowed Chair in Infectious Diseases
 Director, Pediatric Infectious Diseases Section
 University of Arkansas for Medical Sciences and Arkansas Children's
 Hospital
 Little Rock, AR, USA

Suzan H.M. Rooijackers, PhD

Associate Professor
 Medical Microbiology
 University Medical Center Utrecht
 Utrecht, The Netherlands

Daniel Rosenbluth, MD

Tracey C. and William J. Marshall Professor of Medicine
 Division of Pulmonary and Critical Care Medicine
 Washington University School of Medicine in St Louis
 St Louis, MO, USA

Sergio D. Rosenzweig, MD, PhD

Deputy Chief, Immunology Service
 Clinical Center, NIH
 Bethesda, MD, USA

Gian Maria Rossolini, MD

Professor of Microbiology and Clinical Microbiology
 Department of Medical Biotechnologies
 University of Siena
 Siena, Italy
 Department of Experimental and Clinical Medicine
 University of Florence
 Florence, Italy
 Clinical Microbiology and Virology Unit
 Florence Careggi University Hospital
 Florence, Italy

The late Ethan Rubinstein, MD, LLB

Sellers Professor and Head
 Section of Infectious Diseases
 Faculty of Medicine, Winnipeg
 Manitoba, Canada

Greg Ryan, MB, DCH, FRCOG, FRCS

Staff Perinatologist
 Director
 Fetal Medicine Program
 Mount Sinai Hospital
 Professor
 Department of Obstetrics & Gynaecology and Medical Imaging
 Division of Maternal-Fetal Medicine
 University of Toronto
 Toronto, ON, Canada

Steven A. Safren, PhD, ABPP

Professor
Department of Psychology
University of Miami
Coral Gables, FL, USA

Vikrant V. Sahasrabudde, MBBS, MPH, DrPH

Program Director
Division of Cancer Prevention
National Cancer Institute
Rockville, MD, USA

Pekka A.I. Saikku, MD, PhD

Emeritus Professor of Microbiology
University of Oulu
Oulu, Finland

Mohammad M. Sajadi, MD

Associate Professor of Medicine
Institute of Human Virology
University of Maryland School of Medicine
Baltimore, MD, USA

Michelle R. Salvaggio, MD

Associate Professor
Infectious Diseases Section, Department of Internal Medicine
University of Oklahoma Health Sciences Center
Oklahoma City, OK, USA

Carlos A.Q. Santos, MD

Assistant Professor of Medicine
Division of Infectious Diseases
Washington University School of Medicine in St Louis
Saint Louis, MO, USA

Michael J. Satlin, MD, MS

Assistant Professor of Medicine
Department of Internal Medicine
Division of Infectious Diseases
Weill Cornell Medical College
New York, NY, USA

Anthony J. Schaeffer, MD

Chair, Department of Urology
Herman L. Kretschmer Professor of Urology
Professor in Urology
Northwestern University Feinberg School of Medicine
Chicago, IL, USA

Christoph Schimmer, MD

Consultant of Cardiac Surgery
Department of Cardiac Surgery
University of Würzburg
Würzburg, Germany

Robert T. Schooley, MD

Professor and Head
Division of Infectious Diseases
Academic Vice Chair
Department of Medicine
University of California San Diego
San Diego, CA, USA

Richard F. Schumacher, MD

ID Consultant in the Pediatric Hematology-Oncology Unit
Pediatric Infectious Diseases (DGPI)
Pediatric Hematology Oncology Unit
University Children's Hospital, Spedali Civili
Brescia, Italy

Beverly E. Sha, MD

Professor of Medicine
Division of Infectious Diseases
Rush University Medical Center
Chicago, IL, USA

Daniel S. Shapiro, MD

Professor of Internal Medicine
University of Nevada School of Medicine
Reno, NV, USA

Gerard Sheehan, MB, FRCPI

Senior Lecturer
School of Medicine and Medical Sciences
University College Dublin
Consultant in Infectious Diseases
Mater Misericordiae University Hospital
Dublin, Ireland

David M. Shlaes, MD, PhD

Retired (from Anti-infectives Consulting, LLC)
Stonington, CT, USA

Shmuel Shoham, MD

Associate Professor of Medicine
Division of Infectious Diseases
Johns Hopkins University School of Medicine
Baltimore, MD, USA

Cameron P. Simmons, PhD

Senior Research Fellow
Department of Microbiology and Immunology
University of Melbourne
Carlton, Victoria, Australia
Senior Research Fellow
Nuffield Department of Clinical Medicine
University of Oxford
Oxford, UK

Dennis W. Simon, MD

Assistant Professor
Department of Pediatrics and Critical Care Medicine
Children's Hospital of Pittsburgh of UPMC
Pittsburgh, PA, USA

Matthew S. Simon, MD, MS

Assistant Professor of Medicine
Department of Medicine
Weill Cornell Medical College
New York, NY, USA

Kari A. Simonsen, MD

Associate Professor of Pediatrics
Chief, Division of Pediatric Infectious Diseases
University of Nebraska Medical Center
Omaha, NE, USA

Mary P.E. Slack, MA, MBBChir, FRCPath

Professor
School of Medicine
Gold Coast Campus
Griffith University
Queensland, Australia

Tyrel T. Smith

Howard Hughes Med-Grad Fellow
Department of Pediatrics Infectious Diseases
University of Alabama at Birmingham School of Medicine
Birmingham, AL, USA

Jack D. Sobel, MD

Professor of Medicine
Division of Infectious Diseases
Wayne State University School of Medicine
Detroit, Michigan, USA

Maria Souli, MD

Assistant Professor of Medicine and Infectious Diseases
Fourth Department of Medicine
National and Kapodistrian University of Athens
Athens, Greece

Shruti Sridhar, MBBS, MSc, Public Health

Research Assistant
Department of Tropical Diseases
Aix-Marseille University
Marseille, France

James M. Steckelberg, MD

Professor of Medicine
Division of Infectious Diseases
Mayo Clinic College of Medicine
Rochester, MN, USA

Dennis L. Stevens, PhD, MD

Chief, Infectious Disease Section
Veterans Affairs Medical Center
Boise, ID, USA

Heather Strah, MD

Assistant Professor of Medicine
Division of Pulmonary, Critical Care, Sleep and Allergy
Department of Internal Medicine
University of Nebraska Medical Center
Omaha, NE, USA

A. Willem Sturm, MD, PhD

Emeritus Professor Medical Microbiology
Nelson R Mandela School of Medicine
University of KwaZulu-Natal
Congella, South Africa

Somnuek Sungkanuparph, MD

Professor of Medicine
Department of Medicine
Faculty of Medicine Ramathibodi Hospital
Mahidol University
Bangkok, Thailand

