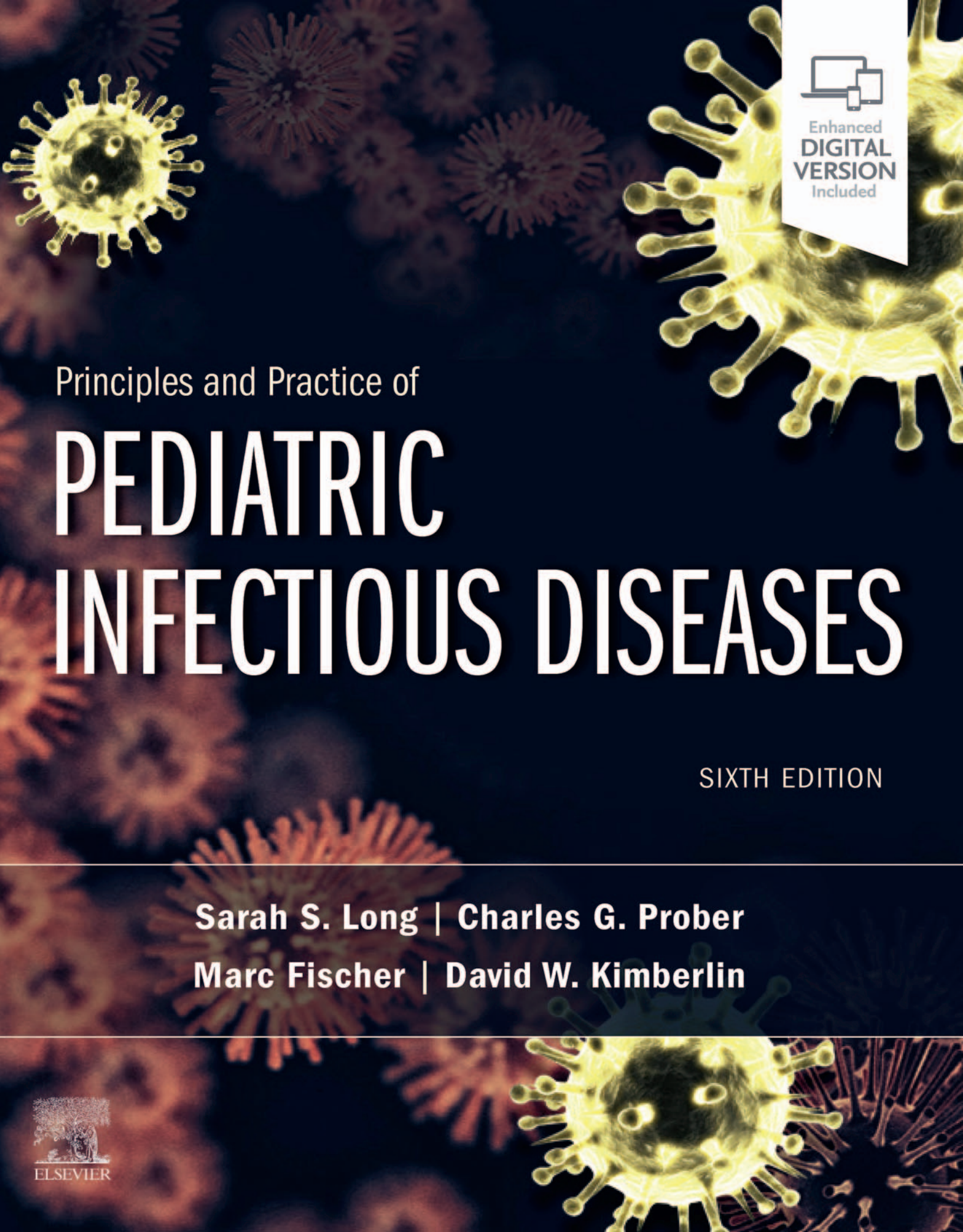


Principles and Practice of

PEDIATRIC INFECTIOUS DISEASES

SIXTH EDITION

Sarah S. Long | Charles G. Prober
Marc Fischer | David W. Kimberlin

ELSEVIER

eBooks for Practicing Clinicians

ELSEVIER

Any screen. Any time. Anywhere.

Activate the eBook version
of this title at no additional charge.

Elsevier eBooks for Practicing Clinicians gives you the power to browse and search content, view enhanced images, highlight and take notes—both online and offline.

Unlock your eBook today.

1. Visit **expertconsult.inkling.com/redeem**
2. Scratch box below to reveal your code
3. Type code into "Enter Code" box
4. Click "Redeem"
5. Log in or Sign up
6. Go to "My Library"

It's that easy!

Place Peel Off Sticker Here

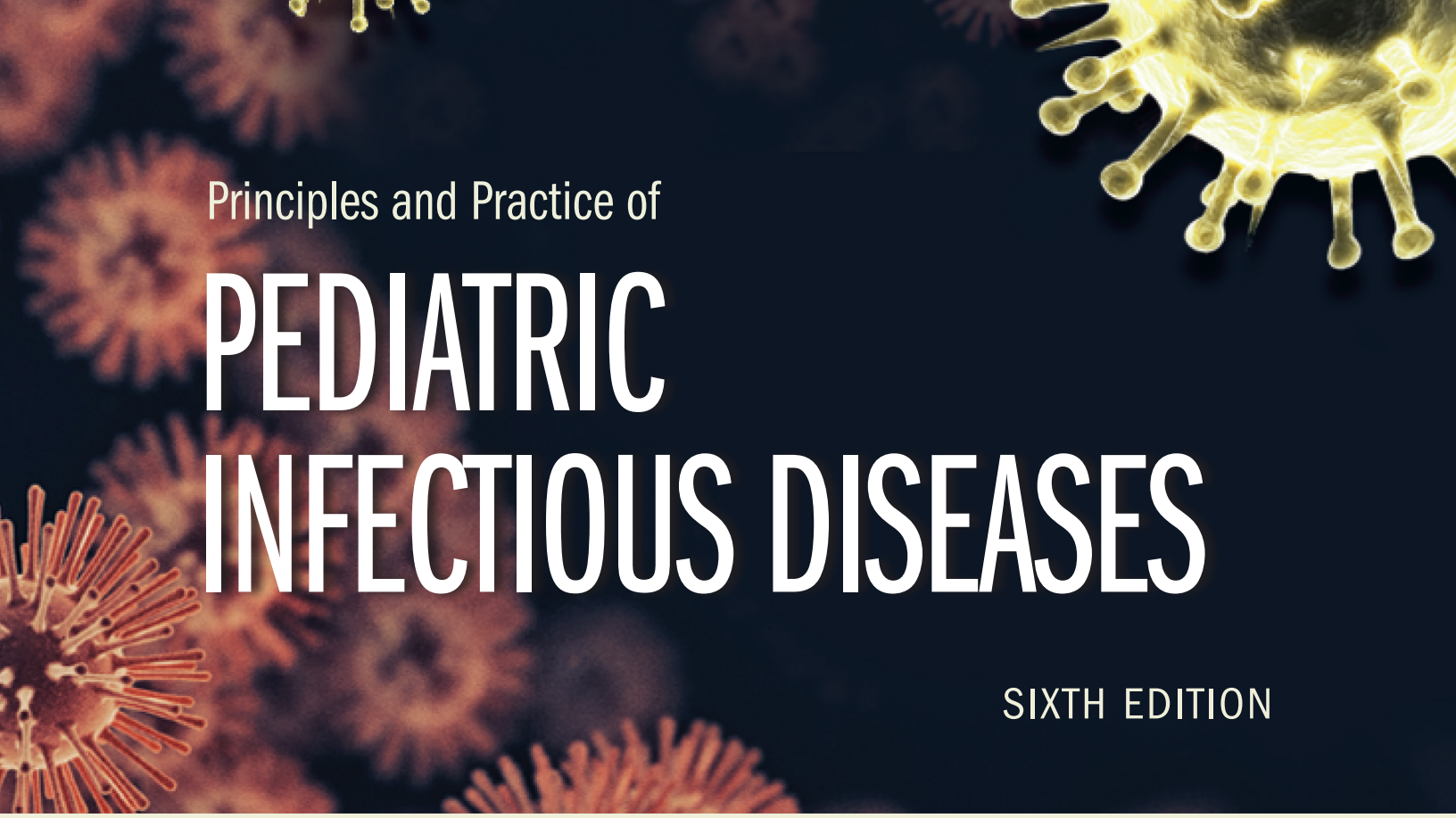
For technical assistance:
email expertconsult.help@elsevier.com
call 1-800-401-9962 (inside the US)
call +1-314-447-8300 (outside the US)

2020_PC

Principles and Practice of

PEDIATRIC INFECTIOUS DISEASES

This page intentionally left blank



Principles and Practice of

PEDIATRIC INFECTIOUS DISEASES

SIXTH EDITION

EDITOR

SARAH S. LONG, MD

Professor of Pediatrics
Drexel University College of Medicine
Chief Emeritus, Section of Infectious Diseases
St. Christopher's Hospital for Children
Philadelphia, Pennsylvania

ASSOCIATE EDITORS

CHARLES G. PROBER, MD
Professor of Pediatrics, Microbiology, and Immunology
Founding Executive Director, Stanford Center for Health Education
Senior Associate Vice Provost for Health Education
Stanford University School of Medicine
Stanford, California

MARC FISCHER, MD, MPH
Medical Epidemiologist
Arctic Investigations Program
Centers for Disease Control and Prevention
Anchorage, Alaska

DAVID W. KIMBERLIN, MD
Professor and Vice Chair for Clinical and Translational Research
Co-Director, Division of Pediatric Infectious Diseases
Department of Pediatrics
University of Alabama at Birmingham Heersink School of Medicine
and the Children's Hospital of Alabama
Birmingham, Alabama

ELSEVIER

Elsevier
1600 John F. Kennedy Blvd.
Ste 1600
Philadelphia, PA 19103-2899

PRINCIPLES AND PRACTICE OF PEDIATRIC INFECTIOUS DISEASES, SIXTH EDITION ISBN-13: 978-0-323-75608-2

ISBN-13: 978-0-323-75608-2

Publisher: Sarah Barth
Senior Content Development Specialist: Ann Anderson
Publishing Services Manager: Catherine Albright Jackson
Senior Project Manager: Doug Turner
Designer: Bridget Hoette

Printed in India

Last digit is the print number: 9 8 7 6 5 4 3 2 1

Preface

The field of infectious diseases is ever changing with emerging pathogens, globalization of people and microbes, escalating antimicrobial resistance, increasing cohorts of children living with immunocompromising conditions, novel diagnostic methods, expanding therapeutic options, and continuous development of vaccines and strategies for implementation. As the conditions on the ground become increasingly complex, so do the roles of infectious diseases experts. On a micro-level, we are entrusted to plan the approach to an individual patient with a potentially previously undescribed infection, while on a macro-level we are challenged to expand the field's knowledge, educate others, and steward the public's health.

Our goal is to provide a comprehensive, reliable, up-to-date reference focused on evidence-based, practical information that is required to care for neonates, infants, children, and adolescents with any infectious disease. We aim to guide the clinician to understand the problem, diagnose the etiology, and effectively manage the patient to optimize outcome. Our scope also includes strategies for prevention and control of infectious diseases and for antimicrobial stewardship that will aid in the management of individual patients and will provide a basis for policy development for institutions. Features permeating the sixth edition include direct links to the referenced primary medical literature in your eBook and addresses for web-based resources, such as to access updates of guidelines, to obtain a restricted therapeutic agent, or to access an expert to aid in management of a rare disease. We have substantially expanded the use of tables, figures, image-illustrated cases, scan- and slide-ready graphics and algorithms, and Key Points boxes to optimize rapid visual access to important information.

We have engaged subject-specific experts to author all chapters and have imposed a prescribed, predictable, and focused format that will reliably reward the reader with answers to the question, what should I do next? With a substantial number of authors from the Centers for Disease Control and Prevention, the American Academy of Pediatrics' Committee on Infectious Diseases and the Section on Infectious Diseases, the Pediatric Infectious Diseases Society, and infection prevention advisory groups, we have attempted to present consistent recommendations and to build a compendium of best practices. Examples of new content are highlighted here, within the context of the four major sections of the book.

Part I. Understanding, Controlling, and Preventing Infectious Diseases: a primer in biostatistics; expanded use of immunoglobulin products; latest vaccine recommendations and schedules for immunizations for healthy and special hosts, and adverse event–reporting systems; listings of resources in electronic, telephone, and paper media; up-to-date recommendations for infection prevention and control for hospitals and offices; special considerations for children who are in out-of-home care, are exposed to pets and exotic animals, or who are traveling or immigrating.

Part II. Clinical Syndromes and Cardinal Features of Infectious Diseases: Approach to Diagnosis and Initial Management: new content on conditions that mimic infectious diseases (such as hemophagocytic lymphohistiocytosis, macrophage activation syndrome, and SARS-CoV-2 related conditions and vaccine adverse events); developmental stages of innate and adaptive immunity; recognition and management of infections and risks due to congenital and acquired immunocompromising conditions; expanded chapters on infections related to receipt of biologic response modifier therapy and corticosteroids; expanded content on central nervous system infectious and parainfectious conditions; a new chapter on maternal chorioamnionitis and its perinatal impact; new morbidities and evidence-based approaches to preventing healthcare-associated infections.

Part III. Etiologic Agents of Infectious Diseases: significant new entries related to molecular and metagenomic diagnostics, antimicrobial resistance, and therapies for bacterial infections, especially infections due to staphylococci, pneumococci, gonococci, mycobacteria, and gram-negative bacilli; SARS-CoV-2 and Zika viruses, new antiviral therapies, new vaccines, and some under development; evidence and guidance where evidence is incomplete for use and monitoring of agents to treat fungal infections; comprehensive and latest guidance for management of protozoal infections, including toxoplasmosis, malaria, and other pathogens of immigrants.

Part IV. Laboratory Diagnosis and Therapy of Infectious Diseases: through the burgeoning world of molecular diagnostics, the *best tests* for laboratory identification of infectious agents; *differentiating features* of commonly used laboratory tests to measure the inflammatory response and predict the cause; *new insights* into principles of use of anti-infective therapies; *expanded primer* on the pharmacodynamic basis of optimal use of antimicrobial agents; mechanisms and *best laboratory techniques* to detect newly emerging antimicrobial resistance; *new antimicrobial agents* for treating bacterial, fungal, viral, and parasitic infections.

The primary audience for our textbook is the subspecialist in infectious diseases who provides care for or advises on policy regarding infants, children, and adolescents. We hope that our book also serves as a daily "consultant" for pediatricians and family physicians and a valuable resource for surgeons, clinical microbiologists, experts in infection control, health policy makers, and other health professionals who care for and about children.

Sarah S. Long
Charles G. Prober
Marc Fischer
David W. Kimberlin

Acknowledgments

With special contributions of clinical images by James H. Brien, DO,
Adjunct Professor of Pediatrics, Infectious Diseases, Texas A&M University College of Medicine, McLane Children's Hospital, Baylor Scott & White Health, Temple, Texas

With our spouses (Bob, Laura, Lisa, and Kim)
our children (Stephen, Suzanne, and Caroline; Meghan and Andrew;
Sydney and Madison; Will, Claire, and Katherine)
and other loved ones
whose patience and endurance are our bedrock,

We share the achievement of this book.

To our mentors and colleagues, who share
knowledge and stimulate learning,

We give credit for the book's value.

To those who practice medicine as an art based on science,
and for the children whom they will serve,
We offer the book's lessons.

To Anthony S. (Tony) Fauci
who has been true north through all of the challenges and advances
that we have experienced for the past two years,
and to our other colleagues who have tirelessly and selflessly advanced the science,
public health, education, training, and frontline patient care throughout the most
historic infectious disease challenge of our lifetime,

We dedicate the sixth edition.

Contributors

Mark J. Abzug, MD
Professor of Pediatrics–Infectious Diseases, University of Colorado School of Medicine; Division of Infectious Diseases, Children's Hospital Colorado, Aurora, Colorado
Introduction to Picornaviridae; Enteroviruses and Parechoviruses

Elisabeth E. Adderson, MD, MSc
Associate Professor of Pediatrics, University of Tennessee Health Sciences Center; Associate Member, Department of Infectious Diseases, St. Jude Children's Research Hospital and St. Jude Graduate School of Biomedical Sciences, Memphis, Tennessee
Infectious Complications of Antibody Deficiency

Aastha Agarwal, MD
Senior Resident, Dermatology, Dr RML Hospital, ABVIMS, Delhi, India
Superficial Fungal Infections

Allison L. Agwu, MD, ScM
Professor of Pediatrics, Johns Hopkins School of Medicine, Baltimore, Maryland
Infectious Complications of HIV Infection

Lindsey Albenberg, DO
Assistant Professor of Pediatrics, University of Pennsylvania Perelman School of Medicine; Attending Physician, Division of Gastroenterology, Hepatology, and Nutrition, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania
Anaerobic Bacteria: Clinical Concepts and the Microbiome in Health and Disease

Jonathan Albert, MD
Fellow, Division of Infectious Diseases, Children's National Hospital, Washington, District of Columbia
Peritonitis

Kevin Alby, PhD, D(ABMM)
Assistant Professor of Pathology and Laboratory Medicine, University of North Carolina School of Medicine; Director, Bacteriology and Susceptibility Testing, UNC Medical Center, Chapel Hill, North Carolina
Mechanisms and Detection of Antimicrobial Resistance

Grace M. Aldrovandi, MD, CM
Professor of Pediatrics, David Geffen School of Medicine at UCLA; Chief, Division of Infectious Diseases, UCLA Mattel Children's Hospital, Los Angeles, California
Immunopathogenesis of HIV-1 Infection

Upton D. Allen, Jr., MBBS, MSc
Professor of Paediatrics, University of Toronto Faculty of Medicine; Division of Infectious Diseases, Hospital for Sick Children, Toronto, Ontario, Canada
Adenoviruses

Gerardo Alvarez-Hernández, MD, PhD, MPH
Professor of Medicine and Health Sciences, Universidad de Sonora, Hermosillo, Mexico
Rickettsia rickettsii (Rocky Mountain Spotted Fever)

Krow Ampofo, MBChB
Professor of Pediatrics, University of Utah School of Medicine; Attending Physician, Infectious Diseases, Primary Children's Hospital, Salt Lake City, Utah
Streptococcus pneumoniae

Evan J. Anderson, MD
Professor of Pediatrics and Medicine, Emory University School of Medicine; Division of Infectious Diseases, Children's Healthcare of Atlanta, Atlanta, Georgia
Campylobacter jejuni and *Campylobacter coli;* Other *Campylobacter* Species

Grace D. Appiah, MD, MS
Medical Epidemiologist, Waterborne Disease Prevention Branch, Centers for Disease Control and Prevention, Atlanta, Georgia
Vibrio cholerae (Cholera)

Monica I. Ardura, DO, MSCS
Associate Professor of Pediatrics, The Ohio State University College of Medicine; Medical Director, Host Defense Program, Division of Infectious Diseases, Nationwide Children's Hospital, Columbus, Ohio
Risk Factors and Infectious Agents in Children With Cancer: Fever and Granulocytopenia; Clinical Syndromes of Infection in Children With Cancer; *Citrobacter* Species

Stephen S. Arnon, MD, MPH
Founder and Chief, Infant Botulism Treatment and Prevention Program, California Department of Public Health, Richmond, California
Clostridium botulinum (Botulism)

Naomi E. Aronson, MD
Professor of Medicine, Director, Infectious Diseases Division, Uniformed Services University of the Health Sciences, Bethesda, Maryland
Leishmania Species (Leishmaniasis)

Ann M. Arvin, MD
Lucile Salter Packard Professor of Pediatrics, Professor of Microbiology and Immunology, Stanford University School of Medicine, Stanford, California
Varicella-Zoster Virus

Shai Ashkenazi, MD, MSc
Professor and Dean, Adelson School of Medicine, Ariel University, Department of Pediatrics A, Schneider Children's Medical Center, Petach Tikva, Israel
Plesiomonas shigelloides; Shigella Species

Liat Ashkenazi-Hoffnung, MD
Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel; Head, Day Hospitalization Department, Attending Physician, Pediatric Infectious Diseases Unit, Schneider Children's Medical Center, Petach-Tikva, Israel
Plesiomonas shigelloides

Edwin J. Asturias, MD
Professor of Pediatrics, University of Colorado School of Medicine; Professor of Epidemiology, Associate Director, Center for Global Health, Colorado School of Public Health; Jules Amer Chair, Department of Community Pediatrics, Children's Hospital Colorado, Aurora, Colorado
Escherichia coli

Kestutis Aukstuolis, DO
Division of Allergy and Infectious Diseases, Department of Medicine, University of Washington, Seattle, Washington
Immunologic Development and Susceptibility to Infection

Vahe Badalyan, MD, MPH, MBA
Attending Physician, Department of Gastroenterology, Hepatology, and Nutrition, Children's National Hospital, Washington, District of Columbia
Acute Hepatitis

Carol J. Baker, MD
Professor of Pediatrics–Infectious Diseases, McGovern Medical School, University of Texas Health Science Center, Houston, Texas
Bacterial Infections in the Neonate; *Streptococcus agalactiae* (Group B *Streptococcus*)

Karthik Balakrishnan, MD, MPH
Associate Professor of Otolaryngology, Stanford University School of Medicine, Lucile Packard Children's Hospital, Stanford, California
Otitis Externa and Necrotizing Otitis Externa

Elizabeth D. Barnett, MD
Professor of Pediatrics, Boston University School of Medicine; Attending Physician, Department of Pediatrics, Boston Medical Center, Boston, Massachusetts
Infectious Diseases in Refugee and Internationally Adopted Children; Protection of Travelers

Kirsten Bechtel, MD
Professor of Pediatrics, Yale School of Medicine; Attending Physician, Pediatric Emergency Medicine, Yale-New Haven Children's Hospital, New Haven, Connecticut
Infectious Diseases Associated With Child Abuse

William E. Benitz, MD
Philip Sunshine Professor in Neonatology Emeritus, Division of Neonatal and Developmental Medicine, Stanford University School of Medicine, Palo Alto, California
Clinical Approach to the Neonate With Suspected Infection; Chorioamnionitis and Neonatal Consequences

Rachel Berkovich, MD
Clinical Assistant Professor, University of Missouri at Kansas City School of Medicine; Medical Director of Imaging, Department of Radiology, Cardinal Glennon Children's Hospital, St. Louis, Missouri; Vice Chair, Department of Radiology, Children's Mercy–Kansas City, Kansas City, Missouri
Focal Suppurative Infections of the Nervous System

David M. Berman, DO, MS
Assistant Professor of Pediatric–Infectious Diseases, Johns Hopkins School of Medicine; Johns Hopkins All Children's Hospital, St Petersburg, Florida
Infections in Hematopoietic Cell Transplant Recipients

Stephanie R. Bialek, MD, MPH
Chief, Parasitic Diseases Branch, Division of Parasitic Diseases and Malaria, Centers for Disease Control and Prevention, Atlanta, Georgia
Intestinal Trematodes

Else M. Bijker, MD, PhD
Postdoctoral Researcher, Oxford Vaccine Group; Paediatrician, Department of Paediatrics, University of Oxford, Oxford, United Kingdom
Neisseria meningitidis

Matthew J. Bizzarro, MD
Professor of Pediatrics, Yale University School of Medicine; Medical Director, Yale Neonatal Intensive Care Network, Yale–New Haven Children's Hospital, New Haven, Connecticut
Healthcare-Associated Infections in the Neonate

Karen C. Bloch, MD, MPH
Professor of Medicine and Infectious Diseases, Vanderbilt University Medical Center, Nashville, Tennessee
Encephalitis

Joseph A. Bocchini, Jr., MD
Professor and Vice Chairman, Department of Pediatrics, Tulane University School of Medicine, New Orleans, Louisiana; Director, Willis-Knighton Children's Health Services, Willis-Knighton Health System, Shreveport, Louisiana
Infections Related to Pets and Exotic Animals

Thomas G. Boyce, MD, MPH
Associate Professor of Pediatrics, Infectious Diseases and Immunology, Levine Children's Hospital, Charlotte, North Carolina
Otitis Externa and Necrotizing Otitis Externa

John S. Bradley, MD
Professor of Pediatrics, University of California San Diego School of Medicine; Director, Infectious Diseases, Rady Children's Hospital San Diego, San Diego, California
Antimicrobial Chemoprophylaxis; Principles of Anti-Infective Therapy; Pharmacokinetic and Pharmacodynamic Basis of Optimal Antimicrobial Therapy; Antibacterial Agents

Denise F. Bratcher, DO
Professor of Pediatrics, University of Missouri at Kansas City School of Medicine; Attending Physician, Division of Infectious Diseases, Children's Mercy–Kansas City, Kansas City, Missouri
Arcanobacterium haemolyticum; Bacillus Species (Including Anthrax); Other Corynebacteria; Other Gram-Positive Bacilli

Paula K. Braverman, MD
Professor of Pediatrics, University of Massachusetts Medical School–Baystate; Chief, Adolescent Medicine, Department of Pediatrics, Baystate Children's Hospital, Springfield, Massachusetts
Urethritis, Vulvovaginitis, and Cervicitis

Itzhak Brook, MD
Professor of Pediatrics, Georgetown University School of Medicine, Washington, District of Columbia
Anaerobic Bacteria: Clinical Concepts and the Microbiome in Health and Disease; *Clostridium tetani* (Tetanus); Other *Clostridium* Species; *Bacteroides* and *Prevotella* Species and Other Anaerobic Gram-Negative Bacilli

Kevin Edward Brown, MD, MRCP
Consultant Medical Virologist, Immunisation and Vaccine Preventable Diseases, UK Health Security Agency, London, United Kingdom
Human Parvoviruses (Parvovirus B19 and Bocavirus)

Kristina P. Bryant, MD
Professor of Pediatrics–Infectious Diseases, University of Louisville School of Medicine; Epidemiologist, Norton Children's Hospital, Louisville, Kentucky
Tickborne Infections

Andres F. Camacho-Gonzalez, MD, MSc
Associate Professor of Pediatrics, Emory University School of Medicine; Division of Pediatric Infectious Diseases, Children's Healthcare of Atlanta, Atlanta, Georgia
Trypanosoma Species (Trypanosomiasis)

Connie F. Cañete-Gibas, PhD
Clinical Mycologist, Department of Pathology and Laboratory Medicine, Fungus Testing Laboratory, UT Health San Antonio, San Antonio, Texas
Classification of Fungi; Agents of Hyalohyphomycosis and Phaeohyphomycosis; Agents of Mucormycosis; *Malassezia* Species; *Sporothrix schenckii* Complex (Sporotrichosis)

Joseph B. Cantey, MD, MPH
Associate Professor of Pediatrics, Joe R. & Teresa Lozano Long School of Medicine; Division of Neonatal-Perinatal Medicine, Division of Immunology and Infectious Diseases, University of Texas Health San Antonio, San Antonio, Texas
Pediatric Healthcare: Infection Epidemiology, Prevention and Control, and Antimicrobial Stewardship; Healthcare-Associated Infections in the Neonate

Paul Cantey, MD, MPH
Chief, Parasitic Diseases Branch, Centers for Disease Control and Prevention, Atlanta, Georgia
Blood and Tissue Nematodes: Filarial Worms; *Echinococcus* Species: Agents of Echinococcosis

Cristina V. Cardemil, MD, MPH
Medical Epidemiologist, Division of Viral Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia
Caliciviruses; Astroviruses

Mary T. Caserta, MD
Professor of Pediatrics, University of Rochester School of Medicine and Dentistry; Division of Infectious Diseases, Golisano Children's Hospital, University of Rochester Medical Center, Rochester, New York
Human Herpesvirus 6 and 7 (Roseola, Exanthem Subitum); Human Herpesvirus 8 (Kaposi Sarcoma-Associated Herpesvirus)

Luis A. Castagnini, MD, MPH
Director, Vaccine Clinical Research, Merck & Co., North Wales, Pennsylvania
Helicobacter pylori

Jessica R. Cataldi, MD, MSCS
Assistant Professor of Pediatrics, University of Colorado School of Medicine; Section of Infectious Diseases, Children's Hospital Colorado, Aurora, Colorado
Moraxella Species

Ellen Gould Chadwick, MD
Professor of Pediatrics, Northwestern University Feinberg School of Medicine; Susan B. DePree Founders' Board Professor in Pediatric Adolescent and Maternal HIV Infection, Director, Section of Pediatric, Adolescent and Maternal HIV Infection, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, Illinois
Nocardia Species

Rebecca J. Chancey, MD
Medical Officer, Parasitic Diseases Branch, Center for Global Health, Centers for Disease Control and Prevention, Atlanta, Georgia
Clonorchis, Opisthorchis, Fascioloa, and *Paragonimus* Species; Antiparasitic Agents

Cara C. Cherry, DVM, MPH, DACVPM
Veterinary Epidemiologist, Rickettsial Zoonoses Branch, Centers for Disease Control and Prevention, Atlanta, Georgia
Coxiella burnetii (Q fever)

Silvia S. Chiang, MD
Assistant Professor of Pediatrics, Warren Alpert Medical School of Brown University; Attending Physician, Infectious Diseases, Hasbro Children's Hospital, Providence, Rhode Island
Mycobacterium tuberculosis

Mary Choi, MD, MPH
Medical Officer, Viral Special Pathogens Branch, Centers for Disease Control and Prevention, Atlanta, Georgia
Bunyaviruses; Filoviruses and Arenaviruses

John C. Christenson, MD
Professor of Clinical Pediatrics, Ryan White Center for Pediatric Infectious Diseases and Global Health, Indiana University School of Medicine; Riley Hospital for Children, Indianapolis, Indiana
Histoplasma capsulatum (Histoplasmosis); Laboratory Diagnosis of Infection Due to Bacteria, Fungi, Parasites, and Rickettsiae

Susan E. Coffin, MD, MPH
Professor of Pediatrics, Perelman School of Medicine at the University of Pennsylvania; Division of Infectious Diseases, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania
Healthcare-Associated Infections

Amanda Cohn, MD
Chief Medical Officer, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia
Neisseria meningitidis

Despina G. Contopoulos-Ioannidis, MD
Clinical Associate Professor of Pediatrics, Division of Infectious Diseases, Stanford University School of Medicine, Stanford, California
Toxoplasma gondii (Toxoplasmosis)

James H. Conway, MD
Professor of Pediatrics, University of Wisconsin School of Medicine & Public Health; Associate Director, Global Health Institute, University of Wisconsin–Madison, Madison, Wisconsin
Mastoiditis

Margaret M. Cortese, MD
Captain, United States Public Health Service, Division of Viral Diseases, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia
Rotaviruses

C. Buddy Creech, MD, MPH
Professor in Pediatrics, Director, Vanderbilt Vaccine Research Program, Edie Carell Johnson Chair, Division of Pediatric Infectious Diseases, Vanderbilt University School of Medicine and Medical Center, Nashville, Tennessee
Musculoskeletal Symptom Complexes; Myositis, Pyomyositis, and Necrotizing Fasciitis; Transient Synovitis; *Staphylococcus aureus*

Jonathan D. Crews, MD, MS
Assistant Professor of Pediatric–Infectious Diseases, Baylor College of Medicine/ Children's Hospital of San Antonio, San Antonio, Texas
Other Gastric and Enterohepatic *Helicobacter* Species

Donna Curtis, MD, MPH
Associate Professor of Pediatrics, University of Colorado School of Medicine; Section of Infectious Diseases, Children's Hospital Colorado, Aurora, Colorado
Pneumonia in the Immunocompromised Host

Nigel Curtis, DCH, DTM&H, MRCP, MRCPCH, PhD
Professor of Paediatrics, The University of Melbourne; Head of Infectious Diseases, The Royal Children's Hospital Melbourne, Leader of Infectious Diseases Group, Murdoch Children's Research Institute, Parkville, Victoria, Australia
Infections Related to the Upper and Middle Airways; *Mycobacterium* Nontuberculosis Species

Lara A. Danziger-Isakov, MD, MPH
Professor of Pediatrics, University of Cincinnati College of Medicine; Division of Infectious Diseases, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio
Infectious Complications in Special Hosts

