FOURTH EDITION

HOSPITAL EPIDEMIOLOGY AND INFECTION CONTROL

C. Glen Mayhall, MD, FIDSA, FSHEA

Professor
Division of Infectious Diseases
Department of Internal Medicine
Healthcare Epidemiologist
The University of Texas Medical Branch Health System
The University of Texas Medical Branch
Galveston, Texas

Wolters Kluwer Health | Lippincott Williams & Wilkins

Philadelphia • Baltimore • New York • London
Buenos Aires • Hong Kong • Sydney • Tokyo

Acquisitions Editor: Frances DeStefano
Product Manager: Leanne Vandetty
Development Editor: Sarah M. Granlund
Production Manager: Alicia Jackson
Senior Manufacturing Manager: Benjamin Rivera
Marketing Manager: Kimberly Schonberger
Design Coordinator: Holly McLaughlin
Production Service: SPi Global

Two Commerce Square
2001 Market Street
Philadelphia, PA 19103 USA
LWW.com

Printed in China

Library of Congress Cataloging-in-Publication Data
Hospital epidemiology and infection control / editor, C. Glen Mayhall. — 4th ed.
p. ; cm.
Includes bibliographical references and index.
ISBN-13: 978-1-60831-300-6
ISBN-10: 1-60831-300-X
1. Nosocomial infections—Prevention. 2. Nosocomial infections—Epidemiology. 3. Cross infection–Prevention. I. Mayhall, C. Glen.
[DNLM: 1. Cross Infection—epidemiology. 2. Cross Infection—prevention & control. 3. Bioterrorism. 4. Infection Control—methods. WX 167]
RA969.H635 2012
614.4'4—dc23

2011015849

To purchase additional copies of this book, call our customer service department at (800) 638-3030 or fax orders to (301) 223-2320. International customers should call (301) 223-2300.

Visit Lippincott Williams & Wilkins on the Internet: at LWW.com. Lippincott Williams & Wilkins customer service representatives are available from 8:30 am to 6 pm, EST.

10 9 8 7 6 5 4 3 2 1

With tremendous gratitude to all of my colleagues and authors who have made the commitment and worked so hard to provide excellent chapters for the four editions of this book.

PREFACE FOR THE FOURTH EDITION

Once again, I appreciate the opportunity to edit the Fourth Edition of Hospital Epidemiology and Infection Control. The Fourth Edition has 104 chapters prepared by 184 authors. It has the most changes between editions compared to those between the First and Second Edition and those between the Second and Third Edition. Nineteen chapters from the Third Edition were retired, and ten new chapters were added to the Fourth Edition. The authors of the chapters on computer fundamentals and on the personal computer collaborated on a single chapter for the Fourth Edition entitled "Using the Personal Computer for Healthcare Epidemiology." A chapter on meta-analysis was added to Section I, and another new chapter in this section integrates the information from the other chapters in the section to provide the reader with a useful approach to study design and data analysis. This author cites other chapters in the section by page number.

Once again, my good friend and colleague, Dr. David Birnbaum, provided guidance and direction on revision of Section II on Healthcare Quality Improvement. I particularly appreciate his suggestion on adding a chapter on working with the media on public communication.

Other new chapters include mechanisms of biofilm formation in staphylococci, microbiologic sampling of the environment in healthcare facilities, antimicrobial stewardship, and elements of design in the built environment of the healthcare facility. Biofilms have been recognized to be of importance in infections related to inanimate materials and devices inserted into patients. The chapter on environmental cultures was included, because when culture of the environment is indicated, the best data can be obtained when appropriate techniques are used to obtain the samples. The chapter on elements of design of the built environment is intended to be a companion chapter to the chapter on prevention of infections related to construction. Inclusion of a chapter on antimicrobial stewardship relates to the increasing resistance of healthcare-associated microorganisms and the need for defined programs to prevent antimicrobial resistance. The first two chapters in Section XIII provide an excellent background for the chapter on antimicrobial stewardship.

Many chapters in this edition have new coauthors and several chapters have been revised or rewritten by an entirely new set of authors.

A new feature for the Fourth Edition is that only 15 to 20 key references are located at the end of the chapters in the printed book while all references cited in the chapters are online. The numbers for the references that are only online are italicized in the text whereas the numbers for the references printed at the end of the chapters are not italicized in the text.

As for all of the editions of this reference text, my goal has been, and is, to bring together many of our colleagues with particular areas of expertise in Healthcare Epidemiology and other experts in related fields to provide a comprehensive and up-to-date reference text that the reader will find useful in the daily practice of Healthcare Epidemiology.

CONTRIBUTORS

Joseph H. Abramson, BSc, MB, BCh
Emeritus Professor of Social Medicine
Hebrew University-Hadassah School of Public Health and Community Medicine
Jerusalem, Israel

Joel Ackelsberg, MD
Medical Director, BT Coordinator
Bureau of Communicable Disease
New York City Department of Health and Mental Hygiene
New York, New York

Stuart P. Adler, MD
Professor of Pediatrics
Virginia Commonwealth University
Medical College of Virginia
Richmond, Virginia

Katherine Allen-Bridson, RN, BSN, CIC
Division of Healthcare Quality Promotion
Centers for Disease Control and Prevention
Atlanta, Georgia

Anucha Apisarnthanarak, MD
Associate Professor
Division of Infectious Diseases
Thammasat University Hospital
Pratumthani, Thailand

Lennox K. Archibald, MD, PhD
Hospital Epidemiologist
Division of Infectious Diseases
College of Medicine
University of Florida
Gainesville, Florida

Matthew J. Arduino, MS, DrPH
Acting Chief
Clinical and Environmental Microbiology Branch
Division of Healthcare Quality Promotion
Centers for Disease Control and Prevention
Atlanta, Georgia

Jeffrey D. Band, MD
Director, Infectious Diseases and International Medicine
Corporate Epidemiologist
William Beaumont Hospital
Royal Oaks, Michigan
Clinical Professor of Medicine
Wayne State School of Medicine
Detroit, Michigan

Judene M. Bartley, MS, MPH, CIC
Vice President, Epidemiology Consulting Services, Inc.
Beverly Hills, Michigan

Sara T. Beatrice, PhD
Assistant Commissioner
Public Health Laboratory
New York City Department of Health and Mental Hygiene
New York, New York

Susan E. Beekmann, RN, MPH
Department of Internal Medicine
University of Iowa Carver College of Medicine
Iowa City, Iowa

Debra Berg, MD
Medical Director
Healthcare Emergency Preparedness Program
Bureau of Communicable Disease
New York City Department of Health and Mental Hygiene
New York, New York

Ronald G. Berglund, MPH
Masters of Public Health
University of Michigan
Ann Arbor, Michigan
Assistant Professor Health Care at Central Michigan University
Director of Quality at Dexter Research Center, Inc.
Saline, Michigan

Dennis C.J.J. Bergmans, MD, PhD
Internist/Intensivist
Department of Intensive Care
Maastricht University Medical Center
Maastricht, The Netherlands

David Birnbaum, PhD, MPH
Adjunct Professor
University of British Columbia School of Population and Public Health
University of British Columbia School of Nursing
University of Victoria School of Health Information Science
Principal
Applied Epidemiology
Manager
Washington State Department of Health, Healthcare Associated Infections Program
Vancouver, British Columbia, Canada

Stephanie R. Black, MD, MSc
Medical Director
Acute Disease Surveillance
Communicable Disease Program
Chicago Department of Public Health
Assistant Professor of Medicine
Rush University Medical Center
Chicago, Illinois

Mary Anne Bobinski, JD, LLM
Dean and Professor
Faculty of Law
University of British Columbia
Vancouver, British Columbia, Canada

Walter W. Bond, MS
Consultant Microbiologist
RCSA, Inc.
Lawrenceville, Georgia

Marc J.M. Bonten, MD, PhD
Department of Medical Microbiology
University Medical Center Utrecht
Utrecht, The Netherlands