Sarah J. Tabrizi, BSc(Hons), FRCP, PhD

Professor of Neurology
Department of Neurodegenerative Diseases/MRC Prion Unit
Institute of Neurology
London, UK

Evelina Tacconelli, MD, PhD

Professor of Infectious Diseases
Division of Infectious Diseases, Department of Internal Medicine
University of Tübingen
Tübingen, Germany

Chen Sabrina Tan, MD

Assistant Professor of Medicine
Beth Israel Deaconess Medical Center
Harvard Medical School
Boston, MA, USA

Randy A. Taplitz, MD

Professor of Clinical Medicine
Division of Infectious Diseases
Department of Medicine
University of California
San Diego, CA, USA

Guillemette Thomas, MD

Assistance Publique–Hôpitaux de Marseille
Hôpital Nord
Réanimation des Détresses Respiratoires et des Infections Sévères
Aix–Marseille Université
Marseille, France

Lora D. Thomas, MD, MPH

Assistant Professor
Division of Infectious Diseases
Vanderbilt University School of Medicine
Nashville, TN, USA

Franck Thuny, MD, PhD

Professor of Cardiology
Head of Unit of Heart Failure and Valve Heart Diseases
Department of Cardiology, University Hospital Nord Aix–Marseille
University of Marseille
Marseille, France

Guy Thwaites

Professor of Infectious Diseases
Nuffield Department of Medicine
University of Oxford, Oxford, UK
Director
Oxford University Clinical Research Unit
Ho Chi Minh City
Vietnam

Frederic Tissot, MD

Chief Resident
Infectious Diseases Service
Centre Hospitalier Universitaire Vaudois and Lausanne University
Hospital
Lausanne, Switzerland

Tone Tønjum, MD, PhD

Professor, Chief Physician
Department of Microbiology
Oslo University Hospital
University of Oslo
Oslo, Norway

Francesca J. Torriani, MD

Professor of Clinical Medicine
Division of Infectious Diseases
Department of Medicine
University of California
San Diego, CA, USA

Christian Toso, MD, PhD

Assistant Professor
Divisions of Abdominal and Transplantation Surgery
Geneva University Hospitals and Faculty of Medicine
Geneva, Switzerland

Paul M. Tulkens, MD, PhD

Professor Emeritus
Professor Invited
Pharmacologie Cellulaire et Moléculaire
Louvain Drug Research Institute
Université Catholique de Louvain
Brussels, Belgium

Allan R. Tunkel, MD, PhD

Professor of Medicine
Associate Dean for Medical Education
Warren Alpert Medical School of Brown University
Providence, RI, USA

Claire E. Turner, PhD

Imperial College Junior Research Fellow
Department of Medicine
Imperial College London
London, UK

Andrew P. Ustianowski, FRCP, PhD

Consultant in Infectious Diseases and Tropical Medicine
NW Regional Infectious Diseases Unit
North Manchester General Hospital
Manchester, UK

Françoise van Bambeke, PharmD, PhD

Professor and Senior Research Associate
Pharmacologie Cellulaire et Moléculaire
Louvain Drug Research Institute
Université Catholique de Louvain
Brussels, Belgium

Reinout van Crevel, MD, PhD

Infectious Diseases Specialist
Department of Medicine
Radboud University Medical Centre
Nijmegen, The Netherlands

Diederik van de Beek, MD, PhD

Professor of Neurology
Department of Neurology
Academic Medical Centre
University of Amsterdam
Amsterdam, The Netherlands

Christian van Delden, MD

Associate Professor of Medicine
Service of Infectious Diseases, Department of Medical Specialties
Geneva University Hospitals and Faculty of Medicine
Geneva, Switzerland

Menno M. van der Eerden, MD, PhD

Pulmonologist
Department of Pulmonary Diseases
Erasmus Medical Center
Rotterdam, The Netherlands

Jos W.M. van der Meer, MD, PhD, FRCP, FRCP(Edin), FIDSA, MAE

Emeritus Professor of Medicine
Radboud University Medical Centre
Nijmegen, The Netherlands

Tom van der Poll, MD, PhD

Professor of Medicine
Center of Experimental and Molecular Medicine & Division of
Infectious Diseases
Academic Medical Center
University of Amsterdam
Amsterdam, The Netherlands

Jakko van Ingen, MD, PhD

Clinical Microbiology Resident
Department of Medical Microbiology
Radboud University Medical Center
Nijmegen, The Netherlands

Jos van Putten, MD, PhD

Professor of Infection Biology
Infectious Diseases and Immunology
Utrecht University
Utrecht, The Netherlands

Bernard P. Vaudaux, MD

Former Head, Unit of Pediatric Infectious Diseases and Vaccinology
Department of Pediatrics
Centre Hospitalier Universitaire Vaudois and Hôpital de l'Enfance
de Lausanne
Lausanne, Switzerland

Sten H. Vermund, MD, PhD

Assistant Vice Chancellor for Global Health
Amos Christie Chair and Professor of Pediatrics
Department of Pediatrics and Vanderbilt Institute for Global Health
Vanderbilt University School of Medicine
Nashville, TN, USA

Raphael P. Viscidi, MD

Professor of Pediatrics
Pediatrics
Johns Hopkins University School of Medicine
Baltimore, MD, USA

Kumar Visvanathan, MBBS, PhD

Professor of Medicine
University of Melbourne
ID Physician and Clinical Director
St Vincent's Hospital
Fitzroy, Victoria, Australia

Govinda S. Visvesvara, PhD

Microbiologist
National Center for Emerging and Zoonotic Infectious Diseases
Centers for Disease Control and Prevention
Atlanta, GA, USA

Lorenz von Seidlein, MD, PhD

Project Coordinator
Mahidol-Oxford Tropical Medicine Research Unit (MORU)
Faculty of Tropical Medicine
Mahidol University
Bangkok, Thailand

Florian M.E. Wagenlehner, MD

Professor of Urology
Clinic for Urology, Pediatric Urology and Andrology
Justus-Liebig-University Giessen
Giessen, Germany

Anna Wald, MD, MPH

Professor
Department of Medicine, Epidemiology, and Laboratory Medicine
University of Washington
Member, Vaccines and Infectious Diseases Division
Fred Hutchinson Cancer Research Center
Seattle, WA, USA

Thomas J. Walsh, MD, PhD (hon), FAAM, FIDSA

Director, Transplantation-Oncology Infectious Diseases Program
Professor of Medicine, Pediatrics, and Microbiology & Immunology
Weill Cornell Medicine of Cornell University
New York, NY

David C. Warhurst, BSc, PhD, DSc

Emeritus Professor of Protozoan Chemotherapy
Department of Pathogen Molecular Biology
London School of Hygiene & Tropical Medicine
London, UK