Toni Darville, MD
Professor of Pediatrics, University of North Carolina at Chapel Hill; Chief, Infectious Diseases, Department of Pediatrics, North Carolina Children's Hospital, Chapel Hill, North Carolina
Chlamydia trachomatis

Gregory A. Dasch, PhD
Biotechnology Applications Laboratory Director, Rickettsial Zoonoses Branch, Centers for Disease Control and Prevention, Atlanta, Georgia
Other *Rickettsia* Species

Irini Daskalaki, MD
Global and Community Health Physician Coordinator, Princeton University Health Services, Princeton, New Jersey
Corynebacterium diphtheriae; Leptospira Species (Leptospirosis); Other *Borrelia* Species and *Spirillum minus*

H. Dele Davies, MD, MHCM
Professor of Pediatrics and Public Health, University of Nebraska Medical Center, Omaha, Nebraska
Infections Related to Biologic Response Modifying Drug Therapy; Infectious Complications of Corticosteroid Therapy

Fatimah S. Dawood, MD
Medical Officer, Influenza Division, Centers for Disease Control and Prevention, Atlanta, Georgia
Influenza Viruses

J. Christopher Day, MD
Assistant Professor of Pediatrics, University of Missouri at Kansas City; Attending Physician, Division of Infectious Diseases, Children's Mercy–Kansas City, Kansas City, Missouri
Lymphatic System and Generalized Lymphadenopathy; Mediastinal and Hilar Lymphadenopathy

M. Teresa de la Morena, MD
Professor of Pediatrics, University of Washington School of Medicine; Division of Immunology, Seattle Children's Hospital, Seattle, Washington
Immunologic Development and Susceptibility to Infection

Gregory P. DeMuri, MD
Professor of Pediatrics, University of Wisconsin School of Medicine and Public Health; Division of Infectious Diseases, American Family Children's Hospital, Madison, Wisconsin
Sinusitis; Preseptal and Orbital Infections

Dickson D. Despommier, PhD
Emeritus Professor of Microbiology and Immunology, Columbia University College of Physicians and Surgeons, New York, New York
Tissue Nematodes

Daniel S. Dodson, MS, MD
Assistant Professor of Pediatrics, University of California Davis School of Medicine; Division of Pediatric Infectious Diseases, UC Davis Health, Sacramento, California
Escherichia coli

Stephen J. Dolgner, MD
Assistant Professor of Pediatrics, Baylor College of Medicine; Division of Cardiology, Texas Children's Hospital, Houston, Texas
Endocarditis and Other Intravascular Infections

Clinton Dunn, MD
Department of Medicine, Division of Allergy and Infectious Diseases, University of Washington, Seattle, Washington
Immunologic Development and Susceptibility to Infection

Jonathan Dyal, MD, MPH
Epidemic Intelligence Service Officer, Viral Special Pathogens Branch, Centers for Disease Control and Prevention, Atlanta, Georgia
Filoviruses and Arenaviruses

Kathryn M. Edwards, MD
Professor of Pediatrics, Sarah H. Sell and Cornelius Vanderbilt Chair, Department of Pediatrics, Vanderbilt University School of Medicine, Nashville, Tennessee
Prolonged, Recurrent, and Periodic Fever Syndromes; *Bordetella pertussis* (Pertussis) and Other *Bordetella* Species

Morven S. Edwards, MD
Professor of Pediatrics, Baylor College of Medicine; Attending Physician, Section of Infectious Diseases, Texas Children's Hospital, Houston, Texas
Bacterial Infections in the Neonate; *Streptococcus agalactiae* (Group B *Streptococcus*)

Dawn Z. Eichenfield, MD, PhD
Assistant Clinical Professor of Dermatology, University of California, Rady Children's Hospital San Diego, San Diego, California
Purpura

Lawrence F. Eichenfield, MD
Distinguished Professor of Dermatology and Pediatrics, University of California, Rady Children's Hospital San Diego, San Diego, California
Purpura

Dirk M. Elston, MD
Professor and Chair, Department of Dermatology, Medical University of South Carolina, Charleston, South Carolina
Ectoparasites (Lice and Scabies)

Beth Emerson, MD
Associate Clinical Professor of Pediatrics, Yale University School of Medicine; Section of Pediatric Emergency Medicine, Yale–New Haven Children's Hospital, New Haven, Connecticut
Infectious Diseases Associated With Child Abuse

Leslie A. Enane, MD, MSc
Assistant Professor of Pediatrics, Indiana University School of Medicine; Director, Pediatric HIV Services, Ryan White Center for Pediatric Infectious Diseases and Global Health, Riley Hospital for Children at Indiana University Health, Indianapolis, Indiana
Agents of Eumycotic Mycetoma: *Pseudallescheria boydii* and *Scedosporium apiospermum*

Moshe Ephros, MD
Director, Pediatric Infectious Diseases Unit, Carmel Medical Center; Associate Clinical Professor of Pediatrics (Retired), Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel
Leishmania Species (Leishmaniasis)

Guliz Erdem, MD
Professor of Pediatrics, Ohio State University College of Medicine; Section of Infectious Diseases, Nationwide Children's Hospital, Columbus, Ohio
Acinetobacter Species; Less Commonly Encountered Nonenteric Gram-Negative Bacilli; *Eikenella, Pasteurella,* and *Chromobacterium* Species

Marina E. Eremeeva, MD, PhD, ScD
Professor of Biostatistics, Epidemiology, and Environmental Health Sciences, Jiann-Ping Hsu College of Public Health, Georgia Southern University, Statesboro, Georgia
Other *Rickettsia* Species

Douglas H. Esposito, MD, MPH
Medical Epidemiologist, Office of Refugee Resettlement, Administration for Children and Families, US Department of Health and Human Services, Atlanta, Georgia
Sarcocystis Species

Monica M. Farley, MD
Jonas A. Shulman Professor of Medicine, Director, Division of Infectious Diseases, Emory University School of Medicine, Atlanta, Georgia
Listeria monocytogenes

Anat R. Feingold, MD, MPH
Associate Professor of Pediatrics, Cooper Medical School of Rowan University; Chief, Pediatric Infectious Diseases, Cooper University Hospital, Camden, New Jersey
Anaerobic Cocci; Anaerobic Gram-Positive Nonsporulating Bacilli (Including Actinomycosis)

Kristina N. Feja, MD, MPH
Clinical Associate Professor of Pediatrics, Robert Wood Johnson Medical School, Rutgers University; Chief, Division of Pediatric Infectious Diseases, Saint Peter's University Hospital, New Brunswick, New Jersey
Babesia Species (Babesiosis)

Adam Finn, BA (Hons), MA, BM, BCh, PhD
Professor of Paediatrics, University of Bristol; Honorary Consultant, Bristol Royal Hospital for Children, Bristol, United Kingdom
Neisseria meningitidis

Marc Fischer, MD, MPH
Medical Epidemiologist, Arctic Investigations Program, Centers for Disease Control and Prevention, Anchorage, Alaska
Coltivirus (Colorado Tick Fever); Flaviviruses; Bunyaviruses

Brian T. Fisher, DO, MPH, MSCE
Associate Professor of Pediatrics and Epidemiology, Perelman School of Medicine at the University of Pennsylvania; Division of Infectious Diseases, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania
Candida Species

Randall G. Fisher, MD
Professor of Pediatrics, Eastern Virginia Medical School; Medical Director, Division of Pediatric Infectious Diseases, Children's Hospital of The King's Daughters, Norfolk, Virginia
Evaluation of the Child With Suspected Immunodeficiency; Infectious Complications of Dysfunction or Deficiency of Polymorphonuclear and Mononuclear Phagocytes

Patricia Michele Flynn, MD
Professor of Pediatrics and Preventive Medicine, University of Tennessee Health Sciences Center; Member, Department of Infectious Diseases, St. Jude Children's Research Hospital, Memphis, Tennessee
Cryptosporidium Species; *Cystoisospora (Isospora)* and *Cyclospora* Species

Monique A. Foster, MD, MPH
Medical Epidemiologist, Division of Viral Hepatitis, Centers for Disease Control and Prevention, Atlanta, Georgia
Hepatitis C Virus; Hepatitis A Virus

LeAnne M. Fox, MD, MPH, DTM&H
Chief, Meningitis and Vaccine Preventable Diseases Branch, Division of Parasitic Diseases and Malaria, Center for Global Health, Centers for Disease Control and Prevention, Atlanta, Georgia
Intestinal Trematodes

[†]Michael M. Frank, MD
Professor of Pediatrics and Immunology, Duke University School of Medicine; Attending Physician, Duke University Medical Center, Durham, North Carolina
Infectious Complications of Complement Deficiency and Diseases of Its Dysregulation

Douglas R. Fredrick, MD
Professor of Ophthalmology, Oregon Health & Science University; Casey Eye Institute, Portland, Oregon
Conjunctivitis in the Neonatal Period (Ophthalmia neonatorum); Conjunctivitis Beyond the Neonatal Period; Infective Keratitis; Infective Uveitis, Retinitis, and Chorioretinitis; Endophthalmitis

Robert W. Frenck, Jr., MD
Professor of Pediatrics, University of Cincinnati College of Medicine; Division of Infectious Diseases, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio
Giardia intestinalis (Giardiasis)

James Gaensbauer, MD, MScPH
Associate Professor of Pediatrics, University of Colorado School of Medicine, Center for Global Health, Department of Epidemiology, Colorado School of Public Health, Aurora, Colorado; Pediatric Infectious Diseases, Department of Pediatrics, Denver Health Medical Center, Denver, Colorado
Infection Related to Trauma

[†]Deceased.

Hayley A. Gans, MD
Professor of Pediatrics–Infectious Diseases, Stanford University School of Medicine, Stanford, California
Hemophagocytic Lymphohistiocytosis and Macrophage Activation Syndrome

Gregory M. Gauthier, MD
Associate Professor (CHS) of Medicine, University of Wisconsin–Madison, Madison, Wisconsin
Blastomyces Species (Blastomycosis)

Patrick Gavigan, MD
Assistant Professor of Pediatrics, Penn State University/Hershey Medical Center; Division of Infectious Diseases, Penn State Children's Hospital, Hershey, Pennsylvania
Erythematous Macules and Papules

Jeffrey S. Gerber, MD, PhD
Associate Professor of Pediatrics, Perelman School of Medicine at the University of Pennsylvania; Attending Physician, Division of Infectious Diseases, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania
Principles of Anti-Infective Therapy

Yael Gernez, MD, PhD
Assistant Professor of Pediatrics, Division of Allergy, Immunology, and Rheumatology, Stanford University School of Medicine, Stanford, California
Infectious Complications of Deficiencies of Cell-Mediated Immunity Other Than AIDs: Primary Immunodeficiencies

Francis Gigliotti, MD
Professor of Pediatrics, University of Rochester School of Medicine and Dentistry, Rochester, New York
Pneumocystis jirovecii

Mark A. Gilger, MD
Professor of Pediatrics, Baylor College of Medicine; Pediatrician-in-Chief, Emeritus, The Children's Hospital of San Antonio, CHRISTUS Health, San Antonio, Texas
Helicobacter pylori; Other Gastric and Enterohepatic *Helicobacter* Species

Carol A. Glaser, MD, DVM, MPVM
Medical Officer, California Department of Public Health, Richmond, California
Encephalitis; Parainfectious and Postinfectious Neurologic Syndromes

Jane M. Gould, MD
Medical Director, Healthcare-Associated Infections/Antimicrobial Resistance Program, Philadelphia Department of Public Health, Philadelphia, Pennsylvania
Healthcare-Associated Infections

James Graziano, MS, MPH
Biologist, Viral Special Pathogens Branch, Centers for Disease Control and Prevention, Atlanta, Georgia
Filoviruses and Arenaviruses

Amanda M. Green, MD
Clinical Fellow, Department of Infectious Diseases, St Jude Children's Research Hospital, Memphis, Tennessee
Infectious Complications of Antibody Deficiency

Michael Green, MD, MPH
Professor of Pediatrics, Surgery & Clinical and Translational Research, University of Pittsburgh School of Medicine; Medical Director, Infection Prevention and Antimicrobial Stewardship, Division of Infectious Diseases, UPMC Children's Hospital of Pittsburgh, Pittsburgh, Pennsylvania
Infections in Solid Organ Transplant Recipients

Daniel Griffin, MD, PhD
Clinical Instructor of Medicine, Division of Infectious Diseases, Columbia University College of Physicians and Surgeons, New York, New York
Tissue Nematodes

Patricia M. Griffin, MD
Chief, National Surveillance Team, Division of Foodborne, Waterborne, and Environmental Diseases, National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia
Other *Vibrio* Species

David C. Griffith, MD
Assistant Professor of Medicine and Pediatrics, Johns Hopkins School of Medicine, Baltimore, Maryland
Management of HIV Infection

Piyush Gupta, MD
Professor and Head, Department of Pediatrics, University College of Medical Sciences, Delhi, India
Corynebacterium diphtheriae

Bruce J. Gutelius, MD, MPH
Team Lead, Enteric Diseases Epidemiology Branch, Division of Foodborne, Waterborne, and Environmental Diseases, National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia
Other *Vibrio* Species

Julie R. Gutman, MD, MSc
Strategic and Applied Science Team Lead, Malaria Branch, Center for Global Health, Centers for Disease Control and Prevention, Atlanta, Georgia
Plasmodium Species (Malaria); Antiparasitic Agents

Aron J. Hall, DVM, MSPH
Norovirus Epidemiology Team Lead, Division of Viral Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia
Enteric Diseases Transmitted Through Food, Water, and Zoonotic Exposures; Caliciviruses

Rana F. Hamdy, MD, MPH, MSCE
Assistant Professor of Pediatrics, George Washington University School of Medicine and Health Sciences; Attending Physician, Division of Infectious Diseases, Children's National Hospital, Washington, District of Columbia
Peritonitis; Appendicitis; Intra-abdominal, Visceral, and Retroperitoneal Abscesses

Jin-Young Han, MD, PhD
Associate Professor of Clinical Pediatrics, Weill Cornell Medicine; Attending Pediatrician, Phyllis and David Komansky Children's Hospital at NewYork–Presbyterian/Weill Cornell Medical Center, New York, New York
Bartonella Species (Cat-Scratch Disease)

Lori K. Handy, MD
Clinical Assistant Professor of Pediatrics, Perelman School of Medicine at the University of Pennsylvania; Division of Infectious Diseases, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania
Healthcare-Associated Infections

Benjamin Hanisch, MD
Assistant Professor of Pediatrics, George Washington University School of Medicine and Health Sciences; Attending Physician, Division of Infectious Diseases, Children's National Hospital, Washington, District of Columbia
Infections in Solid Organ Transplant Recipients

Marvin B. Harper, MD
Associate Professor of Pediatrics, Harvard Medical School; Divisions of Emergency Medicine and Infectious Diseases, Boston Children's Hospital, Boston, Massachusetts
Infection Related to Bites

Aaron M. Harris, MD, MPH
Team Lead, Division of Viral Hepatitis, Centers for Disease Control and Prevention, Atlanta, Georgia
Hepatitis B and Hepatitis D Viruses

Christopher J. Harrison, MD
Professor of Pediatrics, University of Missouri at Kansas City School of Medicine; Division of Infectious Diseases, Children's Mercy–Kansas City, Kansas City, Missouri
Chronic Meningitis; Recurrent Meningitis; Focal Suppurative Infections of the Nervous System

David B. Haslam, MD
Professor of Pediatrics, University of Cincinnati College of Medicine; Division of Infectious Diseases, Cincinnati Children's Hospital, Cincinnati, Ohio
Classification of Streptococci; *Enterococcus* Species; Viridans Streptococci, *Abiotrophia* and *Granulicatella* Species, and *Streptococcus bovis* Group; Groups C and G Streptococci; Other Gram-Positive, Catalase-Negative Cocci: *Leuconostoc* and *Pediococcus* Species and Other Genera

Julia C. Haston, MD, MSc
EIS Officer, Division of Foodborne, Waterborne, and Environmental Diseases, National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia
Trypanosoma Species (Trypanosomiasis)

Sarah.J. Hawkes, MBBS, PhD
Professor of Global Public Health, Institute for Global Health, University College London, London, United Kingdom
Treponema pallidum (Syphilis)

Taylor Heald-Sargent, MD, PhD
Assistant Professor of Pediatrics, Northwestern University Feinberg School of Medicine; Attending Physician, Division of Infectious Diseases, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, Illinois
Streptococcus pyogenes (Group A *Streptococcus*)

†J. Owen Hendley, MD
Professor of Pediatric Infectious Diseases, University of Virginia, Charlottesville, Virginia
Rhinoviruses

Adam L. Hersh, MD, PhD
Professor of Pediatrics, University of Utah School of Medicine; Pediatric Infectious Diseases, Primary Children's Hospital and the University of Utah Health, Salt Lake City, Utah
Principles of Anti-Infective Therapy

Joseph A. Hilinski, MD
Clinical Associate Professor of Pediatrics, University of Washington School of Medicine, Seattle, Washington; Attending Physician, Pediatric Infectious Diseases/Children's Infections and Immune Deficiency Clinic, St. Luke's Children's Hospital, Boise, Idaho
Myocarditis; Pericarditis

Susan L. Hills, MBBS, MTH
Medical Epidemiologist, Arboviral Diseases Branch, Centers for Disease Control and Prevention, Fort Collins, Colorado
Flaviviruses

David K. Hong, MD
Associate Professor (Affiliated) of Pediatrics–Infectious Diseases, Stanford University School of Medicine, Stanford, California; Head of Viral Respiratory Infections R&D, Janssen Pharmaceutical Companies of Johnson & Johnson, South San Francisco, California; Staff Physician, Pediatric Infectious Diseases, Santa Clara Valley Medical Center, San Jose, California
Osteomyelitis; Infectious and Inflammatory Arthritis; Diskitis

Peter J. Hotez, MD, PhD
Dean, National School of Tropical Medicine, Professor of Pediatrics and Molecular Virology & Microbiology, Head, Section of Pediatric Tropical Medicine, Baylor College of Medicine; Texas Children's Hospital Endowed Chair of Tropical Pediatrics, Director, Center for Vaccine Development, Texas Children's Hospital, Baker Institute Fellow in Disease and Poverty, Rice University, Houston, Texas
Classification of Parasites; Intestinal Nematodes

Katherine K. Hsu, MD, MPH
Professor of Pediatrics–Pediatric Infectious Diseases, Boston University Medical Center, Boston, Massachusetts; Medical Director, Division of STD Prevention, Bureau of Infectious Diseases Prevention, Response, and Services, Massachusetts Department of Public Health, Jamaica Plain, Massachusetts
Neisseria gonorrhoeae; Other *Neisseria* Species

Felicia Scaggs Huang, MD, MSc
Assistant Professor of Pediatrics, University of Cincinnati College of Medicine; Attending Physician, Division of Infectious Diseases, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio
Clinical Syndromes of Device-Associated Infections

David A. Hunstad, MD
Professor of Pediatrics and Molecular Microbiology, Washington University School of Medicine; Service Chief, Pediatric Infectious Diseases, St. Louis Children's Hospital, St. Louis, Missouri
Infectious Complications in Special Hosts

W. Garrett Hunt, MD, MPH, DTM&H
Associate Professor of Pediatrics, The Ohio State University College of Medicine; Section of Infectious Diseases, Nationwide Children's Hospital, Columbus, Ohio
Enterobacter, Cronobacter, and *Pantoea* Species

Loris Y. Hwang, MD
Associate Professor of Pediatrics, David Geffen School of Medicine at the University of California, Los Angeles; Division of Adolescent and Young Adult Medicine, University of California Los Angeles, Mattel Children's Hospital UCLA, Los Angeles, California
Human Papillomavirus

Christelle M. Ilboudo, MD
Assistant Professor of Child Health, University of Missouri Health Care, Columbia, Missouri
Other Gram-Positive Bacilli

Preeti Jaggi, MD
Associate Professor of Pediatrics, Emory University School of Medicine; Division of Infectious Diseases, Children's Healthcare of Atlanta, Atlanta, Georgia
Kawasaki Disease

Sophonie Jean, PhD, D(ABMM)
Assistant Professor of Pathology and Laboratory Medicine, The Ohio State University College of Medicine; Clinical Microbiology and Immunoserology Laboratories, Nationwide Children's Hospital, Columbus, Ohio
Enterobacter, Cronobacter, and *Pantoea* Species; *Citrobacter* Species; Less Commonly Encountered Enterobacterales

Ravi Jhaveri, MD
Professor of Pediatrics, Northwestern University Feinberg School of Medicine; Interim Division Head, Division of Pediatric Infectious Diseases, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, Illinois
Fever Without Localizing Signs

Kateřina Jirků-Pomajbíková, DVM, PhD
Researcher, Institute of Parasitology, Biology Centre of the Czech Academy of Sciences, České Budějovice, Czech Republic
Balantioides coli (Formerly *Balantidium coli*)

Nadia A. Kadry, PhD
Cell and Molecular Biology, University of Pennsylvania, Philadelphia, Pennsylvania
Haemophilus influenzae

Mary L. Kamb, MD, MPH
Team Lead, Elimination and Control Epidemiology, Parasitic Diseases Branch, Division of Parasitic Diseases and Malaria, Centers for Disease Control and Prevention, Atlanta, Georgia
Blood and Tissue Nematodes: Filarial Worms

Ronak K. Kapadia, MD, MSc, BSc
Assistant Professor of Clinical Neurosciences, University of Calgary, Calgary, Alberta, Canada
Parainfectious and Postinfectious Neurologic Syndromes

Ben Z. Katz, MD
Professor of Pediatrics, Northwestern University Feinberg School of Medicine; Attending Physician, Division of Infectious Diseases, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, Illinois
Epstein-Barr Virus (Mononucleosis and Lymphoproliferative Disorders)

Sophie E. Katz, MD, MPH
Assistant Professor of Pediatrics, Division of Infectious Diseases, Vanderbilt University Medical Center, Nashville, Tennessee
Myositis, Pyomyositis, and Necrotizing Fasciitis; Transient Synovitis

Ishminder Kaur, MD
Assistant Professor of Pediatrics, David Geffen School of Medicine at the University of California, Los Angeles; Attending Physician, Division of Infectious Diseases, UCLA Mattel Children's Hospital, Los Angeles, California
Mucocutaneous Symptom Complexes; Infections Related to Burns; Topical Antimicrobial Agents

†Deceased.

Gilbert J. Kersh, PhD
Branch Chief, Rickettsial Zoonoses Branch, Centers for Disease Control and Prevention, Atlanta, Georgia
Coxiella burnetii (Q fever)

Muhammad Ali Khan, MD, MPH
Assistant Professor of Pediatrics, George Washington University School of Medicine and Health Sciences; Division of Gastroenterology, Hepatology, and Nutrition, Children's National Hospital, Washington, District of Columbia
Chronic Hepatitis

Ananta Khurana, MD, DNB, MNAMS
Professor of Dermatology, Dr RML Hospital, ABVIMS, Delhi, India
Superficial Fungal Infections

David W. Kimberlin, MD
Professor and Vice Chair for Clinical and Translational Research, Co-Director, Division of Pediatric Infectious Diseases, Department of Pediatrics, University of Alabama at Birmingham Heersink School of Medicine and the Children's Hospital of Alabama, Birmingham, Alabama
Introduction to Herpesviridae; Herpes Simplex Virus; Antiviral Agents

Bruce Klein, MD
Professor of Pediatrics, Medicine, and Medical Microbiology, University of Wisconsin–Madison, Madison, Wisconsin
Blastomyces Species (Blastomycosis)

Miwako Kobayashi, MD, MPH
Medical Epidemiologist, Respiratory Diseases Branch, Centers for Disease Control and Prevention, Atlanta, Georgia
Chlamydophila (Chlamydia) psittaci (Psittacosis)

Larry K. Kociolek, MD, MSCI
Assistant Professor of Pediatrics, Northwestern University Feinberg School of Medicine; Medical Director of Infection Prevention and Control, Pediatric Infectious Diseases, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, Illinois
Clostridioides difficile

Andrew Y. Koh, MD
Associate Professor of Pediatrics, University of Texas Southwestern Medical Center; Director, Pediatric Hematopoietic Stem Cell Transplantation, Children's Health, Dallas, Texas
Risk Factors and Infectious Agents in Children With Cancer: Fever and Granulocytopenia; Clinical Syndromes of Infection in Children With Cancer

Karen L. Kotloff, MD
Professor of Pediatrics–Infectious Diseases and Tropical Pediatrics, Department of Medicine, University of Maryland School of Medicine; Principal Investigator, Center for Vaccine Development and Global Health, Baltimore, Maryland
Abdominal Symptom Complexes; Inflammatory Enterocolitis

Andrew T. Kroger, MD, MPH
Medical Officer, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia
Active Immunization

Matthew P. Kronman, MD, MSCE
Associate Professor of Pediatrics, University of Washington School of Medicine; Division of Infectious Diseases, Seattle Children's Hospital, Seattle, Washington
Endocarditis and Other Intravascular Infections

Leah Lalor, MD
Assistant Professor of Dermatology/Pediatrics, Medical College of Wisconsin; Children's Wisconsin Clinics–Milwaukee, Milwaukee, Wisconsin
Urticaria and Erythema Multiforme

Christine T. Lauren, MD, MHA
Associate Professor of Dermatology, Columbia University College of Physicians and Surgeons; Columbia University Irving Medical Center, New York, New York
Papules, Nodules, and Ulcers

Amy Leber, PhD
Professor of Pediatrics and Pathology, The Ohio State University College of Medicine; Director, Clinical Microbiology and Immunoserology, Department of Pathology and Laboratory Medicine, Nationwide Children's Hospital, Columbus, Ohio
Klebsiella and *Raoultella* Species; Less Commonly Encountered Nonenteric Gram-Negative Bacilli; *Eikenella, Pasteurella,* and *Chromobacterium* Species

Eyal Leshem, MD, DTMH
Clinical Associate Professor of Medicine, Tel Aviv University, Tel Aviv, Israel; Consultant, Division of Infectious Diseases, Sheba Medical Center, Tel Hashomer, Israel
Viral Gastroenteritis

David B. Lewis, MD
Professor of Pediatrics, Stanford University School of Medicine, Stanford, California; Chief, Division of Allergy, Immunology, and Rheumatology, Attending Physician, Lucile Salter Packard Children's Hospital, Palo Alto, California
Hemophagocytic Lymphohistiocytosis and Macrophage Activation Syndrome; Infectious Complications of Deficiencies of Cell-Mediated Immunity Other Than AIDs: Primary Immunodeficiencies

Robyn A. Livingston, MD, MPH
Associate Professor of Pediatrics, University of Missouri at Kansas City School of Medicine; Associate Professor of Pediatric Infectious Diseases, Children's Mercy–Kansas City, Kansas City, Missouri
Recurrent Meningitis

Eloisa Llata, MD, MPH
Medical Epidemiologist, Division of STD Prevention, Centers for Disease Control and Prevention, Atlanta, Georgia
Pelvic Inflammatory Disease

Kevin Lloyd, MD
Research Instructor, Department of Pediatrics, George Washington University School of Medicine and Health Sciences; Fellow, Division of Infectious Diseases, Children's National Hospital, Washington, District of Columbia
Appendicitis

Katrina Loh, MD
Pediatric Gastroenterology Fellow, Department of Gastroenterology, Hepatology, and Nutrition, Children's National Hospital, Washington, District of Columbia
Acute Hepatitis; Chronic Hepatitis

Sarah S. Long, MD
Professor of Pediatrics, Drexel University College of Medicine; Emeritus Chief, Section of Infectious Diseases, St. Christopher's Hospital for Children, Philadelphia, Pennsylvania
Mucocutaneous Symptom Complexes; Prolonged, Recurrent, and Periodic Fever Syndromes; Respiratory Tract Symptom Complexes; *Bordetella pertussis* (Pertussis) and Other *Bordetella* Species; Anaerobic Bacteria: Clinical Concepts and the Microbiome in Health and Disease; *Clostridium botulinum* (Botulism); Use of Common Clinical Laboratory Tests to Assess Infectious and Inflammatory Diseases; Principles of Anti-Infective Therapy

Benjamin A. Lopman, PhD, MSc
Professor of Epidemiology and Environmental Health, Rollins School of Public Health, Emory University, Atlanta, Georgia
Viral Gastroenteritis

Yalda C. Lucero, MD, PhD
Associate Professor of Pediatric Gastroenterology, Microbiology and Micology Program, Institute of Biomedical Science and Department of Pediatrics, Hospital Roberto del Río; Faculty of Medicine, University of Chile, Hospital Roberto del Río; Pediatric Gastroenterology, Clínica Alemana de Santiago, Facultad de Medicina, Clínica Alemana-Universidad del Desarrollo, Santiago, Chile
Aeromonas Species

Debra J. Lugo, MD
Assistant Professor of Pediatrics, Duke University School of Medicine; Division of Infectious Diseases, Duke Children's Hospital and Health Center, Durham, North Carolina
Antifungal Agents

Jorge Luján-Zilbermann, MD
Attending Physician, Division of Infectious Diseases, Johns Hopkins All Children's Hospital, Saint Petersburg, Florida
Infections in Hematopoietic Cell Transplant Recipients

Yvonne A. Maldonado, MD
Senior Associate Dean for Faculty Development and Diversity, Taube Professor of Global Health and Infectious Diseases, Professor of Pediatrics and Health Research and Policy, Stanford University School of Medicine; Chief, Division of Pediatric Infectious Diseases, Medical Director, Infection Prevention and Control and Attending Physician, Lucile Packard Children's Hospital at Stanford, Stanford, California
Rubella Virus; Mumps Virus; Rubeola Virus: Measles and Subacute Sclerosing Panencephalitis; Polioviruses

John J. Manaloor, MD
Associate Professor of Pediatrics, Baylor College of Medicine, Division of Pediatric Infectious Diseases, Director of Antimicrobial Stewardship, Children's Hospital of San Antonio, San Antonio, Texas
Agents of Eumycotic Mycetoma: *Pseudallescheria boydii* and *Scedosporium apiospermum;* Laboratory Diagnosis of Infection Due to Bacteria, Fungi, Parasites, and Rickettsiae

Kalpana Manthiram, MD, MSCI
Assistant Clinical Investigator, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland
Prolonged, Recurrent, and Periodic Fever Syndromes

Stacey W. Martin, MSc
Health Scientist, Division of Vector-Borne Diseases, Centers for Disease Control and Prevention, Fort Collins, Colorado
Principles of Epidemiology and Public Health

Roshni Mathew, MD
Clinical Associate Professor of Pediatrics, Stanford University School of Medicine, Stanford, California; Co-Medical Director, Infection Prevention and Control, Lucile Packard Children's Hospital, Palo Alto, California
Osteomyelitis; Infectious and Inflammatory Arthritis; Diskitis

Tony Mazzulli, MD
Professor of Laboratory Medicine and Pathobiology, University of Toronto Faculty of Medicine; Microbiologist-in-Chief, Department of Microbiology, Mount Sinai Hospital/ University Health Network, Toronto, Ontario, Canada
Laboratory Diagnosis of Infection Due to Viruses, *Chlamydia,* and *Mycoplasma*

Elizabeth J. McFarland, MD
Professor of Pediatrics, University of Colorado School of Medicine; Chief, Section of Infectious Diseases, Children's Hospital Colorado, Aurora, Colorado
Diagnosis and Clinical Manifestations of HIV Infection

Kathleen A. McGann, MD
Professor of Pediatrics, Duke University Medical Center; Attending Physician, Section of Infectious Diseases, Duke Children's Hospital, Durham, North Carolina
Respiratory Tract Symptom Complexes

Lucy A. McNamara, PhD
Epidemiologist, Division of Bacterial Diseases, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia
Principles of Epidemiology and Public Health

Debrah Meislich, MD
Assistant Professor of Pediatrics, Pediatric Clerkship Director, Cooper Medical School of Rowan University; Attending Physician, Pediatric Infectious Diseases, Cooper University Hospital, Camden, New Jersey
Anaerobic Cocci; Anaerobic Gram-Positive Nonsporulating Bacilli (Including Actinomycosis)