Susan E. Boruchoff, MD
Professor of Medicine
Division of Infectious Diseases
Robert Wood Johnson Medical School
Hospital Epidemiologist
Robert Wood Johnson University Hospital
New Brunswick, New Jersey

Jason E. Bowling, MD
Assistant Professor
Department of Medicine/Division of Infectious Diseases
University of Texas Health Science Center at San Antonio
San Antonio, Texas
Hospital Epidemiologist University Health System
San Antonio, Texas

Patrick J. Brennan, MD
Professor of Medicine
Senior Vice President and Chief Medical Officer
Penn Medicine
University of Pennsylvania Health System
Philadelphia, Pennsylvania

Barbara A. Brown-Elliott, MS, MT(ASCP)SM
Research Assistant Professor
Microbiology Supervisor
Mycobacteria/Nocardia Laboratory
The University of Texas Health Science Center
Tyler, Texas

Kristina Bryant, MD
Associate Professor of Pediatrics
Pediatric Infectious Diseases
University of Louisville School of Medicine
Hospital Epidemiologist
Kosair Children's Hospital
Louisville, Kentucky

John P. Burke, MD
Professor of Medicine
University of Utah School of Medicine
Chief
Department of Clinical Epidemiology and Infectious Diseases
Information Healthcare
Salt Lake City, Utah

Jose Cadena, MD
Assistant Professor
Department of Medicine, Infectious Diseases
University of Texas Health Science Center at San Antonio (UTHSCSA)
Medical Director, Infection Control
Acting Chief, Infectious Diseases
Department of Medicine
South Texas Veterans Healthcare System
San Antonio, Texas

David P. Calfee, MD, MS
Associate Professor of Medicine
Weill Cornell Medical College
Chief Hospital Epidemiologist
New York Presbyterian Hospital
Weill Cornell Campus
New York, New York

Anne-Marie Chaftari, MD
Instructor
Department of Infectious Diseases, Infection Control and Employee Health
The University of Texas M. D. Anderson Cancer Center
Houston, Texas

Eyad Cheikh, MD
Fellow in Infectious Diseases
Department of Internal Medicine, Division of Infectious Diseases
Carilion Roanoke Memorial Hospital
Roanoke, Virginia

Carol E. Chenoweth, MD
Clinical Professor
Division of Infectious Diseases
Department of Internal Medicine
Department of Epidemiology
Hospital Epidemiologist
University of Michigan Health System
Ann Arbor, Michigan

Tom M. Chiller, MD, MPHTM
Deputy Chief
Mycotic Diseases Branch
National Center for Emerging and Zoonotic Infectious Diseases
Centers for Disease Control and Prevention
Adjunct Assistant Professor
Department of Infectious Diseases
Emory University School of Medicine
Atlanta, Georgia

David C. Classen, MD, MS
Associate Professor
Department of Internal Medicine
University of Utah
Salt Lake City, Utah

Kerry O. Cleveland, MD
Associate Professor of Medicine
University of Tennessee Health Science Center
Methodist Healthcare of Memphis
Memphis, Tennessee

Eva P. Clontz, Med
School of Medicine
University of North Carolina at Chapel Hill
Chapel Hill, North Carolina

Sara E. Cosgrove, MD
John Hopkins University
Baltimore, Maryland

Kent B. Crossley, MD
VA Medical Center
Education Service
Minneapolis, Minnesota

Burke A. Cunha, MD, MACP
Professor of Medicine
State University of New York School of Medicine
Stony Brook, New York
Chief, Infectious Disease Division
Winthrop-University Hospital
Mineola, New York

Cheston B. Cunha, MD
Department of Medicine
Brown University Alpert School of Medicine
Rhode Island Hospital & The Miriam Hospital
Providence, Rhode Island

Inger K. Damon, MD, PhD
Chief, Poxvirus and Rabies Branch
Centers for Disease Control and Prevention
Atlanta, Georgia

Titus L. Daniels, MD, MPH
Assistant Professor of Medicine (Infectious Diseases)
Vanderbilt University School of Medicine
Associate Hospital Epidemiologist
Vanderbilt University Medical Center
Hospital Epidemiologist
Williamson Medical Center
Nashville, Tennessee

Rabih O. Darouiche, MD
Professor
Department of Physical Medicine and Rehabilitation
Baylor College of Medicine
Houston, Texas

Whitni B. Davidson, MD
Centers for Disease Control and Prevention
Atlanta, Georgia

Michael D. Decker, MD, MPH
Adjunct Professor of Preventative Medicine
Vanderbilt University School of Medicine
Nashville, Tennessee
Vice President
Scientific and Medical Affairs
Sanofi Pasteur
Swiftwater, Pennsylvania

Markus Dettenkofer, MD, Prof. Dr. Med.
Head, Division of Hospital Infection Control
Assistant Medical Director
Institute für Umweltmedizin und Krankenhaushygiene
University Medical Center
Freiburg, Germany

Herbert L. DuPont, MD
Chief, Internal Medicine Service
St. Luke's Episcopal Hospital
Professor and Director
Center for Infectious Diseases
Professor of Epidemiology
The University of Texas-Houston School of Public Health
The Baylor College of Medicine H. Irving Schweppe, Jr., M.D.
Chair in Internal Medicine and Vice Chairman
Department of Medicine
Mary W. Kelsey Chair of Medical Sciences
The University of Texas-Houston Medical School
Houston, Texas

Marlene L. Durand, MD
Massachusetts Eye & Ear Infirmary
Boston, Massachusetts

Winfried Ebner, MD
Institute für Umweltmedizin und Krankenhaushygiene
Department of Environmental Health Sciences
Freiburg, Germany

Martin E. Evans, MD
Professor of Infectious Diseases
University of Kentucky School of Medicine
Associate Medical Director
Infection Control and Prevention
University of Kentucky Healthcare Enterprise
Lexington, Kentucky

Pamela S. Falk, MPH
Director Healthcare Epidemiology
University of Texas Medical Branch Hospitals and Clinics
Galveston, Texas

Paul D. Fey, PhD
Associate Professor
Department of Pathology and Microbiology
University of Nebraska Medical Center
Omaha, Nebraska

John P. Flaherty, MD
Professor of Medicine
Northwestern University Feinberg School of Medicine
Division of Infectious Diseases
Chicago, Illinois

Ursula Flückiger, MD
Professor of Infectious Diseases and Internal Medicine
Faculty of Medicine
University of Basel
Basel, Switzerland
Head of Infectious Diseases
Zentrum für Innere Medizin
Hirslanden Klinik Aarau
Aarau, Switzerland

Patricia M. Flynn, MD, MS
Member
Department of Infectious Diseases
St. Jude Children's Research Hospital
Professor
Departments of Pediatrics and Preventative Medicine
University of Tennessee Health Science Center
Memphis, Tennessee

Gary L. French, MD
Professor
Infectious Diseases Services
St. Thomas' Hospital
London, England, United Kingdom

Kathleen M. Gallagher, DSc MPH
National Center for Immunizations and Respiratory Diseases
Centers for Disease Control and Prevention
Division of Viral Diseases
Atlanta, Georgia

Aditya H. Gaur, MD
Assistant Member
Department of Infectious Diseases
St. Jude Children's Research Hospital
Memphis, Tennessee

Michael S. Gelfand, MD
Professor of Medicine
University of Tennessee, Memphis
Memphis, Tennessee

Dale N. Gerding, MD
Hines VA Hospital
Hines, Illinois

Angella M. Goetz, RN, MNEd, CIC
Infection Preventionist
Special Pathogens Laboratory
Pittsburgh, Pennsylvania

Suzanne P. Goodrich, MD
Fellow
Division of Infectious Diseases
Indiana University School of Medicine
Indianapolis, Indiana

Justin V. Graham, MD, MS
Chief Medical Information Officer
NorthBay Health System
Fairfield, California
Assistant Clinical Professor of Medicine
Department of Medicine
University of California, San Francisco
San Francisco, California