David W. Warnock, BSc, PhD, FAAM, FRCPath

Honorary Professor of Medical Mycology
Faculty of Medical and Human Sciences
University of Manchester
Manchester, UK

David A. Warrell, DM, DSc, FRCP, FRCPE, FMedSci

International Director (Hans Sloane Fellow), Royal College of Physicians, London, UK
Emeritus Professor of Tropical Medicine, Nuffield Department of Clinical Medicine and Honorary Fellow of St Cross College, University of Oxford, Oxford, UK
Principal Fellow, Australian Venom Research Unit, Department of Pharmacology and Therapeutics, University of Melbourne, Melbourne, Australia
International Advisor, Australian DFAT Myanmar Snake-Bite Project, University of Adelaide, Adelaide, Australia

Mary J. Warrell, MB, BS, FRCP, FRCPath

Honorary Senior Researcher
Oxford Vaccine Group
Centre for Clinical Vaccinology & Tropical Medicine
University of Oxford
Oxford, UK

Adilia Warris, MD, PhD

Professor of Paediatric Infectious Diseases
Institute of Medical Sciences
University of Aberdeen
Aberdeen, UK

Richard R. Watkins, MD, MS, FACP

Associate Professor of Internal Medicine
Northeast Ohio Medical University
Rootstown, OH, USA
Division of Infectious Diseases
Akron General Medical Center
Akron, OH, USA

David J. Weatherall, MD, FRCP, FRS

Regius Professor Emeritus
Weatherall Institute of Molecular Medicine
University of Oxford
Oxford, UK

Rainer Weber, MD

Professor of Infectious Diseases
Division of Infectious Diseases and Hospital Epidemiology
University Hospital
Zurich, Switzerland

Wolfgang Weidner, MD, PhD

Professor of Urology
Clinic for Urology, Pediatric Urology and Andrology
Justus-Liebig University Giessen
Giessen, Germany

Jonathan R. White, MBChB, MRCP

Clinical Research Fellow in Gastroenterology
NIHR Biomedical Research Unit in Gastrointestinal and Liver Diseases
Nottingham University Hospitals NHS Trust
University of Nottingham, Queen's Medical Centre
Nottingham, UK

Peter J. White, PhD

Head, Modelling and Economics Unit
Public Health England Centre for Infectious Disease Surveillance and Control, London, UK
MRC Centre for Outbreak Analysis and Modelling and NIHR HPRU in Modelling Methodology
Department of Infectious Disease Epidemiology
Imperial College London
London, UK

James Whitehorn, PhD, MRCP

Research Fellow
Department of Clinical Research
London School of Hygiene and Tropical Medicine
London, UK
Oxford University Clinical Research Unit Vietnam
Oxford, UK

Richard J. Whitley, MD

Distinguished Professor
Loeb Chair in Pediatrics
Professor of Pediatrics, Microbiology,
Medicine and Neurosurgery
University of Alabama
Birmingham, AL, USA

Christopher J.M. Whitty, FRCP, DTM&H

Consultant Physician
The Hospital for Tropical Diseases
Professor of International Health
London School of Hygiene & Tropical Medicine
London, UK

Willem Joost Wiersinga

Consultant, Internal Medicine and Infectious Diseases
Principal Investigator
Department of Medicine
Division of Infectious Diseases and Center for Experimental Molecular Medicine (CEMM)
Academic Medical Center
University of Amsterdam
Amsterdam, The Netherlands

Mark H. Wilcox, BMedSci, BM, BS, MD, FRCPath

Consultant and Professor of Medical Microbiology
Department of Microbiology
Leeds Teaching Hospitals
University of Leeds & Public Health England
Leeds, UK

Thomas N. Williams, MBBS, MRCP, PhD

Professor of Haemoglobinopathy Research
Department of Medicine
Imperial College,
London, UK

Cara C. Wilson, MD

Professor
Infectious Diseases Division
University of Colorado School of Medicine
Denver, CO, USA

Mary Elizabeth Wilson, MD

Adjunct Professor
Global Health and Population
Harvard T.H. Chan School of Public Health
Boston, MA, USA
Visiting Professor of Epidemiology and Biostatistics
School of Medicine
University of California San Francisco
San Francisco, CA, USA

Hilmar Wisplinghoff, MD

Physician
Institute for Medical Microbiology, Immunology and Hygiene
University of Cologne
Cologne, Germany

Robin Wood, MD, DSC (Med)

Emeritus Professor of Medicine
Desmond Tutu HIV Centre
Institute of Infectious Disease & Molecular Medicine and
Department of Medicine
University of Cape Town
Cape Town, South Africa

Richard G. Wunderink, MD

Professor of Medicine
Division of Pulmonary and Critical Care
Northwestern University Feinberg School of Medicine
Chicago, IL, USA

David Wyles, MD

Associate Professor of Medicine
Division of Infectious Diseases
University of California San Diego
San Diego, CA, USA

Zhi-Tao Yang, MD, PhD

Doctor in Charge of ICU
Emergency Department/Pôle Sino-Français de Recherches en Science
du Vivant et Génomique
Ruijin Hospital
Shanghai Jiaotong University, School of Medicine
Shanghai, China

Jonathan S. Yoder, MSW, MPH

Water Preparedness and Response Coordinator
National Center for Emerging and Zoonotic Infectious Diseases
Centers for Disease Control and Prevention
Atlanta, GA, USA

Najam A. Zaidi, MD, FACP, FIDSA

Consulting Infectious Disease Attending
Division of Infectious Disease
Roger Williams Medical Center
Providence, RI, USA
Medical Director
Infection Control and Antibiotic Stewardship
St Luke's Hospital
New Bedford, MA, USA
Assistant Professor of Medicine (Clinical)
Warren Alpert School of Medicine
Brown University
Providence, RI, USA

Andrea J. Zimmer, MD

Assistant Professor of Medicine
Department of Medicine, Division of Infectious Diseases
University of Nebraska Medical Center
Omaha, NE, USA

Jane N. Zuckerman, MD, FRCP, FRCPath, FFPH, FFTM

Consultant in Travel Medicine
Department of Infection
Royal Free London NHS Foundation Trust
Honorary Senior Lecturer
Department of Infection
University College London
London, UK

Alimuddin Zumla, GCDS, FRCP(Lond), FRCP(Edin), FRCPath(UK), PhD(Lond), FSB(UK)

Professor of Infectious Diseases and International Health
Division of Infection and Immunity
University College London
Consultant Infectious Diseases Physician
University College London Hospitals NHS Foundation Trust
London, UK

We dedicate this work to our teachers, who inspired and encouraged us; our students for their enthusiasm and new ideas; and our families for putting up with us for all these years.