H. Cody Meissner, MD
Professor of Pediatrics, Tufts University School of Medicine; Chief, Pediatric Infectious Diseases, Department of Pediatrics, Tufts Medical Center, Boston, Massachusetts
Passive Immunization; Bronchiolitis; Respiratory Syncytial Virus

Asuncion Mejias, MD, PhD, MsCS
Associate Professor of Pediatrics, The Ohio State University College of Medicine; Division of Infectious Diseases, Nationwide Children's Hospital and Principal Investigator, Department of Pediatrics, Abigail Wexner Research Institute at Nationwide Children's Hospital, Columbus, Ohio
Fever and the Inflammatory Response; Parainfluenza Viruses

Jussi Mertsola, MD
Professor of Pediatrics and Adolescent Medicine, Turku University Hospital, Turku, Finland
Bordetella pertussis (Pertussis) and Other *Bordetella* Species

Kevin Messacar, MD
Associate Professor of Pediatrics, University of Colorado School of Medicine; Division of Infectious Diseases, Children's Hospital Colorado, Aurora, Colorado
Introduction to Picornaviridae; Enteroviruses and Parechoviruses

Mohammad Nael Mhaissen, MD
Medical Director, Pediatric Infectious Diseases, Valley Children's Healthcare, Madera, California
Cryptosporidium Species; *Cystoisospora (Isospora)* and *Cyclospora* Species

Marian G. Michaels, MD, MPH
Professor of Pediatrics, University of Pittsburgh School of Medicine; Division of Pediatric Infectious Diseases, UPMC Children's Hospital of Pittsburgh, Pittsburgh, Pennsylvania
Eosinophilic Meningitis; Infections in Solid Organ Transplant Recipients

Melissa B. Miller, PhD, D(ABMM), F(AAM)
Professor of Pathology and Laboratory Medicine, University of North Carolina School of Medicine; Director, Clinical Microbiology and Molecular Microbiology Laboratories, UNC Medical Center, Chapel Hill, North Carolina
Mechanisms and Detection of Antimicrobial Resistance

Hilary Miller-Handley, MD
Clinical Instructor, Department of Pediatrics, University of Cincinnati College of Medicine; Division of Infectious Diseases, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio
Infectious Complications in Special Hosts

Eric Mintz, MD, MPH
Medical Epidemiologist, Waterborne Diseases Prevention Branch, Centers for Disease Control and Prevention, Atlanta, Georgia
Vibrio cholerae (Cholera)

Parvathi Mohan, MD, MBBS
Professor of Pediatrics, George Washington University School of Medicine and Health Sciences; Director of Hepatology, Department of Gastroenterology, Hepatology, and Nutrition, Children's National Hospital, Washington, District of Columbia
Chronic Hepatitis

Susan P. Montgomery, DVM, MPH
Parasitic Diseases Branch, Centers for Disease Control and Prevention, Atlanta, Georgia
Diphyllobothriidae, *Dipylidium* and *Hymenolepis* Species; Blood Trematodes: Schistosomiasis

Jose G. Montoya, MD
Director of Laboratory Medicine, Dr. Jack S. Remington Laboratory for Specialty Diagnostics, Palo Alto, California
Toxoplasma gondii (Toxoplasmosis)

Anne C. Moorman, MPH
Epidemiologist, Division of Viral Hepatitis, Centers for Disease Control and Prevention, Atlanta, Georgia
Hepatitis C Virus

Pedro L. Moro, MD, MPH
Medical Epidemiologist, Immunization Safety Office, Division of Healthcare Quality Promotion, National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia
Echinococcus Species: Agents of Echinococcosis

Anna-Barbara Moscicki, MD
Professor of Pediatrics, David Geffen School of Medicine at the University of California Los Angeles; Division of Adolescent and Young Adult Medicine, Mattel Children's Hospital UCLA, Los Angeles, California
Human Papillomavirus

William J. Muller, MD, PhD
Associate Professor of Pediatrics, Northwestern University Feinberg School of Medicine; Attending Physician, Division of Infectious Diseases, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, Illinois
Epstein-Barr Virus (Mononucleosis and Lymphoproliferative Disorders)

Angela L. Myers, MD, MPH
Professor of Pediatrics, University of Missouri-Kansas City; Director, Division of Infectious Diseases, Children's Mercy–Kansas City, Kansas City, Missouri
Abdominal and Retroperitoneal Lymphadenopathy; Localized Lymphadenitis, Lymphadenopathy, and Lymphangitis

Simon Nadel, MBBS, MRCP
Consultant Paediatric Intensivist, St Mary's Hospital and Imperial College, London, United Kingdom
Acute Bacterial Meningitis Beyond the Neonatal Period

Jennifer Lynn Nayak, MD
Associate Professor of Pediatrics, University of Rochester School of Medicine and Dentistry; Division of Infectious Diseases, Golisano Children's Hospital, University of Rochester Medical Center, Rochester, New York
Human Herpesvirus 6 and 7 (Roseola, Exanthem Subitum); Human Herpesvirus 8 (Kaposi Sarcoma-Associated Herpesvirus)

Michael Noel Neely, MSc, MD
Professor of Pediatrics, Keck School of Medicine, University of Southern California; Chief, Pediatric Infectious Diseases, Children's Hospital Los Angeles, Los Angeles, California
Pharmacokinetic and Pharmacodynamic Basis of Optimal Antimicrobial Therapy; Antibacterial Agents

Karen P. Neil, MD, MSPH
Epidemiologist, Division of Foodborne, Waterborne, and Environmental Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia
Enteric Diseases Transmitted Through Food, Water, and Zoonotic Exposures

Christina A. Nelson, MD, MPH
Medical Officer, Division of Vector-Borne Diseases, Centers for Disease Control and Prevention, Fort Collins, Colorado
Francisella tularensis (Tularemia)

Noele P. Nelson, MD, PhD, MPH
Medical Epidemiologist, Division of Viral Hepatitis, Centers for Disease Control and Prevention, Atlanta, Georgia
Hepatitis A Virus

Megin Nichols, DVM, MPH, DACVPM
Epidemiologist, Division of Foodborne, Waterborne, and Environmental Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia
Enteric Diseases Transmitted Through Food, Water, and Zoonotic Exposures

William Nicholson, PhD
Activity Chief, Rickettsial Zoonoses Branch, Centers for Disease Control and Prevention, Atlanta, Georgia
Family Anaplasmataceae (Anaplasmosis, Ehrlichiosis, Neorickettsiosis, and Neoehrlichiosis)

Amy Jo Nopper, MD
Professor of Pediatrics, University of Missouri at Kansas City School of Medicine; Division Director, Dermatology, Children's Mercy–Kansas City, Kansas City, Missouri
Superficial Bacterial Skin Infections and Cellulitis

Laura E. Norton, MD
Assistant Professor of Pediatrics, University of Minnesota Medical School, Minneapolis, Minnesota
Arcanobacterium haemolyticum; Other Corynebacteria

Theresa J. Ochoa, MD
Associate Professor, Instituto de Medicina Tropical Alexander von Humboldt, Universidad Peruana Cayetano Heredia, Lima, Peru; Associate Professor of Epidemiology, Center for Infectious Diseases, University of Texas Health Science Center at Houston, Houston, Texas
Yersinia Species

Liset Olarte, MD, MSc
Assistant Professor of Pediatrics, University of Missouri at Kansas City School of Medicine; Division of Infectious Diseases, Children's Mercy–Kansas City, Kansas City, Missouri
Streptococcus pneumoniae; Bacillus Species (Including Anthrax)

Timothy R. Onarecker, MD
Assistant Professor of Pediatrics, University of Arkansas for Medical Sciences; Division of Infectious Diseases, Arkansas Children's Hospital, Little Rock, Arkansas
Aseptic and Viral Meningitis

Walter A. Orenstein, MD, DSc (Hon)
Professor of Medicine, Pediatrics, Epidemiology, and Global Health, Emory University School of Medicine; Associate Director, Emory Vaccine Center, Atlanta, Georgia
Active Immunization

Miguel O'Ryan, MD
Professor, Microbiology and Mycology Program, Institute of Biomedical Sciences, Faculty of Medicine, University of Chile, Santiago, Chile
Yersinia Species; *Aeromonas* Species

William R. Otto, MD
Attending Physician, Pediatrics, Division of Infectious Diseases, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania
Candida Species

Christopher P. Ouellette, MD
Assistant Professor of Pediatrics, The Ohio State University College of Medicine; Division of Infectious Diseases and Host Defense Program, Nationwide Children's Hospital, Columbus, Ohio
Proteus, Providencia, and *Morganella* Species

Christopher D. Paddock, MD, MS, MPHTM
Research Medical Officer, Rickettsial Zoonoses Branch, Centers for Disease Control and Prevention, Atlanta, Georgia
Rickettsia rickettsii (Rocky Mountain Spotted Fever)

Debra L. Palazzi, MD, MEd
Professor of Pediatrics, Baylor College of Medicine; Chief, Pediatric Infectious Diseases Clinic, Texas Children's Hospital, Houston, Texas
Eosinophilic Meningitis

Suresh Kumar Panuganti, MBBS, DCH, DNB (Paediatrics)
Fellow in Pediatric Critical Care Medicine, Consultant Pediatric Intensivist, Department of Pediatrics, Yashoda Hospital, Somajiguda, Hyderabad, India
Acute Bacterial Meningitis Beyond the Neonatal Period

Diane E. Pappas, MD, JD
Professor of Pediatrics, University of Virginia School of Medicine; Division of General Pediatrics, University of Virginia Health System, Charlottesville, Virginia
The Common Cold; Rhinoviruses

Michal Paret, MD
Division of Pediatric Infectious Diseases, Department of Pediatrics, NYU Langone Health/Hassenfeld Children's Hospital, New York, New York
Epididymitis, Orchitis, and Prostatitis

Daniel M. Pastula, MD, MHS
Associate Professor of Neurology, Medicine (Infectious Diseases and Epidemiology), University of Colorado School of Medicine, Aurora, Colorado
Parainfectious and Postinfectious Neurologic Syndromes

Thomas F. Patterson, MD
Professor of Medicine, University of Texas Health Sciences Center at San Antonio; Chief, Division of Infectious Diseases, Director, San Antonio Center for Medical Mycology, UT Health San Antonio, San Antonio, Texas
Classification of Fungi; Agents of Hyalohyphomycosis and Phaeohyphomycosis; Agents of Mucormycosis; *Malassezia* Species; *Sporothrix schenckii* Complex (Sporotrichosis); *Cryptococcus* Species

Brett W. Petersen, MD, MPH
Captain, US Public Health Service, Poxvirus and Rabies Branch, Division of High Consequence Pathogens and Pathology, National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia
Poxviridae

Mikael Petrosyan, MD, MBA
Associate Professor of General and Thoracic Surgery, George Washington University School of Medicine; Associate Chief, Department of General and Thoracic Surgery, Children's National Medical Center, Washington, District of Columbia
Appendicitis

Larry K. Pickering, MD
Adjunct Professor of Pediatrics, Emory University School of Medicine, Atlanta, Georgia
Active Immunization

Talia Pindyck, MD, MPH
Medical Epidemiologist, Waterborne Disease Prevention Branch, Centers for Disease Control and Prevention, Atlanta, Georgia
Vibrio cholerae (Cholera)

Swetha Pinninti, MD
Assistant Professor, University of Alabama at Birmingham Heersink School of Medicine; Division of Infectious Diseases, Children's Hospital of Alabama at the University of Alabama, Birmingham, Alabama
Viral Infections in the Fetus and Neonate

Laure F. Pittet, MD, PhD
Clinical Research Fellow, Infectious Diseases Unit, Department of General Paediatrics, University Hospitals of Geneva, Faculty of Medicine of the University of Geneva, Geneva, Switzerland; Honorary Fellow, Department of Paediatrics, The University of Melbourne; Clinical Research Fellow, Infectious Diseases Group, Murdoch Children's Research Institute, Parkville, Victoria, Australia
Mycobacterium Nontuberculosis Species

Paul J. Planet, MD, PhD
Assistant Professor of Pediatrics, Perelman School of Medicine at the University of Pennsylvania; Attending Physician, Division of Infectious Diseases, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania
Pseudomonas aeruginosa

Andrew J. Pollard, MBBS, BSC, MRCP(UK), DIC, PhD
Professor of Paediatric Infection and Immunity, Oxford Vaccine Group, Department of Paediatrics, University of Oxford, Oxford, United Kingdom
Neisseria meningitidis

Klara M. Posfay-Barbe, MD
Professor, Department of Pediatrics, Gynecology, and Obstetrics, University of Geneva School of Medicine; Head, Infectious Diseases Unit, Children's Hospital of Geneva, University Hospitals of Geneva, Geneva, Switzerland
Eosinophilic Meningitis

Casper S. Poulsen, PhD
Faculty of Health and Medical Sciences, University of Copenhagen; Novo Nordisk Foundation Center for Basic Metabolic Research, Copenhagen, Denmark
Endolimax nana

Susan M. Poutanen, MD, MPH
Associate Professor of Laboratory Medicine and Pathobiology & Medicine, University of Toronto Faculty of Medicine; Medical Microbiologist & Infectious Diseases Physician, Mount Sinai Hospital & University Health Network, Toronto, Ontario, Canada
Human Coronaviruses

Ann M. Powers, PhD
Lead, Virology Team, Arboviral Diseases Branch, Centers for Disease Control and Prevention, Fort Collins, Colorado
Togaviridae: Alphaviruses

Nina Salinger Prasanphanich, MD, PhD
Pediatric Infectious Diseases Fellow, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio
Giardia intestinalis (Giardiasis)

Bobbi S. Pritt, MD, MSc, (D)TMH
Professor of Laboratory Medicine and Pathology, Director, Clinical Parasitology, Mayo Clinic, Minneapolis, Minnesota
Family Anaplasmataceae (Anaplasmosis, Ehrlichiosis, Neorickettsiosis, and Neoehrlichiosis)

Charles G. Prober, MD
Professor of Pediatrics, Microbiology, and Immunology, Founding Executive Director, Stanford Center for Health Education, Senior Associate Vice Provost for Health Education, Stanford University School of Medicine, Stanford, California
Introduction to Herpesviridae; Herpes Simplex Virus

Neha Puar, MD
Clinical Assistant Professor of Pediatrics, University of Missouri at Kansas City School of Medicine; Children's Mercy–Kansas City, Kansas City, Missouri
Superficial Bacterial Skin Infections and Cellulitis

Laura A.S. Quilter, MD, MPH
Medical Officer, Division of STD Prevention, Centers for Disease Control and Prevention, Atlanta, Georgia
Genitourinary Skin and Mucous Membrane Infections and Inguinal Lymphadenopathy; *Trichomonas vaginalis*

Octavio Ramilo, MD
Henry G. Cramblett Chair in Pediatric Infectious Diseases and Professor, Department of Pediatrics, The Ohio State University College of Medicine; Chief, Division of Infectious Diseases, Nationwide Children's Hospital, Columbus, Ohio
Fever and the Inflammatory Response; Parainfluenza Viruses

Suchitra Rao, MBBS, MSCS
Associate Professor of Pediatrics, University of Colorado School of Medicine; Divisions of Infectious Diseases and Hospital Medicine, Children's Hospital Colorado, Aurora, Colorado
BK, JC, and Other Human Polyomaviruses; Influenza Viruses

Adam J. Ratner, MD, MPH
Associate Professor of Pediatrics and Microbiology, NYU Grossman School of Medicine; Chief, Division of Pediatric Infectious Diseases, NYU Langone Health, New York, New York
Sexually Transmitted Infection Syndromes; Epididymitis, Orchitis, and Prostatitis

Sarah A. Rawstron, MD
Associate Professor of Pediatrics, Hackensack Meridian School of Medicine; Attending Physician, Infectious Diseases, K. Hovnanian Children's Hospital at Jersey Shore University Medical Center, Neptune, New Jersey
Treponema pallidum (Syphilis); Other *Treponema* Species

Jennifer S. Read, MD, MPH, DTM&H
Clinical Professor of Pediatrics, University of Vermont Medical Center, Burlington, Vermont
Epidemiology and Prevention of HIV Infection in Infants, Children, and Adolescents

Ryan F. Relich, PhD, D(ABMM), MLS(ASCP)CMSMCM
Associate Professor of Clinical Pathology and Laboratory Medicine, Indiana University School of Medicine; Medical Director, Division of Clinical Microbiology, Indiana University Health; Medical Director, Clinical Microbiology and Serology Laboratories, Eskenazi Health, Indianapolis, Indiana
Laboratory Diagnosis of Infection Due to Bacteria, Fungi, Parasites, and Rickettsiae

Megan E. Reller, MD, PhD, MPH, DTM&H
Associate Professor of Medicine, Duke University School of Medicine; Division of Infectious Diseases and International Health, Duke Hubert-Yeargan Center for Global Health and Duke Global Health Institute, Durham, North Carolina
Salmonella Species

Candice L. Robinson, MD, MPH
Medical Officer, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia
Active Immunization

José R. Romero, MD
Professor of Pediatrics, Division of Pediatric Infectious Diseases, University of Arkansas for Medical Sciences; Arkansas Secretary of Health, Director, Arkansas Department of Health, Little Rock, Arkansas
Aseptic and Viral Meningitis

David A. Rosen, MD, PhD
Assistant Professor of Pediatrics and Molecular Microbiology, Washington University School of Medicine; Division of Infectious Diseases, St. Louis Children's Hospital, St. Louis, Missouri
Infectious Complications in Special Hosts

Shannon A. Ross, MD, MSPH
Associate Professor of Pediatrics, University of Alabama at Birmingham Heersink School of Medicine; Division of Infectious Diseases, Children's Hospital of Alabama at the University of Alabama, Birmingham, Alabama
Cytomegalovirus

G. Ingrid J.G. Rours, MD, PhD, MSc
Pediatrics, Kinderplein, Medical Center for Quality of Life; Physician, Medical Microbiology and Infectious Diseases, Erasmus Medical Center, Rotterdam, Zuid Holland, the Netherlands
Chlamydia trachomatis

Peter C. Rowe, MD
Professor of Pediatrics, Johns Hopkins University School of Medicine; Division of Adolescent and Young Adult Medicine, Department of Pediatrics, Johns Hopkins Children's Center, Baltimore, Maryland
Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)

Anne H. Rowley, MD
Professor of Pediatrics and Microbiology/Immunology, Northwestern University Feinberg School of Medicine; Attending Physician, Infectious Diseases, The Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, Illinois
Kawasaki Disease

Lorry G. Rubin, MD
Professor of Pediatrics, Zucker School of Medicine at Hofstra/Northwell, Hempstead, New York; Director, Infectious Diseases, Cohen Children's Medical Center of New York, New Hyde Park, New York
Capnocytophaga Species; *Francisella tularensis* (Tularemia); *Legionella* Species; *Streptobacillus moniliformis* (Rat-Bite Fever); Other Gram-Negative Coccobacilli

Edward T. Ryan, MD
Professor of Medicine, Harvard Medical School; Professor of Immunology, Harvard T.H. Chan School of Public Health; Director, Global Infectious Diseases, Massachusetts General Hospital, Boston, Massachusetts
Antiparasitic Agents

Alexandra Sacharok, BS
Graduate Student Researcher, Department of Pediatrics, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania
Classification of Bacteria

Thomas J. Sandora, MD, MPH
Associate Professor of Pediatrics, Harvard Medical School; Hospital Epidemiologist, Department of Pediatrics, Division of Infectious Diseases, Boston Children's Hospital, Boston, Massachusetts
Clostridioides difficile

Sarah G.H. Sapp, PhD
Biologist, Division of Parasitic Diseases and Malaria, Centers for Disease Control and Prevention, Atlanta, Georgia
Diphyllobothriidae, *Dipylidium* and *Hymenolepis* Species

Kabir Sardana, MD, DNB, MNAMS
Professor and Director of Dermatology, Dr RML Hospital, ABVIMS, Delhi, India
Superficial Fungal Infections

Jason B. Sauberan, PharmD
Clinical Research Pharmacist, Neonatal Research Institute, Sharp Mary Birch Hospital for Women and Newborns; Consultant Pharmacist, Helen Bernardy Center for Medically Fragile Children, Rady Children's Hospital, San Diego, California
Pharmacokinetic and Pharmacodynamic Basis of Optimal Antimicrobial Therapy; Antibacterial Agents

Joshua K. Schaffzin, MD, PhD
Associate Professor of Pediatrics, University of Cincinnati College of Medicine; Division of Infectious Diseases, Director, Infection Prevention & Control Program, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio
Granulomatous Hepatitis; Acute Pancreatitis; Cholecystitis and Cholangitis; Clinical Syndromes of Device-Associated Infections

Sarah Schillie, MD, MPH, MBA
Medical Epidemiologist, Division of Viral Hepatitis, Centers for Disease Control and Prevention, Atlanta, Georgia
Hepatitis B and Hepatitis D Viruses

Jennifer E. Schuster, MD, MSCI
Associate Professor of Pediatrics, University of Missouri-Kansas City School of Medicine; Division of Infectious Diseases, Children's Mercy–Kansas City, Kansas City, Missouri
Human Metapneumovirus

Kevin L. Schwartz, MD, MSc, DTM&H
Assistant Professor, Dalla Lana School of Public Health, University of Toronto Faculty of Medicine; Physician, Infectious Diseases, Unity Health Toronto; Infectious Diseases Physician, Infection Prevention and Control, Public Health Ontario, Toronto, Ontario, Canada
Protection of Travelers

Bethany K. Sederdahl, MD, MPH
Attending Physician, Department of Obstetrics & Gynecology, Christiana Care Healthcare System, Newark, Delaware
Other *Campylobacter* Species

Jose Serpa-Alvarez, MD
Associate Professor of Medicine–Infectious Diseases, Baylor College of Medicine, Houston, Texas
Taenia solium, Taenia asiatica, and *Taenia saginata:* Taeniasis and Cysticercosis; *Taenia (Multiceps) multiceps* and *Taenia serialis:* Coenurosis

Kara N. Shah, MD, PhD
Optima Dermatology, Liberty Township, Ohio
Urticaria and Erythema Multiforme

Samir S. Shah, MD, MSCE
Professor of Pediatrics, University of Cincinnati College of Medicine; Director, Division of Hospital Medicine, Attending Physician in Infectious Diseases and Hospital Medicine, James M. Ewell Endowed Chair, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio
Acute Pneumonia and Its Complications; *Chlamydophila (Chlamydia) pneumoniae; Mycoplasma pneumoniae;* Other *Mycoplasma* Species; *Ureaplasma urealyticum*

Nader Shaikh, MD, MPH
Professor of Pediatrics, University of Pittsburgh School of Medicine; Attending Physician, UMPC Children's Hospital of Pittsburgh, Pittsburgh, Pennsylvania
Otitis Media

Andi L. Shane, MD, MPH, MSc
Marcus Professor of Hospital Epidemiology and Infection Prevention, Emory University School of Medicine and Children's Healthcare of Atlanta, Atlanta, Georgia
Infections Associated With Group Childcare; Approach to the Diagnosis and Management of Gastrointestinal Tract Infections

Eugene D. Shapiro, MD
Professor of Pediatrics and Epidemiology (Microbial Diseases and Investigative Medicine), Yale University School of Medicine; Attending Physician, The Children's Hospital at Yale–New Haven, New Haven, Connecticut
Fever Without Localizing Signs; *Borrelia burgdorferi* (Lyme Disease)

Jana Shaw, MD, MPH
Professor of Pediatrics, SUNY Upstate Medical University, Syracuse, New York
Infections of the Oral Cavity

Avinash K. Shetty, MD
Associate Dean for Global Health, Professor of Pediatrics, Director, Global Health Education, Wake Forest School of Medicine; Chief, Section of Pediatric Infectious Diseases, Director, Pediatric HIV Program, Atrium Health-Wake Forest Baptist, Brenner Children's Hospital, Winston-Salem, North Carolina
Rubella Virus; Mumps Virus; Rubeola Virus: Measles and Subacute Sclerosing Panencephalitis

Timothy R. Shope, MD, MPH
Professor of Pediatrics, University of Pittsburgh School of Medicine; Attending Physician, Children's Hospital of Pittsburgh of UPMC, Pittsburgh, Pennsylvania
Infections Associated With Group Childcare

Linda M. Dairiki Shortliffe, MD
Stanley McCormick Memorial Professor Emerita, Department of Urology, Stanford University School of Medicine, Stanford, California
Urinary Tract Infections, Renal Abscess, and Other Complex Renal Infections

Stanford T. Shulman, MD
Virginia H. Rogers Emeritus Professor of Pediatrics, Division of Infectious Diseases, Northwestern University Feinberg School of Medicine, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, Illinois
Pharyngitis; *Streptococcus pyogenes* (Group A *Streptococcus*)

Gail F. Shust, MD
Clinical Associate Professor of Pediatrics, NYU Grossman School of Medicine; Division of Pediatric Infectious Diseases, NYU Langone Health, New York, New York
Sexually Transmitted Infection Syndromes; Management of HIV Infection

George Kelly Siberry, MD, MPH
Medical Officer, Office of HIV/AIDS, US Agency for International Development (USAID), Washington, District of Columbia
Management of HIV Infection

Jane D. Siegel, MD
Public Health Medical Officer III, Healthcare Associated Infections Program, California Department of Public Health, Richmond, California
Pediatric Healthcare: Infection Epidemiology, Prevention and Control, and Antimicrobial Stewardship

Robert David Siegel, MD, PhD
Professor of Microbiology and Immunology, Stanford University School of Medicine, Stanford, California
Classification of Human Viruses

Kari A. Simonsen, MD
Professor of Pediatrics, Division of Infectious Diseases, University of Nebraska Medical Center, Omaha, Nebraska
Infectious Complications of Corticosteroid Therapy

Upinder Singh, MD
Professor and Division Chief, Division of Infectious Diseases and Geographic Medicine, Department of Medicine, Stanford University School of Medicine, Stanford, California
Entamoeba histolytica (Amebiasis); Other *Entamoeba,* Amebae, and Intestinal Flagellates; *Naegleria fowleri; Acanthamoeba* Species

Christiana Smith, MD, MSCS
Assistant Professor of Pediatrics, University of Colorado School of Medicine; Section of Infectious Diseases, Children's Hospital Colorado, Aurora, Colorado
Pneumonia in the Immunocompromised Host; Diagnosis and Clinical Manifestations of HIV Infection

Lauren L. Smith, MD
Assistant Professor of Pediatrics, Eastern Virginia Medical School; Medical Director, Division of Allergy and Immunology, Children's Hospital of the King's Daughters, Norfolk, Virginia
Evaluation of the Child With Suspected Immunodeficiency; Infectious Complications of Dysfunction or Deficiency of Polymorphonuclear and Mononuclear Phagocytes

Eunkyung Song, MD
Assistant Professor of Pediatrics, The Ohio State University College of Medicine; Division of Infectious Diseases, Nationwide Children's Hospital, Columbus, Ohio
Serratia Species

Emily Souder, MD
Assistant Professor of Pediatrics, Drexel University College of Medicine; Section of Infectious Diseases, St. Christopher's Hospital for Children, Philadelphia, Pennsylvania
Other *Haemophilus* Species and *Aggregatibacter* Species

Paul Spearman, MD
Albert B. Sabin Professor, Department of Pediatrics, University of Cincinnati College of Medicine; Director, Division of Infectious Diseases, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio
Acute Pneumonia and Its Complications

Joseph W. St. Geme III, MD
Professor of Pediatrics and Microbiology, Perelman School of Medicine at the University of Pennsylvania; Chairman, Department of Pediatrics, Children's Hospital of Philadelphia and University of Pennsylvania; Physician-in-Chief, Department of Pediatrics, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania
Classification of Bacteria; Classification of Streptococci; *Enterococcus* Species; Viridans Streptococci, *Abiotrophia* and *Granulicatella* Species, and *Streptococcus bovis* Group; Groups C and G Streptococci; Other Gram-Positive, Catalase-Negative Cocci: *Leuconostoc* and *Pediococcus* Species and Other Genera; *Haemophilus influenzae*

Mary Allen Staat, MD, MPH
Professor of Pediatrics, University of Cincinnati College of Medicine; Director, International Adoption Center, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio
Infectious Diseases in Refugee and Internationally Adopted Children

J. Erin Staples, MD, PhD
Lead, Surveillance and Epidemiology Team, Arboviral Diseases Branch, Centers for Disease Control and Prevention, Fort Collins, Colorado
Coltivirus (Colorado Tick Fever); Togaviridae: Alphaviruses; Bunyaviruses

Jeffrey R. Starke, MD
Professor of Pediatrics, Baylor College of Medicine; Section of Infectious Diseases, Texas Children's Hospital, Houston, Texas
Mycobacterium tuberculosis

Victoria A. Statler, MD, MSc
Associate Professor of Pediatrics, University of Louisville School of Medicine; Physician, Division of Infectious Diseases, Norton Children's Hospital, Louisville, Kentucky
Tickborne Infections

William J. Steinbach, MD
Robert H. Fiser, Jr., MD Endowed Chair in Pediatrics, Chair, Department of Pediatrics, Associate Dean for Child Health, College of Medicine, University of Arkansas for Medical Sciences; Pediatrician-in-Chief, Arkansas Children's Hospital, Little Rock, Arkansas
Candida Species, *Aspergillus* Species; Antifungal Agents

Christen Rune Stensvold, BMedSc, MSc, PhD
Senior Scientist, Department of Bacteria, Parasites, and Fungi, Statens Serum Institut, Copenhagen, Denmark
Balantioides coli (Formerly *Balantidium coli*); *Blastocystis* Species; *Endolimax nana*

Erin K. Stokes, MPH
Surveillance Epidemiologist, Division of Foodborne, Waterborne, and Environmental Diseases, National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia
Other *Vibrio* Species

Bradley P. Stoner, MD, PhD
Professor and Head, Department of Public Health Sciences, Queen's University, Kingston, Ontario, Canada
Klebsiella granulomatis: Granuloma Inguinale (Donovanosis)

Gregory A. Storch, AB, MD
Ruth L. Siteman Professor of Pediatrics, Washington University School of Medicine, St. Louis, Missouri
Use of Common Clinical Laboratory Tests to Assess Infectious and Inflammatory Diseases

Anne Straily, DVM, MPH, DACVPM
Parasitic Diseases Branch, Division of Parasitic Diseases and Malaria, Centers for Disease Control and Prevention, Atlanta, Georgia
Blood Trematodes: Schistosomiasis

Kathleen E. Sullivan, MD, PhD
Professor of Pediatrics, Perelman School of Medicine at the University of Pennsylvania; Chief, Division of Allergy and Immunology, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania
Infectious Complications of Complement Deficiency and Diseases of Its Dysregulation

Douglas S. Swanson, MD
Associate Professor of Pediatrics, University of Missouri at Kansas City School of Medicine; Division of Infectious Diseases, Children's Mercy–Kansas City, Kansas City, Missouri
Chronic Meningitis

Robert R. Tanz, MD
Professor Emeritus of Pediatrics, Division of Advanced General Pediatrics & Primary Care, Northwestern University Feinberg School of Medicine, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, Illinois
Streptococcus pyogenes (Group A *Streptococcus*)

Gillian Taormina, DO, MS
Assistant Professor of Pediatrics, Albany Medical College; Attending Physician, Division of Pediatric Infectious Diseases, Albany Medical Center, Albany, New York
Intra-abdominal, Visceral, and Retroperitoneal Abscesses

Jacqueline E. Tate, PhD
Epidemiologist, Division of Viral Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia
Astroviruses

Jeanette Taveras, DO
Assistant Professor of Pediatrics, Drexel University College of Medicine; Section of Infectious Diseases, St. Christopher's Hospital for Children, Philadelphia, Pennsylvania
Fever and the Inflammatory Response

Marc Tebruegge, DTM&H, MRCPCH, MSc, MD, PhD
Clinical Senior Lecturer, Department of Paediatrics, The University of Melbourne, Parkville, Victoria, Australia; Honorary Associate Professor, Department of Infection, Immunity, and Inflammation, UCL Great Ormond Street Institute of Child Health, London, United Kingdom
Infections Related to the Upper and Middle Airways; *Mycobacterium* Nontuberculosis Species