John N. Greene, MD
Chief, Infectious Diseases and Hospital Epidemiology
Moffitt Cancer Center
Professor of Internal Medicine and Oncological Sciences
University of South Florida College of Medicine
Tampa, Florida

Margaret A. Hamburg, MD
Commissioner
U.S. Food and Drug Administration

Stephan I. Harbarth, MD, MS
Associate Hospital Epidemiologist
Associate Professor of Medicine
Attending Physician in Geriatric and General Infectious Diseases
Geneva University Hospitals
Geneva, Switzerland

Alan R. Hauser, MD, PhD
Associate Professor
Departments of Microbiology/Immunology and Medicine
Northwestern University
Chicago, Illinois

David K. Henderson, MD
Deputy Director for Clinical Care
Clinical Center
National Institutes of Health
Bethesda, Maryland

Loreen A. Herwaldt, MD
Professor of Internal Medicine
UI Carver College of Medicine
Professor of Epidemiology
UI College of Public Health
Hospital Epidemiologist
University of Iowa Hospital and Clinics
Iowa City, Iowa

Angela L. Hewlett, MD, MS
Assistant Professor
Section of Infectious Diseases
Department of Internal Medicine
University of Nebraska Medical Center
Omaha, Nebraska

Jennifer Ho, MBBS, MPH+TM
Doctor
National University Hospital Singapore
Singapore, Singapore

Karen K. Hoffmann, RN, BSN, MS
Clinical Instructor
Division of Infectious Disease
Associate Director
NC Statewide Program for Infection Control and Epidemiology
University of North Carolina School of Medicine
Chapel Hill, North Carolina

John Holton, MD
Department of Bacteriology
Windeyer Institute of Medical Sciences
College Royal Free and University London Medical School
London, England, United Kingdom

Teresa C. Horan, MPH
Division of Healthcare Quality Promotion
Centers for Disease Control and Prevention
Atlanta, Georgia

Nordiah A. Jalil, MD, MSc
Professor
Department of Medical Microbiology & Immunology
Universiti Kebangsaan Malaysia
Kuala Lumpur, Malaysia
Infection Control Doctor
Infection Control Unit
Universiti Kebangsaan Malaysia Medical Centre
Kuala Lumpur, Malaysia

William R. Jarvis, BS, MD
Jason and Jarvis Associates, LLC
Hilton Head Island, South Carolina

Joseph F. John Jr., MD
Ralph H. Johnson Medical Center
Charleston, South Carolina

Stuart Johnson, MD
Hines VA Hospital
Hines, Illinois

Jennie Johnstone, MD
Assistant Professor
Department of Medicine
McMaster University
Infectious Disease Physician
Department of Medicine
Hamilton Health Sciences (Juravinski Hospital)
Hamilton, Ontario, Canada

Keith S. Kaye, MD, MPH
Professor of Medicine
Wayne State University School of Medicine
Corporate Director
Infection Prevention, Hospital Epidemiology and Antimicrobial Stewardship
Detroit Medical Center and Wayne State University
Detroit, Michigan

Thomas J. Kirn, MD, PhD
Assistant Professor
Department of Pathology & Laboratory Medicine
Department of Medicine (Infectious Disease)
Associate Director
Microbiology Laboratory
Robert Wood Johnson University Hospital
New Brunswick, New Jersey

Matthew D. Koff, MD, MS
Assistant Professor in Anesthesiology Critical Care Medicine and Emergency Medicine
Dartmouth-Hitchcock Medical Center
Dartmouth Medical School
Lebanon, New Hampshire

Andreas M. Kogelnik, MD, PhD
Director
Open Medicine Institute
Mountain View, California
Consulting Assistant Professor
Stanford University School of Medicine
Stanford, California

Amy Beth Kressel, MD
Associate Professor of Clinical Medicine
Clinical Director, Division of Infectious Diseases
Indiana University School of Medicine
Medical Director, Infection Control
Indiana University Hospital
Indianapolis, Indiana

Stephen B. Kritchevsky, PhD
Professor
Internal Medicine/Gerontology and Geriatric Medicine
Director
Sticht Center on Aging
Deputy Director
Translational Science Institute
Wake Forest University School of Medicine
Winston-Salem, North Carolina

Marjorie Kruvand, PhD
Assistant Professor
School of Communication
Loyola University Chicago
Chicago, Illinois

Preeta K. Kutty, MD, MPH
Medical Epidemiologist
Division of Viral Diseases, Epidemiology Branch
Centers for Disease Control and Prevention
Atlanta, Georgia

Marcelle Layton, MD
Assistant Commissioner, Bureau of Communicable Disease
New York City Department of Health and Mental Hygiene
New York, New York

Ingi Lee, MD, MSCE
Assistant Professor of Medicine
University of Pennsylvania School of Medicine
Division of Infectious Diseases
Philadelphia, Pennsylvania

Daniel P. Lew, MD
Department of Infectious Diseases
University of Geneva Hospitals
Geneva, Switzerland

W. Matthew Linam, MD, MS
Instructor
Department of Pediatrics
University of Arkansas for Medical Sciences
Pediatric Infectious Diseases Section
Arkansas Children's Hospital
Little Rock, Arkansas

Mark Loeb, BSc, MD, MSc, FRCPC
McMaster University
Hamilton, Ontario, Canada

Randy W. Loftus, MD
Assistant Professor
Department of Anesthesiology and Critical Care Medicine
Dartmouth-Hitchcock Medical Center
Lebanon, New Hampshire

Dror Marchaim, MD
Infection Control Fellow
Division of Infectious Diseases
Detroit Medical Center
Wayne State University
Detroit, Michigan

C. Glen Mayhall, MD, FIDSA, FSHEA
Professor
Division of Infectious Diseases
Department of Internal Medicine
Healthcare Epidemiologist
The University of Texas Medical Branch Health System
University of Texas Medical Branch
Galveston, Texas

Elizabeth Linner McClure, MD, MPH
Medical Director
AHC Office of Emergency Response
University of Minnesota
Minneapolis, Minnesota

Andrea M. McCollum, PhD, MS
Centers for Disease Control and Prevention
Atlanta, Georgia

Michael M. McNeil, M.D., MPH
Division of Healthcare and Quality Protection
Centers for Disease Control and Prevention
Decatur, Georgia

Nicolas A. Melgarejo, MD
Infectious Disease Fellow
University of Texas Medical School Houston
Center of Infectious Diseases–UT School of Public Health
University of Texas Medical Center
M.D. Anderson Cancer Center
Houston, Texas

James M. Melius, MD, Dr PH
NYS Laborers' Health and Safety Trust Fund
Albany, New York

Douglas K. Mitchell, MD
Professor of Pediatrics
Pediatric Infectious Diseases
Eastern Virginia Medical School
General Booth Pediatrics
Children's Hospital of The King's Daughters
Virginia Beach, Virginia

Gloria C. Morrell, RN, MS, MSN, CIC
Division of Healthcare Quality Promotion
Centers for Disease Control and Prevention
Atlanta, Georgia

Linda M. Mundy, MD, PhD
LM Mundy, LLC
Bryn Mawr, Pennsylvania

Dilip Nathwani, MB, FRCP, DTM&H
Consultant Physician
Honorary Professor of Infection
Ninewells Hospital & Medical School
Dundee, Scotland, United Kingdom

Dionissios Neofytus, MD, MPH
Assistant Professor
Department of Medicine
The Johns Hopkins University
Attending, Transplant and Oncology Infectious Disease Service
Department of Medicine
The Johns Hopkins University
Baltimore, Maryland

Mary D. Nettleman, MD, MS
Professor and Chair
Department of Medicine
College of Human Medicine
Michigan State University
East Lansing, Michigan

Judith Noble-Wang, PhD
Division of Healthcare Quality Promotion
Centers for Disease Control and Prevention
Atlanta, Georgia

Russell N. Olmsted, MPH, CIC
Epidemiologist
Infection Prevention & Control Services
Saint Joseph Mercy Health System
Ann Arbor, Michigan