The Evolution of Koch's Postulates

JONATHAN COHEN

KEY CONCEPTS

- Robert Koch developed his famous postulates as a way of trying to bring some order and scientific rigor into the debate surrounding the microbial cause of disease.
- Although his ideas were helpful, even Koch himself recognized the limitations of his approach. These limitations became even more apparent with the emergence of clinical virology as a discipline. Viruses proved to be particularly challenging to fit in to Koch's structures.
- The emergence in the 1980s of the field of the molecular pathogenesis of microbial disease created new challenges, and led to the idea of 'molecular' Koch's postulates.
- Finally, it was recognized that Koch's postulates were not helpful when thinking about immunocompromised patients, or in those cases where infection played an 'indirect' role, such as in the pathogenesis of cancer.
- Today, Koch's postulates are primarily of historical interest although they continue to provide a useful framework in which to consider the pathogenesis of disease.

Introduction

At one time diseases were thought to be caused by the wrath of the gods, configuration of the stars or miasmas.¹ It was not until the latter part of the 19th century that micro-organisms began to be accepted – at least by some scientists – as the cause of infectious diseases, and it was then that Robert Koch developed his famous principles (postulates) as a way of trying to bring some order and scientific rigor into what had become a sometimes difficult debate. Since that time Koch's postulates have achieved almost totemic significance in biology and medicine, yet it became clear very quickly that they had serious limitations. This chapter discusses what role they play, if any, in understanding the modern world of infection.

A Historical Perspective

In 1840 the German anatomist Friedrich Henle wrote a paper considering what would be required to confidently attribute causation to micro-organisms that had been associated with various infectious diseases (for a detailed account of the historical background see [reference 2](#)). Robert Koch entered medical school at the University of Göttingen in 1862 and came to know Henle well, but it was not until 1882 that Koch formulated what have come to be known as Koch's postulates, or sometimes as Henle–Koch's postulates. Koch was working at a time that has been called the 'bacteriological revolution' of 19th century medicine, although some historians have challenged this.³ What is certainly true is that during the latter part of the 19th century there was an explosion of knowledge about micro-organisms and, of course, Koch himself was pivotal in demonstrating the microbial etiology of tuberculosis and anthrax. But it was not always easy to persuade detractors, and he hoped that these principles, presented to a scientific meeting in Berlin in 1890, would bring some order into the debate ([Box 1-1](#)).

Koch's ideas undoubtedly helped, but as we shall see, even Koch himself recognized the limitations of his approach. These limitations became even more apparent as the new century dawned and with it

the emergence of clinical virology as a discipline. Viruses proved to be particularly challenging to fit into Koch's structures and a number of writers, notably Thomas Rivers¹ and Robert Huebner,⁴ developed alternative paradigms to try to get round the problem. By the 1970s the problems had multiplied, not least because of the discovery of 'slow viruses' and the recognition of the possible role of micro-organisms in some chronic diseases. The British writer Alfred Evans revised the original Koch's postulates, and Evans' ideas remain useful⁵ ([Box 1-2](#)).

The advent of molecular microbiology allowed not only the identification of micro-organisms without the requirement for their cultivation on solid media, but also the notion that 'virulence' and 'pathogenicity' could be attributed to certain microbial genes or gene

BOX 1-1 KOCH'S POSTULATES

Based on Koch's presentation to the Tenth International Congress of Medicine in Berlin, 1890.

1. The parasite occurs in every case of the disease in question and under circumstances which can account for the pathological changes and clinical course of the disease.
2. The parasite occurs in no other disease as a fortuitous and nonpathogenic parasite.
3. After being fully isolated from the body and repeatedly grown in pure culture, the parasite can induce the disease anew.
4. The parasite can be re-isolated from an experimentally inoculated host.*

*The fourth postulate was in fact added by later writers.

BOX 1-2 EVANS' PRINCIPLES OF THE CAUSATION OF DISEASE, 1976⁵

Based on the original Koch's postulates, Evans' principles were important because they incorporated both the epidemiological principles first developed by Sir Austin Bradford Hill, and also the immunological notion of a specific host response as providing evidence that an organism was contributing to the cause of a disease.

- Prevalence of the disease should be significantly higher in those exposed to the putative cause than in control cases not so exposed.
- Exposure to the putative cause should be present more commonly in those with the disease than in controls without the disease when all risk factors are held constant.
- Incidence of the disease should be significantly higher in those exposed to the putative cause than in those not exposed, as shown in prospective studies.
- Temporally, the disease should follow exposure to the putative agent with a distribution of incubation periods on a bell-shaped curve.
- A spectrum of host responses should follow exposure to the putative agent along a logical biologic gradient from mild to severe.
- A measurable host response following exposure to the putative cause should regularly appear in those lacking this before exposure or should increase in magnitude if present before exposure.
- Experimental reproduction of the disease should occur in higher incidence in animals or humans appropriately exposed to the putative cause than in those not so exposed; this exposure may be deliberate in volunteers, experimentally induced in the laboratory, or demonstrated in a controlled regulation of natural exposure.
- Elimination or modification of the putative cause or of the vector carrying it should decrease the incidence of the disease.
- Prevention or modification of the host's response on exposure to the putative cause should decrease or eliminate the disease (e.g., immunization or drug).
- The whole thing should make biologic and epidemiologic sense.

TABLE
1-1**The Growing List of Situations in Which It Has Become Difficult or Impossible to Apply Koch's Postulates as Originally Conceived, Despite Very Clear Evidence for Causation**

Colonization vs carrier state vs infection	<i>Candida albicans</i> ; <i>Neisseria meningitidis</i>
Inability to isolate the organism in pure culture	<i>Mycobacterium leprae</i>
Inability to isolate the organism in cell-free culture	<i>Plasmodium falciparum</i>
Organisms for which humans are the only host	Herpes simplex virus
Subclinical infection	<i>Mycobacterium tuberculosis</i>
Organisms that cause 'distant' infection	<i>Streptococcus pyogenes</i> /rheumatic fever; measles virus/SSPE
Disease caused by toxins	<i>Staphylococcus aureus</i> /toxic shock syndrome
Diseases that require coinfection	Hepatitis D virus/hepatitis B virus <i>Wucheria</i> and <i>Wolbachia</i> endosymbionts (filariasis)
Organisms associated with tumors	EBV (Burkitt lymphoma); HHV-8 (Kaposi's sarcoma); <i>Helicobacter pylori</i> (gastric cancer)
Bacteria that require phage DNA to acquire virulence	<i>Corynebacterium diphtheriae</i>
Organisms identified only by molecular probes	<i>Tropheryma whipplei</i> (Whipple's disease) (subsequently successfully cultivated)

EBV, Epstein-Barr virus; HHV-8, human herpesvirus 8; SSPE, subacute sclerosing panencephalitis.

families. Falkow's paper in 1988 on 'molecular Koch's postulates' was an attempt to reconcile 20th century science with 19th century deterministic principles,⁶ and this debate has continued.^{2,7}

Limitations of Koch's Postulates

It became apparent almost immediately that there were instances where causation was very likely but the postulates could not be made to 'fit' the evidence. Koch himself believed *Vibrio cholerae* to be the cause of cholera, but because the organism had also been isolated from otherwise healthy carriers his second principle was breached. As time passed, more and more examples emerged that stretched the utility of Koch's postulates right up to – and indeed beyond – the limit of plausibility (Table 1-1).