Eyasu H. Teshale, MD
Medical Officer, Division of Viral Hepatitis, Centers for Disease Control and Prevention, Atlanta, Georgia
Hepatitis C Virus; Hepatitis E Virus

George R. Thompson III, MD
Professor of Medicine, Division of Infectious Diseases, UC Davis Medical Center, Sacramento, California
Cryptococcus Species; *Coccidioides immitis* and *Coccidioides posadasii* (Coccidioidomycosis)

Robert Thompson-Stone, MD
Associate Professor of Neurology and Pediatrics, University of Rochester School of Medicine & Dentistry; Division of Child Neurology, Golisano Children's Hospital, University of Rochester Medical Center, Rochester, New York
Neurologic Syndromes

Isaac Thomsen, MD, MSCI
Associate Professor–Pediatric Infectious Diseases, Vanderbilt University Medical Center, Nashville, Tennessee
Staphylococcus aureus

Richard B. Thomson, Jr., PhD, D(ABMM)
Clinical Professor of Pathology, The University of Chicago Pritzker School of Medicine; Medical Microbiologist, Department of Pathology and Laboratory Medicine, NorthShore University HealthSystem, Evanston, Illinois
Nocardia Species

Emily A. Thorell, MD, MSCI
Associate Professor of Pediatrics, University of Utah School of Medicine; Director, Antimicrobial Stewardship Program, Associate Hospital Epidemiologist, Division of Infectious Diseases, Primary Children's Medical Center, Salt Lake City, Utah
Cervical Lymphadenitis and Neck Infections

Vivian Tien, MD
Fellow, Division of Infectious Diseases and Geographic Medicine, Department of Medicine, Stanford University School of Medicine, Stanford, California
Entamoeba histolytica (Amebiasis); Other *Entamoeba,* Amebae, and Intestinal Flagellates; *Naegleria fowleri; Acanthamoeba* Species

Nicole H. Tobin, MD
Associate Adjunct Professor, Department of Pediatrics, David Geffen School of Medicine at the University of California, Los Angeles; Attending Physician, Division of Infectious Diseases, UCLA Mattel Children's Hospital, Los Angeles, California
Immunopathogenesis of HIV-1 Infection

Philip Toltzis, MD
Professor of Pediatrics, Case Western Reserve University School of Medicine; Infectious Diseases Specialist, Division of Pediatric Pharmacology and Critical Care, Rainbow Babies and Children's Hospital, Cleveland, Ohio
Coagulase-Negative Staphylococci and Micrococcaceae

James Treat, MD
Professor of Pediatrics, Perelman School of Medicine at the University of Pennsylvania; Fellowship Director, Education Director and Attending Physician, Pediatric Dermatology, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania
Vesicles and Bullae

Stephanie B. Troy, MD
Medical Officer, Division of Antivirals, Office of Infectious Diseases/Office of New Drugs, Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, Maryland
Polioviruses

Russell B. Van Dyke, MD
Professor of Pediatrics, Tulane University School of Medicine, New Orleans, Louisiana
Infectious Complications of HIV Infection

Louise Elaine Vaz, MD, MPH
Associate Professor of Pediatrics, Oregon Health & Sciences University; Division of Infectious Diseases, Doernbecher Children's Hospital, Portland, Oregon
The Systemic Inflammatory Response Syndrome, Sepsis, and Septic Shock

Vini Vijayan, MD
Pediatric Infectious Diseases Specialist, Division of Infectious Diseases, Valley Children's Hospital, Madera, California
Bartonella Species (Cat-Scratch Disease)

Jennifer Vodzak, MD
Assistant Professor of Pediatrics, Geisinger Commonwealth School of Medicine, Scranton, Pennsylvania; Director, Division of Infectious Diseases and Director, Pediatric Quality, Safety and Best Practice, Geisinger Janet Weis Children's Hospital, Danville, Pennsylvania
Other *Haemophilus* Species and *Aggregatibacter* Species; *Fusobacterium* Species; Use of Common Clinical Laboratory Tests to Assess Infectious and Inflammatory Diseases

Thor A. Wagner, MD
Associate Professor of Pediatrics, University of Washington, Center for Global Infectious Diseases Research, Seattle Children's Research Institute, Seattle, Washington
Introduction to Retroviridae; Human T-Cell Lymphotropic Viruses; Human Immunodeficiency Virus

Ellen R. Wald, MD
Alfred Dorrance Daniels Professor of Diseases of Children, Chair, Department of Pediatrics, University of Wisconsin School of Medicine & Public Health; Pediatrician-in-Chief, Department of Pediatrics, American Family Children's Hospital, Madison, Wisconsin
Mastoiditis; Sinusitis; Preseptal and Orbital Infections

Rebecca Wallihan, MD
Attending Physician, Division of Infectious Diseases, Nationwide Children's Hospital and The Ohio State University College of Medicine, Columbus, Ohio
Less Commonly Encountered Enterobacterales

Huanyu Wang, PhD, DABMM
Assistant Professor of Pathology and Laboratory Medicine, The Ohio State University College of Medicine; Assistant Director, Clinical Microbiology and Immunoserology Laboratories, Nationwide Children's Hospital, Columbus, Ohio
Proteus, Providencia, and *Morganella* Species; *Serratia* Species; *Acinetobacter* Species

Zoon Wangu, MD
Assistant Professor of Pediatrics–Infectious Diseases and Immunology, UMass Chan Medical School, UMass Memorial Children's Medical Center, Worcester, Massachusetts; Clinical Faculty, Ratelle STD/HIV Prevention Training Center, Massachusetts Department of Public Health, Jamaica Plain, Massachusetts
Protection of Travelers; *Neisseria gonorrhoeae;* Other *Neisseria* Species

Matthew Washam, MD, MPH
Assistant Professor of Pediatrics, The Ohio State University College of Medicine; Division of Infectious Diseases, Nationwide Children's Hospital, Columbus, Ohio
Klebsiella and *Raoultella* Species

Valerie Waters, MD, MSc
Professor of Paediatric Infectious Diseases, Senior Associate Scientist, Research Institute, The Hospital for Sick Children, Toronto, Ontario, Canada
Pseudomonas Species and Related Organisms; *Burkholderia cepacia* Complex and Other *Burkholderia* Species; *Stenotrophomonas maltophilia*

Joshua R. Watson, MD
The Ohio State University College of Medicine; Attending Physician, Division of Infectious Diseases, Nationwide Children's Hospital, Columbus, Ohio
Less Commonly Encountered Enterobacterales

Jill E. Weatherhead, MD, PhD
Director of Medical Education, National School of Tropical Medicine, Assistant Professor of Infectious Diseases and Pediatric Tropical Medicine, Baylor College of Medicine, Houston, Texas
Classification of Parasites; Intestinal Nematodes

Geoffrey A. Weinberg, MD
Professor of Pediatrics, University of Rochester School of Medicine & Dentistry; Director, Clinical Pediatric Infectious Diseases & Pediatric HIV Program, Golisano Children's Hospital, University of Rochester Medical Center, Rochester, New York
Neurologic Syndromes

Mark K. Weng, MD, MSc
Medical Epidemiologist, Division of Viral Hepatitis, Centers for Disease Control and Prevention, Atlanta, Georgia
Hepatitis A Virus

Nathan P. Wiederhold, PharmD
Professor of Pathology and Laboratory Medicine, Director, Fungus Testing Laboratory, UT Health San Antonio, San Antonio, Texas
Classification of Fungi; Agents of Hyalohyphomycosis and Phaeohyphomycosis; Agents of Mucormycosis; *Malassezia* Species; *Sporothrix schenckii* Complex (Sporotrichosis)

Harold C. Wiesenfeld, MD, CM
Professor of Obstetrics, Gynecology, and Reproductive Sciences, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania
Pelvic Inflammatory Disease

Cydni Williams, MD, MCR
Associate Professor of Pediatrics, Oregon Health & Science University; Director, Pediatric Critical Care and Neurotrauma Recovery Program, OHSU Doernbecher Children's Hospital, Portland, Oregon
The Systemic Inflammatory Response Syndrome, Sepsis, and Septic Shock

John V. Williams, MD
Henry L. Hillman Professor of Pediatrics, Microbiology & Molecular Genetics, University of Pittsburgh School of Medicine; Chief, Pediatric Infectious Diseases, UPMC Children's Hospital of Pittsburgh, Pittsburgh, Pennsylvania
Human Metapneumovirus

Rodney E. Willoughby, Jr., MD
Professor of Pediatrics, Medical College of Wisconsin, Milwaukee, Wisconsin
Rabies Virus

Robert R. Wittler, MD
Professor of Pediatrics, Kansas University School of Medicine—Wichita, Wichita, Kansas
Persistent and Recurrent Pneumonia

James B. Wood, MD, MSCI
Assistant Professor of Pediatrics, Indiana University School of Medicine; Ryan White Center for Pediatric Infectious Diseases and Global Health, Division of Pediatric & Adolescent Clinical Effectiveness Research, Riley Hospital for Children, Indianapolis, Indiana
Musculoskeletal Symptom Complexes; *Histoplasma capsulatum* (Histoplasmosis)

Charles Reece Woods, MD
Professor and Chair, Department of Pediatrics, University of Tennessee College of Medicine Chattanooga; Chief Executive Officer, Children's Hospital, Erlanger Health System, Chattanooga, Tennessee
Subcutaneous Tissue Infections and Abscesses

Kimberly A. Workowski, MD
Professor of Medicine and Infectious Diseases, Emory University School of Medicine; Clinical Consultant, Epidemiology and Surveillance Branch, Division of STD Prevention, Centers for Disease Control and Prevention, Atlanta, Georgia
Genitourinary Skin and Mucous Membrane Infections and Inguinal Lymphadenopathy; *Trichomonas vaginalis*

Terry W. Wright, PhD
Associate Professor of Pediatrics, University of Rochester School of Medicine and Dentistry, Rochester, New York
Pneumocystis jirovecii

Hsi-Yang Wu, MD
Director of Pediatric Urology; Warren Alpert Medical School of Brown University, Providence, Rhode Island
Urinary Tract Infections, Renal Abscess, and Other Complex Renal Infections

Huan Xu, MD
Assistant Professor of Medicine, Baylor College of Medicine; Division of Infectious Diseases, Michael E. Debakey Veteran's Administration Medical Center, Houston, Texas
Taenia solium, Taenia asiatica, and *Taenia saginata:* Taeniasis and Cysticercosis; *Taenia (Multiceps) multiceps* and *Taenia serialis:* Coenurosis

Pablo Yagupsky, MD
Professor of Pediatrics and Clinical Microbiology, Director, The Joyce and Irving Goldman Medical School, Ben-Gurion University of the Negev; Director, The Clinical Microbiology Laboratory, Soroka University Medical Center, Beer-Sheva, Israel
Kingella Species

Jumi Yi, MD
Director, Global Regulatory Affairs and Clinical Safety, Merck & Co., Rahway, New Jersey
Approach to the Diagnosis and Management of Gastrointestinal Tract Infections; *Campylobacter jejuni* and *Campylobacter coli*

Jonathan Yoder, MSW, MPH
Epidemiologist, Division of Foodborne, Waterborne, and Environmental Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia
Enteric Diseases Transmitted Through Food, Water, and Zoonotic Exposures

[†]Edward J. Young, MD
Professor of Medicine, Baylor College of Medicine; Michael E. DeBakey Veteran's Administration Medical Center, Houston, Texas
Brucella Species (Brucellosis)

Andrea L. Zaenglein, MD
Professor of Dermatology and Pediatrics, Penn State University; Attending Physician in Dermatology, Hershey Medical Center, Penn State Children's Hospital, Hershey, Pennsylvania
Erythematous Macules and Papules

Petra Zimmermann, MD, PhD
Consultant in Paediatric Infectious Diseases and Senior Lecturer, Faculty of Science and Medicine, University of Fribourg, Fribourg, Switzerland; Honorary Fellow, Infectious Diseases Research Group, Murdoch Children's Research Institute Melbourne, Parkville, Victoria, Australia
Infections Related to the Upper and Middle Airways

Wenjing Zong, MD
Instructor of Pediatrics, Perelman School of Medicine at the University of Pennsylvania; Attending Physician, Division of Pediatric Gastroenterology, Hepatology, and Nutrition, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania
Anaerobic Bacteria: Clinical Concepts and the Microbiome in Health and Disease

[†]Deceased.

Contents

F. Central Nervous System Infections

G. Genitourinary Tract Infections

H. Gastrointestinal and Tract Infections and Intoxications

I. Intra-abdominal Infections

J. Skin and Soft-Tissue Infections

K. Bone and Joint Infections

L. Eye Infections

M. Infections Related to Trauma, Animals, and Ticks

N. Infections of the Fetus and Newborn

†Deceased.

Nonenterobacteriaceae: Gram-Negative Bacilli

Gram-Negative Coccobacilli

Treponemataceae (Spiral Organisms)

Anaerobic Bacteria

[†]Deceased.

†Deceased.

RNA Viruses: Caliciviridae

C. Fungi

D. Human Parasites and Vectors

Protozoa

Nematodes

Cestodes

Trematodes

PART IV: Laboratory Diagnosis and Therapy for Infectious Diseases

A. The Clinician and the Laboratory

B. Anti-Infective Therapy

PART I

Understanding, Controlling, and Preventing Infectious Diseases

SECTION A: Epidemiology and Control of Infectious Diseases

1 Principles of Epidemiology and Public Health

Lucy A. McNamara and Stacey W. Martin

Epidemiology is the study of the distribution and determinants of disease or other health-related states or events in specified populations and the application of this study to the control of health problems.[1] A key component of this definition is that epidemiology focuses on populations, an emphasis that distinguishes epidemiology from clinical case studies, which focus on individual subjects.

Health events can be characterized by their distribution (descriptive epidemiology) and by factors that influence their occurrence (analytic epidemiology). In both descriptive and analytic epidemiology, health-related questions are addressed using quantitative methods to identify patterns or associations from which inferences can be drawn and interventions developed, applied, and assessed.

DESCRIPTIVE EPIDEMIOLOGY

Surveillance

The goals of descriptive epidemiology are to define the frequency of health-related events and determine their distribution by person, place, and time. The foundation of descriptive epidemiology is surveillance, or case detection. Retrospective surveillance identifies health events from existing data, such as clinical or laboratory records, hospital discharge data, and death certificates. Prospective surveillance identifies and collects information about cases as they occur, for example, through ongoing laboratory-based reporting.

With *passive surveillance,* case reports are supplied voluntarily by clinicians, laboratories, health departments, or other sources. The completeness and accuracy of passive reporting are affected by whether reporting is legally mandated, the ease of establishing a definitive diagnosis for the disease under surveillance, illness severity, interest in and awareness of the medical condition among the public and the medical community, and by whether a report will elicit a public health response. Because more severe illness is more likely to be diagnosed and reported, the severity and clinical spectrum of passively reported cases often differ from those of all cases of an illness. Weekly and annual state counts of passively collected reports of nationally notifiable diseases are available on the National Notifiable Diseases System (NNDSS) Data and Statistics web page (https://wwwn.cdc.gov/nndss/data-and-statistics.html).

In *active surveillance,* an effort is made to ascertain all cases of a condition occurring in a defined population. Active case finding can be prospective (through routine contacts with reporting sources), retrospective (through record audit), or both. Population-based active surveillance, in which all cases in a defined geographic area are identified and reported, provides the most complete and unbiased ascertainment of disease and is optimal for describing the rate of a disease and its clinical spectrum. By contrast, active surveillance conducted at only one or several participating facilities, often referred to as sentinel surveillance, can yield biased information on disease frequency or spectrum based on the representativeness of the patient population and the size of the sample obtained. The range and severity of clinical symptoms also influence whether active surveillance is able to ascertain all cases of a disease; individuals with mild disease may not present to a physician for diagnosis.

Case Definition

Establishing a standard case definition is a necessary first step for surveillance and description of the epidemiology of a disease or health event.[2] Formulation of a case definition is particularly important when laboratory diagnostic testing results are not definitive. More restrictive case definitions have greater specificity and minimize misclassification of persons without the condition of interest as cases; however, they can exclude true cases and may be most useful when investigating a newly recognized condition, in which the ability to determine etiology, pathogenesis, or risk factors is decreased by inclusion of noncases in the study population. A more inclusive definition can be important in an outbreak setting to increase sensitivity to detect potential cases for further investigation or to inform application of preventive interventions (e.g., reactive vaccination campaigns). Multiple research or public health objectives can be addressed by developing a tiered case definition that incorporates varying degrees of diagnostic certainty for confirmed, probable, and suspected cases. The Council of State and Territorial Epidemiologists (CSTE) provides uniform surveillance case definitions for nationally notifiable infectious and noninfectious conditions (https://wwwn.cdc.gov/nndss/case-definitions.html).

Sensitivity, Specificity, and Predictive Value

Sensitivity, specificity, and predictive values can be used to quantify the performance of a case definition or the results of a diagnostic test or algorithm (Table 1.1). Sensitivity and specificity are intrinsic measures of a case definition or diagnostic test, whereas predictive values vary with the prevalence of a condition within a population. Even with a highly specific diagnostic test, if a disease is uncommon among the people tested, a large proportion of positive test results will be false positives, and the positive predictive value will be low (Table 1.2). If the test is applied more selectively, such that the proportion of people tested who truly have disease is greater, the test's predictive value will be improved. Thus, predictive values depend both on test sensitivity and specificity, and on the disease prevalence in the population in which the test is applied, also called the pre-test probability.

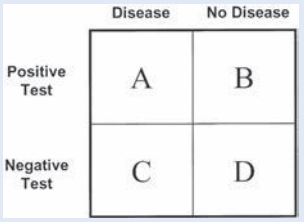
Often, the sensitivity and specificity of a test are inversely related. Selecting the optimal balance of sensitivity and specificity depends on the purpose for which the test is used. Generally, a screening test should be highly sensitive, whereas a follow-up confirmatory test should be highly specific.

Incidence and Prevalence

Characterizing disease frequency is one of the most important aspects of descriptive epidemiology. Frequency measures typically include a count of new or existing cases of disease as the numerator and a quantification of the population at risk as the denominator. *Cumulative incidence* is expressed as a proportion and describes the number of new cases of an illness occurring in a fixed at-risk population over a specified period of time. The *incidence density* or *incidence rate* is the rate of new cases

TABLE 1.1 Definitions and Formulas for the Calculation of Important Epidemiologic Parameters

Measures of test accuracy	*Sensitivity:* Proportion of true positive (diseased) with a positive test result	A/(A + C)
	Specificity: Proportion of true negative (nondiseased) with a negative test result	D/(B + D)
	Positive predictive value (PPV): Proportion of positive test results that are true positives	A/(A + B)
	Negative predictive value (NPV): Proportion of negative test results that are true negatives	D/(C + D)
Measures of data dispersion and precision	*Variance:* Statistic describing variability among individual members of a population	$[1/(n-1)][(x_1-\bar{x})^2 + (x_2-\bar{x})^2 + \ldots + (x_n-\bar{x})^2]$
	Standard deviation (SD): A second, more commonly used statistic describing variability among individual members of a population	$\sqrt{\text{Variance}}$
	Standard error (SE): Statistic describing the variability of sample-based point estimates (P) around the true population value being estimated	$\frac{SD}{\sqrt{n}}$
	Confidence interval: A range of values that is believed to contain the true value within a defined level of certainty (usually 95%)	—



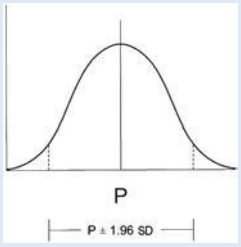


TABLE 1.2 Positive and Negative Predictive Values for a Hypothetical Diagnostic Test Having a Sensitivity of 90% and a Specificity of 90%

Proportion With Condition	Positive Predictive Value	Negative Predictive Value
1%	8%	>99%
10%	50%	99%
20%	69%	97%
50%	90%	90%

of disease in a dynamic at-risk population; the denominator typically is expressed as the population-time at-risk (e.g., person-time).

Because the occurrence of many infections varies with season, extrapolating annual incidence from cases detected during a short observation period can be inaccurate. In describing the risk of acquiring illness during a disease outbreak, the *attack rate,* defined as the number of new cases of disease occurring in a specified population and time period, is a useful measure. Finally, the *case-fatality rate*, or proportion of cases of a disease that result in death, is used to quantify the mortality resulting from a disease in a particular population and time period.

Prevalence refers to the proportion of the population having a condition at a specific point in time. As such, it is a better measure of disease burden for chronic conditions than is incidence or attack rate, which identify only new (incident) cases. Prevalent cases of disease can be ascertained in a cross-sectional survey, whereas determining incidence requires longitudinal surveillance. When disease prevalence (P) is low and incidence (I) and duration (D) are stable, prevalence is a function of disease incidence multiplied by its average duration ($P = I \times D$).

Describing Illness by Person, Place, and Time

Characterizing disease by person, place, and time is often useful. Demographic variables, including age, sex, socioeconomic status, and race or ethnicity, often are associated with the risk of disease. Describing a disease by place can help define risk groups, for example, when an illness is caused by an environmental exposure or is vector borne, or during an outbreak with a point source exposure. Time also is a useful descriptor of disease occurrence. Evaluating long-term (secular) trends provides information that can be used to identify emerging health problems or to assess

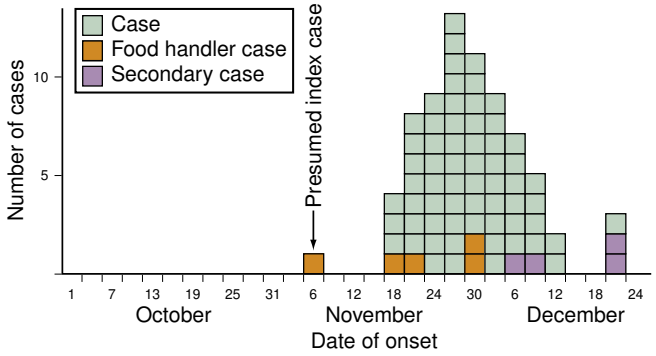


FIGURE 1.1. Example of an epidemic curve for a common source outbreak with continuous exposure. Cases of hepatitis A by date of onset in Fayetteville, Arkansas, from November to December 1979. (From Centers for Disease Control and Prevention, unpublished data.)

the impact of prevention programs. The timing of illness in outbreaks can be displayed in an epidemic curve (Fig. 1.1) and can be useful in defining the mode of transmission or incubation period, or for assessing the effectiveness of control measures.

ANALYTIC EPIDEMIOLOGY

Study Design

The goal of analytic epidemiologic studies is to assess for and quantify the association between an exposure and a health outcome. This goal can be addressed in experimental or observational studies. In *experimental studies,* hypotheses are tested by systematically allocating an exposure of interest to subjects in separate groups to achieve the desired comparison. Such studies include randomized, controlled, double-blind treatment trials as well as laboratory experiments. By carefully controlling study variables, investigators can restrict differences among groups and thereby increase the likelihood that the observed differences are a consequence of the specific factor being studied. Because experiments are prospective, the temporal sequence of exposure and outcome can be established, making it possible to define cause and effect.

By contrast, *observational studies* test hypotheses using observational methods to assess exposures and outcomes among individual subjects in

TABLE 1.3 Types of Observational Studies and Their Advantages and Disadvantages

Type of Study	Design and Characteristics	Advantages	Disadvantages
Cohort	Prospective or retrospective	Ideal for outbreak investigations in defined populations	Unsuited for rare diseases or those with long latency
	Select study group	Prospective design ensures that exposure preceded disease	Expensive
	Observe for exposures and disease	Selection of study group is unbiased by knowledge of disease status	Can require long follow-up periods
	Outcome measures used: Relative risk (RR) or hazard ratio (HR) of disease given exposure	RR and HR accurately describe risk given an exposure	Difficult to investigate multiple exposures
Cross-sectional	Nondirectional	Rapid, easy to perform, and inexpensive	Timing of exposure and disease can be difficult to determine
	Select study group	Ideal to determine knowledge, attitudes, and behaviors	Biases can affect recall of past exposures
	Determine exposure and disease status		
	Outcome measures used: Prevalence ratio for disease given exposure		
Case-control	Retrospective	Rapid, easy to perform, and inexpensive	Timing of exposure and disease can be difficult to determine
	Identify cases with disease	Ideal for studying rare diseases, those with long latency, new diseases	Biases can occur in selecting cases and controls and determining exposures
	Identify controls without disease		OR only provides an estimate of the RR if disease is rare
	Determine exposures in cases and controls		
	Outcome measures used: Odds ratio (OR) for an exposure given disease		

populations and to identify statistical associations from which inferences regarding causation are drawn. Although observational studies cannot be controlled to the same degree as experiments, they are practical in circumstances in which exposures or behaviors cannot be assigned. Moreover, the results often are more generalizable to a real population having a wide range of attributes. The 3 basic types of observational studies are cohort studies, cross-sectional studies, and case-control studies (Table 1.3). Hybrid study designs, incorporating components of these 3 types, also have been developed.[3] In planning observational studies, care must be taken in the selection of participants to minimize the possibility of bias. Selection bias results when study subjects have differing probabilities of being selected and the probability of selection is related to the risk factors or outcomes under evaluation.

In contrast to experimental or observational studies that analyze information about individual subjects, *ecologic studies* draw inferences from data on a population level. Causal inferences from ecologic studies must be made with caution because relationships observed on a population level do not necessarily apply on the individual level (a problem known as the *ecologic fallacy*). Because of these drawbacks, ecologic studies are suited best for generating hypotheses that can be tested using other study methods.

Cohort Studies

In a *cohort study,* subjects are categorized based on their exposure to a suspected risk factor and are observed for the development of disease or other health-related outcome. Associations between exposure and disease are expressed by the *relative risk* of disease, or *risk ratio*, in exposed and unexposed groups (Table 1.4). Cohort studies typically are prospective, with exposure defined before disease occurs. However, cohort studies also can be retrospective, in which the cohort is selected after the outcome has occurred. In this case, exposures are determined from existing records that preceded the outcome, and thus the directionality of the exposure-disease relationship is still forward. Characterizing exposures before development of disease is a major benefit of cohort studies because this approach minimizes selection bias and simplifies inference of cause and effect. Another advantage of cohort studies is that they can be used to assess multiple potential outcomes resulting from an exposure. However, in a cohort study it can be difficult to investigate multiple exposures as risk factors for a single outcome. Cohort studies also are impractical for studying rare diseases or conditions with a long latent period between exposure and the onset of clinical illness. In general, cohort studies are unsuited for investigating risk factors for new or rare diseases or for generating new hypotheses about possible exposure-disease relationships.

Cohort studies provide data not only on whether an outcome occurs but also, for those experiencing the outcome, on when it occurs. Analysis of time-to-event data for outcomes such as death or illness is a powerful approach to assess or compare the impacts of preventive or therapeutic interventions. The probability of remaining event-free over time can be expressed in a *survival curve* where the event-free probability is initially 1 and declines in a step-function as the outcomes of interest occur (Fig. 1.2A). Time-to-event data also can be displayed as the *cumulative hazard* of an event occurring among members of a cohort that increases from 0 at enrollment (Fig. 1.2B). These 2 approaches are related in that the hazard reflects the incident event rate, whereas survival reflects the cumulative nonoccurrence of that outcome.[4,5] With time-to-event analysis, the association between exposure and disease often is expressed as a hazard ratio. Like relative risk, the hazard ratio is a comparative measure of risk between exposed and unexposed groups. The primary difference is that the hazard ratio compares event experience over the entire time period, whereas the relative risk compares cumulative event occurrence at the study endpoint.[6]

Cross-Sectional Studies

In a *cross-sectional study,* or survey, a sample is selected, and at a single point in time exposures and outcome are determined. Outcomes can include disease status or behaviors and beliefs, and multiple exposures can be evaluated as explanations for the outcome. Associations are characterized by the *prevalence ratio*, similar to the risk ratio in cohort studies. Because neither exposures nor outcomes are used in selection of the study group, prevalence is an estimate of that in the overall population from which the sample was drawn. National survey data characterizing health status, behaviors, and medical care are available from the National Center for Health Statistics (http://www.cdc.gov/nchs/index.htm).

TABLE 1.4 Measures of Association, Risk, and Impact

Absolute measures of association and risk	*Absolute risk reduction* (ARR), *excess risk,* or *attributable risk:* Difference in the incidence of the outcome between exposed and unexposed	(A/(A + B)) – (C/(C + D))
	Number needed to treat (NNT): Number of individual subjects who must receive an intervention (or exposure) to prevent one negative outcome	1/ARR
Relative measures of association and risk	*Relative risk* or *risk ratio* (RR): Risk (probability) of a health event in those with a given exposure divided by the risk in those without the exposure	$\frac{A/(A+B)}{C/(C+D)}$
	Odds ratio (OR): Odds of a given exposure among those with a health event divided by odds of exposure among those without the health event	AD/BC
Measure of impact	*Population attributable fraction:* The proportion of disease in a population that results from the specific exposure	$[P_e (RR - 1)]/[1 + P_e (RR - 1)]$ [Proportion exposed, $P_e = (A + B)/(A + B + C + D)$]
	Vaccine efficacy/effectiveness (VE): The percentage reduction in incidence of a disease among persons who have received a vaccine compared with the incidence in persons who have not received the vaccine	(1 – RR) × 100 or (1 – OR) × 100

	Disease	No Disease
Exposed	A	B
Unexposed	C	D

Case-Control Studies

In a *case-control study,* the investigator identifies a group of people with a disease or outcome of interest (cases) and compares their exposures with those in a selected group of people who do not have disease (controls). Differences between the groups are expressed by an *odds ratio,* which compares the odds of an exposure in case and control groups (Table 1.4). The odds ratio is not the same as a risk ratio; however, it provides an estimate of the risk ratio if the disease or outcome in question is rare. Case-control studies are retrospective in that disease status is known and serves as the basis for selecting the 2 comparison groups; exposures are then determined by reviewing available records or by interview.

A major advantage of case-control studies is their efficiency in studying uncommon diseases or diseases with a long latency. Case-control studies also can evaluate multiple exposures that may contribute to a single outcome; study subjects frequently can be identified from existing sources (e.g., hospital or laboratory records, disease registries, or surveillance reports), and after identification of suitable control subjects, data on previous exposures can be collected rapidly. Case-control studies also have several drawbacks. Bias can be introduced during selection of cases and controls and in determining exposures retrospectively, and inferring causation from statistically significant associations can in some situations be complicated by difficulty in determining the temporal sequence of exposure and disease.

Causal Inference and the Impact of Bias

The impact of potential bias is particularly important in observational studies. The *validity* of a study is the degree to which inferences drawn from a study are warranted. *Internal validity* refers to the correctness of study conclusions for the population from which the study sample was drawn, whereas *external validity* refers to the extent to which the study results can be generalized beyond the population sampled. The validity of a study can be affected by bias, or *systematic error,* in selecting the study participants (sampling), in ascertaining their exposures, or in analyzing and interpreting study data. For errors to result in bias, they must be systematic, or directional. *Nonsystematic error* (random misclassification) decreases the ability of a study to identify a true association but does not usually result in detection of a spurious association.

Several sources of bias can occur in selection of study participants (Box 1.1).[7] *Diagnosis bias* results when persons with a given exposure are more likely to be diagnosed as having disease than are people without the exposure (or vice versa); this can occur because diagnostic testing is more or less likely to be done based on exposure or because the interpretation of a test may be affected by knowledge of exposure status. For hospital-based studies, differential referral also can bias selection of a study sample. This bias would occur if, for example, the frequency of an exposure varied with socioeconomic status and a hospital predominantly admitted persons from either a high-income group or a low-income group. Bias also can occur when eligible subjects refuse to participate in a study.

Determination of exposures can also be affected by several types of bias. Recall of exposures can be different for persons who have had an illness compared with people who were well. This bias occurs in either direction: patients may be more likely to remember an exposure that they associate with their illness (e.g., what was eaten before an episode of diarrhea) or less likely to recall an exposure if a severe illness affected memory. Interviewers can introduce bias by questioning cases and controls differently about their exposures. Misclassification of exposures can also result from errors in measurement such as can occur with the use of an inaccurate laboratory test. Although systematic misclassification can result in bias, misclassification of exposure often is random rather than systematic.