Ryosuke Osawa, MD
Fellow
University of Pittsburgh Medical Center
Pittsburgh, Pennsylvania

Michael Osterholm, PhD, MPH
University of Minnesota
Center for Infectious Disease Research and Policy
Minneapolis, Minnesota

Luis Ostrosky-Zeichner, MD
Division of Infectious Diseases
University of Texas Medical School at Houston
Houston, Texas

Leilani Paitoonpong, MD, MSc
Instructor
Department of Medicine
Chulalongkorn University
Infectious Disease Specialist
Department of Medicine
King Chulalongkorn Memorial Hospital
Bangkok, Thailand

Marc Paladini, MPH
Director, Syndromic Surveillance
Bureau of Communicable Disease
New York City Department of Health and Mental Hygiene
New York, New York

Adelisa L. Panlilio, MD, MPH
Medical Consultant
Division of Healthcare Quality Promotion
Centers for Disease Control and Prevention
Atlanta, Georgia

Priti R. Patel, MD
Medical Epidemiologist
Prevention and Response Branch
Division of Healthcare Quality Promotion
Centers for Disease Control and Prevention
Atlanta, Georgia

Jan Evans Patterson, MD
University of Texas Health Science Center
Health Science Center at San Antonio
San Antonio, Texas

Trish M. Perl, MD, MSc
John Hopkins Medical Institutions
Hospital Epidemiology and Infection Control
Baltimore, Maryland

C.J. Peters, MD
John Sealy Distinguished University Chair in Tropical Medicine and Emerging Virology
Professor
Departments of Microbiology & Immunology and Pathology
University of Texas Medical Branch
Galveston, Texas

Larry K. Pickering, MD, FAAP
Senior Advisor to the Director
National Center for Immunization and Respiratory Diseases
Executive Secretary
Advisory Committee on Immunization Practices
Centers for Disease Control and Prevention
Atlanta, Georgia

Didier Pittet, MD, MS
Professor of Medicine
University of Geneva Faculty of Medicine
Director, Infection Control Program
University of Geneva Hospitals
Geneva, Switzerland

David J. Pombo, MD
Department of Clinical Epidemiology and Infectious Diseases
LDS Hospital
Division of Infectious Diseases
University of Utah School of Medicine
Salt Lake City, Utah

Jean M. Pottinger, MA, RN, CIC
Infection Preventionist
Program of Hospital Epidemiology
The University of Iowa Hospitals and Clinics
Iowa City, Iowa

Issam Raad, MD
Professor and Chairman
Department of Infectious Diseases
Infection Control and Employee Health
The University of Texas M. D. Anderson Cancer Center
Houston, Texas

John H. Rex, MD
Vice President Clinical Infection
AstraZeneca Pharmaceuticals
Macclesfield, United Kingdom
Adjunct Professor of Medicine
University of Texas Medial School-Houston
Houston, Texas

Bruce S. Ribner, MD, MPH
Associate Professor of Medicine
Emory University School of Medicine
Epidemiologist
Emory University Hospital and the Emory Clinic
Atlanta, Georgia

Louis B. Rice, MD
VA Medical Center
Cleveland, Ohio

Robin L. Roach, MS, BSN, BFA, CIC
Clinical Assistant Professor
Department of Medicine
Michigan State University
Director
Infection and Prevention and Epidemiology
Sparrow Health System
Lansing, Michigan

Mary A.M. Rogers, PhD
Research Assistant Professor
University of Michigan
Ann Arbor, Michigan

Laura J. Rose, MS
Division of Healthcare Quality Promotion
Clinical and Environmental Laboratory Branch
Centers for Disease Control and Prevention
Atlanta, Georgia

Manfred L. Rotter, MD, Dip Bact
Medical University Vienna, Austria
Vienna, Austria

Ulises Ruiz, MD, PhD, FACS, CPHQ
University Institute for Health Service Assessment
Facultad de Medicina
Universidad Complutense de Madrid
Madrid, Spain

Mark E. Rupp, MD
Professor, Infectious Diseases
University of Nebraska Medical Center
Medical Director, Department of Healthcare
Epidemiology
Nebraska Medical Center
Omaha, Nebraska

William A. Rutala, PhD, MPH
University of North Carolina School of Medicine
Chapel Hill, North Carolina

Nasia Safdar, PhD
Medical Director of Infection Control
University of Wisconsin Hospital and Clinics
Assistant Professor
Infectious Diseases
University of Wisconsin School of Medicine and Public Health
William S. Middleton VA Medical Center
Madison, Wisconsin

Sanjay Saint, MD, MPH
Associate Chief of Medicine
Ann Arbor VA Medical Center
Director
VA/UM Patient Safety Enhancement Program
Professor of Internal Medicine
University of Michigan Medical School
Ann Arbor, Michigan

Cassandra D. Salgado, MD, MS
Associate Professor of Medicine
Medical University of South Carolina
Hospital Epidemiologist
Medical University of South Carolina
Charleston, South Carolina

Matthew Samore, MD
University of Utah
Salt Lake City, Utah

Melissa K. Schaefer, MD
Division of Healthcare Quality Promotion
Centers for Disease Control and Prevention
Atlanta, Georgia

William A. Schaffner, MD
Professor and Chairman
Department of Preventive Medicine
Professor of Medicine (Infectious Diseases)
Vanderbilt University School of Medicine
Associate Hospital Epidemiologist
Vanderbilt University Medical Center
Nashville, Tennessee

W. Michael Scheld, MD
Bayer-Coewald L. Mandell Professor of Infectious Diseases
Professor of Medicine
Clinical Professor of Neurology
University of Virginia School of Medicine
Director, Pfizer Initiative in Infectious Health
Charlottesville, Virginia

Charles J. Schleupner, MSc, MD
Professor of Internal Medicine
Virginia Tech-Carilion School of Medicine and Research Institute
Director, Fellowship in Infectious Diseases
Section of Infectious Diseases
Department of Internal Medicine
Carilion Clinic
Roanoke, Virginia

Eileen Schneider, MD, MPH
Centers for Disease Control and Prevention
Division of Viral Diseases
Atlanta, Georgia

Marisel Segarra-Newnham, PharmD, MPH
Clinical Pharmacy Specialist, Infectious Diseases/HIV
Veterans Affairs Medical Center
Patient Support Service
West Palm Beach, Florida
Clinical Assistant Professor of Pharmacy Practice
University of Florida College of Pharmacy
Gainesville, Florida

Lynne M. Sehulster, PhD
Prevention and Response Branch
Division of Healthcare Quality Promotion
Centers for Disease Control and Prevention
Atlanta, Georgia

John A. Sellick Jr, DO, MS
Associate Professor of Medicine
University of Buffalo, SUNY
Hospital Epidemiologist
VA Western New York Healthcare System
Kaleida Health
Buffalo, New York

Jane F. Seward, MBBS, MPH
Acting Director, Division of Viral Diseases
National Center for Immunizations and Respiratory Diseases
Centers for Disease Control and Prevention
Atlanta, Georgia

Andi L. Shane, MD, MPH
Assistant Professor
Division of Pediatric Infectious Diseases
Emory University School of Medicine
Atlanta, Georgia

Ronald I. Shorr, MD, MS
Geriatric Research Education and Clinical Center
Malcom Randall VAMC
Professor of Aging and Genetic Research
University of Florida
Gainesville, Florida

Sanjay K. Shukla, PhD
Research Scientist Center for Human Genetics
Marshfield Clinic Research Foundation
Marshfield, Wisconsin

Emily K. Shuman, MD
Clinical Lecturer
Division of Infectious Diseases
Department of Internal Medicine
University of Michigan Health System
Ann Arbor, Michigan

José Simón, MD
University Institute for Health Service Assessment
Universidad Complutense de Madrid
Madrid, Spain

Nina Singh, MD
Associate Professor of Medicine
University of Pittsburgh
Chief Transplant
Infectious Diseases
VA Pittsburgh Healthcare System
Pittsburgh, Pennsylvania