As others have observed, the problem with Koch's postulates is not that they are wrong, but rather, that they apply only to a very limited number of circumstances. The rapid growth in microbiology led to the recognition not only of many more bacterial species, but crucially, to the discovery of the role that viruses play in human disease. As Huebner trenchantly commented in 1957:

*it is quite obvious that the clinician seldom if ever knows that the illness he describes actually is caused by a virus or, if so, what virus is implicated. Similarly, the virologist reporting new and prevalent agents very often has only slightly more information and, usually, no greater certainty about the clinical behavior and importance of his viruses than does the clinician.*⁴

The problems remain, and are well illustrated by the difficulties in understanding what role, if any, a newly identified virus such as bocavirus might have in causing disease.⁸

Pari passu with the growth of diagnostic microbiology came an explosive growth in the understanding of pathogenesis of microbial disease, the concepts of the carrier state and of colonization, of coinfection and the notion that micro-organisms could cause 'distant' disease. Nowadays we accept that *Streptococcus pyogenes* is the primary cause of rheumatic fever, that Reiter's syndrome can follow an episode of shigellosis, that hepatitis virus can be the antigen of cryoglobulinemia, or that Brill-Zinsser disease is a late complication of rickettsial infection, but these examples completely overturn the classical concept of an 'infectious disease'. Tumor viruses pose similar challenges. Unequivocal evidence now exists implicating Epstein-Barr virus (EBV) in the pathogenesis of Burkitt lymphoma, of hepatitis B in hepatoma, and of KSHV (Kaposi's sarcoma-associated herpesvirus, or human herpesvirus 8 [HHV-8]) in Kaposi's sarcoma and multicentric Castleman's disease (MCD). Yet Koch's postulates are completely unsuited to proving causality in these situations,⁹ and indeed if we had

BOX 1-3 'MOLECULAR' KOCH'S POSTULATES

An attempt to update the original concepts to create a framework that would allow the identification of genes associated with bacterial virulence.⁶

- The phenotype or property under investigation should be associated with pathogenic members of a genus or pathogenic strains of a species.
- Specific inactivation of the gene(s) associated with the suspected virulence trait should lead to a measurable loss in pathogenicity or virulence, or the gene(s) associated with the supposed virulence trait should be isolated by molecular methods. Specific inactivation or deletion of the gene(s) should lead to loss of function in the clone.
- Reversion or allelic replacement of the mutated gene should lead to restoration of pathogenicity, or the replacement of the modified gene(s) for its allelic counterpart in the strain of origin should lead to loss of function and loss of pathogenicity or virulence. Restoration of pathogenicity should accompany the reintroduction of the wild-type gene(s).

relied on them we would not have been in the position of being certain that human papillomaviruses were implicated in the cause of cervical cancer and we would not today have an effective vaccine against this disease.

Finally, Koch's postulates are not helpful when it comes to ascribing causality in immunocompromised patients. We know that recognized organisms of very low virulence¹⁰ or even entirely unknown bacteria¹¹ can cause clinically significant disease in heavily immunocompromised individuals even though they would certainly not fulfil Koch's criteria.

Virulence, Pathogenicity and Causation

The emergence in the 1980s of the field of the molecular pathogenesis of microbial disease created new challenges, and led to Falkow developing the idea of 'molecular' Koch's postulates⁶ (Box 1-3). At that early stage it seemed reasonable to suppose that it would be possible to identify single genes that conferred virulence to an organism, and the updated postulates were designed to help identify where this could be safely imputed from the data. The subsequent explosion of our knowledge has led to a much more complex picture: we now have complete genome sequences for a large number of important human pathogens, we understand that there are groups, or islands of genes associated with pathogenicity, and we have new experimental models such as the zebra fish or the fruit fly in which to study molecular virulence factors.⁷ A detailed discussion of the concepts of virulence, pathogenesis and

causation is beyond the scope of this chapter and suffice it to say they are not identical. But as an example, consider a strain of *Staphylococcus aureus* containing TSST-1, the gene for toxic shock syndrome toxin. This same strain might be found as a harmless commensal in the nose, or causing a simple superficial skin abscess, as a destructive lesion of the aortic valve in a patient with endocarditis or associated with a fulminating toxic shock syndrome. TSST-1 is certainly a 'virulence gene' but it is probably only contributing to the disease in the last of these scenarios.

Beyond Infection: Micro-organisms and Chronic Disease

We have already noted conditions such as rheumatic fever or Reiter's disease in which micro-organisms are clearly implicated, and also several malignancies that are either directly or indirectly caused by tumor viruses. But beyond these relatively clear-cut cases lies a huge range of conditions in which micro-organisms have been implicated, usually on the basis of either epidemiological evidence (be that serological or based on prevalence data) or histopathological findings (Table 1-2). The subject was reviewed exhaustively in a 2004 Institute of Medicine report¹² and again more recently in a paper that used published data and aligned these with Koch's and Hill's criteria to gauge the level of evidence supporting a role for micro-organisms in chronic diseases.¹³ They concluded that there was reasonably strong evidence to implicate five organisms (HIV, hepatitis B, hepatitis C, *Helicobacter pylori* and *Chlamydia pneumoniae*) in as many as 37 different chronic conditions.

Most recently, scientists have begun to consider the huge biomass of bacteria in the human gut and have developed the idea of the gut microbiota and the influence that these organisms can have on conditions as diverse as allergies, irritable bowel disease, Crohn's disease and even obesity.¹⁴ With a pleasing circularity, Zhao has recently used Koch's postulates to discuss how we might try to identify causality in this very difficult area.¹⁵

Conclusions – and a Note of Caution

Koch's postulates were invaluable at the time they were developed and remain largely valid for a relatively small number of defined

TABLE
1-2

Examples of Chronic Diseases in Which Micro-organisms Have Been Implicated in the Cause

Disease	Suggested Causative Organisms
Kawasaki disease	Unknown (multiple candidates: EBV; <i>Mycoplasma pneumoniae</i> ; VZV; adenoviruses)
Kikuchi's disease	Unknown (multiple viral candidates)
Crohn's disease	<i>Mycobacterium paratuberculosis</i>
Acne	<i>Propionibacterium acnes</i>
Sarcoidosis	Mycobacteria; <i>P. acnes</i> ; herpesviruses
Type I diabetes mellitus	Enteroviruses
Schizophrenia	Endogenous retroviruses
Multiple sclerosis	Measles (and many other viruses)
Atherosclerosis	<i>Chlamydia pneumoniae</i> ; CMV
Chronic fatigue syndrome	<i>Borrelia burgdorferi</i> ('chronic neuroborreliosis'); <i>Candida albicans</i> ('Candida syndrome'); EBV; XMRV

*Note that in none of these cases has causation been proved, and in most the association is tenuous at best. The list is intended simply to demonstrate the wide range of diseases and potential causes, and is not exhaustive.