Even a carefully designed study that minimizes potential biases can lead to erroneous causal inferences. An exposure can falsely appear to be associated with disease because it is closely linked to the true, but undetermined, risk factor. For example, race often is found to be associated with the risk of a disease, but in many instances the true risk factor is likely an unmeasured variable that is associated with race, such as socioeconomic status. The risk of making incorrect inferences can be minimized by considering certain general criteria for establishing causation. These criteria include the strength of an association, the presence of a dose-response effect, a clear temporal sequence of exposure to disease, the consistency of findings with those of other studies, and the biologic plausibility of the hypothesis.[8]

Statistical Analysis

Characteristics of Populations and Samples

While epidemiologic analysis seeks to draw valid conclusions about populations, the entire population rarely is included in a study. An assumption underlying statistical analysis is that the sample evaluated was selected randomly from the population. Often, this criterion is not met and calls into question the appropriateness and interpretation of statistical analyses.

The mean, median, and mode describe central values for samples and populations. The arithmetic *mean* is the average, determined by summing individual values and dividing by the sample size. When data are not normally distributed, or skewed, calculation of a geometric mean can limit the impact of outlying values. The geometric mean is calculated by

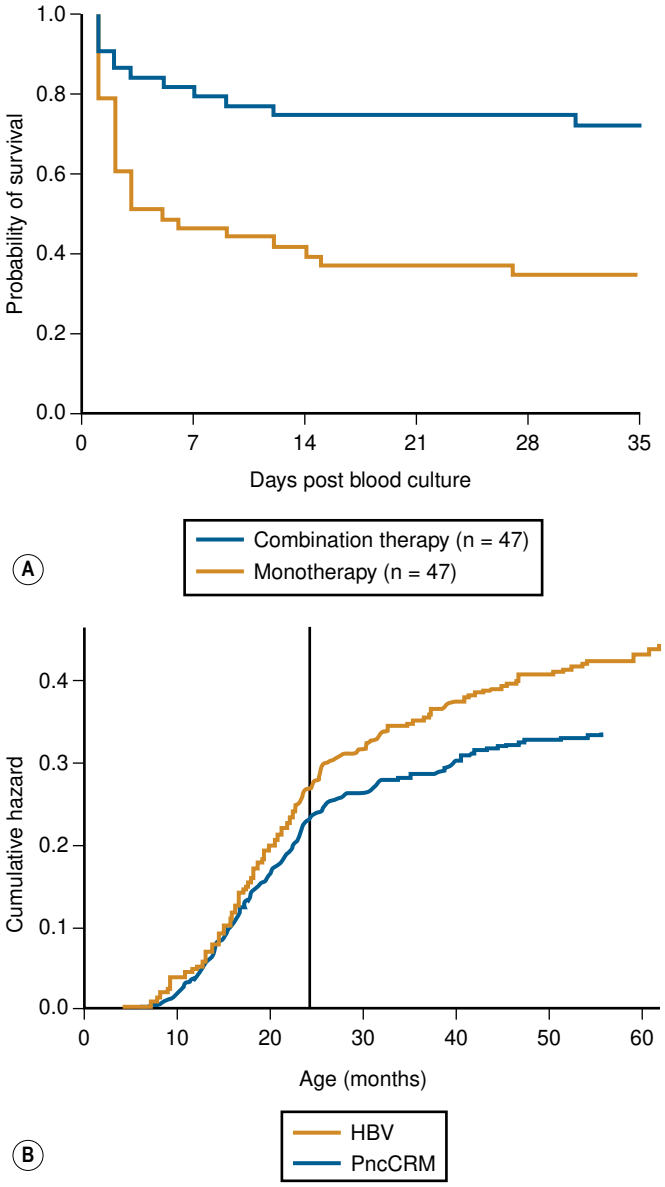


FIGURE 1.2. Example of Kaplan-Meier and cumulative hazard curves. (A) Survival plot for critically ill patients with *Streptococcus pneumoniae* bacteremia treated with monotherapy or combination therapy. (B) Cumulative hazard of tympanostomy tube placement from 2 months until 4–5 years of age in children who received pneumococcal conjugate vaccine *(PncCRM)* or a control vaccine (hepatitis B vaccine *[HBV]*). ([A] Redrawn from Baddour LM, Yu VL, Klugman KP, et al. Combination antibiotic therapy lowers mortality among severely ill patients with pneumococcal bacteremia. *Am J Respir Crit Care Med*. 2004;170:440–444. [B] Redrawn from Palmu AAI, Verho J, Jokinen J, et al. The seven-valent pneumococcal conjugate vaccine reduced tympanostomy tube placement in children. *Pediatr Infect Dis J*. 2004;23:732–738.)

taking the *n*th root of the *product* of all the individual values, where *n* is the total number of individual values. For example, immunogenicity of vaccines is usually expressed by the geometric mean titer. The *median,* or middle value, is another way to describe nonnormally distributed data. The *mode,* or most commonly occurring value in a sample, rarely is used.

Several measures can be used to describe the variability in a sample. The *range* describes the difference between the highest and lowest value, whereas the *interquartile range* defines the difference between the 25th and 75th percentiles. Variation among individual elements most often is characterized by the variance or standard deviation. The *variance* is the mean of the squared deviation of each observation from the sample's mean. The *standard deviation* is the square root of the variance

BOX 1.1 Potential Sources of Bias in Observational Studies[a]

BIAS IN CASE ASCERTAINMENT AND CASE/CONTROL SELECTION

- Surveillance bias: differential surveillance or reporting for exposed and unexposed
- Diagnosis bias: differential use of diagnostic tests in exposed and unexposed
- Referral bias: differential admission to hospital based on an exposure or a variable associated with exposure
- Selection bias: differential sampling of cases based on an exposure or a variable associated with exposure
- Nonresponse bias: differential outcome or exposures of responders and nonresponders
- Survival bias: differential exposures between those who survive to be included in a study and those who die following an illness
- Misclassification bias: systematic error in classification of disease status

BIAS IN ESTIMATION OF EXPOSURE

- Recall bias: differential recall of exposures based on disease status
- Interviewer bias: differential ascertainment of exposures based on disease status
- Misclassification bias: systematic errors in measurement or classification of exposure

[a]A more complete listing is provided by Sackett.[7]

(Table 1.1). For a normally distributed population, 68% of values fall within 1 standard deviation of the mean, and 95% of values fall within 1.96 standard deviations.

When analyzing a sample, the mean or other statistics describing the sample represent a *point estimate* of that parameter for the entire population. If another random sample were drawn from the same population, the point estimate for the parameter of interest likely would be different, depending on the variability in the population and the sample size selected. The *standard error* is used to describe the precision of a point estimate (e.g., mean, odds ratio, relative risk) and depends on sample standard deviation and the sample size (Table 1.1).

A *confidence interval* defines a range of values that includes the true population value within a defined level of certainty. Most often, the 95% confidence interval is presented (Table 1.1).

Absolute and Relative Measures of Association

Measures of association are used to assess the strength of an association between an exposure and an outcome. In a cohort study, the *absolute risk reduction* (also known as *excess risk, attributable risk,* or *risk difference*) is the difference in the incidence of the outcome between exposed and unexposed subjects. The *number needed to treat* (NNT) is a measure of the number of individual subjects who must receive a treatment to prevent a single negative outcome and is calculated as the reciprocal of the *absolute risk reduction*. In addition to absolute measures, relative measures also are useful for describing the strength of an association. In a cohort study or survey, the relative risk or risk ratio compares the risk of disease for subjects with versus subjects without an exposure (Table 1.4). In case-control studies, association is assessed by the odds ratio, which compares the odds of exposure among subjects with and without a disease or health outcome; when disease is uncommon (<10%) in both exposed and unexposed groups, the odds ratio approximates the relative risk. For time-to-event analyses, the comparative risk is expressed as the *hazard ratio.* Odds ratios, relative risks, and hazard ratios >1 signify increased risk given exposure, and values <1 suggest that exposure decreases the risk of an outcome. Because observational studies generally do not include all members of a population, these measures of association represent an estimate of the true value within the entire population. Statistical analyses

can help guide investigators in making causal inferences based on point estimates of these measures of association.

Statistical Significance

Statistical tests are applied to assess the likelihood that the study results were obtained by chance alone rather than representing a true difference within the population. Most investigators consider a P value <0.05 as being *statistically significant*, indicating a <5% risk that the observed association is the result of chance alone (designated a *type I error,* the probability of which is the *alpha level*). Although use of this cutoff for significance testing has become conventional, ignoring higher P values can lead to missing a real and important association, whereas blind faith in the significance of lower P values can lead to erroneous conclusions. Statistical testing should contribute to, but not replace, criteria for evaluating possible causation.

Statistical significance also can be defined based on 95% confidence intervals, which approximately correspond to a P value of 0.05. An odds ratio, relative risk, or hazard ratio is considered statistically significant if the 95% confidence interval does not include 1. An advantage of using confidence intervals to define statistical significance is that they provide information on whether a finding is statistically significant and on the possible range of values for the point estimate in the population, with 95% certainty.

One pitfall in interpreting statistical significance is ignoring the *magnitude* of an effect in favor of its "significance." A very large, overpowered study can identify as significant a small, perhaps trivial, difference among study groups. Some epidemiologists have proposed that, despite statistical significance, odds ratios <2 or 3 in an observational study should not be interpreted because unidentified bias or confounding could account for a difference of this magnitude.[9] Conversely, the relative risk or odds ratio associating an exposure and outcome can be large, but if the exposure is uncommon in both groups, it cannot explain most cases of illness. The public health importance of an exposure can be described by the *population-attributable fraction,* or the proportion of the disease in a population that is related to the exposure of interest.

Sample Size

Another type of error in epidemiologic studies is when a study fails to identify a true risk factor as statistically significant (designated a *type II error,* the probability of which is the *beta level*). The probability of a type II error is higher when the sample size is small. Often, the type II error rate is set at 0.2, indicating acceptance of a 20% likelihood that a true difference exists but would not be identified by the study. Statistical power is defined as $1 - \beta$ and is the complement of the probability of committing a type II error (β); that is, power is the probability of correctly identifying a difference of specified size among groups, if such a difference truly exists. The problem of inadequate sample size in clinical studies was highlighted in an analysis of "negative" randomized controlled trials reported in 3 leading medical journals between 1975 and 1990. Of 70 reports, only 16% and 36% had sufficient statistical power (80%) to detect a true 25% or 50% relative difference, respectively, among treatment groups.[10]

In calculating sample sizes for testing hypotheses, investigators must select acceptable rates of type I and type II errors and define the magnitude of the difference in outcomes that is deemed clinically important. Sample size calculations can be performed using a range of computer software. The program Epi-Info can be used to perform sample size calculations as well as other statistical functions and is available at no charge from the Centers for Disease Control and Prevention (www.cdc.gov/epiinfo/).

Ensuring an adequate sample size is particularly important for studies attempting to prove *equivalence* or *noninferiority* of a new treatment compared with standard therapy. Food and Drug Administration guidance recommends that noninferiority trials adopt a null hypothesis that a difference exists among treatments; this hypothesis is rejected if the lower 95% confidence limit for the new treatment is within a specified margin of the point estimate for standard therapy. Because the null hypotheses can never be proven or accepted, the failure to reject a null hypothesis of no difference among treatments or exposure does not prove equivalence. The importance of this distinction is illustrated by an analysis of 25 studies claiming equivalence of therapies for pediatric bacterial meningitis. Twenty-three studies claimed equivalence based on a failure to detect a significant difference among treatment groups. However, only 3 of these trials were adequately powered to exclude a 10% difference in mortality, thus showing that many studies potentially missed a clinically significant difference.[11]

In some situations, an investigator would want to detect a significant difference among study groups as soon as possible, for example, when a therapeutic or preventive intervention could be applied once a risk group is identified or when concerns exist about the safety of a drug or vaccine. One approach to this situation is to include in the study design an *interim analysis* after a specified number of subjects are evaluated. Because the likelihood of identifying chance differences as significant increases with the number of analyses, it is recommended that the threshold for defining statistical significance should become more stringent as the number of planned analyses increases.[12] If each interim analysis can lead the investigators to stop the trial, this study design is considered a group sequential method.[13] Another example of a group sequential design is when concordance or discordance in outcome is tabulated for each matched set exposed to alternate treatments. Results for each set are plotted on a graph, and data collection continues until a preset threshold for a significant difference among study groups is crossed or no significant difference is detected at a given power.[12]

Statistical Inference

Statistical testing is used to determine the significance of differences among study groups, and thus it provides guidance on whether to accept or reject the null hypothesis. Although providing details of specific statistical tests is outside the scope of this chapter, Table 1.5 gives examples of statistical tests that can be applied in analyzing different types of exposure and outcome variables.

Using appropriate analytic and statistical methods is important in identifying significant predictors of an outcome (i.e., risk factors) correctly. *Confounding variables* are associated with the disease of interest and with other exposure variables and are not part of the causal pathway between the other exposure(s) and the outcome. For example, consider a study attempting to determine whether meningococcal vaccination decreases nasopharyngeal carriage of *Neisseria meningitidis*. If frequent attendance at social events is associated with increased carriage and also with a decreased chance of receiving vaccine, then failure to adjust for social event attendance as a confounding variable could lead to overestimation of the relationship between vaccination and carriage reduction. Meanwhile, *effect modifiers* interact with other risk factors to affect their impact on outcome but may or may not be associated with the outcome on their own. Frequently, age is an effect modifier, with an exposure associated significantly with an outcome in one age group but not in another.

Several approaches are used to control for confounding variables and effect modifiers. In study design, an extraneous variable can be controlled

TABLE 1.5 Types of Statistical Tests Used to Evaluate the Significance of Associations Among Categorical and Continuous Variables

Independent Variable (Exposure, Risk Factor)	Dependent Variable (Disease, Outcome)	
	Categorical and Dichotomous	Continuous
CATEGORICAL		
Dichotomous	Chi-square test	Student t-test (parametric)
	Fisher exact test	Wilcoxon rank sum test (nonparametric)
>2 categories	Chi-square test	Analysis of variance (parametric)
		Kruskal-Wallis test (nonparametric)
CONTINUOUS	Logistic regression	Linear regression
		Correlation (Pearson: parametric; Spearman: nonparametric)

for by randomization, restricting sampling to one category of the variable or by *frequency matching* to obtain similar proportions of cases and controls in each stratum of the variable. A more extreme form of matching is to select control subjects who are similar to individual cases for extraneous variables (e.g., age, sex, underlying disease) and to analyze whether exposures are concordant or discordant within matched sets. A newer approach to study design is the *case-crossover*[14] or *case series*[15] analysis. In this method, exposures occurring in a defined risk period before the outcome are compared with exposures occurring outside the risk window for the same individual subjects. This approach has been adapted to the study of adverse events after vaccination. If the vaccine causes the event, the rate of the event will be greater within a defined risk window than predicted by chance alone based on the expected distribution of the event.[16] The strength of this approach is that each subject, or case, serves as his or her own control, thereby decreasing confounding.

At the analysis stage, the impact of confounding variables and effect modifiers can be limited by performing a stratified analysis or using a multivariable model. In a *stratified analysis,* the possible association between a risk factor and an outcome is determined separately within different categories, or strata, of the extraneous variable. If the extraneous variable is a confounder, the stratum-specific estimates should be similar to each other and can be combined into a single estimate using an appropriate statistical test (e.g., a *Mantel-Haenszel odds ratio*). If a stratification variable is an effect modifier, the relative risk or odds ratio will differ substantially among the strata; for example, an exposure can be a strong risk factor in one age group but not another. In this setting, a summary statistic should not be presented, and results for each stratum should be presented separately. When the extraneous variable is confounding, stratifying the analysis by the confounding variable may eliminate an apparent association between the exposure and the outcome in the unstratified analysis and indicate that the exposure is not an independent risk factor for disease.

Because stratified analyses become confusing rapidly as the number of strata increases, techniques of *statistical modeling* have been developed that permit simultaneous control of multiple variables. Significant risk factors determined in a *multivariable model* are interpreted as each contributing independently and significantly to the outcome, as the model controls for potential confounding from each included variable. Effect modification can be taken into account by including terms expressing the interaction between a risk factor and effect modifier in the model. Various multivariable models are appropriate for discrete, continuous, and time-dependent outcomes.

A limitation of multivariable modeling is *multicollinearity,* which occurs when 2 or more explanatory variables of interest are highly correlated and can result in inaccurate measures of association and decreased statistical power. The risk of multicollinearity can be reduced by assessing correlations among potential risk factors and selecting which variables to include in the model. Various methods to identify and minimize multicollinearity have been developed.[17]

VACCINE EFFICACY AND EFFECTIVENESS STUDIES

Most prelicensure efficacy studies are experimental, randomized, double-blind, controlled trials in which *vaccine efficacy* (VE) is calculated by comparing the attack rates (AR) for disease in the vaccinated and unvaccinated groups: VE (%) = (AR unvaccinated − AR vaccinated) / AR unvaccinated) × 100; or (1 − RR) × 100.

After licensure, conducting controlled studies, which requires withholding vaccine from a control group, is no longer ethical. Therefore, further studies must be observational rather than experimental, by comparing persons who have chosen to be immunized with those who have not. Such observational studies are said to assess *vaccine effectiveness* rather than *vaccine efficacy*; however, the two measures use the same abbreviation, VE. In *case-control vaccine effectiveness studies,* vaccination status of persons with disease is compared with vaccination status of healthy control subjects in a real-world setting. The number of vaccinated and unvaccinated cases and controls is included in a 2×2 table, and vaccine effectiveness is calculated as 1 minus the odds ratio: VE (%) = (1 − OR) × 100. When the proportion of cases vaccinated is less than the proportion of vaccinated controls, the odds ratio is <1, and the point estimate for VE indicates that immunization is protective. The precision of the estimate is expressed by the 95% confidence interval. A lower 95% confidence limit that is >0% indicates statistically significant protection. However, the expected lower confidence limit often is much >0 to be consistent with meaningful levels of protection. The most important component of a case-control effectiveness study is selecting control subjects who have the same opportunity for immunization as do cases. If cases have less opportunity to be immunized, results will be biased toward showing protection. Factors such as low socioeconomic status, which can increase the risk of disease and decrease the chance of being immunized, are potential confounding variables and can be controlled for by matching control subjects to cases for those factors.

Cohort studies also can be used to determine vaccine effectiveness after licensure. A study design called the *indirect-cohort method* was developed by researchers at the Centers for Disease Control and Prevention to evaluate the effectiveness of the pneumococcal polysaccharide vaccine by using data collected by disease surveillance.[18] In this study, the cohort included persons identified with invasive pneumococcal infections. The study hypothesis was that if pneumococcal vaccines were protective, the proportion of vaccinated persons infected with pneumococcal serotypes that are included in the vaccine formulation would be less than the proportion of unvaccinated persons infected with vaccine-type strains. Vaccine effectiveness was calculated from the relative serotype distributions overall and for each individual serotype. The point estimate of vaccine effectiveness for preventing invasive infection was 57% (95% confidence interval, 45%–66%)[19]; this estimate is similar to that obtained in a case-control effectiveness study.[20]

DISEASE CONTROL AND PUBLIC HEALTH POLICY

Outbreak Investigations

Outbreak investigations require knowledge of disease transmission and use of descriptive and analytic epidemiologic tools. Possible outbreaks can be identified from surveillance data showing an increased rate of an infection or an unusual clustering of infection by person, place, or time. Comparing the incidence rate of disease with a baseline rate from a previous period is helpful in validating the occurrence of an outbreak. Other explanations for changes in the apparent rate of disease occurrence, such as diagnostic error, seasonal variations, and changes in reporting, must be considered.

After identifying a potential outbreak, the next steps of an investigation are to develop a case definition, identify cases, and characterize the descriptive epidemiology of the outbreak. An *epidemic curve* depicts the number of cases over time and can provide information on possible transmission (Fig. 1.1). In an outbreak with a *point source exposure,* an index case may be identified, with other cases occurring after an incubation period or at multiples of an incubation period. Plotting the location of cases on a spot map can also be helpful in determining possible exposures. Describing patients' characteristics can be important in identifying at-risk populations for further investigation or targeting of control measures, as well as for developing hypotheses that can be investigated in an analytic study.

Not all outbreaks can be traced to a point source exposure. Outbreaks and epidemics also can result from increased transmission of an *endemic* disease (i.e., a disease or condition that normally occurs in a specific population or area). In this situation, it can be challenging to determine when an increase in disease constitutes an outbreak rather than a normal fluctuation in disease incidence. To determine whether an outbreak is occurring, the current incidence of the disease must be compared with the baseline disease incidence in that area. Often, no standard definition exists for when an increase in endemic disease incidence constitutes an outbreak or epidemic. For instance, in US pertussis epidemics the threshold for declaring an epidemic has varied by state. In California in 2010 and 2014, an epidemic was declared when the statewide case counts had reached 5 times the number of cases observed in a year with baseline pertussis incidence. By contrast, in Washington State in 2012, an epidemic was declared when the incidence of pertussis reached 2 standard deviations above the statewide 10-year average.

Cohort studies are optimal for investigating outbreaks that occur in small, well-defined populations, including in schools, childcare settings, social gatherings, and hospitals. In populations that are large and/or not well defined, a case-control study is the most feasible approach. It is important to select control subjects who had an opportunity equal to that

of cases for exposure to potential risk factors and development of disease. When the number of cases is relatively small, enrolling multiple control subjects per case increases the power of the study to find significant risk factors. After a standard questionnaire is administered, significant risk factors are determined by comparing exposures of cases and controls. The results of analyses can lead to inferences of causation and development of prevention and control strategies or to further hypotheses that can be evaluated later. The impact of intervention can be determined by ongoing surveillance and continued plotting of additional cases on the epidemic curve.

Impact and Economic Analysis of Disease Prevention

Assessing health and economic impacts of public health interventions is important in developing or supporting policy decisions. Health impacts can be expressed directly as cases of disease, deaths, and sequelae prevented. Vaccine efficacy is a specific example of the *prevented fraction* (PF), where PF = P (1 − RR), with P representing the proportion exposed to an intervention. Secondary measures of health impact include *years of potential life lost (YPLLs)* or *quality-adjusted life-years (QALYs)* lost, which quantify the impact of death, or death and disability, respectively, based on the age at which these events occur.[21] A measure of the efficiency of an intervention is the *number needed to treat* which, as described above, indicates how many persons must be exposed to an intervention to avoid a single case of an adverse health outcome.

Cost-effectiveness analyses determine the cost per health outcome achieved, such as the cost per death or complication averted, and permit comparison of an intervention with other potential uses of resources. In a cost-effectiveness formula, costs appear in the numerator, and health benefits appear in the denominator. The numerator includes expenditures for the prevention program, from which cost savings occurring with disease prevention are subtracted. In addition to direct costs averted (e.g., savings from decreased medical care), indirect cost savings occur from increased productivity of people who do not become ill or miss time from work while receiving care or caring for ill family members. *Cost-utility* calculations are similar to cost-effectiveness but assess cost per quality-adjusted life-year saved or year of potential life lost averted.

Cost-benefit analyses differ from cost-effectiveness analyses in that the calculation is made entirely in economic terms. Health benefits are assigned an economic value, and expenditures are compared with savings. One problem with this approach lies in the difficulty of assigning an economic value to a health effect. For example, the value of a life saved may be quantified as the estimated value of a person's earnings over his or her lifetime, lost earnings as a result of premature death, or by a standard amount; both economic and ethical issues can be raised by the choice of approach. Because the parameters used in economic analyses often are uncertain or based on limited data, and because choices made by the investigator (e.g., regarding the value of life) can be influential to the analysis, *sensitivity analyses* often are performed in which parameters are varied across a range of potential values. In addition to defining a range of possible economic outcomes, sensitivity analyses can identify the factors that most strongly influence the results, thus elucidating where further studies may be important.

EVALUATING THE MEDICAL LITERATURE

Steps in reviewing published medical research are shown in Box 1.2.[22] The ability to assess published studies carefully often is limited by the information presented in the report. To improve reporting of randomized controlled trials, a group of investigators and editors developed the Consolidated Standards of Reporting Trials (CONSORT)[23] (http://www.consort-statement.org/) and later extended these recommendations to reporting randomized trials of noninferiority and equivalences.[24] Reporting often still does not adhere to the quality standards proposed.[25,26] Although the guidelines refer to experimental rather than observational studies, most criteria apply to observational studies as well.

In assessing the medical literature, it is important to examine all published work on a particular topic rather than relying on a single report and to evaluate the strength of the combined evidence from these reports. One framework for evaluating the literature on a topic is the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, adopted by the US Advisory Committee on Immunization Practices (ACIP) in 2010 (www.cdc.gov/vaccines/acip/recs/GRADE/about-grade.html). In GRADE, the strength of evidence for the relationship between a particular intervention or exposure and an outcome is categorized into 4 hierarchical levels, from greatest to least[27]:

1. Randomized controlled trials, or overwhelming evidence from observational studies
2. Randomized controlled trials with important limitations, or exceptionally strong evidence from observational studies
3. Observational studies, or randomized controlled trials with notable limitations
4. Clinical experience and observations, observational studies with important limitations, or randomized controlled trials with several major limitations

To offset the impact of *publication bias* (i.e., the tendency to more often submit or publish reports of effectiveness than of noneffectiveness of a treatment), many countries require all clinical trials to be officially registered so that a record shows that the study was conducted even if the results are never published. Reviewing information on all registered clinical trials on a topic in addition to reviewing the published literature can provide a more complete picture of the effect of a particular intervention or exposure. In the US, all clinical trials must be registered at clinicaltrials.gov; similar sites exist for other countries.

BOX 1.2 Steps in the Critical Evaluation of Epidemiologic Literature

1. Consider the research hypothesis
2. Consider the study design
   - Type of study
   - Selection of study participants
   - Selection and definition of outcome variables
   - Selection and definition of exposure (predictor) variables
   - Sample size and power
3. Consider the analysis
   - Complete accounting of study subjects and outcomes
   - Appropriateness of statistical tests
   - Potential sources and impact of bias
   - Potential impact of confounding and effect modification
4. Consider the interpretation of results
   - Magnitude and importance of associations
   - Study limitations
   - Ability to make causal inferences

From Greenberg RS. *Medical Epidemiology*. Norwalk, CT: Appleton and Lange; 1993.

Understanding a Medical or Epidemiologic Study

Assessing the *research hypothesis* allows readers to determine the relevance of the study to their practice and to judge whether the analyses were done to test the hypothesis or to identify other associations of interest. The ability to make causal inferences from a confirmatory study that tests a single hypothesis is greater than from an exploratory study in which multiple exposures are considered as potential explanations for an outcome.

Several components of *study design* are important to consider. Details should be presented regarding the criteria for selecting the cohort or cases and controls. *Exposure* and *outcome variables* should be clearly defined, and the potential for misclassification and its impact should be considered. Quantifying exposure can be important to establish a dose-response relationship. *Sample size estimates* should be presented, making clear the magnitude of difference among study groups considered clinically meaningful and the type I and type II error levels.

In the *analysis*, it is important that outcomes for all study subjects are reported, even if that outcome is "lost to follow-up." *Intent-to-treat* analyses consider outcomes for all enrolled subjects, whether or not they completed the therapy (e.g., subjects who were nonadherent to therapy or who received only part of a vaccination series). By contrast, *per protocol* analyses include only those subjects who followed the study protocol

throughout the full study duration. Usually, an intent-to-treat analysis is considered more conservative than a per protocol analysis, but this is not necessarily the case for noninferiority trials.

The appropriateness of the statistical tests should be assessed; for example, if data are not normally distributed, they can be transformed to a scale that is more normally distributed (e.g., geometric mean titers), or nonparametric statistical tests should be used. In assessing a multivariable model, the reader should critically evaluate the type of model chosen, the variables included, and whether interaction terms were considered. Missing data pose a particular problem for some modeling approaches in that study subjects may be included only if data are available for each variable in the model; thus, the power of a multivariable model can be much less than that predicted in a sample size calculation. Missing data are also a potential source of bias. Multiple imputation methods may be used in some situations to minimize problems arising from missing data.

Bias can have an important impact on study results and must be carefully considered. Approaches to minimize bias should be described clearly. The direction and potential magnitude of remaining bias should be estimated and its impact on results considered. Potential confounding, the presence of important unmeasured variables, and possible effect modification can have a major impact on the results. Investigators should openly discuss the potential limitations of the investigation and describe the strategies applied to overcome those limitations.

Interpretation of study results includes assessing the magnitude of the associations, their relevance to practice, and the likelihood that the relationships observed are causal. The importance of an exposure in explaining an outcome can be expressed by the attributable proportion. However, the *external validity* of the results and the potential impact on one's own patient population still must be assessed.

All references are available online at Elsevier eBooks for Practicing Clinicians.

2 Pediatric Healthcare: Infection Epidemiology, Prevention and Control, and Antimicrobial Stewardship

Jane D. Siegel and Joseph B. Cantey

Pediatric healthcare epidemiology is the study and analysis of the distribution (who, when, where) of patterns and determinants of health and disease conditions in healthcare settings where children receive healthcare or gather in locations where disease conditions could be present. Prevention of healthcare-associated infections (HAIs) is the major goal and is an important component of quality and patient safety programs. Healthcare epidemiologists must be ready to meet the needs of the ever-changing healthcare systems and disease threats that emerge, often without warning. Healthcare facilities have learned from high-reliability organizations (e.g., the aviation industry) the importance of adopting changes that include the leadership's commitment to achieving zero patient harm, a fully functional culture of safety throughout the organization, and the widespread deployment of highly effective process improvement tools.[1] The five principles of high reliability organizations are (1) preoccupation with failure; (2) reluctance to simplify (embracing complexity); (3) commitment to resilience; (4) sensitivity to operations; and (5) deference to expertise.[2] Involvement of new stakeholders for improving patient safety and outcomes related to HAIs has broadened the arena for HAI prevention efforts. Regional and national collaboratives have facilitated the performance of well-designed studies to generate data that inform recommended practices applicable specifically to the pediatric population.

Knowledge of the complexities of prevention and control of HAIs in children is critical to many different leaders in children's healthcare facilities. The mere imposition of policies for adults on children could be inappropriate on one hand and would miss opportunities to prevent infections unique to children on the other hand. Active involvement of bedside staff and medical directors within the various pediatric subspecialties has enhanced the implementation of effective infection control practices in areas such as pediatric intensive care units (PICUs), neonatal intensive care units (NICUs), oncology and transplant units, gastroenterology units, and interventional radiology areas. As more disciplines in healthcare become engaged in prevention of HAIs and in antimicrobial stewardship, it is the responsibility of the healthcare epidemiologist and the infection prevention and control (IPC) staff (infection preventionists, healthcare epidemiologists) to educate the facility leadership on the discipline of IPC.

IPC for the pediatric population is a unique discipline that requires understanding of various host factors, sources of infection, routes of transmission, behaviors required for care of infants and children, pathogens and their virulence factors, treatments, preventive therapies, and behavioral theory. Although the term *nosocomial* is applied accurately to infections that are acquired in acute care hospitals, the more general term, *healthcare-associated infections* (HAIs), is preferred because much care of high-risk patients, including patients with medical devices (e.g., central venous catheters, ventilators, ventricular shunts, peritoneal dialysis catheters), has shifted to ambulatory settings, rehabilitation or long-term care facilities, and the home. Additionally, much opportunity for IPC of HAIs exists in office practice settings. Thus, the geographic location of acquisition of the infection often cannot be determined.