Philip W. Smith, MD
Professor and Chief
Section of Infectious Diseases
University of Nebraska Medical Center
Omaha, Nebraska

Usha Stiefel, MD
Assistant Professor
Case Western Reserve University School of Medicine
Chief
Infectious Diseases Section
Cleveland VA Medical Center
Cleveland, Ohio

Valentina Stosor, MD
Assistant Professor
Division of Infectious Diseases and Organ Transplantation
Northwestern University Feinberg School of Medicine
Chicago, Illinois

Janet E. Stout, PhD
Special Pathogens Laboratory
Pittsburgh, Pennsylvania

Charles W. Stratton IV, MD
Associate Professor of Pathology and Medicine
Director, Clinical Microbiology Laboratory
Department of Pathology
Vanderbilt University Medical Center
Nashville, Tennessee

Andrew J. Streifel, MPH
Hospital Environmental Health Specialist
Department of Environmental Health and Safety
University of Minnesota
Minneapolis, Minnesota

John J. Szela, MD
Attending Physician
Division of Infectious Diseases
William Beaumont Hospital
Royal Oak, Michigan

Paul A. Tambyah, MD
Associate Professor of Medicine
National University of Singapore
Singapore, Singapore

Jeffrey M. Tessier, MD, FACP
Assistant Professor of Medicine
Division of Infectious Diseases
Virginia Commonwealth University
Richmond, Virginia

Nicola D. Thompson, PhD
Epidemiology Research Team
Division of Viral Hepatitis
Centers for Disease Control and Prevention
Atlanta, Georgia

Jerome I. Tokars, MD, MPH
Medical Epidemiologist
National Center for Public Health Informatics
Centers for Disease Control and Prevention
Atlanta, Georgia

Elizabeth A. Tolley, PhD
Professor
Department of Preventive Medicine
University of Tennessee Health Science Center
Memphis, Tennessee

Ronald B. Turner, MD
University of Virginia
Department of Pediatrics
Charlottesville, Virginia

Ilker Uçkay, MD
Service of Infectious Diseases
Infection Control Program
Geneva University Hospital
Geneva, Switzerland

William M. Valenti, MD
Clinical Associate Professor of Medicine
University of Rochester School of Medicine and Dentistry
Founding Medical Director/Staff Physician/Physician-at-Large
AIDS Care, Inc.
Rochester, New York

Trevor C. VanSchooneveld, MD
Assistant Professor
Department of Internal Medicine
Division of Infectious Disease
Director, Antimicrobial Stwardship Program
University of Nebraska Medical Center College of Medicine
Omaha, Nebraska

Richard J. Wallace, Jr., MD
University of Texas Health Center
Tyler, Texas

David J. Weber, MD, MPH
University of North Carolina at Chapel Hill
Chapel Hill, North Carolina

Melvin P. Weinstein, MD
Professor of Medicine and Pathology
Chief, Division of Infectious Diseases, Allergy and Immunology
Director, Microbiology Laboratory
Robert Wood Johnson University Hospital
New Brunswick, New Jersey

Robert A. Weinstein, MD
The C. Anderson Hedberg, MD, Professor of Medicine
Rush University Medical Canter
Chairman of Medicine
Cook County (Stroger) Hospital
Chicago, Illinois

Richard P. Wenzel, MD, MSc
Professor and Former Chairman
Department of Internal Medicine
School of Medicine
Virginia Commonwealth University
Richmond, Virginia

Cynthia J. Whitener, MD
Professor of Medicine
Division of Infectious Diseases
Penn State Milton S. Hershey Medical Center
Hershey, Pennsylvania

Ann I. Winters, MD
Bureau of Communicable Disease
New York City Department of Health and Mental Hygiene
New York, New York

Keith F. Woeltje, MD, PhD
Associate Professor of Medicine in Infectious Diseases
Washington University School of Medicine
Medical Director for Infection Prevention
BJC Healthcare
St. Louis, Missouri

Sarah Y. Won, MD, MPH
Assistant Professor
Virginia Commonwealth University
McGuire Veterans Affairs Hospital
Richmond, Virginia

Edward S. Wong, MD
Chief, Infectious Disease
McGuire Veterans Affairs Medical Center
Professor of Medicine
Department of Medicine
Virginia Commonwealth University Health System
Richmond, Virginia

Rebecca Wurtz, MD, MPH
Associate Professor
Department of Preventative Medicine
Northwestern University Feinberg School of Medicine
Chicago, Illinois

Terry Yamauchi, MD
Professor of Pediatrics
UAMS College of Medicine
Chair of Infection Control Committee
Arkansas Children's Hospital
Inaugural Professor
Clinton School of Public Service
University of Arkansas
Member, Arkansas State Board of Health
Little Rock, Arkansas

Victor L. Yu, MD
Specials Pathogens Laboratory
Pittsburgh, Pennsylvania

John A. Zaia, MD
Professor and Chair
Department of Virology
Beckman Research Institute of City of Hope
Director, Pediatric Infectious Diseases
City of Hope
Duarte, California

Wilma Ziebuhr, MD
Institute for Molecular Infection Biology
University of Wuerzburg
Wuerzburg, Bavaria, Germany

ACKNOWLEDGMENTS

I greatly appreciate the excellent contributions made by my administrative assistant Denise R. Morris and the developmental editors Louise Bierig and Sarah Granlund for Lippincott Williams & Wilkins.

CONTENTS

SECTION V: EPIDEMIOLOGY AND PREVENTION OF HEALTHCARE-ASSOCIATED INFECTIONS CAUSED BY SPECIFIC PATHOGENS

SECTION XVI: HEALTHCARE EPIDEMIOLOGY AND INFECTION CONTROL IN SPECIAL SETTINGS FOR HEALTHCARE DELIVERY

SECTION XVII: BIOTERRORISM

SECTION I

Applied Epidemiology and Biostatistics in Healthcare Epidemiology and Infection Control

CHAPTER 1

Principles of Infectious Diseases Epidemiology

Lennox K. Archibald

Epidemiology is defined as the study of the factors determining the occurrence of diseases in human populations. It is an indispensable tool for characterizing infectious disease occurrences in medical institutions, communities, regions, or industry, and for determining the exposure–disease relationship in humans and the modes of acquisition and spread that are critical for treatment, control, and prevention of these infectious disease occurrences. Clinicians, microbiologists, and other personnel involved in the preventive and public health professions use epidemiologic methods for disease surveillance, outbreak investigations, infectious diseases outcome measurements, and observational studies to identify risk factors for various infectious diseases. Knowledge of these risk factors is essential for making decisions regarding further epidemiologic or microbiological investigations, directing research activities, implementing relevant prevention and control measures or interventions, and establishing public health policies. In the pharmaceutical and biomedical industries, the application of epidemiologic methods is integral to the investigation of intrinsic contamination of products, ascertainment and characterization of risk factors for contamination, and maintenance of quality assurance practices in the laboratory or manufacturing operations before distribution of products.

The use of epidemiology and the use of statistical methods to analyze epidemiologic data grew out of attempts to understand, predict, and control the great epidemics of our past; the diseases associated with those early epidemics were largely infectious. The study and implementation of infection control practices and interventions grew out of the need to understand and control the institutional epidemics of infectious diseases that complicate the care of the ill *(1,2)*. Thus, discussions of the principles of epidemiology begin with examples of methods that were first formalized in the study of transmissible microorganisms, many of which continue to cause problems today.

The term *hospital epidemiology* was a modern addition by workers in the United States *(3)*, as was the recognition of the potential use of epidemiologic methods in hospitals for the study and control of noninfectious diseases *(4)*. The term *nosocomial* infection has traditionally defined acute infections acquired in the hospital inpatient setting *(5)*. However, in the current era of managed care, healthcare systems in the United States have evolved from the traditional acute care hospital inpatient setting to a new integrated, extended care model that now encompasses hospitals, outpatient clinics, ambulatory centers, long-term care facilities, and the home. As expected, infections (and antimicrobial resistance among implicated pathogens) may be acquired at any of these levels of care. For this reason, the term *nosocomial infection* has been replaced by *healthcare-associated infection*. Except for the acute care hospitals, however, the relative importance of each of these levels of care as risk factors for the acquisition of healthcare-associated infections remains largely uncharacterized or unknown.