CMV, cytomegalovirus; EBV, Epstein-Barr virus; VZV, varicella-zoster virus; XMRV, xenotropic murine leukemia virus-related-virus.

circumstances in which bacteria can be precisely tied to the cause of a particular clinical syndrome. But in a world in which viruses cause cancer and noncultivable bacteria can be demonstrated by molecular probes, Koch's postulates are no longer fit for purpose. What is more, used uncritically they have the potential to mislead.¹⁶ Their main purpose now is to provide a framework to ensure that scientific rigor is applied when proposing an organism as the cause of a disease – exactly as Koch intended when he first conceived them.

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Nature and Pathogenicity of Micro-organisms

JOSHUA FIERER | DAVID LOONEY | JEAN-CLAUDE PECHÈRE†

KEY CONCEPTS

- Micro-organisms and higher organisms have evolved together and interact in complex ways. Only a small percentage of microbes are inherently pathogenic.
- Pathogenicity, the ability of infectious agents to cause disease, must be interpreted in the context of the properties of both transmissible agent and host.
- Understanding this interplay is important to developing methods to prevent infection and reduce the severity of disease.
- The initial step in infection is usually adherence, mediated by the interaction of surface structures on the pathogen with host cell membrane proteins or carbohydrates. This often presents excellent targets for immunity.
- Intracellular pathogens have evolved methods to neutralize the cellular defenses that can destroy invaders.

Introduction

The micro-organisms that surround us play roles critical to human existence, through processes as diverse as photosynthesis, nitrogen fixation, production of vitamins in the intestine, and decomposition of organic matter. They are a major driving force behind evolution, providing organelles for photosynthesis and respiration in present-day eukaryotes, and facilitating genome rearrangement in infected host cells. The lifestyle of a micro-organism is intimately related to its environment, be it the human body or a polluted riverbed. Some highly specialized micro-organisms can survive in harsh environmental conditions, while others, such as root-colonizing bacteria and our own intestinal flora, take advantage of the abundant resources provided by higher organisms.

THE NORMAL MICROBIAL FLORA OF THE HUMAN HOST

The fetus normally starts acquiring its indigenous microflora from its mother during vaginal delivery and nursing. The human body can be thought of as an ecosystem for microbes. Each part of the body exposed to the outside environment has its own characteristic mixture of microbes. The microbial population is especially dense in the large intestine, where each gram of stool contains $\sim 10^{12}$ bacteria. The normal flora is well adapted to its niche and forms a complex, metabolically interacting community. Although age, diet and exogenous factors such as antibiotic treatment may induce important variations, the microbial population of the gastrointestinal tract seems to be stable in each individual. The fecal flora is much more diverse in vegetarians than in omnivores or carnivores, probably reflecting the difficulty of digesting complex carbohydrates found in plants. Facultative anaerobes such as *Escherichia coli*, which are frequently used as markers for environmental pollution with human feces, represent less than 1% of the normal flora.

†Deceased

Our intimate symbiosis with microbes is often peaceful and mutually beneficial (mutualism), as when bacteria shelter in the intestine and in turn supply vitamins, aid in digesting endogenous or exogenous carbohydrates, assist in maintaining oral tolerance and the development of the innate immune system.¹ Alternatively, if the micro-organism benefits while the host is indifferent, the relationship (and organism) is termed commensal. Parasitism occurs when the invading organisms produce harm to the host.

This chapter focuses on the lifestyle of pathogenic micro-organisms and how they infect us, reproduce and cause disease. We shall use the word ‘pathogenicity’ to indicate the capacity to cause disease (or damage) in nonimmune individuals. Although the word ‘virulence’ is often used in the same sense, we mean it to refer to the severity of the illness that is caused. Communicability refers to the transmissibility or infectiousness of micro-organisms.

Definition and Comparison of Infectious Agents

The definition of an ‘infectious agent’ was proposed by Jacob Henle in 1840 and refined by Robert Koch. In 1876, Koch reported experiments on mice with *Bacillus anthracis* showing that:

- *B. anthracis* could be isolated from all animals suffering from naturally occurring anthrax;
- disease could be reproduced in an experimental host by infection with a pure culture of this *B. anthracis*;
- *B. anthracis* could subsequently be re-isolated from the experimental host.

As discussed in more detail in Chapter 1, this definition of a pathogen is correct but inadequate because many pathogenic microbes have never been cultured (e.g. *Mycobacterium leprae* and *Treponema pallidum*), others lack a suitable animal host in which the infection can be reproduced (e.g. *Salmonella enterica* serovar Typhi), and some microbes cause disease only under specific conditions that may not be reproducible in experimental animals (e.g. varicella-zoster virus).

Infectious agents can be divided into four groups:

- Prions, which consist of only a single protein (PrP). The infectious form (PrP^{TSE})² is transmissible as spongiform encephalopathy (see Chapter 23).
- Viruses, which contain proteins, lipids and nucleic acids. Virioids consist of only nucleic acid. These organisms characteristically disassemble after cell entry and then assemble their progeny during replication³ (see Chapters 162 to 175).
- Bacteria, including archaea and eubacteria. Unlike eukaryotes, the DNA genomes of prokaryotes are not separated from the cell by a membrane. Unlike viruses, they remain enclosed within their own cell envelope throughout their life cycle (see Chapters 176 to 188).
- Eukaryotes, including fungi (see Chapters 189 and 190), protozoa (see Chapters 191 to 194) and multicellular parasites (see Chapter 195). These organisms have subcellular compartments, including the nucleus.