The principles of transmission of infectious agents in healthcare settings and recommendations for prevention are reviewed in the Healthcare and Infection Control Practices Advisory Committee (HICPAC) Guideline for Isolation Precautions: Preventing Transmission of Infectious Agents in Healthcare Settings, 2007,[3] and in the Core Infection Prevention and Control Practices for Safe Healthcare Delivery in All Settings, 2017.[4] The Council for Outbreak Response: Healthcare-Associated Infections and Antimicrobial Resistant Pathogens (CORHA)[5] was formed in 2015 to bring together stakeholder organizations to improve practices and policies at the local, state and national levels for detection, investigation, control, and prevention of HAI/AR outbreaks across the healthcare continuum, including emerging infections and other risks with potential for healthcare transmission. Guidance on infection control practices related to antimicrobial resistant pathogens may be found on the Centers for Disease Control and Prevention (CDC) website[6] and outbreak response on the CORHA website.[5] The Society of Healthcare Epidemiology of America (SHEA) has published guidance for outbreak response and incident management to assist healthcare epidemiologists.[7] The reader should consult the Handbook of Pediatric Infection Prevention and Control[8] for more specific information related to the pediatric population. The World Health Organization (WHO) website should be consulted for new information concerning emerging pathogens worldwide. A detailed discussion of HAIs can be found in Chapters 99 and 100. This chapter focuses on the components of an effective pediatric hospital epidemiology program.

REFERENCES

1. Last JM, ed. *Dictionary of Epidemiology*. 4th ed. New York: Oxford University Press; 2001:61.
2. Wharton M, Chorba TL, Vogt RL, et al. Case definitions for public health surveillance. *MMWR Recomm Rep (Morb Mortal Wkly Rep)*. 1990;39(RR-13):1–43.
3. Kleinbaum DG, Kupper LL, Morgenstern H. *Epidemiologic Research: Principles and Quantitative Methods*. New York: Van Nostrand Reinhold; 1982:62–95.
4. Bland JM, Altman DG. Survival probabilities (the Kaplan-Meier method). *BMJ*. 1998;317:1572.
5. Clark TG, Bradburn MJ, Love SB, et al. Survival analysis. Part 1: basic concepts and first analyses. *Br J Cancer*. 2003;89:232–238.
6. Hosmer W, Lemeshow S, May S. *Applied Survival Analysis*. New York: Wiley; 2008.
7. Sackett DL. Bias in analytic research. *J Chronic Dis*. 1979;32:51–63.
8. Hill AB. In: *Principles of Medical Statistics*. 9th ed. New York: Oxford University Press; 1971:309–323.
9. Hoffmeister H. Small effects as a main problem in epidemiology. In: Hoffmeister H, Szklo M, Thamm M, eds. *Epidemiological Practices in Research on Small Effects*. Berlin: Springer; 1998:1–4.
10. Moher D, Dulberg CS, Wells GA. Statistical power, sample size, and their reporting in randomized controlled trials. *J Am Med Assoc*. 1994;272:122–124.
11. Krysan DJ, Kemper AR. Claims of equivalence in randomized controlled trials of the treatment of bacterial meningitis in children. *Pediatr Infect Dis J*. 2002;21:753–757.
12. Armitage P, Berry G. In: *Statistical Methods in Medical Research*. 2nd ed. New York: Wiley; 1987.
13. Whitehead J. Sequential methods. In: Redmond CK, Colton T, eds. *Biostatistics in Clinical Trials*. New York: Wiley; 2001:414–422.
14. Maclure M, Mittleman MA. Should we use a case-crossover design? *Annu Rev Public Health*. 2000;21:193–221.
15. Farrington CP, Nash J, Miller E. Case series analysis of adverse reactions to vaccines: a comparative evaluation. *Am J Epidemiol*. 1996;143:1165–1173.
16. Murphy TV, Gargiullo PM, Massoudi MS, et al. Intussusception among infants given an oral rotavirus vaccine. *N Engl J Med*. 2001;344:564–572.
17. Graham MH. Confronting multicollinearity in ecological multiple regression. *Ecology*. 2003;84:2809–2815.
18. Broome CV, Facklam RR, Fraser DW. Pneumococcal disease after pneumococcal vaccination: an alternative method to estimate the efficacy of pneumococcal vaccine. *N Engl J Med*. 1980;303:549–552.
19. Butler JC, Breiman RF, Campbell JF, et al. Pneumococcal polysaccharide vaccine efficacy. *J Am Med Assoc*. 1993;270:1826–1831.
20. Shapiro ED, Berg AT, Austrian R. The protective efficacy of polyvalent pneumococcal polysaccharide vaccine. *N Engl J Med*. 1991;325:1453–1460.
21. World Bank. *World Development Report 1993: Investing in Health*. Oxford, United Kingdom: Oxford University Press; 1993.
22. Greenberg RS. *Medical Epidemiology*. Norwalk, CT: Appleton and Lange; 1993:120.
23. Moher D, Schulz KF, Altman DG, for the CONSORT Group. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomized trials. *Lancet*. 2001;357:1191–1194.
24. Piaggio G, Elbourne DR, Altman DG, et al. Reporting of noninferiority and equivalence randomized trials: an extension of the CONSORT statement. *J Am Med Assoc*. 2006;295:1152–1160.
25. Stevanovic A, Schmitz S, Rossaint R, et al. CONSORT item reporting quality in the top ten ranked journals of critical care medicine in 2011: a retrospective analysis. *PloS One*. 2015;10:e0128061. https://doi.org/10.1371/journal.pone.0128061.
26. Peters JPM, Hooft L, Grolman W, Stegeman I. Assessment of the quality of reporting of randomised controlled trials in otorhinolaryngologic literature — Adherence to the CONSORT statement. *PloS One*. 2015;10:e0122328. https://doi.org/10.1371/journal.pone.0122328.
27. Centers for Disease Control and Prevention. New framework (GRADE) for development of evidence-based recommendations by the Advisory committee on immunization practices. *MMWR Morb Mortal Wkly Rep*. 2012;61:327.

RISK FACTORS FOR HEALTHCARE-ASSOCIATED INFECTIONS IN CHILDREN

Unique aspects of the pediatric population and their risk factors for HAIs are summarized in the following sections. Specific risks and pathogens are addressed in several other chapters in this textbook.

Host or Intrinsic Factors

PICUs, NICUs, oncology services, and gastroenterology services caring for patients with intestinal failure who are dependent on total parenteral nutrition (including lipids) have the highest rates of bacterial and fungal infection associated with central venous catheters. The definition of mucosal barrier injury laboratory-confirmed bloodstream infection (MBI-LCBI) currently is used by the National Healthcare Safety Network (NHSN) of the CDC to distinguish bacteremia that represents translocation of gut microorganisms related to mucosal barrier injury in patients with oncologic conditions, hematopoietic stem cell transplantation (HSCT), and intestinal failure from bacteremia associated with central venous catheters (CLABSI) and are not publicly reported.[9] This distinction is important because the bundled practices that focus on line insertion and maintenance do not prevent MBI-LCBI.[10] HAIs can result in substantial morbidity and mortality, as well as lifetime physical, neurologic, and developmental disabilities. Host (i.e., intrinsic) factors that make children particularly vulnerable to infection include immaturity of the immune system, congenital abnormalities, and congenital or acquired immunodeficiencies. Children with congenital anomalies and developmental disabilities have an increased risk of HAI because their unique anatomic features predispose them to contamination of normally sterile sites, and their physiologic functions may be impaired. Moreover, these children require prolonged and repeated hospitalizations, undergo many complex surgical procedures, and have extended exposure to invasive supportive and monitoring equipment.

Innate deficiencies of the immune system in prematurely born infants, who may be hospitalized for prolonged periods and exposed to intensive monitoring, supportive therapies, and invasive procedures, contribute to the relatively high rates of infection in the NICU. All components of the immune system are compromised in neonates, and the degree of deficiency is proportional inversely to gestational age (see Chapter 9). The underdeveloped skin of the very low birth weight (<1000 g) infant provides another mode of pathogen entry.

Populations of immunosuppressed children have expanded with the advent of more intense and innovative immunosuppressive therapeutic regimens used for oncologic conditions, HSCT, solid-organ transplantation, and rheumatologic conditions and inflammatory bowel disease for which immunosuppressive drugs and biologic response modifying agents are used. Genetic mutations in the genes for the transmembrane conductance regulator (CFTR) in children with cystic fibrosis result in thick secretions, chronic endobronchial infections, and gastrointestinal malabsorption. Knowledge of the epidemiology of infection of patients with cystic fibrosis and effective methods to prevent patient-to-patient transmission have expanded with the use of newer molecular diagnostic methods; a guideline for prevention of transmission of infectious agents of particular concern for this population was developed and updated.[11] Fortunately, the population of children with perinatally acquired HIV infection and AIDS has decreased dramatically since 1994, but new cases of sexually transmitted HIV infection continue to be diagnosed in teens who receive care in children's hospitals; therefore, HIV screening is an important routine practice for those >13–15 years of age. Additionally, young infants who have not yet been immunized, or immunosuppressed children who do not respond to vaccines or who lose antibody during disease or treatment (e.g., patients with nephrotic syndrome), have increased susceptibility to vaccine-preventable diseases.

Sources or Extrinsic Factors

The source of many HAIs is the endogenous flora of the patient. A colonizing pathogen can invade a patient's bloodstream or be transmitted to other patients on the hands of healthcare personnel (HCP) or on shared equipment. Water can be an important source of infections caused by gram-negative bacilli (GNB); therefore, exposure of wounds or mucous membranes to tap water should be avoided in high risk hospitalized patients.[12] Other important sources of HAIs in infants and children include the mother in the case of neonates, invasive monitoring and supportive equipment, contaminated infusates such as blood, total parenteral nutrition fluids, lipids, and infant formula, nutritional supplements, and human milk. Intrinsically contaminated powdered formulas and infant formulas prepared in contaminated blenders or improperly stored or handled have resulted in sporadic and epidemic infections in the nursery (e.g., *Cronobacter sakazakii*), but such infections have become less frequent since the pathogenesis was defined and contamination reduced.[13] Human milk that has been contaminated by maternal flora or by organisms transmitted through breast pumps has caused isolated serious infections and outbreaks. The risks of neonatal hepatitis, cytomegalovirus (CMV) infection, and HIV infection from human milk warrant further caution for handling and use of banked breast milk.

Maternal infection with *Neisseria gonorrhoeae, Treponema pallidum,* HIV, hepatitis B virus, parvovirus B19, *Mycobacterium tuberculosis,* herpes simplex virus, group B *Streptococcus*, or colonization with multidrug-resistant organisms (MDROs) poses substantial threats to the neonate. Group B *Streptococcus* is rarely transmitted nosocomially and is prevented by following recommended screening and prophylaxis protocols. During perinatal care, procedures such as fetal monitoring using scalp electrodes, fetal transfusion and surgical procedures, umbilical cannulation, and circumcision are potential risk factors for infection. Other contacts, including adult and sibling visitors, may introduce RSV and vaccine preventable infections into pediatric healthcare settings.

The use of invasive devices for monitoring or treatment is associated with an increased infection risk, and devices should be used only for the period of time when necessary and according to evidence based protocols for insertion and care. With increasing numbers of procedures being performed by pediatric interventional radiologists,[14] an understanding of appropriate aseptic technique, as well as prevention and management of infectious complications, by interventional radiologists is important.[15]

Construction, renovation, demolition, and excavation in and near healthcare facilities[16] and contaminated linen[17] are important sources of environmental fungi (e.g., *Aspergillus* spp., agents of mucormycoses, *Fusarium* spp., *Scedosporium* spp., *Bipolaris* spp.), but these pathogens are not transmitted patient to patient. Immunocompromised patients, and patients in the PICU are at greatest risk for fungal infection, and case fatality rates may be ≥50%, especially if diagnosis and treatment are delayed. Infection control risk assessments and implementation of effective practices can prevent exposure to these pathogens.

Several practices must be evaluated with respect to the potentially associated risk of infection for infants and young children. Theoretical concerns exist that infection risk also will increase in association with the innovative skin-to-skin practices (kangaroo Care) and co-bedding of twins. The experience with skin-to-skin practices has been safe and beneficial as long as parents are advised about potential risks if they have an infection. Neither the benefits nor the safety of co-bedding multiple-birth infants in the hospital setting has been demonstrated.

TRANSMISSION

Routes

The principal modes of transmission of infectious agents are through direct and indirect contact, droplet, and airborne routes.[3,4] Many pathogens can be transmitted by more than one route. During the 2020 pandemic of SARS-CoV-2, additional evidence has been published to support aerosol transmission as an important mode of transmission that varies from traditional droplet or airborne routes.[18–20] Whole genome sequencing has become a critically important tool in outbreak investigations of bacteria, fungi, and viruses to define routes of transmission more precisely and is now available widely.

Indirect Contact. Most infectious agents are transmitted horizontally by the indirect contact route on the hands of HCP or through contaminated shared items or contaminated surfaces; this is known as *fomite transmission*. Toddlers often share waiting rooms, playrooms, toys, books, and other items and therefore have the potential of transmitting pathogens directly and indirectly to one another. Contaminated bath toys were implicated in an outbreak of multidrug-resistant *Pseudomonas*

aeruginosa in a pediatric oncology unit.[21] Although the source of most *Candida* HAIs is the patient's endogenous flora, horizontal transmission, most likely via HCP hands, has been demonstrated in studies using molecular typing in the NICU[22] and in a pediatric oncology unit.[23] Hand hygiene and environmental cleaning and disinfection are most important to prevent transmission by this route.

Direct Contact. Direct contact transmission occurs when microorganisms are transferred directly from one infected person to another person without a contaminated intermediate person or object and occurs less frequently than indirect contact transmission.

Droplet. Infectious respiratory droplets >5 μm in diameter are generated from the respiratory tract by coughing, sneezing, or talking or during such procedures as suctioning, intubation, chest physiotherapy, or pulmonary function testing. Transmission of infectious agents by the droplet route requires exposure of mucous membranes to large respiratory droplets within 6 feet (2 meters) of the infected person. Large respiratory droplets do not remain suspended in the air for prolonged periods, and they settle on environmental surfaces. Adenovirus, influenza virus, and rhinovirus are transmitted primarily by the droplet route, whereas RSV is transmitted primarily by the contact route.[24] Although influenza virus can be transmitted by the airborne route under unusual conditions of reduced air circulation or low absolute humidity, ample evidence indicates that transmission of influenza is prevented by droplet precautions and, in the care of infants, the addition of contact precautions.[25]

Airborne. Droplet nuclei that arise from desiccation of respiratory droplets are usually <5 μm in diameter, contain infectious agents, remain suspended in the air for prolonged periods of time, and can travel long distances on air currents. Susceptible persons who have not had face-to-face contact or been in the same room as the source person can inhale such infectious particles. *M. tuberculosis*, varicella-zoster virus (VZV), and rubeola virus are the agents most frequently transmitted by the airborne route. Although transmission of *M. tuberculosis* by the airborne route can occur rarely from an infant or young child with active tuberculosis, the more frequent source of *M. tuberculosis* in a healthcare setting is the adult visitor with active pulmonary tuberculosis that has not yet been diagnosed; thus, screening of visiting family members is an important component for control of tuberculosis in pediatric healthcare facilities.[26]

Aerosol. A clear distinction between droplet and aerosol-based transmission is overly simplistic. Aerosols are liquid or solid particles that contain an infectious agent, most often a virus, remain suspended in the air, and can be inhaled by a nearby individual, whereas droplets containing an infectious agent fall to the ground and may be sprayed onto a nearby individual's respiratory mucosa via a contact route. The term *aerosol* is also used to describe the collection or cloud of respiratory droplets that remain suspended in the air. The size of aerosols has been defined as <5 μm but can be as large as 50 μm. These particles remain suspended in the air but do not travel long distances under usual circumstances. Individuals infected with SARS CoV-2 produce a much greater quantity of aerosols than droplets. The amount of respiratory particles that are produced routinely varies in number and in size. There are several factors that influence production and transmission of respiratory aerosols laden with virus that can be inhaled by others: (1) Humidity: With higher humidity, respiratory particles are heavier and drop to the ground more quickly and are therefore less likely to be inhaled by others; (2) force with which air is forced over moist respiratory particles; (3) amount of coughing, sneezing, heavy breathing; (4) close proximity to the source; (5) ventilation of the enclosed space, number of air exchanges per hour; (6) filtration; and (7) duration of exposure to the source. Some agents (e.g., SARS-CoV and SARS-CoV-2) can be transmitted as small-particle aerosols under special circumstances of performing aerosol-generating procedures (AGPs) (e.g., endotracheal intubation, bronchoscopy). SARS-CoV-2 may be transmitted in small particle aerosols for distances between 3 and 6 feet, even when AGPs are not being performed.[18,20] An N95 or higher respirator is recommended whenever caring for a patient with suspected or confirmed COVID-19 to prevent inhalation of small particle aerosols. AGPs should be performed in an airborne infection isolation room (AIIR) and if, not available, in a single occupancy room with the door closed. There is still much to be learned about the role of aerosols in transmission of infectious agents.

The following classification was proposed in 2003 for aerosol transmission when evaluating routes of SARS-CoV transmission: (1) *Obligate:* Under natural conditions, disease occurs following transmission of the agent only through small-particle aerosols (e.g., tuberculosis); (2) *Preferential:* Natural infection results from transmission through multiple routes, but small-particle aerosols are the predominant route (e.g., measles, varicella); and (3) *Opportunistic:* Agents naturally cause disease through other routes, but under certain environmental conditions they can be transmitted by fine-particle aerosols.[28] This conceptual framework can explain rare occurrences of airborne transmission of agents that are transmitted most frequently by other routes (e.g., smallpox, SARS-CoV, influenza, noroviruses). Concern about airborne transmission of influenza arose during the 2009 influenza A (H1N1) pandemic. However, the conclusion from all published experiences during the 2009 pandemic was that droplet transmission is the usual route of transmission, and surgical masks were noninferior to N95 respirators in preventing laboratory-confirmed influenza in HCP.[29] Concerns about unknown or possible routes of transmission of agents that can cause severe disease and have no known treatment often result in more extreme prevention strategies. Therefore, recommended precautions could change as the epidemiology of emerging agents is defined and these controversial issues are resolved. Although no evidence supports airborne transmission of the Ebola virus under usual circumstances in the field, the aerosolization of body fluids that contain high titers of Ebola virus requires additional protection.[30]

Role of Healthcare Personnel

Transmission of microbes between children and HCP when recommended hand hygiene is not performed is an especially important risk because of the very close contact that occurs during care of infants and young children. HCP as vehicles of infectious agents is facilitated by overcrowding, understaffing, and too few appropriately trained nurses in pediatric facilities.[3,31] Adequate staffing levels and the composition of staff in high-risk clinical units are important components of an effective IPC program. HCP rarely are the *source* of outbreaks of HAIs caused by bacteria and fungi[32] and, therefore, performing screening cultures among HCP as part of an outbreak investigation rarely is indicated. Observations of HCP for specific risk factors (e.g., dermatitis, skin abscesses, onychomycosis, wearing of artificial nails) and querying about the presence of conditions (e.g., sinusitis, draining otitis externa, respiratory tract infections) that may increase the risk of transmission is more helpful than performing widespread cultures of hand swabs during an outbreak investigation unless there is a specific epidemiologic link.[32] Persons with direct patient contact who were wearing artificial nails have been implicated in outbreaks of *P. aeruginosa* and ESBL-producing *Klebsiella pneumoniae* in NICUs; therefore, the use of artificial nails or extenders is prohibited in persons who have direct contact with high-risk patients.[3] Several published studies have shown that infected pediatric HCP, including resident physicians, transmitted *Bordetella pertussis* to patients[33] and can be the source of other vaccine-preventable infections in healthcare.[34]

EPIDEMIOLOGICALLY IMPORTANT PATHOGENS

The following characteristics provide a useful framework for determining when a pathogen is epidemiologically important: (1) A propensity for transmission within and across healthcare facilities and the occurrence of temporal or geographic clusters of infection in >2 patients. A single case of healthcare-associated invasive disease caused by certain pathogens (e.g., group A *Streptococcus* postoperatively, peripartum, or in burn units; *Legionella* sp.; *Aspergillus* sp.; *Candida auris*) should trigger an investigation; (2) Association with antimicrobial resistance that could render infections difficult to treat or untreatable. Infections caused by intrinsically resistant GNB also suggest possible contamination of water or medication. The CDC has published reports in 2013 and in 2019 of the Antibiotic Resistance Threats in the United States (www.cdc.gov/drugresistance/pdf/threats-report/2019-ar-threats-report-508.pdf) that provide classification of MDROs according to threat level (e.g., urgent, serious, concerning, and watch list) to assist clinicians in planning surveillance and control programs; (3) Association with serious clinical disease and increased morbidity and mortality; and (4) A newly discovered or re-emerging pathogen.

Pathogens associated with HAIs in children differ from those in adults in that respiratory viruses are more frequently associated with transmission in pediatric healthcare facilities. Respiratory viruses (e.g., RSV, parainfluenza, adenovirus, human metapneumovirus) have been implicated in outbreaks in high-risk units and in pediatric long-term care facilities.

One exception is the SARS-CoV-2 agent associated with the 2019–2020 pandemic. Children were affected less frequently than adults early in the pandemic, and very young children may not transmit SARS-CoV-2 as effectively as do adults. As more respiratory viruses and gastrointestinal pathogens are identified by using highly sensitive methods, epidemiologic studies will be required to define further the risk of transmission in healthcare facilities and the clinical significance of detection by antigen or molecular testing.[35,36] Previously prominent healthcare-associated outbreaks of varicella, measles, and rotavirus infection now are rare events because of the consistent use of vaccines for children and HCP.

It is often challenging to distinguish pathogens that are first acquired in the community and then become responsible for healthcare-associated outbreaks. The emergence of methicillin-resistant *Staphylococcus aureus* (MRSA) characterized by the unique SCC *mec* type IV element was first observed among infants and children in the community (CA-MRSA). As rates of colonization with CA-MRSA at the time of hospital admission increased, so did transmission of community strains, most often USA 300, within the hospital and especially within the NICU, thus making prevention especially challenging. Other MDROs (e.g., VRE, ESBLs, and CRE, especially *K. pneumoniae*) have emerged as the most challenging healthcare-associated pathogens in both pediatric and adult settings, and otherwise healthy children in the community can be colonized asymptomatically with these MDROs. GNB, including ESBL-producing organisms and other multidrug-resistant isolates, are more frequent than MRSA and VRE in many PICUs and NICUs. Patients who are transferred from other healthcare facilities, especially chronic care facilities, can be colonized with MDR GNB at the time of admission to the PICU. HAIs caused by MDROs are associated with increased length of stay, increased morbidity and mortality, and increased cost, in part because of the delay in initiating effective antimicrobial therapy. Although the prevalence of specific MDROs is lower in pediatric institutions, the same principles of target identification and interventions to control MDROs apply in all settings.

Information on other epidemiologically important healthcare associated pathogens in pediatrics including *C. difficile*, *Candida* spp., and environmental fungi can be found in other chapters. Of note, *Candida auris,* a difficult-to-treat, rapidly spreading pathogen in adult facilities, has had little impact on the pediatric population to date.

PREVENTION PROGRAMS

Prevention remains the mainstay of IPC programs and requires special considerations in children. The primary goal of IPC programs is to prevent the transmission of infectious agents among individual patients or groups of patients, visitors, and HCP who care for them. Checklists, adherence monitoring, and prevention bundles are important tools for infection prevention. Prevention bundles are groups of 3–5 evidence-based best practices with respect to a process that individually improve care, but when applied together result in substantially greater reduction in infection rates. Adherence to the individual measures within a bundle is readily measurable. Bundled practices are used most frequently for prevention of device- or procedure-related HAIs but can be applied to prevention of any type of HAI. For example, a healthcare-associated virus infection bundle developed in a large tertiary care children's hospital that included visitor symptom screening and restriction and adherence to employee sick leave policy in addition to the basics of infection control practices was associated with a reduction in healthcare associated viral illnesses.[37] One important component of such a bundle is mandatory influenza vaccine for all staff members.

Most outbreak investigations identify gaps in the basic infection control practices that led to transmission. The most important components of a prevention program are continuous emphasis of the basics such as hand hygiene, proper use and donning and doffing of gowns and gloves, N95 and surgical masks, eye protection, and environmental cleaning, with adherence monitored using trained observers. As new pathogens emerge, new strategies for prevention of transmission emerge. The experience with Ebola virus in the US in 2014 and 2015[30] and SARS-CoV-2 in the 2019–2020 pandemic[38] are recent examples of requirements for change in the usual infection prevention paradigms, with a renewed emphasis on the 3 tiers of the hierarchy of controls (e.g., engineering, administration, and use of personal protective equipment [PPE]), donning and doffing of PPE, and the use of trained observers. If prevention cannot always be achieved, strategies for early diagnosis, treatment, and containment are critical.

A series of IPC guidelines have been developed and updated at varying intervals by the HICPAC/CDC, SHEA, the Infectious Diseases Society of America (IDSA), the American Academy of Pediatrics (AAP), the Association for Professionals in Infection Control and Epidemiology (APIC), and others to provide evidence-based, rated recommendations for practices that are associated with reduced rates of HAIs, especially those infections associated with the use of medical devices and surgical procedures. Recommended isolation precautions by infectious agent also can be found in the CDC guidelines[3,4] and in the most recent edition of the *Red Book Report of the Committee on Infectious Diseases* of the American Academy of Pediatrics that is updated every 3 years.

Administrative Factors

The importance of certain administrative measures for a successful IPC program has been demonstrated. A white paper published by SHEA summarizes the necessary infrastructure for an effective IPC program in modern times.[39] This paper addresses the expansion of IPC responsibilities from a relatively narrow focus on acute infectious disease events in the acute care hospital, surveillance, and implementation of recommended isolation precautions to a much broader set of activities across the continuum of care requiring teamwork within and beyond individual facilities, often including large networks. Because IPC comprises one component of the institutional culture of safety, it is critical to obtain support from the senior leadership of healthcare organizations to provide necessary fiscal and human resources for a proactive, successful IPC program. Critical elements requiring administrative support include access to the following: (1) Appropriately trained healthcare epidemiologists and IPC personnel; (2) clinical microbiology laboratory services needed to support infection control outbreak investigations, including ability to perform molecular diagnostic testing; (3) data-mining programs and information technology specialists; (4) multidisciplinary programs to ensure judicious use of antimicrobial agents and control of resistance; (5) development of effective educational information for delivery to HCP, patients, families, and visitors; (6) well-trained occupational health personnel familiar with infectious diseases; and (7) local and state health department resources for preparedness.

Infection Prevention and Control Team

An effective IPC program improves safety of patients and HCP and decreases short-term and long-term morbidity, mortality, and healthcare costs. The IPC committee of a facility establishes policies and procedures to prevent or reduce the incidence and costs associated with HAIs. This committee should be one of the strongest and most accessible committees in the facility; committee composition should be considered carefully and limited to active, authoritative participants who have well-defined committee responsibilities and who represent major groups within the hospital. The chairperson should be a good communicator with expertise in IPC issues, healthcare epidemiology, and clinical pediatric infectious diseases. Important functions of the IPC committee are continuous monitoring of institutional HAIs, education of HCP and intervention when necessary, and regular review of IPC policies with development of new policies as needed. Annual review of all policies is required by The Joint Commission and can be accomplished optimally by careful review of a few policies each month. With the advent of unannounced inspections, a constant state of readiness is required.

The hospital epidemiologist or medical director of the pediatric IPC department usually is a physician with specialized training in pediatric infectious diseases and healthcare epidemiology. In multispecialty medical centers where infants and children comprise a relatively small proportion of patients, pediatric infectious disease and infection control experts should be consulted for management of pediatric IPC issues and report to the broader IPC leadership. The skillsets, training, and competencies needed for success as a healthcare epidemiologist were summarized in another white paper published by the SHEA.[40] Certification for healthcare epidemiologists has not yet been developed.

Provision of adequate numbers of well-trained IPs and bedside nursing staff are critical for success. Infection preventionists are specialized professionals with advanced training, and preferably certification, in

IPC. Although most IPs are registered nurses, other professionals such as microbiologists, medical technologists, pharmacists, and epidemiologists are successful in this position. Pediatric patients should have IP services provided by professionals with expertise and training in the care of children. In a large, general hospital, at least one infection preventionist should be dedicated to IPC services for children. The responsibilities of IPs continue to expand and include but are not limited to the following:

1. Surveillance and IPC in facilities affiliated with primary acute care hospitals (e.g., ambulatory clinics, day-surgery centers, long-term care facilities, rehabilitation centers, home care) in addition to the primary hospital
2. Collaboration and frequent communication with occupational health services related to IPC (e.g., assessment of risk and administration of recommended prophylaxis following exposure to infectious agents, tuberculosis screening, influenza and pertussis vaccination, respiratory protection fit testing, administration of other vaccines as indicated during infectious disease crises such as pre-exposure smallpox vaccine in 2003 and pandemic influenza A [H1N1] vaccine in 2009 and COVID-19 vaccines in 2020)
3. Preparedness planning for annual influenza outbreaks, pandemic influenza, SARS, Middle East respiratory syndrome (MERS), bioweapons attacks, Ebola Virus Disease, SARS-CoV-2, or other pandemics
4. Adherence monitoring for selected IPC practices
5. Oversight of risk assessment and implementation of preventive measures associated with construction, renovation, and other environmental conditions associated with increased infection risk
6. Participation in antimicrobial stewardship programs, focusing on prevention of transmission of MDROs
7. Evaluation of new products and medical devices that could be associated with increased infection risk (e.g., endoscopes, contaminated injectable medications) and introduction and assessment of performance after implementation of modified products
8. Mandatory public reporting of HAI rates according to enacted state legislation
9. Direct and frequent communication with the public and with local public health departments concerning infection control–related issues
10. Participation in local and multicenter reporting and research projects

IPC programs must be adequately staffed to perform all the assigned activities. Thus, the ratio of 1 infection preventionist to 250 beds that was associated with a 30% reduction in the rates of nosocomial infection in the Study on Efficacy of Nosocomial Infection Control (SENIC) performed in the 1970s[41] is no longer sufficient because of the increased complexity of patient populations and ever-expanding IPC responsibilities. Experience with the 2019–2020 SARS-CoV-2 pandemic highlighted the critical importance of an adequate number of IP staff. While it is unlikely that a study similar to the SENIC study will be repeated in the current era, data have been gathered by several groups to support the need for 1.0–1.25 IPs per 100 beds in the Acute Care Hospital.[42–44] IP staffing may be supported by the addition of support staff with diverse roles and abilities (e.g., a hand hygiene program manager, infection prevention associates, a clinical practice analyst, infection control liaisons from various clinical units). This type of program was associated with a significant reduction in rates of harm across 5 key HAI indicators at a time when patient days, central venous catheter days, and ventilator days increased in a large children's hospital.[45] Appointment of a clinical staff member in a high-risk unit as an IPC liaison enhances the infection preventionist's effectiveness.[3] No information is available on the number of IPC personnel required outside acute care, but it is clear that persons well trained in IPC must be available for all sites where healthcare is delivered. For example, during the pandemic, the state of California mandated a full-time IP for every skilled nursing facility in the state and is planning to maintain that requirement post pandemic.

Surveillance

Facility-Wide and System-Wide Surveillance

Surveillance for HAIs consists of a systematic method of determining the incidence and distribution of infections acquired by hospitalized patients. The CDC recommends the following: (1) Prospective surveillance on a regular basis by trained infection preventionists, using standardized definitions and available data mining software; (2) analysis of infection rates using established epidemiologic and statistical methods (e.g., calculation of rates using appropriate denominators that reflect duration of exposure; use of statistical process control charts for trending rates); (3) regular use of data in decision making; (4) feedback to bedside staff; and (5) employment of an effective and trained healthcare epidemiologist who develops IPC strategies and policies and serves as a liaison with the medical community and administration.[46-48] The CDC has established a set of standard definitions of HAIs that have been validated and accepted widely with updates posted on the CDC NHSN website. Standardization of surveillance methodology has become especially important with the advent of state legislation for mandatory reporting of HAI infections to the public. NHSN is the nation's most widely used HAI tracking system in the US and now receives, analyzes, and reports data from >25,000 medical facilities in the US. A standardized infection ratio (SIR) that takes into account differences in risk among healthcare settings, unit types, procedures, and patient populations has been included in summary reports of HAI rates since 2009. The Centers for Medicare and Medicaid Services and most states use the NHSN data for public reporting of HAI rates to HCP and the public on their websites. Although much effort has been directed toward making these data understandable and useful to consumers, interpretation of these data by the public remains difficult, and more research is needed to optimize methods of data display to the public.[49] NHSN publishes reports of the data analyzed at various intervals and links may be found on the NHSN website.[50] The report that is posted on the state health department website presents data by facility, specific HAI type, and year-to-year trends, and describes improvements that have occurred and identifies other areas in need of improvement.