The terms *hospital epidemiology* and *infection control* remain synonymous in the minds of many, and both the terms and their associated programs have grown in definition and function over the past five decades. Interest in infection control has broadened from focused concerns

with puerperal sepsis and surgical site infection to full, scientifically tested programs of surveillance, prevention, and control of healthcare-associated infections acquired at other anatomic sites. Hospital epidemiology programs were among the earliest projects used to demonstrate the utility of the scientific method and statistics for characterizing and analyzing infectious diseases data and using the results of these analyses to improve the quality of care and patient outcomes. In the special environment of the acute care hospital, a natural repetition of earlier studies of population-based infectious diseases provided the basis for epidemiologic investigations.

Surveillance data generated from epidemiologic studies may be used to determine the need for clinical or public health action; assess the effectiveness of prevention, intervention, or control programs, or diagnostic algorithms; or set priorities for rational or appropriate use of limited microbiology resources, planning, and research. An understanding of epidemiology is important for quantifying and interpreting microbiology and pharmaceutical data, and for application of these data to clinical practice, quality assurance, hypothesis generation during investigation of outbreaks and other adverse events, rational prescribing policies, and public health.

Data from epidemiologic and microbiological studies can inform diagnostic and therapeutic practice and indicate areas for allocation of already scarce resources. For example, one of the perennial problems that clinicians and microbiologists face is how to differentiate between true bacteremia and blood culture contamination resulting from coagulase-negative staphylococci, which are the most frequently isolated microorganisms in blood cultures (6). Blood culture contamination can occur during venipuncture if the skin is not adequately cleaned, after the blood draw at the time of inoculation of blood into the culture bottle, or at some point during processing of blood culture bottles in the microbiology laboratory. To make an informed decision on true bacteremia versus contamination, clinicians and microbiologists need to be familiar with the epidemiology of bloodstream infections in different clinical settings and be able to integrate these data with the relevant clinical and microbiology information at hand so that a decision could be made whether or not to initiate antimicrobial therapy or request additional, supplemental investigations that might facilitate the decision-making process.

DEFINITIONS

In the application and discussion of epidemiologic principles, standard definitions and terminology have been widely accepted *(7,8)*. The definitions of some commonly used terms are outlined in this section:

Attack rate A ratio of the number of new infections divided by the number of exposed, susceptible individuals in a given period, usually expressed as a percentage. Other terms are the *incidence rate* and the *case rate*.

Attributable mortality indicates that an exposure was a contributory cause of or played an etiologic role leading to death.

Attributable risk The measure of impact of a causative factor. The attributable risk establishes how much of the disease or infection is attributable to exposure to a specific risk factor. It is a proportion where the numerator is the difference between the incidence in exposed and unexposed groups and the denominator is the incidence for the exposed group.

Bias The difference between a true value of an epidemiologic measure and that which is estimated in a study. Bias may be random or systematic. There are three types of bias: selection bias, information bias, and confounding. Selection bias is a distortion in the estimate of effect resulting from the manner in which parameters are selected for the study population. Information bias depends on the accuracy of the information collected. Confounding arises from unrecognized factors that may affect interpretation of epidemiologic data. Unrecognized, systematic bias presents the greatest danger in studies by suggesting relationships that are not valid (see also Chapter 2).

Carrier An individual (host) who harbors a microorganism (agent) without evidence of disease and, in some cases, without evidence of host immune response. This carriage may take place during the latent phase of the incubation period as a part of asymptomatic disease or may be chronic following recovery from illness. Carriers may shed microorganisms into the environment intermittently or continuously, and this shedding may lead to transmission. Shedding and potential transmission may be increased by other factors affecting the host, including infection by another agent.

Case An individual in a population or group recognized as having a particular disease or condition under investigation or study. This definition may not be the same as the clinical definition of a case.

Case–fatality rate A ratio of the number of deaths from a specific disease divided by the number of cases of disease, expressed as a percentage.

Cluster An aggregation of relatively uncommon events or diseases in time and/or space in numbers that are believed to be greater than are expected by chance alone.

Colonization The multiplication of a microorganism at a body site or sites without any overt clinical expression or detected immune reaction in the host at the time that the microorganism is isolated. Colonization may or may not be a precursor of infection. Colonization may be a form of carriage and is a potential source of transmission.

Communicability The characteristic of a human pathogen that enables it to be transmitted from one person to another under natural conditions. Infections may be communicable or noncommunicable. Communicable infections may be endemic, epidemic, or pandemic.

Communicable period The time in the natural history of an infection during which transmission to susceptible hosts may take place.

Confounding An illusory association between two factors when in fact there is no causal relationship between the two. The apparent association is caused by a third variable that is both a risk factor for the outcome or disease

and is associated with but not a result of the exposure in question.

Contact An exposed individual who might have been infected through transmission from another host or the environment.

Contagious Having the potential for transmission.

Contamination The presence of an agent (e.g., microorganism) on a surface or in a fluid or material—therefore, a potential source for transmission.

Cumulative incidence The proportion of at-risk persons who become diseased during a specified period of time.

Endemic The usual level or presence of an agent or disease in a defined population during a given period.

Epidemic An unusual, higher-than-expected level of infection or disease by an agent in a defined population in a given period. This definition assumes previous knowledge of the usual, or endemic, levels.

Epidemic curve A graphic representation of the distribution of defined cases by the time of onset of their disease.

Epidemic period The time period over which the excess cases occur.

Hyperendemic The level of an agent or disease that is consistently present at a high incidence and/or prevalence rate.

Immunity The resistance of a host to a specific agent, characterized by measurable and protective surface or humoral antibody and by cell-mediated immune responses. Immunity may be the result of specific previous experience with the agent (wild infection), from transplacental transmission to the fetus, or from active or passive immunization to the agent. Immunity is relative and governed through genetic control. Immunity to some agents remains throughout life, whereas for others, it is short-lived, allowing repeat infections by the same agent. Immunity may be reduced in extremes of age, through disease, or through immunosuppressive therapy.

Immunity: cell-mediated versus humoral Cell-mediated immune protection, largely related to specific T-lymphocytic activity, as opposed to humoral immunity, which is measured by the presence of specific immunoglobulins (antibodies) in surface body fluids or circulating in noncellular components of blood. Antibodies are produced by B lymphocytes, also now recognized to be under the influence of T-lymphocytic functions.

Immunogenicity An agent's (microorganism's) intrinsic ability to trigger specific immunity in a host. Certain agents escape host defense mechanisms by intrinsic characteristics that fail to elicit a host immune response. Other agents evoke an immune response that initiates a disease process in the host that increases cellular damage and morbidity beyond the direct actions of the microorganism itself. These disease processes may continue beyond the presence of living microorganisms in the host.

Incidence The ratio of the number of new infections or disease in a defined population in a given period to the number of individuals at risk in the population. "At risk" is frequently defined as the number of potentially exposed susceptible persons. Incidence is a measure of the transition from a nondiseased to a diseased state and is usually expressed as numbers of new cases per thousands (1,000, 10,000, or 100,000) per year.

Incidence rate or density Similar to the incidence but members of the at-risk population may be followed for different lengths of time. Thus, the denominator is the sum of each person's time at risk (i.e., total person-time of observation).