Table 2-1 compares the properties that define prokaryotes with eukaryotes and Table 2-2 emphasizes the differences between bacteria

TABLE 2-1 Comparison of Prokaryotes and Eukaryotes

Feature	Prokaryotes	Eukaryotes
Chromosome	Single, circular or linear	Yes
Gene organization	Operon-polycistronic mRNA	Single genes and block of genes
Nucleosomes	No	Yes
Nuclear membrane	No	Yes
Mitosis	No	Yes
Introns in genes	No	Yes
Transcription	Coupled with translation	Separate from translation
mRNA	No terminal polyadenylation (except archaeobacteria); polygenic	Terminal polyadenylation; usually monogenic
First amino acid	Unstable formylmethionine (except archaeobacteria)	Methionine
Ribosome	70S (30S + 50S)	80S (40S + 60S)
Cell wall	Presence of muramic acid, D-amino acids, peptidoglycan (except archaeobacteria and mycoplasma)	No muramic acid, D-amino acids or peptidoglycan
Membrane	No sterols or phosphatidyl-choline (except mycoplasma)	Sterols and phosphatidyl-choline
Endoplasmic reticulum	No	Yes
Mitochondria	No	Yes (<i>Entamoeba histolytica</i> , <i>Giardia</i> and microsporidia have vestigial remnants of mitochondria)
Lysosomes and peroxisomes	No	Yes
Movement	By flagella, composed of a single fiber	Ameboid, by cilia or cilia-like flagella

TABLE 2-2 Comparison of Bacteria and Fungi

Characteristics	Bacteria	Fungi
Cell volume (μL)	0.6–5.0	Yeast: 20–50; molds: greater than yeast
Nucleus	No membrane	Membrane
Mitochondria	No	Yes
Endoplasmic reticulum	No	Yes
Sterol in cytoplasmic membrane	No (except for mycoplasma)	Yes
Cell wall components	Muramic acids and teichoic acids; no chitin, glucans or mannans	Chitin, glucans and mannans; no muramic acids or teichoic acids
Metabolism	Autotrophic or heterotrophic	Heterotrophic
Sensitivity to polyenes	No	Yes

Adapted from Kobayashi G.S.: *Fungi*. In: Davis B.D., Dulbecco R., Elsen H.N., Ginsberg H.S., ed. *Microbiology*, 4th ed. Philadelphia: JB Lippincott; 1990:737–765.

and fungi, many of which determine the specificity of antimicrobial agents.

General Properties and Classification of Viruses

TAXONOMY OF VIRUSES

Viruses are classified into families (-viridae), genera (-virus or -viruses) and species (-virus), based on the type (DNA or RNA) and nature (single-stranded or double-stranded, segmented or nonsegmented) of genetic material, and structural features⁴ (size, symmetry and presence or absence of a lipid envelope; Table 2-3). For example, Picornaviridae

is a family of small, non-enveloped RNA viruses containing the *Enterovirus* genus, which in turn includes poliovirus species of serotypes 1, 2 and 3.⁵ Other schemes emphasize the relationship of the genetic material of the virus and the viral replication scheme.⁶ For example, Baltimore group IV contains viruses with single-stranded (ss) RNA genomes where the mRNA shares the same sense as the viral RNA (+ssRNA), including the Picornaviridae, enteroviruses and poliovirus.

COMMON STEPS IN VIRAL REPLICATION

Virus replication involves the following steps:

1. Attachment: Virus particles (virions) attach to specific receptor(s) on the surface of a host cell.
2. Entry: Virions fuse to the outer cell membrane or are endocytosed and fuse to endosomal membranes at reduced pH.
3. Uncoating and transport: The virion disassembles, freeing its nucleic acid and proteins, which are transported into the cytoplasm and/or nucleus.
4. Transcription and translation: Viral RNA and proteins are expressed. Intermediates such as viral complementary RNA or integrated proviral DNA may be involved.
5. Assembly and release: New virions are formed and released from the cell via lysis, or budding from surface or internal membranes.

STRUCTURE OF VIRUSES

Virions serve to protect the viral genome and facilitate infection of new host cells. The smallest viruses are only 25–30 nm in diameter, while the largest (e.g. mimivirus, an infectious agent of amoebae) are 400 nm or more in size.⁷ The viral genome is tightly associated with nucleoprotein(s) in a highly organized core structure, the nucleocapsid. In some virus families, such as negative-strand RNA viruses and retroviruses, the virion contains enzymes required for early steps in virus replication. The viral capsid or tegument comprises the outer proteinaceous covering. Some viruses have a surrounding outer lipid layer (the envelope) derived from host cell membranes during budding. Clefs, vertices, or spikes in the capsid or proteins inserted into the envelope layer serve to attach to host receptor molecule(s).⁸

TABLE 2-3
Classification of Viruses

Family Name	Example	Genome Size (kb), Polarity (+ or -) and Segments	Morphology	Envelope
DNA VIRUSES				
Single-stranded (Class II)				
Parvoviridae	Human parvovirus B19	5 (±) single	Icosahedral	No
Mixed-stranded (Class VII)				
Hepadnaviridae	Hepatitis B	3 (±) single	Icosahedral	Yes
Double-stranded (Class I)				
Papovaviridae	Wart virus	8 (±) single	Icosahedral	No
Polyomaviridae	JC virus	5 (±) single	Icosahedral	No
Adenoviridae	Adenovirus	36–38 (±) single	Icosahedral	No
Herpesviridae	Herpes simplex	120–220 (±) single	Icosahedral	Yes
Poxviridae	Vaccinia	120–280 (±) single	Complex	Yes
RNA VIRUSES				
Positive-sense (Class IV)				
Picornaviridae	Poliovirus	7.2–8.4 (+) single	Icosahedral	No
Togaviridae	Rubella	12 (+) single	Icosahedral	Yes
Flaviviridae	Yellow fever	10 (+) single	Icosahedral	Yes
Coronaviridae	Infectious bronchitis	16–21 (+) single	Helical	Yes
Negative-sense (Class V)				
Rhabdoviridae	Rabies	13–16 (-) single	Helical	Yes
Paramyxoviridae	Measles	16–20 (-) single	Helical	Yes
Orthomyxoviridae	Influenza	14 (-) 8	Helical	Yes
Bunyaviridae	California encephalitis	13–21 (-) 3	Helical	Yes
Arenaviridae	Lassa fever	10–14 (-) 2	Helical	Yes
Filoviridae	Marburg, Ebola	19 (-) single	Helical	Yes
Reverse (Class VI)				
Retroviridae	HIV-1	3–9 (+) diploid	Icosahedral	Yes
Double-stranded (Class III)				
Reoviridae	Rotavirus	16–27 (±) 10–12	Icosahedral	No

The Viral Genome

Viral genomes usually consist of either DNA or RNA, though some contain both: Cytomegalovirus (CMV) virions include viral RNAs that promote infectivity and human immunodeficiency virus (HIV) virions include partially reverse transcribed DNA.⁹ Genomes range from 1.7 kb to 1.2 Mb in size, and may encode only a single gene, or hundreds. For example, Parvoviridae have only two open reading frames, whereas the vaccinia poxvirus has 263 known genes. Genomes may be linear or circular, segmented or nonsegmented. Genome segmentation facilitates genetic exchange between coinfecting virions in a process known as reassortment. Many viral nucleic acids contain modified nucleotides, which inhibit host cell nucleases and/or mediate recognition by viral polymerase. Linear genomes often contain conserved terminal sequences. When complementary, these allow partial circularization of the genome via formation of panhandle or tube-like structures. Terminal sequences may also allow incomplete replication products to recombine or mediate recognition by proteins that prime transcription or replication. Retroviral proviral DNA is flanked by repeat sequences similar to those of transposable genetic elements.