Although various surveillance methods are used, the basic goals and elements are similar and include using standardized definitions of infection, finding and collecting cases of HAIs, tabulating data, using appropriate denominators that reflect duration of risk, analyzing and interpreting the data, reporting important deviations from endemic rates (epidemic, outbreaks) to the bedside care providers and to the facility administrators, implementing appropriate control measures, auditing adherence rates for recommended processes, and assessing efficacy of the control measures. Medical centers can use different methods of surveillance, as outlined in Box 2.1. Most experts agree that a combination of methods enhances surveillance and reliability of data, and some combination of clinical chart review and database retrieval is important. Whatever data collection systems are used, validation is required. Administrative databases created for the purposes of billing should not be used as the sole source to identify HAIs because of overestimates and underestimates that result from inaccurate coding of HAIs. Internal validation of data reported to NHSN is recommended, and validation tools are available on the NHSN website. Use of software designed specifically for IPC data entry and analysis facilitates real-time tracking of trends and timely intervention when clusters are identified. The IPC team should participate in the development and update of electronic medical record systems for a healthcare organization to ensure that surveillance needs will be met.

Targeted Pathogen-Specific Active Surveillance Cultures

Targeted pathogen-specific active surveillance of microbial cultures or point prevalence cultures is an important tool for investigation of outbreaks associated with a specific pathogen.[5–7] Much controversy has surrounded the role of obtaining active surveillance cultures from all patients admitted to an acute care hospital, especially to an ICU, to detect asymptomatic colonization with MRSA or VRE and then to place those persons under Contact Precautions in an endemic setting, a practice referred to as a *vertical approach*.[51] A *horizontal approach* is advantageous because it reduces the risk of transmission of a broad variety of pathogens and does not focus on a single pathogen. Contributing factors to the effectiveness of the horizontal approach for prevention of transmission include the following: (1) widespread implementation of bundled prevention practices, including limiting use of unnecessary medical devices; (2) improved understanding and more consistent implementation of Standard Precautions, especially hand hygiene; (3) widespread use of adherence monitoring to ensure consistent implementation of recommended practices; (4) improved environmental cleaning with adherence monitoring; and (5) promotion of

BOX 2.1 Sources of Data for Surveillance

Clinical rounds with physicians or nurses, or both
Review of:
- Patients' orders
- Radiology reports and databases
- Pharmacy reports and databases
- Operating room diagnoses and procedures
- Microbiology: bacteriology, virology, mycology, mycobacteriology, serology reports, autopsy reports, data-mining reports

Post-discharge surveillance, especially for surgical site infections
Public health surveillance
Review of:
- Employee health reports
- Admission diagnoses
- Outpatient diagnoses
- Administrative databases, but these should not be used as a sole source because of inaccurate coding of healthcare-associated infections
- Electronic data mining systems that integrate microbiology laboratory data and pharmacy data

antimicrobial stewardship. At this time, there is insufficient experience to make a broad recommendation to discontinue routine use of Contact Precautions for patients with asymptomatic colonization with MRSA or VRE in an endemic setting.[52] Special considerations for the NICU may be found in a HICPAC CDC guidance document.[53] Each IPC program must determine practice based on local conditions and follow with close auditing and surveillance for potential adverse outcomes.

Control of unusual infections or outbreaks in the community generally is the responsibility of the local or state public health department; however, the individual facility must be responsible for preventing transmission within that facility. Public health agencies can be helpful, particularly in alerting hospitals of community outbreaks so that outpatient and inpatient diagnosis, treatment, necessary isolation, and other preventive measures are implemented promptly to avoid further spread. Conversely, designated persons in the hospital must notify public health department personnel of reportable infections to facilitate early diagnosis, treatment, and infection control in the community. Benefits of community or regional collaboratives of individual healthcare facilities and local public health departments for prevention of HAIs, especially those caused by MDROs, have been demonstrated, and such collaboration should be encouraged.

Microbiology laboratory personnel can provide culture information online about individual patients, outbreaks of infection, antibiograms (antibiotic susceptibility patterns of pathogens summarized periodically), and employee infection data. The laboratory also can assist with surveillance cultures and facilitation of molecular typing of isolates during outbreak investigations. Rapid diagnostic testing of clinical specimens for identification of respiratory and gastrointestinal tract viruses and *B. pertussis* is especially important for pediatric facilities. The IPC division and the microbiology laboratory personnel must communicate daily because even *requests* for cultures or other diagnostic testing from physicians (e.g., *M. tuberculosis*, *Neisseria meningitidis*, *C. difficile*) can identify patients early who are infected, are at high risk of infection, or require isolation. If microbiology laboratory work is outsourced, it is important to ensure that the services and communication needed to support effective IPC are available, as delineated in a 2018 guideline developed by the IDSA and the American Society for Microbiology.[54]

ANTIMICROBIAL STEWARDSHIP

Antimicrobial stewardship is inextricably linked to effective IPC. Increasingly, patients are colonized or infected with MDROs rather than more susceptible strains, and MDROs are a major public health threat worldwide. Antibiotic exposure imposes selective pressure on pathogens by eliminating susceptible organisms, which drives the proliferation of antibiotic-resistant strains and promotes the development or acquisition of genetic factors that confer antimicrobial resistance to previously susceptible organisms. In closed units, drug-resistant strains can be identified within weeks of an antibiotic regimen change.[55] Rotation of the antibiotic regimen, or cycling, has not been shown to reduce resistance; overall reduction in antibiotic use is required to slow the development of resistance.[56] Unfortunately, antimicrobial agents are among the most overused classes of drugs in the US. The CDC estimates that up to one-third of all antibiotic use is either inappropriate or unnecessary.[6,57] Therefore, a systematic approach to reducing prolonged or unnecessary antimicrobial therapy can slow the development of MDROs and prevent antibiotic-associated infections (e.g., *Clostridioides difficile* diarrhea).

Antimicrobial stewardship was defined in a consensus statement by the IDSA, SHEA, and Pediatric Infectious Diseases Society in 2012 as "coordinated interventions designed to improve and measure the appropriate use of antibiotic agents by promoting the selection of the optimal antibiotic regimen, including dosing, duration, and route of administration." A stewardship program is most effective when there is collaboration between the patient care team, clinical pharmacist, infectious diseases physician, infection preventionist, healthcare epidemiologist, and microbiologist.[58,59] Hospital administrative support for the infrastructure required to facilitate ongoing measurement and reporting of antimicrobial use and related outcome measures (e.g., antimicrobial use dashboard in the electronic medical record, individual provider feedback) is critical to the success of the antimicrobial stewardship program. The NHSN publishes the Antimicrobial Use and Resistance Module that facilities can use to analyze antimicrobial use and resistance data in a way that supports IPC efforts and antimicrobial stewardship.[60] In 2019, the CDC updated the Core Elements of Hospital Antibiotic Stewardship Programs to include an emphasis on commitment of hospital leadership and the inclusion of a pharmacist, ideally as a coleader, of the stewardship program. Additionally, the importance of formal inclusion of bedside nurses in antimicrobial stewardship remains underappreciated; nursing participation has been shown to improve patient outcomes and clinician confidence.[61–63]

An antimicrobial stewardship program can optimize clinical outcomes while decreasing the adverse consequences of prolonged or unnecessary antimicrobial use, including the emergence of resistant organisms. A variety of strategies have been proven as effective components of an antimicrobial stewardship program. Audit and feedback, in which antibiotic use is measured, analyzed, and used to inform and educate prescribers in real time, perhaps is the single most effective tool and is the backbone of effective stewardship. Preauthorization, in which certain restricted antimicrobial agents can be prescribed only after approval by the stewardship team, is also effective but is a far less collaborative strategy.[64,65] An intermediate step is to use an antibiotic timeout, in which restricted agents can be prescribed but then are systematically reviewed by the stewardship team at a specified time (e.g., 48 hours).[66] When done effectively, education and feedback ideally will shift the responsibility for appropriate antibiotic prescribing towards the prescribing team and away from the stewardship program.[67] The use of facility-specific treatment guidelines for specific conditions also can optimize prescribing by establishing clear recommendations for common conditions (e.g., pneumonia, intra-abdominal infection, neonatal sepsis). The inclusion of relevant providers in the development and maintenance of these clinical guidelines (e.g., surgeons for intra-abdominal infection, pediatric hospital medicine providers for pneumonia) has been shown to improve adherence and efficacy.[68,69] Finally, the concept of diagnostic stewardship has emerged as a corollary to effective antimicrobial stewardship; specifically, understanding that correctly distinguishing an infection from a noninfectious condition is a prerequisite to using antimicrobial agents effectively. Clinicians must prioritize obtaining relevant diagnostic tests, particularly bacterial and fungal cultures before initiating antimicrobial therapy in order to clarify subsequent decisions. Investigating viral diagnostics, sepsis biomarkers, and predictive modeling are all important potential strategies to prevent unnecessary antimicrobial use.[70]

Finally, it is critical to emphasize that "all antimicrobial stewardship is local." Strategies that are effective at a large, tertiary, free-standing children's hospital may not be applicable to a rural critical access hospital that lacks pediatric-specific pharmacists or infectious diseases support. Similarly, an antimicrobial stewardship program tailored to a PICU would not necessarily be effective in a NICU, in which patients and pathologic events differ dramatically. Studies show that even a referral NICU in which most or all infants are born at other facilities has drastically

TABLE 2.1 Recommendations for Application of Standard Precautions for the Care of All Patients in All Healthcare Settings

Component	Recommendations for Performance
Hand hygiene	Perform before touching patients and before donning gloves; after touching blood, body fluids, secretions, excretions, and contaminated items; immediately after removing gloves; between patient contacts. Alcohol-containing antiseptic hand rubs are preferred except when hands are visibly soiled with blood or other proteinaceous materials or if exposure to spores (e.g., *Clostridioides difficile, Bacillus anthracis*) is likely to have occurred
Gloves	Use for touching blood, body fluids, secretions, excretions, contaminated items; for touching mucous membranes and nonintact skin
Gown	Wear during procedures and patient care activities when contact of clothing or exposed skin with blood or body fluids, secretions, or excretions is anticipated
Mask,[a] eye protection (goggles), face shield	Wear during procedures and patient care activities likely to generate splashes or sprays of blood, body fluids, or secretions (especially suctioning, endotracheal intubation) to protect healthcare personnel. For patient protection, the person inserting an epidural anesthesia needle or performing myelograms should use a mask when prolonged exposure of the puncture site is likely to occur
Soiled patient-care equipment	Handle in a manner that prevents transfer of microorganisms to others and to the environment; wear gloves if equipment is visibly contaminated; perform hand hygiene
Environmental control	Develop procedures for routine care, cleaning, and disinfection of environmental surfaces, especially frequently touched surfaces in patient care areas. Include objective measures of effectiveness of cleaning (e.g., Glo-Germ marking or ATP measurements)
Textiles and laundry	Handle in a manner that prevents transfer of microorganisms to others and to the environment
Safe injection practices (use of needles and other sharps)	Do not recap, bend, break, or hand-manipulate used needles; if recapping is required, use a one-handed scoop technique only; use needle-free safety devices when available; place used sharps in a puncture-resistant container. Use a sterile, single-use, disposable needle and syringe for each injection given. Single-dose medication vials are preferred when medications are administered to >1 patient
Patient resuscitation	Use a mouthpiece, resuscitation bag, or other ventilation device to prevent contact with mouth and oral secretions
Patient placement	Prioritize for a single-patient room if the patient is at increased risk of transmission, is likely to contaminate the environment, does not maintain appropriate hygiene, or is at increased risk of acquiring infection or developing adverse outcome following infection
Respiratory hygiene and cough etiquette[b]	Instruct symptomatic persons to cover the mouth or nose when sneezing or coughing; use tissues and dispose in no-touch receptacle; observe hand hygiene after soiling of hands with respiratory secretions; wear a surgical mask if tolerated or maintain spatial separation, >1–2 m (3–6 feet) if possible

[a]During aerosol-generating procedures on patients with suspected or proven infections transmitted by aerosols (e.g., SARS-CoV and SARS-CoV-2), wear a fit-tested N95 or higher respirator in addition to gloves, gown, and face and eye protection.

[b]Source containment of infectious respiratory secretions in symptomatic patients, beginning at the initial point of encounter (e.g., triage and reception areas in emergency departments and physician offices).

Modified with permission from Siegel JD, Rhinehart E, Jackson M, et al. Guideline for isolation precautions: preventing transmission of infectious agents in healthcare settings, 2007. *Am J Infect Control.* 2007;35(Suppl 2):S65–S164.

different prescribing patterns and stewardship requirements than an inborn NICU in which the infants are born at that hospital.[71] Antimicrobial stewardship programs should be tailored to the specific environment to ensure optimal impact.[72] The use of implementation science to identify barriers to adoption and effectiveness is particularly valuable when instituting an antimicrobial stewardship program. Ultimately, a well-designed antimicrobial stewardship program that is tailored for a specific purpose is an invaluable component of infection control and prevention.

ISOLATION PRECAUTIONS

Isolation of patients with potentially transmissible infectious diseases is a strategy proven to prevent transmission of infectious agents in healthcare settings. Many published studies, performed in both adult and pediatric settings, provide a strong evidence base for most recommendations for isolation precautions and for limiting outbreaks. However, controversies exist concerning the most clinically and cost-effective measures for preventing certain HAIs, especially those associated with MDROs.

Since 1970, the guidelines for isolation precautions developed by CDC have responded to the needs of the evolving US healthcare systems and the growing bodies of evidence. For example, universal precautions became a required standard in response to the HIV epidemic that emerged in the 1980s and the need to prevent acquisition of bloodborne pathogens (e.g., HIV, hepatitis B and C viruses) by HCP through skin, eye, mucous membrane, or parenteral contact with blood or other potentially infectious materials from persons not known to be or suspected of being infected. Universal precautions were modified and now are standard precautions since publication of the 1996 Guideline for Isolation.[3] The federal Needlestick Safety and Prevention Act, signed into law in November 2000, authorized the Occupational Safety and Health Administration's revision of its Bloodborne Pathogens Standard more explicitly to require the use of safety-engineered sharp devices.

Evidence and recommendations are provided for the prevention of transmission of MDROs such as MRSA, VRE, VISA, VRSA, and GNB.[3–6] The components of a protective environment for prevention of environmental fungal infections in HSCT recipients are described in the HICPA/CDC 2007 Isolation Guideline.[3] Updates of evidence-based, rated recommendations are posted on the HICPAC website as they become available.

Standard Precautions

The most recent Guideline for Isolation Precautions published in 2007[3] reaffirms Standard Precautions, a combination of universal precautions and body substance isolation, as the foundation of transmission prevention measures. Critical thinking is required for HCP to recognize the importance of body fluids, excretions, and secretions in the transmission of infectious pathogens and take appropriate protective precautions by using PPE (e.g., masks, gowns, gloves, face shields, or goggles) and safety devices when exposure is likely even if an infection is not suspected or known. In addition, updated guidelines[4] provide recommendations for Standard Precautions in all settings in which healthcare is delivered (acute care hospitals, ambulatory surgical and medical centers, long-term care facilities, and home health agencies). The components of Standard Precautions are summarized in Table 2.1. In the most recent HICPAC/CDC isolation guidelines,[3,4] safe injection practices are included as a component of Standard Precautions. Despite the emphasis on safe injection practices, transmission of hepatitis B and C viruses continues to be reported in ambulatory care settings as a result of failure

to follow recommended practices, thus indicating a need to reiterate the established effective practices. A review of clusters of transmission of hepatitis C virus in dialysis centers from 2005 to 2015 identified the following potential infection control breaches: (1) Use of multidose vials for heparin or saline administration; (2) poor compliance with hand hygiene before and after patient contacts or after touching a possibly contaminated surface; (3) failure to change gloves between patient contacts or after contact with a potentially contaminated surface; (4) failure to disinfect environmental surfaces adequately; (5) unsafe injection practices; (6) failure to disinfect shared equipment between patient uses; (7) lack of a separate area for medication preparation; and (8) failure to have clean and dirty utility rooms clearly separated.

Two additions were made to Standard Precautions in 2007: (1) Respiratory hygiene or cough etiquette for source containment by people with signs and symptoms of respiratory tract infection and (2) use of a mask by personnel inserting an epidural anesthesia needle or performing a myelogram when prolonged exposure of the puncture site is likely. Both components have a strong evidence base.

Implementation of Standard Precautions requires the availability of PPE in proximity to all patient care areas. HCP with exudative lesions or weeping dermatitis must avoid direct patient care and handling of patient care equipment. Persons having direct patient contact should be able to anticipate exposure incurring risks and steps to take if a high-risk exposure occurs. Exposures of concern are as follows: Exposures to blood or other potentially infectious material defined as an injury with a contaminated sharp object (e.g., needlestick, scalpel cut); a spill or splash of blood or other potentially infectious material onto nonintact skin (e.g., cuts, hangnails, dermatitis, abrasions, chapped skin) or onto a mucous membrane (e.g., mouth, nose, eye); or blood exposure covering a large area of normal skin. Patient-related duties that do not constitute high-risk exposures include handling food trays or furniture, pushing wheelchairs or stretchers, using restrooms or telephones, having personal contact with patients (e.g., giving information, touching intact skin, bathing, giving a back rub, shaking hands), or performing clerical or administrative functions for a patient.

If hands or other skin surfaces are exposed to blood or other potentially infectious material, the area should be washed immediately with soap and water for at least 10 seconds and rinsed with running water for at least 10 seconds. For an eye, nose, or mouth splashed with blood or body fluids, the area should be irrigated immediately with a large volume of water. If a skin cut, puncture, or lesion is exposed to blood or other potentially infectious material, the area should be washed immediately with soap and water for at least 10 seconds and rinsed with 70% isopropyl alcohol. Any exposure incident should be reported immediately to the occupational health department to determine whether blood samples are required from the source patient and the exposed person and if immediate prophylaxis is indicated.

All HCP should know where to find the exposure control plan specific to each area of care, whom to contact, where to go, and what to do if inadvertently exposed to blood or body fluids. Important resources include the occupational health department, the emergency department, and the infection control or hospital epidemiology division. The most important recommendation in any accidental exposure is to seek advice immediately to determine whether intervention is required.

Transmission-Based Precautions

Transmission-Based Precautions are designed for patients with documented or suspected infection with pathogens for which additional precautions beyond Standard Precautions are needed to prevent transmission. The three categories of Transmission-Based Precautions are Contact Precautions, Droplet Precautions, and Airborne Precautions, and they are based on the likely routes of transmission of specific infectious agents. It is likely that specific precautions for prevention of aerosol transmission will be developed by CDC in the future. Transmission-Based Precautions are combined for infectious agents that have more than one route of transmission. When used singly or in combination, such precautions always are used in addition to Standard Precautions. Transmission-Based Precautions applied at the time of initial contact, based on the clinical presentation and the most likely pathogens, are referred to as *Empiric Precautions* or *Syndromic Precautions*. This approach is useful especially for emerging agents (e.g., SARS-CoV, avian influenza, pandemic influenza), for which information concerning routes of transmission is evolving. The categories of clinical presentation are as follows: diarrhea, central nervous system, generalized rash or exanthem, respiratory, skin or wound infection. Single-patient rooms always are preferred for children needing Transmission-Based Precautions. If single-patient rooms are unavailable, cohorting of patients, and preferably of staff (dedicating specific staff members to a cohort of patients without cross over to other uninfected patients), according to clinical and laboratory confirmed diagnosis and exposure history is recommended. The experience of patients with Ebola virus infection in the US in 2014 led to the development of special precautions after viral transmission to 2 nurses occurred as a result of patients' extraordinarily high viral loads and large volumes of emitted body fluids.[30] PPE for all transmission-based precautions is donned upon entry into the room to protect against acquisition of pathogens from contaminated surfaces, even if direct contact with the patient is not intended. Evidence supports the importance of applying Contact Precautions only when indicated, obtaining training on the use of PPE, having effective PPE readily available, and practicing consistent and precise use of PPE.

Table 2.2 lists the 3 categories of isolation based on routes of transmission and their necessary components. Table 2.3 lists precautions by syndromes, to be used when a patient has an infectious disease, and the agent is not yet identified. For infectious agents that are more likely to be transmitted by the droplet route (e.g., pandemic influenza), droplet precautions (with use of surgical mask) are appropriate. When caring for individuals with infections transmitted by aerosols, such as SARS-CoV-2, an N95 or higher respirator and a face shield or goggles are recommended. When aerosol-generating procedures are administered to individuals with an aerosol or airborne infection, place the patient in a negative pressure isolation room (AIIR) and wear an N95 or higher respirator and a face shield or goggles.[3,38]

ENVIRONMENTAL MEASURES

Cleaning

Contaminated environmental surfaces and noncritical medical items have been implicated in transmission of several infectious agents, including VRE, *C. difficile, Acinetobacter* spp., MRSA, and RSV in healthcare settings.[73] Pathogens on surfaces are transferred to the hands of HCP and are then transferred to patients or items to be shared. Occupying a room previously occupied by a patient with a key pathogen is a risk factor for acquiring that pathogen during a hospital stay. *Cleaning* is the removal of all foreign material from surfaces and objects. This process is accomplished using soap and enzymatic products. Failure to remove all organic material from items before disinfection and sterilization reduces the effectiveness of these processes. Most often, the failure to follow recommended procedures for cleaning and disinfection contributes more than does the specific pathogen to the environmental reservoir during outbreaks. A program of environmental cleaning developed and implemented collaboratively by the IPC and environmental services departments are associated with sustained improvement in cleaning.[74,75] Use of a standardized cleaning checklist and implementation of monitoring for adherence to recommended environmental cleaning practices are important determinants of success. Visual markers (e.g., invisible fluorescein powder) and adenosine triphosphate bioluminescence technologies are also useful for monitoring effective environmental cleaning and providing immediate feedback to workers. Cost effectiveness of an environmental cleaning bundle with five evidence-based components targeting audit, communication, technique, training, and product has been demonstrated.[76]

Disinfection, Sterilization, and Removal of Infectious Waste

Disinfection is a process that eliminates all forms of microbial life except the endospore. Disinfection usually requires liquid chemicals. Disinfection of an inanimate surface or object is affected adversely by the following: the presence of organic matter; a high level of microbial

TABLE 2.2 Transmission-Based Precautions[a]

Component	Contact	Droplet	Airborne/Aerosol
Hand hygiene	Per Standard Precautions Perform 5 "moments" of hand hygiene (see text), and ***upon entry*** into room Soap and water preferred over alcohol hand rub for *Clostridioides difficile, Bacillus anthracis* spores	Per Standard Precautions Perform 5 "moments" of hand hygiene (see text), and ***upon entry*** into room	Per Standard Precautions Perform 5 moments of hand hygiene (see text), and ***upon entry*** into room
Gown	Yes; don before or ***upon entry*** into room	Per Standard Precautions Add to droplet precautions for infants, young children, or presence of diarrhea	Per Standard Precautions and, if infectious, draining skin lesions present
Gloves	Yes; don before or ***upon entry*** into room	Per Standard Precautions. Add for infants, young children, and/or presence of diarrhea	Per Standard Precautions Add for infants, young children, or presence of diarrhea
Mask	Per Standard Precautions	Yes; don before or ***upon entry*** into room	Don N95 particulate respirator or higher ***before entry*** into room
Goggles or face shield	Per Standard Precautions	Per Standard Precautions Always for SARS-CoV, SARS-CoV-2, avian influenza	Per Standard Precautions Always for SARS-CoV, SARS-CoV-2, avian influenza
N95 or higher respirator (always don *before entry* into room)	When aerosol-generating procedures performed for influenza, SARS-CoV, SARS-CoV-2VHF[b]	When aerosol-generating procedures performed for influenza, SARS-CoV, SARS-CoV-2, VHF	Yes; don ***before entry*** into room
Room placement	Single-patient room preferred Cohort similar infections if single-patient rooms unavailable	Single-patient room preferred Cohort similar infections if single-patient rooms unavailable	Single-patient room Negative air pressure (Airborne Infection isolation room, AIIR); 12 air changes/hr for new construction, 6 air changes/hr for existing rooms. AIIRs not needed for pathogens transmitted by aerosol if no aerosol generating procedure
Environmental measures	Increased frequency, especially in the presence of diarrhea, transmission of *C. difficile*, norovirus Bleach for VRE, *C. difficile,* norovirus, *C. auris*	Routine	Routine
Transport	Mask patient if coughing Cover infectious skin lesions PPE not routinely required for transporter	Mask patient	Mask patient Cover infectious skin lesions

[a]In addition to Standard precautions, use Transmission-Based Precautions for patients with highly transmissible or epidemiologically important pathogens for which additional precautions are needed.
[b]Includes Ebola virus. Consult most recent Centers for Disease Control and Prevention and World Health Organization guidelines for recommended infection control precautions for Ebola virus disease.
Modified with permission from Siegel JD, Rhinehart E, Jackson M, et al. Guideline for isolation precautions: preventing transmission of infectious agents in healthcare settings, 2007. *Am J Infect Control* 2007;35(Suppl 2):S65–S164.
PPE, personal protective equipment; SARS, severe acute respiratory syndrome; VHF, viral hemorrhagic fever; VRE, vancomycin-resistant *Enterococcus*.

contamination; use of too dilute germicide; inadequate disinfection contact time; an object that can harbor microbes in protected cracks, crevices, and hinges; pH; and temperature. Certain infectious agents (e.g., rotavirus, noroviruses, *C. difficile*) can be resistant to some routinely used hospital disinfectants; thus, a 1:10 dilution of 5.25% sodium hypochlorite (household bleach) or other special disinfectants are indicated to prevent transmission of such agents despite appropriate cleaning procedures.

No-touch automated room decontamination technologies have been developed and added to room turnover procedures in some facilities. At specific wavelengths, ultraviolet light breaks the molecular bonds in DNA, thus destroying the organisms. Ultraviolet light irradiation and hydrogen peroxide vapor systems have been shown to reduce surface contamination with common pathogens, such as *C. difficile* and VRE, and decrease the risk of acquiring HAIs caused by those pathogens when these systems are added to a terminal cleaning regimen; however, no beneficial effect for MRSA or gram-negative MDROs was demonstrated in one systematic review and metanalysis.[77] These technologies supplement, but do not replace, standard cleaning and disinfection because surfaces must be physically cleaned of particulate matter and debris first. Other disadvantages of these systems are that they cannot be used when people are in the rooms, room turnover is delayed, and the systems are expensive to purchase. No recommendations have been made for routine use or specific indications because research on antimicrobial effectiveness, cost effectiveness, and feasibility of these systems is ongoing.

Self-disinfecting surfaces can be created by altering the structure of the surface material or by incorporating a material that has antimicrobial activity.[78] Copper has antimicrobial activity against a wide range of organisms including bacteria and fungi. Thus, incorporating copper into high-touch surfaces such as toilet seats, bed rails, door handles, or countertops is a novel infection prevention strategy that has been shown to reduce bacterial colony counts compared with control surfaces in healthcare settings. However, no recommendation for routine use yet has been made.

Sterilization is the eradication of all forms of microbial life, including fungal and bacterial spores. Sterilization is achieved by physical and chemical processes such as steam under pressure, dry heat, ethylene oxide, and liquid chemicals. The Spaulding classification of patient care equipment as critical, semi-critical, and noncritical items regarding sterilization and disinfection is used by the CDC. Critical items require sterilization because they enter sterile body tissues and carry a high risk of causing infection if they are contaminated; semi-critical items require disinfection because they may contact mucous membranes and nonintact skin; and noncritical items require routine cleaning because they come in contact only with intact skin. If noncritical items used on patients requiring Transmission-Based Precautions, especially Contact Precautions, must be shared, then these items should be disinfected between uses. Guidelines for specific objects and specific disinfectants are published and updated by the CDC. Multiple published reports and manufacturers similarly recommend

TABLE 2.3 Clinical Syndromes or Conditions Warranting Empiric Transmission-Based Precautions in Addition to Standard Precautions Pending Confirmation of Diagnosis[a]

Clinical Syndrome or Condition[b]	Potential Pathogens[c]	Empiric Precautions (Always Includes Standard Precautions)
DIARRHEA		
Acute diarrhea with a likely infectious cause in an incontinent or diapered patient	Enteric pathogens[d]	Contact Precautions (pediatrics and adult)
MENINGITIS	Neisseria meningitidis Enteroviruses Mycobacterium tuberculosis	Droplet Precautions for first 24 hrs of antimicrobial therapy; mask, face, and eye protection for intubation Contact Precautions for infants and childrenZ Airborne Precautions if pulmonary infiltrate Airborne Precautions plus Contact Precautions if potentially infectious draining body fluid present
RASH OR EXANTHEMS, GENERALIZED, ORIGIN UNKNOWN		
Petechial or ecchymotic exanthem with fever (general)	*N. meningitidis*	Droplet Precautions for first 24 hrs of antimicrobial therapy
If traveled in an area with an ongoing outbreak of viral hemorrhagic fever in the 10 days before onset of fever	Ebola, Lassa, Marburg viruses	Airborne Precautions plus Contact Precautions, with face and eye protection, emphasizing safety sharps and barrier precautions when blood exposure likely In the United States, asymptomatic persons can be managed in Ebola assessment centers. Transfer symptomatic persons with infection to biocontainment units Use a single-use fluid-resistant or impermeable gown that extends to at least midcalf or a coverall without an integrated hood. Two pairs of gloves should be worn. Use a single-use fluid-resistant or impermeable boot cover. A single-use fluid resistant or impermeable apron should be worn to cover the torso if the patient has vomiting or diarrhea Consult CDC, WHO websites for current recommendations
Vesicular	Varicella-zoster, herpes simplex, variola (smallpox), vaccinia viruses	Airborne plus Contact Precautions Contact Precautions only if herpes simplex, localized zoster in an immunocompetent host, or vaccinia viruses most likely
Maculopapular with cough, coryza, and fever	Rubeola (measles) virus	Airborne Precautions
RESPIRATORY INFECTIONS		
Cough, fever, or upper-lobe pulmonary infiltrate in an HIV-negative patient or a patient at low risk for HIV infection	*M. tuberculosis,* respiratory viruses, *Streptococcus pneumoniae, Staphylococcus aureus* (MSSA or MRSA)	Airborne Precautions plus Contact Precautions until *M. tuberculosis* ruled out Droplet Precautions if respiratory viruses most likely
Cough, fever, or pulmonary infiltrate in any lung location in an HIV-infected patient or a patient at high risk for HIV infection	*M. tuberculosis,* respiratory viruses, *Streptococcus pneumoniae, Staphylococcus aureus* (MSSA or MRSA)	Airborne Precautions plus Contact Precautions Use eye and face protection if aerosol-generating procedure performed or contact with respiratory secretions anticipated If tuberculosis is unlikely and no AIIRs or respirators are available, use Droplet Precautions instead of Airborne Precautions Tuberculosis more likely in HIV-infected than in HIV-uninfected persons
Cough, fever, or pulmonary infiltrate in any lung location in a patient with a history of recent travel (10–21 days) to a country with an outbreak of SARS or avian influenza	*M. tuberculosis*, SARS-CoV, SARS-CoV-2, avian influenza	Airborne Precautions plus Contact Precautions in addition to eye protection If SARS and tuberculosis unlikely, use Droplet Precautions instead of Airborne Precautions
Respiratory infections, particularly bronchiolitis and pneumonia, in infants and young children	Respiratory syncytial virus, parainfluenza virus, adenovirus, influenza virus, human metapneumovirus	Contact Precautions plus Droplet Precautions Droplet Precautions can be discontinued when adenovirus and influenza have been ruled out
SKIN OR WOUND INFECTION		
Abscess or draining wound that cannot be covered	*Staphylococcus aureus* (MSSA or MRSA), group A *Streptococcus*	Contact Precautions Add droplet precautions for the first 24 hrs of appropriate antimicrobial therapy if invasive group A streptococcal disease is suspected

[a]Infection control professionals should modify or adapt this table according to local conditions. To ensure that appropriate empiric precautions are always implemented, hospitals must have systems in place to evaluate patients routinely according to these criteria as part of preadmission and admission care.