Incubation period The period between exposure to an agent and the first appearance of evidence of disease in a susceptible host. Incubation periods are typical for specific agents and may be helpful in the diagnosis of unknown illness. Incubation periods may be modified by extremes of dose or by variations in host immune function. The first portion of the incubation period following colonization and infection is frequently a silent period, called the *latent period*. During this time, there is no evidence of host response(s) and evidence of the presence of the infecting agent may not be measurable. However, transmission of the microorganism to other hosts, though reduced during this period, is a recognized risk (e.g., chicken pox, hepatitis B virus, human immunodeficiency virus [HIV]). Measurable early immune responses in the host may appear shortly before the first signs and symptoms of disease, marking the end of the latent period. Signs and symptoms of disease commonly appear shortly thereafter, marking the end of the incubation period.

Index case The first case to be recognized in a series of transmissions of an agent in a host population. In semiclosed populations, as typified by chronic disease hospitals, the index case may first introduce an agent not previously active in the population.

Infection The successful transmission of a microorganism to the host with subsequent multiplication, colonization, and invasion. Infection may be clinical or subclinical and may not produce identifiable disease. However, it is usually accompanied by measurable host response(s), either through the appearance of specific antibodies or through cell-mediated reaction(s) (e.g., positive tuberculin test results). An infectious disease may be caused by the intrinsic properties of the agent (invasion and cell destruction, release of toxins) or by associated immune response in the host (cell-mediated destruction of infected cells, immune responses to host antigens similar to antigens in the agent).

Infectivity The characteristic of the microorganism that indicates its ability to invade and multiply in the host. It is frequently expressed as the proportion of exposed patients who become infected.

Isolation The physical separation of an infected or colonized host, including the individual's contaminated body fluids and environmental materials, from the remainder of the at-risk population in an attempt to prevent transmission of the specific agent to the latter group. This is usually accomplished through individual environmentally controlled rooms or quarters, hand washing following contact with the infected host and environment, and the use of barrier protective devices, including gowns, gloves, and, in the case of airborne agents, an appropriate mask.

Morbidity rate The ratio of the number of persons infected with a new clinical disease to the number of persons at risk in the population during a defined period; an *incidence rate* of disease.

Mortality rate The ratio of those infected who have died in a given period to the number of individuals in the defined population. The rate may be *crude*, related to all causes, or *disease-specific*, related or *attributable* to a specific disease in a population at risk for the disease.

Odds The ratio of the probability of an event occurring to the probability of it not occurring.

Pandemic An epidemic that spreads over several countries or continents and affects many people.

Pathogenicity The ability of an agent to cause disease in a susceptible host. The pathogenicity of a specific agent may be increased in a host with reduced defense mechanisms. For some agent–host interactions, the resultant disease is due to the effects of exaggerated or prolonged action of defense mechanisms of the host.

Prevalence The ratio of the number of individuals measurably affected or diseased by an agent in a defined population at a particular point in time. The proportion of the population having the disease during a specified time period, without regard to when the process or disease began, defines the period prevalence.

Pseudo-outbreak Real clustering of false infections or artifactual clustering of real infections. Often it is identified when there is increased recovery of unusual microorganisms.

Rate An expression of the frequency with which an event occurs in a defined population. All rates are ratios. Some rates are proportions; that is, the numerator is a part of the denominator. A comparable rate is a rate that controls for variations in the distribution of major risk factors associated with an event.

Ratio An expression of the relationship between a numerator and a denominator where the two are usually distinct and separate quantities, neither being a part of the other.

Relative risk The ratio of the incidence rate of infection in the exposed group to the incidence rate in the unexposed group. Used to measure the strength of an association between exposures or risk factors and disease.

Reservoir Any animate or inanimate niche in the environment in which an infectious agent may survive and multiply to become a source of transmission to a susceptible host. Medical care workers and patients constitute the main animate reservoir for microorganisms associated with healthcare-associated infections; water-related sources are important inanimate reservoirs that have been implicated in outbreaks related to dialysis units and to air conditioning systems.

Secular trend Profile of the changes in measurable events or in the incidence rate of infection or disease over an extended period of time; also called a *temporal trend*.

Sensitivity For surveillance systems, the ratio of the number of patients reported to have an infection divided by the number of patients who actually had an infection.

Specificity For surveillance systems, the ratio of the number of patients who were reported not to have an infection divided by the number of patients who actually did not have an infection.

Sporadic Occurring irregularly and usually infrequently over a period of time.

Surveillance The ongoing systematic collection, analysis, and interpretation of healthcare data essential to the planning, implementation, and evaluation of public health practice, closely integrated with the timely dissemination of these data to those contributing data or to other interested groups who need to know. Surveillance was popularized by Langmuir and others at the Centers for Disease Control and Prevention (CDC) and has been the basic method in infection control programs in the United States since the 1960s.

Susceptibility A condition of the host that indicates absence of protection against infection by an agent. This is usually marked by the absence of specific antibodies or specific measures of cell-mediated immunity against the infecting microorganism.

Transmission The method by which any potentially infecting agent is spread to another host. Transmission may be direct or indirect. *Direct transmission* may take place by touching between hosts, by the projection of large droplets in coughing and sneezing onto another host, or by direct contact by a susceptible host with an environmental reservoir of the agent. *Indirect transmission* may be vehicle-borne, airborne, or vector-borne. In *vehicle-borne transmission*, contaminated environmental sources, including water, food, blood, and laundry, may act as an intermediate source of an infectious agent for introduction into a susceptible host. The agent may have multiplied or undergone biologic development in the vehicle. In *airborne transmission,* aerosols containing small (1–5 μm) particles may be suspended in air for long periods and inspired into the lower respiratory tract to become a site of infection in a host. These infectious particles may be generated by evaporation of larger particles produced in coughing and sneezing (*Mycobacterium tuberculosis*), by mechanical respiratory aerosolizers (*Legionella*), or by wind or air currents (fungal spores). In *vector-borne transmission,* arthropods or other invertebrates may carry or transmit microorganisms, usually through inoculation by biting or by contamination of food or other materials. The vector may be infected itself or act only as a mechanical carrier of the agent. If the vector is infected, the agent may have multiplied or undergone biologic development in the vector. This type of transmission has been of little importance for healthcare-associated infections in the United States.

Virulence The intrinsic capabilities of an agent to infect a host and produce disease and a measure of the severity of the disease produced. In the extreme, this is represented by the number of patients with clinical disease who develop severe illness or die—the case–fatality rate.

EPIDEMIOLOGIC METHODS APPLIED TO INFECTIOUS DISEASES

The classic epidemiologic methods are essential for the study, characterization, and understanding of the various infections that occur in healthcare settings, communi-

ties, or regions. Such methods are used to determine the exposure–disease relationship in humans; establish the modes of acquisition, mechanisms of transmission, and spread; identify risk factors associated with infection and disease; characterize and relate causal factors to an infectious disease; determine or select appropriate methods of prevention and control; or guide rational application and practice of clinical microbiology methods. These epidemiologic methods were developed in an attempt to control common errors in observations that occur when one studies the association of one event (a risk or causal factor) with another later event (the outcome or disease).

Epidemiologic study methods are grouped as either *observational* or *experimental*. Observational epidemiologic methods are further classified as either *descriptive* or *analytic. Observational studies* are conducted in natural, everyday community or clinical settings, where the investigators observe the appearance of an outcome but have no control over the environment or the exposure of people or product to a risk factor or suspected etiologic agent, a specific intervention or preventive measure, or a particular therapeutic regimen.

Descriptive Epidemiology

Observational descriptive studies establish the case definition of an infectious disease event by obtaining data for analysis from available primary (e.g., medical records) or secondary (e.g., infection control surveillance) sources. These data enable the characteristics of the population that has acquired the infection to be delineated according to (a) "person" (age, sex, race, marital status, personal habits, occupation, socioeconomic status, medical or surgical procedure or therapy, device use, underlying disease, or other exposures or events); (b) "place" (geographic occurrence of the health event or outbreak, medical or surgical service, place of acquisition of infection, or travel); and (c) "time" (preepidemic and postepidemic periods, seasonal variation, secular trends, or duration of stay in hospital). The information from descriptive studies might provide important clues regarding the risk factors associated with infection, and in each case it is hoped that an analysis of the collected data might be used to generate hypotheses regarding the occurrence and distribution of disease or infection in the population(s) being studied.