The viral RNA (vRNA) of positive-strand RNA viruses acts directly as mRNA for protein synthesis; they resemble eukaryotic RNAs with a cap at the 5' end and are polyadenylated (poly-A) at the 3' end. In

contrast, the RNA-dependent RNA polymerase of (-)ssRNA viruses uses vRNA as a template for mRNA transcription. Negative-strand RNA genomes may lack cap structures and poly-A tails, often parasitizing cap structures from cellular pre-mRNA or mRNA. Retroviruses synthesize a dsDNA copy of the positive-strand RNA genome, which then integrates into cellular DNA.

The Capsid

The viral genome is protected by one or more protein coats, the nucleocapsid and/or capsid. The capsid is made of viral protein structures known as capsomeres, accounting for a large portion of the viral mass. Papillomavirus produces only two capsid proteins and poliovirus four, but more complex viruses may encode a larger variety.

Picornaviruses, adenoviruses and papovaviruses have a nucleocapsid structure with icosahedral symmetry (each capsid consists of 20 triangular facets and 12 apices). Influenza, measles and rabies virus form capsids with helical or cylindrical symmetry. The central core is formed by the nucleic acid genome, around which the nucleocapsid proteins are arranged like the steps of a spiral staircase (Figure 2-1).

More complex virion morphologies also exist. Bacteriophages, viruses that infect bacteria, have complex attachment structures fixed

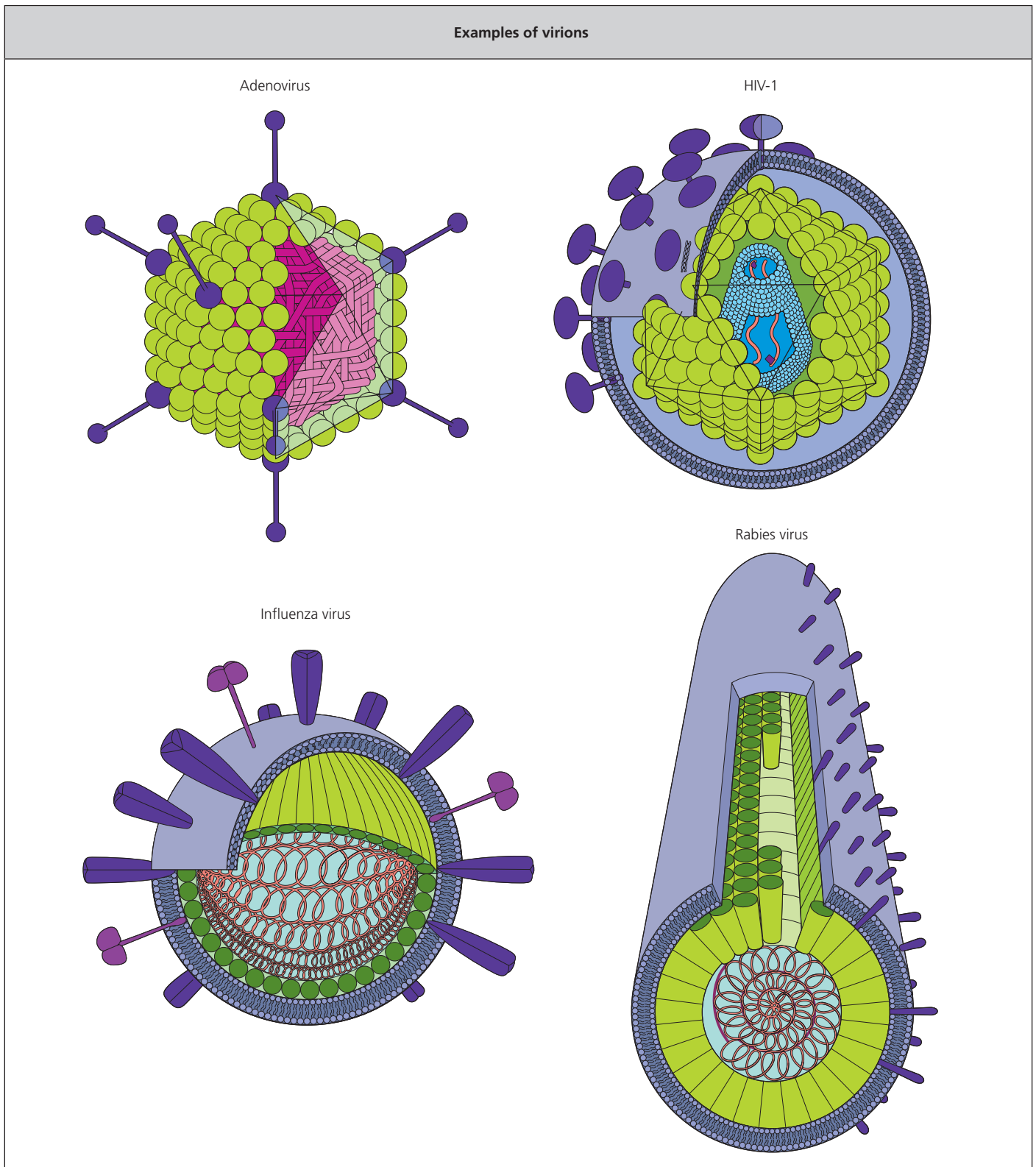


Figure 2-1 Examples of virions. Adenovirus is an icosahedral DNA virus without an envelope; fibers extend from the 12 points of the icosahedral coat; DNA forms a ribbon-like molecule. Approximate size 8 nm. HIV-1; glycoprotein (GP) molecules protrude through the lipid membrane; the icosahedral capsid encloses a truncated conical nucleocapsid in which the diploid RNA is enclosed. Approximate size 100 nm. Influenza virus is an enveloped RNA virus containing nucleocapsid of helical symmetry; spikes of hemagglutinin and neuraminidase protrude from the lipid bilayer. Approximate size 100–200 nm (variable). Rabies virus is a helical RNA nucleocapsid with a bullet-shaped lipoprotein envelope in which approximately 200 GPs are embedded. Approximate size 150 nm. (The diagram is not to relative scale.) (Adapted from Collier L., *Oxford J.: Human virology*. Oxford: Oxford University Press; 1990:8 by permission of Oxford University Press.)