[b]Patients with the syndromes or conditions listed may have atypical signs or symptoms (e.g., neonates and adults with pertussis may not have paroxysmal or severe cough). The clinician's index of suspicion should be guided by the prevalence of specific conditions in the community, as well as clinical judgment.

[c]The organisms listed under the column "Potential Pathogens" are not intended to represent the complete, or even most likely, diagnoses, but rather possible etiologic agents that require additional precautions beyond standard precautions until they can be excluded.

[d]These pathogens include enterohemorrhagic *Escherichia coli* O157:H7, *Shigella* spp., hepatitis A virus, noroviruses, rotavirus, and *Clostridium difficile.*

AIIR, airborne infection isolation room; CDC, Centers for Disease Control and Prevention; CoV, coronavirus; HIV, human immunodeficiency virus; MRSA, methicillin-resistant *Staphylococcus aureus;* MSSA, methicillin-susceptible *Staphylococcus aureus;* SARS, severe acute respiratory syndrome; VHF, viral hemorrhagic fever; WHO, World Health Organization.

the use and reuse of objects with appropriate sterilization, disinfection, or cleaning recommendations.

Outbreaks of MDR GNB infections have been associated with exposure to duodenoscopes used for retrograde cholangiopancreatography. These endoscopes have a complex design with long, narrow channels, crevices that are difficult to access with a cleaning brush, right-angle turns, and heavy microbial contamination following procedures. Recommendations in guidelines for reprocessing endoscopes to avoid contamination focus on training of personnel, meticulous manual cleaning, high-level disinfection followed by rinsing and air-drying, and proper storage.[79] Medical devices that are designed for single use (e.g., specialized catheters, electrodes, biopsy needles) must be reprocessed by third parties or hospitals according to the guidance issued by the US Food and Drug Administration (FDA) in August 2000 with amendments in September 2006; such reprocessors are regulated as manufacturers. Available data show that single-use devices reprocessed according to the FDA regulatory requirements are as safe and effective as new devices.

Deficiencies in disinfection and sterilization leading to infection have resulted either from failure to adhere to scientifically based guidelines or failures in the disinfection or sterilization processes. When such failures are discovered, an investigation must be completed, including notification of patients and, in some cases, testing for infectious agents. A guidance document for risk assessment and communication to patients in such situations is published.[80]

Healthcare facility waste is all biologic or nonbiologic waste that is discarded and not intended for further use. Medical waste is material generated as a result of use with a patient, such as for diagnosis, immunization, or treatment, and it includes soiled dressings and intravenous tubing. Infectious waste is that portion of medical waste that potentially could transmit an infectious disease. Microbiologic waste, pathologic waste, contaminated animal carcasses, blood, and sharps are all examples of infectious waste. Methods of effective disposal of infectious waste include incineration, steam sterilization, drainage to a sanitary sewer, mechanical disinfection, chemical disinfection, and microwave treatment. State and local regulations guide the treatment and disposal of regulated medical waste.

VISITATION POLICIES

People

Special visitation policies are required in pediatric units, especially the high-risk units, because acquisition of a seemingly innocuous viral infection in neonates and in children with underlying diseases can result in unnecessary evaluations and empiric therapies for suspected septicemia as well as serious, life-threatening disease. All visitors with signs or symptoms of respiratory or gastrointestinal tract infection should be restricted from visiting patients in healthcare facilities. Increased restrictions may be required during a community outbreak (e.g., SARS-CoV-2, pandemic influenza, Ebola virus). During respiratory virus season, the number of visitors can be limited and the age restriction increased. It is preferred for all visitors to be immunized against influenza during influenza season. Several children's hospitals provide influenza vaccine or tetanus, diphtheria, and acellular pertussis (Tdap) vaccine, or both, to household contacts at no charge, thereby supporting the cocooning strategy endorsed by the Advisory Committee on Immunization Practices of the CDC and the American Academy of Pediatrics.

For patients requiring Contact Precautions, the use of PPE by visitors is determined by the nature of the interaction with the patient and the likelihood that the visitor will frequent common areas on the patient's unit or interact with other patients and their families. It is important to distinguish parents or guardians from nonhousehold visitors when determining whether the visitor should wear PPE. The risk-benefit decision should weigh not only the specific pathogen in question, but also the effect of parental or guardian PPE on breastfeeding, bonding, and family participation in the child's medical care. For family members who are rooming in with children who have prolonged hospitalizations, restriction of visitation to other patients is emphasized. A SHEA expert guidance document has been published to summarize the principles to follow to prevent transmission of infectious agents by visitors to patients because few data are available to inform evidence-based recommendations.[81]

Although most pediatricians encourage visits by siblings in inpatient areas, the medical risk must not outweigh the psychosocial benefit. Families favorably regard sibling visitation, and no evidence indicates increased bacterial colonization or subsequent bacterial infection in the neonate or older child who has been visited by siblings. Strict guidelines for sibling visitation should be established and enforced in an effort to maximize visitation opportunities and minimize risks of transmission of infectious agents, most frequently viruses. The following recommendations regarding visitation can guide policy development:

1. Sibling visitation is encouraged in the well-child nursery and NICU, as well as in areas for care of older children.
2. Before visitation, parents should be interviewed by a trained staff nurse concerning their current health status and that of the patient's sibling. Siblings should not be allowed to visit if they are delinquent in recommended vaccines, have fever or symptoms of an acute illness, or are within the incubation period following exposure to a known infectious disease. After the interview, the physician or nurse should place a written consent for sibling visitation in the patient's permanent record and a nametag indicating that the sibling has been approved for visitation for that day.
3. Asymptomatic siblings who recently were exposed to varicella but who previously were immunized can be assumed to be immune.
4. The visiting sibling should visit only his or her sibling and not be allowed in playrooms with groups of patients.
5. Visitation should be limited to periods of time that ensure adequate screening, observation, and monitoring of visitors by medical and nursing staff members.
6. Children should perform hand hygiene before and after contact with the patient or upon entry and departure from the patient's room.
7. During the entire visit, parents or another responsible adult should supervise sibling activity.

Animals

Animal-assisted therapy can be of substantial clinical benefit to the child hospitalized for prolonged periods; therefore, it is important for healthcare facilities to provide guidance for safe visitation. Many zoonoses and infections are attributable to animal exposure (see Chapter 88). Most infections result from inoculation of animal flora through a bite or scratch or self-inoculation after contact with the animal, the animal's secretions or excretions, or contaminated environment. Although few data support a true evidence-based guideline for animal visitation (including personal pets) in healthcare facilities, updated expert guidance is provided in the SHEA Expert Guidance on Animals in Healthcare Facilities: Recommendations to Minimize Potential Risk, which includes a review of the literature related to animal-assisted activities.[82]

Prudent visitation policies should limit visitation to animals that (1) are domesticated; (2) do not require a water environment; (3) do not bite or scratch; (4) can be brought to the hospital in a carrier or easily walked on a leash; (5) are trained to defecate and urinate outside or in appropriate litter boxes; (6) can be bathed before visitation; and (7) are known to be free of respiratory, dermatologic, and gastrointestinal tract disease. Despite the established risk of salmonellosis associated with reptiles (e.g., turtles, iguanas), many reports of outbreaks of invasive disease associated with reptiles continue to be reported; reptiles should be excluded from pet visitation programs, and families should be advised not to have pet reptiles in the home with young infants or immunocompromised persons. Exotic animals that are imported should be excluded because of unpredictable behavior and the potential for transmission of unusual pathogens (e.g., monkeypox in the US in 2003).[83] Visitation should be limited to short periods and confined to designated areas. Visiting pets must have a certificate of immunization from a licensed veterinarian. Children should observe hand hygiene after contact with animals. Most pediatric facilities restrict pet interaction with severely immunosuppressed patients and patients in ICUs.

OCCUPATIONAL HEALTH

The Occupational Safety and Health Administration requires occupational health and student health collaboration with the IPC department

of a healthcare facility. HCP are at increased risk of infection in hospitals caring for children because (1) children have a high incidence of infectious diseases; (2) personnel can be susceptible to many pediatric pathogens; (3) pediatric care requires close physical contact; (4) children may lack good personal hygiene; (5) infected children can be asymptomatic; and (6) HCP are exposed to multiple family members who also may be infected.

Routine Infection Prevention and Control Practices

The CDC has provided updated guidance on the Infrastructure and Routine Practices for Occupational Infection Prevention and Control Services.[84] The occupational health department is an educational resource for information on infectious pathogens in the healthcare workplace. In concert with the IPC service, occupational health provides preemployment education and respirator fit testing and annual retraining for all employees regarding routine health maintenance, available recommended and required vaccines, Standard and Transmission-Based Precautions, and exposure control plans. Reporting a work-related exposure is required for subsequent medical care and workers' compensation.

Screening for tuberculosis at regular intervals, as determined by the facility's risk assessment, can use either tuberculin skin testing or interferon-γ release assays. With new pathogens being isolated, new diseases and their transmission described, and new prophylactic regimens and treatment available, it is mandatory that occupational health personnel have an up-to-date working knowledge of IPC and know where and what services, equipment, and therapies are available for HCP.

All HCP should be screened by history or serologic testing, or both, to document their immune status to specific agents, and immunization should be provided for the following for all employees who are nonimmune and who do not have contraindications to receiving the vaccine: hepatitis B virus, influenza (yearly), mumps, rubella, rubeola, varicella, Tdap, and, since 2021, COVID-19. The 2006 Advisory Committee on Immunization Practices recommendation to administer a single dose of Tdap to certain HCP was amended in 2011 to have no restriction based on age or time interval since the last Td dose. Providing vaccines at no cost to HCP increases acceptance.

Influenza vaccine coverage among HCP has increased over time to 81% overall for the 2019–2020 influenza season and was 94% in facilities with an employer vaccination requirement.[85] Although mandatory influenza vaccination programs for all employees in healthcare facilities are endorsed by many professional societies,[86] some facilities have had success using novel strategies that include incentives, without a mandate.[87] Publications from several large institutions, including children's hospitals, indicate that mandatory programs with only medical exemptions are well received, and only rarely are employees terminated for failure to be vaccinated.[88]

Special Concerns of Healthcare Personnel

HCP who have common underlying medical conditions should be able to obtain general information on wellness and screening when needed from the occupational health service. HCP with direct patient contact who have infants <1 year of age at home often are concerned about acquiring infectious agents from patients and transmitting them to their susceptible children. An immune healthcare worker who is exposed to VZV does not become a silent carrier of VZV. However, pathogens to which the healthcare worker is partially immune or nonimmune can cause a severe, mild, or asymptomatic infection in the employee that can be transmitted to family members. Examples include influenza, pertussis, RSV and other respiratory viruses, norovirus, and tuberculosis. Important preventive procedures for HCP with infants at home or who are pregnant are as follows: (1) consistent training and observance of Standard Precautions, Transmission-Based Precautions, and especially hand hygiene according to published recommendations; (2) annual influenza and 1-time Tdap immunization (unless pregnant, when a Tdap immunization during each pregnancy is recommended); (3) routine tuberculosis screening; (4) assurance of immunity or immunization against poliomyelitis, measles, mumps, hepatitis B, and rubella; (5) early medical evaluation for acute infectious illnesses; (6) routine, on-time immunization of infants; and (7) prompt initiation of prescribed prophylaxis or therapy following exposure or development of certain infections.

HCP who are, could be, or anticipate becoming pregnant should feel comfortable and safe working in the healthcare workplace. In fact, with Standard Precautions and appropriate adherence to environmental cleaning and Transmission-Based Precautions, vigilant HCP can be at less risk than a preschool teacher, childcare provider, or mother of children with many playmates in the home. Pathogens of potential concern to pregnant HCP include cytomegalovirus, hepatitis B virus, influenza, measles, mumps, parvovirus B19, rubella, VZV, *M. tuberculosis,* Zika virus, and SARS-CoV-2. The causal association between Zika virus and microcephaly and other neurodevelopmental abnormalities[89] has led to recommended precautions. Although Zika virus is more frequently acquired outside of the healthcare setting, pregnant HCP are advised to follow safe injection practices for prevention of exposure to infectious blood.[3] Pregnancy is an indication for influenza vaccine to prevent the increased risk of serious disease and hospitalization that occurs in women who develop influenza in the second or third trimester of pregnancy. In 2011, the CDC recommended universal immunization with Tdap (if previously not immunized with Tdap) for pregnant women after 20 weeks of gestation, and since 2012, the CDC recommends a dose of Tdap with each pregnancy.[90] COVID-19 vaccine is recommended for pregnant women and to date, there have not been pregnancy-related adverse events associated with vaccination during the first four months of administration in the US. The CDC website will continue to update information about safety of vaccine in pregnant women as it accumulates. Pregnant HCP should assume that all patients potentially are infected with CMV and other silent pathogens and should use hand hygiene and gloves when handling body fluids, secretions, and excretions. Table 2.4 summarizes information about infectious agents that are relevant to the pregnant woman working in healthcare. Chapters on each agent may be consulted for more specific information.

INFECTION PREVENTION AND CONTROL IN THE NONACUTE CARE SETTING

The risk of HAIs in pediatric ambulatory settings is substantial, and it usually is associated with lack of adherence to routine IPC practices and procedures, especially cleaning and disinfection, sterilization, and hand hygiene. Respiratory viral agents and *M. tuberculosis* are noteworthy pathogens transmitted in ambulatory settings. One example is transmission of RSV in an HSCT outpatient clinic has been demonstrated using molecular techniques.[91] Crowded waiting rooms, toys, furniture, lack of isolation of children, unwell children, contaminated hands, contaminated secretions, and susceptible HCP are only some of the factors that result in sporadic and epidemic illness in outpatient settings. Patient-to-patient transmission of *Burkholderia* species and *P. aeruginosa* in outpatient clinics for patients with cystic fibrosis has been confirmed and prevented by implementing recommended IPC practices.[11] IPC guidelines and policies for pediatric outpatient settings, including office practices, were updated by the American Academy of Pediatrics in 2017.[92] Prevention strategies include definition of policies, education, and strict adherence to guidelines. In pediatrics, among the most important interventions are separation of children with respiratory tract illnesses from well children and consistent implementation of respiratory hygiene or cough etiquette. A guideline for IPC for outpatient settings with a checklist and a guideline for outpatient oncology settings can be found on the CDC website.[93] Principles and recommendations for Safe Living after HSCT[94] and for patients with cystic fibrosis[11] are valuable contributions to management of infectious risks for specific populations in the ambulatory setting. A guideline based on data and expert consensus opinion for IPC in residential facilities for pediatric patients and their families provides practical guidance for settings where high-risk patients live with their families for varying periods of time.[95] IPC challenges now are being addressed in long-term care facilities for children.[96] More data are needed to determine the most effective and least restrictive practices.

TABLE 2.4 Pregnant Healthcare Personnel: Guide to Management of Occupational Exposure to Selected Infectious Agents

Agent or Disease	In-Hospital Source	Potential Effect on the Fetus	Perinatal Transmission	Maternal Screening	Prevention
***Bordetella pertussis* Pertussis ("whooping cough")**	Respiratory droplets from a coughing patient, HCP, visitor	No congenital syndrome	Maternal respiratory secretions	Documentation of date of vaccination with Tdap; Tdap recommended during each pregnancy. History of pertussis disease is *not* protective and does not replace vaccine	Tdap early in third trimester of each pregnancy (to prevent young infant from acquiring pertussis) and for every adult coming in contact with infant <12 months of age Breastfeeding *not* contraindicated *Standard Precautions* plus *Droplet Precautions*
Cytomegalovirus (CMV)/ congenital infection syndrome,[a] hearing loss	Patient populations: neonates, toddlers in childcare, hemodialysis patients, immunocompromised hosts, transplant recipients HCP acquisition during pregnancy unlikely to be occupational Urine, saliva, blood, semen, vaginal secretions, breast milk, respiratory secretions if pneumonia present	Symptomatic congenital infection syndrome[a] 5%–10%; hearing loss 10%–15%; asymptomatic congenital infection; hepatitis, anemia, thrombocytopenia Hearing loss can have later onset	Primary infection 25%–50% Recurrent infection or second infection with new strain: 69% reduction in risk of transmission Symptomatic <5%–15%	Routine screening not recommended Preexisting maternal antibody incompletely protective for fetus	Efficacy of CMV immune globulin or ganciclovir for pregnant woman with primary infection not established No vaccine available Breastfeeding *not* contraindicated Pregnant HCP does not need to be restricted from care of known CMV-infected patient *Standard Precautions*, especially *Safe Injection Practices*
Ebola virus	Blood and body fluids from infected, clinically ill patients, especially large-volume diarrhea	Spontaneous abortion, stillbirth Neonatal survival rare	Data on perinatal transmission limited and anecdotal; likely very high because Ebola virus is present in products of conception when tested	Routine screening not recommended, but a low threshold for diagnosing EVD in the pregnant woman is recommended PCR on blood is the recommended diagnostic test Case fatality rate of EVD in pregnant women is 90%	Restriction of pregnant women from care of persons with EVD Prolonged shedding of Ebola virus in breast milk Breastfeeding contraindicated, but duration unknown When caring for people not suspected of EVD, but during an EVD epidemic: *Standard Precautions,* especially *Safe Injection Practices* plus *Enhanced Precautions* in a biocontainment unit as defined on CDC and WHO websites
Hepatitis A virus (HAV)	Feces (most common), highest titer just before onset of jaundice; blood *very* rare Transmission in healthcare settings rare	None; transmission can occur at the time of delivery if mother still in the infectious phase and can cause hepatitis in infant	None	Routine screening not recommended	Vaccine is a killed virus vaccine and can be used safely in pregnancy Breastfeeding *not* contraindicated *Standard Precautions* Add *Contact Precautions* in acute phase
Hepatitis B virus (HBV)	Blood, body fluids, vaginal secretions, semen	Hepatitis; if acquired perinatally or at young age, increased risk for hepatocellular carcinoma	$HBeAg^-$ and $HBsAg^+$ (10%) $HBeAg^+$ and $HBsAg^+$ (90%)	Routine HBsAg testing advised Documentation of vaccination	HBV vaccine during pregnancy if immunity not previously documented Neonate: HBIG in addition to routine vaccine at birth if mother $HBsAg^+$ or status unknown Breast feeding *not* contraindicated *Standard Precautions*, especially *Safe Injection Practices*
Hepatitis C virus (HCV)	Blood, body fluids	Hepatitis	Transmission 5% (range 0%–25%)	Screening only if risk factors present: illicit IV drug user (mother or partner who is illicit IV drug user); history of organ transplant, transfusion of blood or blood products before 1992; hemodialysis; HBV or HIV infection; unexplained elevation of serum hepatic enzymes; history of tattooing; HCP with history of percutaneous exposure to blood test for HCV antibody (if positive, HCV RNA)	No vaccine or immune globulin available; postexposure treatment with antiviral agents investigational; consult current guidelines for updates Breastfeeding *not* contraindicated *Standard Precautions*, especially *Safe Injection Practices*

Continued

TABLE 2.4 Pregnant Healthcare Personnel: Guide to Management of Occupational Exposure to Selected Infectious Agents—cont'd

Agent or Disease	In-Hospital Source	Potential Effect on the Fetus	Perinatal Transmission	Maternal Screening	Prevention
Herpes simplex virus (HSV) **Fever blisters, cold sores, genital ulcers, encephalitis**	Vesicular fluid, oropharyngeal and vaginal secretions, amniotic fluid	Sepsis, encephalitis, meningitis, mucocutaneous lesions, congenital malformation (rare)	Primary genital infection 33%–50% Recurrent genital infection 1%–2%	Routine antibody testing minimally useful Maternal type-specific serology for HSV-1 and HSV-2 antibodies should be considered when evaluating an asymptomatic neonate following vaginal or cesarean delivery to a woman with genital lesions that are characteristic of HSV	Since genital infection with HSV is the risk for the fetus, occupational acquisition unlikely to occur Oral suppressive antiviral therapy at or beyond 36 wks of gestation decreases shedding in women with a history of genital HSV lesions Breastfeeding contraindicated only if herpetic lesions are located on the breast *Standard Precautions* Add *Contact Precautions* for patients with skin lesions
HIV **AIDS**	Blood, body fluids, vaginal secretions, semen	No congenital syndrome Transmission primarily during delivery If infected, onset of symptoms usually at 12–18 months of age	Risk of transmission determined by maternal HIV viral load, duration of exposure to maternal blood, body fluids (including breast milk), and use of ART during pregnancy, labor, and postnatally in the infant If no ART: maternal viral load <1000 copies/mL virus, rate of 2%; if load ≥10,000, rate up to 25% Rate reduced to <3% with perinatal and neonatal ART	Routine prenatal screening advised with repeat at end of pregnancy if high-risk behaviors HIV-exposed infants who receive ART from birth: repeated screens during first year HIV antibody screen with fourth-generation test; if positive, quantitative PCR	Antiretroviral chemoprophylaxis for occupational and nonoccupational exposures as recommended in most recent guidelines Treatment of infected woman with ART during pregnancy according to guidelines ART during labor and for infant of infected mother Repeated screening of treated HIV-exposed infant during first 4–6 months of life; check most recent guidelines Cesarean delivery reduces risk of HIV infection in infant if maternal viral load >1000 copies/mL or unknown near time of delivery Breastfeeding *not* recommended if alternative source of nutrition available *Standard Precautions*, especially *Safe Injection Practices*
Influenza virus **Influenza (flu)**	Respiratory droplets or sneezing; coughing patient, HCP, visitor	No congenital syndrome Influenza in mother can cause fetal hypoxia, premature labor, and fetal death Increased morbidity during third trimester of pregnancy Increased morbidity and mortality in pregnant women with 2009 influenza A (H1N1)	Maternal respiratory secretions	Documentation of vaccine received during current season	Inactivated influenza vaccine (IIV4) for all pregnant women during each influenza season to decrease risk of hospitalizations for cardiopulmonary complications in mother No risk if exposed to persons who received live-attenuated influenza vaccine (LAIV) Breastfeeding *not* contraindicated *Standard Precautions plus Droplet Precautions* Add *Contact Precautions* for infants and others who cannot contain their secretions Consider fitted N95 filtering facepiece respirator (or equivalent N95 respirator) for aerosol-generating procedures (e.g., bronchoscopy, nebulizer treatment), but AIIR not indicated
Measles (rubeola)	Respiratory secretions, coughing patient	Prematurity, spontaneous abortion; no congenital syndrome	Rare	Serology (IgG) if question after an exposure, but not routinely checked if adequate documentation provided Provider-documented disease or 2 doses measles-containing vaccine ≥12 months of age	Vaccine[b] Immune globulin IM or IGIV within 6 days of exposure if nonimmune *Standard Precautions* plus *Airborne Precautions*

TABLE 2.4 Pregnant Healthcare Personnel: Guide to Management of Occupational Exposure to Selected Infectious Agents—cont'd

Agent or Disease	In-Hospital Source	Potential Effect on the Fetus	Perinatal Transmission	Maternal Screening	Prevention
***Mycobacterium tuberculosis*, active disease (tuberculosis [TB])**	Sputum, skin lesions, CSF if meningitis present	Neonatal tuberculosis; liver most frequently infected	Rare	PPD, IGRA (interferon-γ release assay) (e.g., Quantiferon-Gold, T-Spot) Chest radiograph if indicated clinically or a past known positive PPD or IGRA result	Varies with PPD reaction size and chest radiograph result Anti-TB agents for active TB during pregnancy recommended PPD reliable and safe during pregnancy *Standard Precautions* plus *Airborne Precautions* for pulmonary or laryngeal TB. Add *Contact Precautions* if draining skin lesions
***Neisseria meningitidis*, meningococcal disease, meningococcal meningitis, sepsis**	Blood, respiratory secretions	No congenital syndrome Fetus at risk if mother develops severe disease during pregnancy	Rare	No routine screening	Prompt chemoprophylaxis if close (within 3–6 feet) contact with respiratory secretions of patient with meningococcal disease with IM ceftriaxone or oral azithromycin Routine vaccine only if microbiologist and routinely exposed to isolates of *N. meningitidis* *Standard Precautions* plus *Droplet Precautions* until 24 hr after effective therapy initiated
Parvovirus B19 Fifth disease (slapped cheeks), anemia, fetal hydrops	Respiratory secretions; blood of immunocompromised patients and patients with sickle cell disease during aplastic crisis Patient with Fifth disease no longer contagious once rash appears	Fetal hydrops, stillbirth No congenital syndrome Approximately 25% Fetal death <10%	Rare	No routine screening. Parvovirus B19 DNA can be detected in serum, leukocytes, respiratory secretions, urine, tissue specimens Specific IgM, IgG if exposure has occurred	No vaccine available Pregnant HCP can choose to defer care of immunocompromised patients with chronic infection or sickle cell disease during aplastic crisis *Standard Precautions*, especially *Safe Injection Practices*; for infected immunocompromised patient, add *Droplet Precautions*
Rubella	Respiratory secretions	Congenital infection syndrome[a] 90% affected in first trimester 40%–50% affected overall	Rare	Documentation of 2 doses rubella-containing vaccine before pregnancy Routine rubella IgG testing during pregnancy Preconception screening recommended	Vaccine[b] Immune globulin after exposure of a susceptible woman to rubella does *not* provide protection against congenital rubella No congenital rubella syndrome described in association with vaccine given inadvertently during pregnancy Rubella-containing vaccine post partum if woman is nonimmune *Standard Precautions* *Droplet Precautions plus Contact Precautions* for patients with congenital rubella until ≥1 year of age
Severe acute respiratory syndrome-coronavirus 2019 (SARS-CoV-2, COVID)	Respiratory droplets and aerosolized particles; contaminated equipment and surfaces	No fetal syndrome identified to date	Vertical uncommon; horizontal transmission may occur	Nasopharyngeal, midturbinate, anterior nares PCR test	Standard, Droplet, Aerosol (N95 respirator or higher for patient contact; AIIR for aerosol generating procedures), Eye protection, Contact Precautions; Mask for source control; COVID-19 vaccine for pregnant women
Syphilis Rash, skin and genital lesions, central nervous system disease	Blood, lesion (especially large bullae of congenital syphilis), amniotic fluid	Congenital infection syndrome[a] Variable 10%–90%; depends on stage of maternal disease and trimester of the infection	Transmission possible, related to contagiousness of maternal lesions	Serum VDRL, RPR Serum FTA-ABS	Post exposure prophylaxis with penicillin or ceftriaxone if percutaneous exposure *Standard Precautions*, especially *Safe Injection Practices* (wear gloves when caring for patients with congenital, primary, and secondary syphilis until 24 hrs of treatment completed)

Continued

TABLE 2.4 Pregnant Healthcare Personnel: Guide to Management of Occupational Exposure to Selected Infectious Agents—cont'd

Agent or Disease	In-Hospital Source	Potential Effect on the Fetus	Perinatal Transmission	Maternal Screening	Prevention
Varicella-zoster virus (VZV) Chickenpox, shingles	Respiratory secretions, vesicle fluid	Congenital infection syndrome Malformations, skin, limb, CNS, eye: chickenpox zoster Congenital syndrome 2%	High risk of infection and severe disease if maternal varicella within 5 days before or 2 days after delivery	Varicella IgG serology Past history of chickenpox unreliable	Vaccine (2 doses)[b]; VariZIG or IGIV, ideally within 96 hours of exposure if nonimmune Use the following precautions for patients with chickenpox and disseminated zoster: *Standard Precautions* plus *Airborne Precautions* plus *Contact Precautions*
Zika virus	Blood, body fluids of infected patients; mosquitoes in endemic area. Acquisition in the community more likely than in healthcare settings	Microcephaly, other neurodevelopmental abnormalities	Undefined at time of publication	RT-PCR on blood Serum IgG, IgM	Avoid outdoor work assignments in endemic areas Check CDC website for updated recommendations *Standard Precautions*, especially *Safe Injection Practices*

[a]Congenital syndrome: varying combinations of jaundice, hepatosplenomegaly, microcephaly, thrombocytopenia, anemia, retinopathy, skin and bone lesions, and "blueberry muffin spots" (extramedullary hematopoiesis).
[b]Live virus vaccine given before or after pregnancy.
ART, antiretroviral therapy; CDC, Centers for Disease Control and Prevention; CNS, central nervous system; CSF, cerebrospinal fluid; EVD, Ebola virus disease; FTA-ABS, Fluorescent treponema antigen-antibody test; HBeAg, hepatitis B e antigen; HBIG, hepatitis B immune globulin; HBsAg, hepatitis B surface antigen; HCP, healthcare personnel; IgG, immunoglobulin G; IgM, immunoglobulin M; IGIV, immune globulin intravenous; IM, intramuscular; IV, intravenous; PCR, polymerase chain reaction; PPD, purified protein derivative; RPR, rapid plasma reagin test; Tdap, tetanus-diphtheria-acellular pertussis; VDRL, Venereal Disease Research Laboratory test; WHO, World Health Organization.

All references are available online at Elsevier eBooks for Practicing Clinicians.

3 Infections Associated With Group Childcare

Timothy R. Shope and Andi L. Shane

On average, 12.5 million (61%) of the 20.4 million children in the United States who are younger than 5 years of age were enrolled in a regular childcare arrangement during the spring of 2011.[1] Children in group childcare experience increased frequency of certain infectious diseases and amplify outbreaks of illness (Table 3.1). Aggregation of young children potentiates transmission of organisms that can produce disease in other children, adult care providers, parents, and community contacts. As group size increases, so does the incidence of respiratory illnesses; however, once group sizes of 8 or more children are reached, this effect diminishes.[2] Respiratory infections are much more common than gastrointestinal infections, which comprise only 10% of these illnesses.[3] Children newly entered into group childcare are at especially high risk of respiratory tract and enteric infections. However, mothers whose children were enrolled in group childcare before 2.5 years of age reported their children had less frequent respiratory and gastrointestinal tract infections and episodes of otitis media during elementary school years.[4] The relationship between group childcare exposure and development of asthma is complex and influenced by multiple variables such as early childhood exposure to bacterial and viral antigens, environmental triggers, and genetic inheritance. Not surprisingly, studies have produced conflicting results. In a study of two longitudinal birth cohorts, childcare attendance overall demonstrated a protective effect for subsequent development of asthma. However, there was an interaction between childcare attendance and the Toll-like receptor 2 gene status; carriage of the T allele for TLR2/-16934 was associated with protection from asthma, but AA homozygosity was not.[5] An increase in antibiotic use as an attempt to facilitate earlier return to care enhances the potential for emergence of resistant organisms, thus resulting in an increased economic burden to individual persons and society.[6–8] Despite the challenges of frequent respiratory and gastrointestinal illness exacerbations among children enrolled in group childcare, these arrangements facilitate opportunities for socialization and enable primary caregivers to be employed outside the home.

TYPES OF CHILDCARE SETTINGS

Quantifying the number of children participating in each type of childcare setting is challenging because of different ascertainment methods used in several data sources. Types of facilities can be classified by size of enrollment, age of enrollees, and environmental characteristics of the facility. Grouping of children by age varies by setting, but in organized care facilities children usually are separated into the following groups: infants (6 weeks through 12 months), toddlers (13 through 35 months), preschoolers (36 months through 59 months), and school-aged children (5 through 12 years). These designations have relevance to the epidemiology of infectious diseases as well as to regulation and monitoring. Licensed childcare in centers and family childcare homes is subject to state regulation; however, the majority of childcare is provided by family members and others in their homes and is not subject to state regulations and monitoring.

The US Census Bureau conducts the Survey of Income and Program Participation (SIPP), which collects information about childcare arrangements for children <15 years of age. In 2011, 51% of children <5 years of age with working mothers were cared for by a relative, 33% were in organized care including center-based care or family childcare homes, 27% had multiple