Analytic Epidemiology

Observational analytic studies are designed to test hypotheses raised by the findings in descriptive investigations. The objectives of these studies are (a) to establish the cause and effects of infection in a population and (b) determine why a population acquired a particular infection in the first place. The three most common types of observational analytic studies are cohort studies, case–control studies, and prevalence or cross-sectional studies.

Cohort Studies In cohort studies, hypotheses that have been generated from previous (descriptive) studies are tested in a new population. A population of individuals (a cohort) that is free of the infection or disease of interest is recruited for study. The presence or absence of the suspected (hypothesized) risk factors for the disease is recorded at the beginning of the study and throughout the observation period. All members of the cohort population (e.g., all premature infants admitted to a neonatal intensive care unit during a defined time period) are followed over time for evidence or appearance of the infection or disease and classified accordingly as exposed or unexposed to specific risk factors. If the observation period begins at the present time and continues into the future or until the appearance of disease, the study is called a *prospective cohort study*. If the population studied is one that in the past was apparently free of the markers of disease on examination of records or banked laboratory specimens, it may be chosen for study if data on exposure to the suspected risk factors for disease also are available. The population may be followed to the present or until the appearance of disease. This type of study, common in occupational epidemiology, is called a *historical* or *retrospective cohort study*.

A key requirement of a cohort study is that participants be reliably categorized into exposed and unexposed groups. *Relative risk*, that is, the ratio of the incidence of the outcome in the exposed group to the incidence in the unexposed group, is used to measure the strength of an association between exposures or risk factors and disease. Cohort studies have the advantage of enabling identification and direct measurement of risk factors associated with disease, determination of the incidence of infection and disease, and ascertainment of the temporal relationship between exposure and disease. In cohort studies, observational bias may be less of a limitation on the validity or results, since the information on the presence of risk factors is recorded before the outcome of disease is established. To ensure sufficient numbers for analysis, cohort studies require continual follow-up of large populations for long periods unless the disease under investigation is one of high incidence. Cohort studies are, in general, more expensive and time-consuming to conduct and are not suitable for the investigation of uncommon infections or conditions. However, they render the most convincing nonexperimental approach for establishing causation.

Case–Control Studies In a case–control study, individuals (cases) who are already infected, ill, or meet a given case definition are compared with a group of individuals (controls) who do not have the infection, disease, or other outcome of medical interest. In contrast to cohort studies, participants in a case–control study are selected by manifestation of symptoms and signs, laboratory parameters, or a specific condition, disease, or outcome. Thus, the search for exposure of case and control subjects to potential risk factors remains a retrospective one. For case–control studies, the measure of association between exposures or risk factors and health outcome is expressed as an odds ratio, that is, the ratio of the odds of an exposure, event, or outcome occurring in a population to the odds in a control group, where the odds of an event is the ratio of the probability of it occurring to the probability of it not occurring.

The presence of significant differences in the exposure to risk factors among case versus control subjects suggests an etiologic (causal) association between those factors and the infection or disease defined by cases. Case–control methods are useful for studying infections, events, or outcomes likely associated with multiple risk factors or

low incidence rates; for investigating situations in which there is a long lag-time between exposure and outcome of interest; and for establishing etiologic associations or causation of a disease, infection, or other outcome when there is no existing information about the cause or source. In an attempt to reduce bias, control subjects might be selected from individuals matched with cases for selected characteristics, such as age, gender, socioeconomic status, or other variables not suspected or under investigation as risk factors. Compared with cohort studies, case–control studies may be conducted in relatively shorter time, are relatively less expensive, or may require a smaller sample size to execute. Limitations of case–control studies include selection bias in choosing case and control subjects; recall bias in which study subjects might have difficulty in remembering possible exposures; incomplete information on specific exposures; or risk factor data may be difficult to find (or remember). Case–control studies are not used to measure incidence or prevalence rates and, generally, are not capable of establishing temporal relationships between an exposure and outcome.

Prevalence or Cross-Sectional Studies In prevalence studies, the presence of putative risk factors and the disease under investigation is recorded in a survey of a study population at a specific point in time or within a (short) time period. The rates of disease among those with and without the suspected risk factors are compared. Thus, cross-sectional studies can establish association but not causation for suspected risk factors. Prevalence studies are relatively inexpensive and can be carried out rapidly if well-planned. However, they do not allow the ascertainment of risk factors at the beginning of disease nor do they enable one to establish a temporal sequence of risk factors preceding the infection or other outcome of interest. Point prevalence, period prevalence, and seroprevalence surveys are examples of cross-sectional studies.

Experimental Epidemiology

In *experimental studies*, the investigator controls an exposure of individuals in a population to a suspected causal factor, a prevention measure, a therapeutic regimen, or some other specific intervention. These exposure modalities are *randomly* allocated to comparable groups, thereby minimizing confounding factors. Both the exposed and unexposed groups are monitored thereafter for specific outcomes (e.g., appearance of infection or disease, evidence of effective prevention or control of the disease, or cure). Experimental studies often are used to evaluate antimicrobial or vaccine treatment regimens and are generally expensive to conduct. Within healthcare settings, studies that examine restriction of certain antimicrobials or promotion of use of alternative antimicrobials for the control of antimicrobial resistance could be considered under the category of experimental. For ethical reasons, it is rarely possible to expose human populations to potential pathogens or to withhold a preventive measure that could potentially be beneficial to the patient. Unfortunately, animal hosts are not naturally susceptible to many agents of human disease. Thus, one has to be careful when extrapolating epidemiologic findings in animal experimental studies to the control of infections in human subjects.

Quasi-experimental studies: more recently, there has been an increase in the number of published papers describing results from these studies. This type of study shares the design characteristics of experimental studies but lacks random assignments of study subjects. Quasi-experimental studies are useful where randomization is impossible, impractical, or unethical. The main drawbacks of quasi-experimental studies are their inability to eliminate confounding bias or establish causal relationships.

EPIDEMIOLOGY OF INFECTION AND DISEASE

The epidemiology of infectious disease presents two processes for discussion: (a) the epidemiology of the determinants leading to infections in hosts and (b) the epidemiology of the appearance and extent of disease related to the infection in those hosts. It is common to discuss health and disease as the result of a series of complex interactions between an agent of change, the host that is the target of the agent's actions, and the mutual environment in which the host and agent are found. In studies of healthcare-associated infections, the agents are the microorganisms associated with the infections, the hosts are the patients under care or their healthcare workers, and the common environment is the acute care hospital, intensive care unit, outpatient, home, or other healthcare venues.

The interactions determining the probability of a microbiologic agent causing infection in a host may be simply presented by an equation of infection:

$$I_p = (D \times S \times T \times V)/H_d,$$

where I_p is the probability of infection, D is the dose (number of microorganisms) transmitted to the host, S is the receptive host site of contact with the agent, T is the time of contact (sufficient for attachment and multiplication or not), and V represents virulence, the intrinsic characteristics of the microorganism that allow it to infect. The denominator in the equation (H_d) represents the force of the combined host defenses attempting to prevent this infection.

Any reduction in host defenses (represented by the denominator) in such an equation allows infection to take place with a similar reduction in one or more of the agent factors in the numerator. Infection may take place with a smaller dose of microorganisms. Infection may take place at an unusual site. The contact time for a microorganism to fix to an appropriate surface may be briefer, or infection may take place with an agent of lesser virulence, one that does not cause infection in the normal host. These reductions in the host defense characteristics, represented by the denominator, and the reduction of requirements to infect for the agent are typical of the interactions that allow opportunistic infections in compromised hosts, represented by many patients under care in modern hospitals. In this model, equation of infection, the environment might be considered the background or playing field on which the agent–host interaction takes place. A number of additional models of the interaction of agent, host, and environment have been suggested to help understand these processes. The three models in Figure 1-1—the seesaw model, the

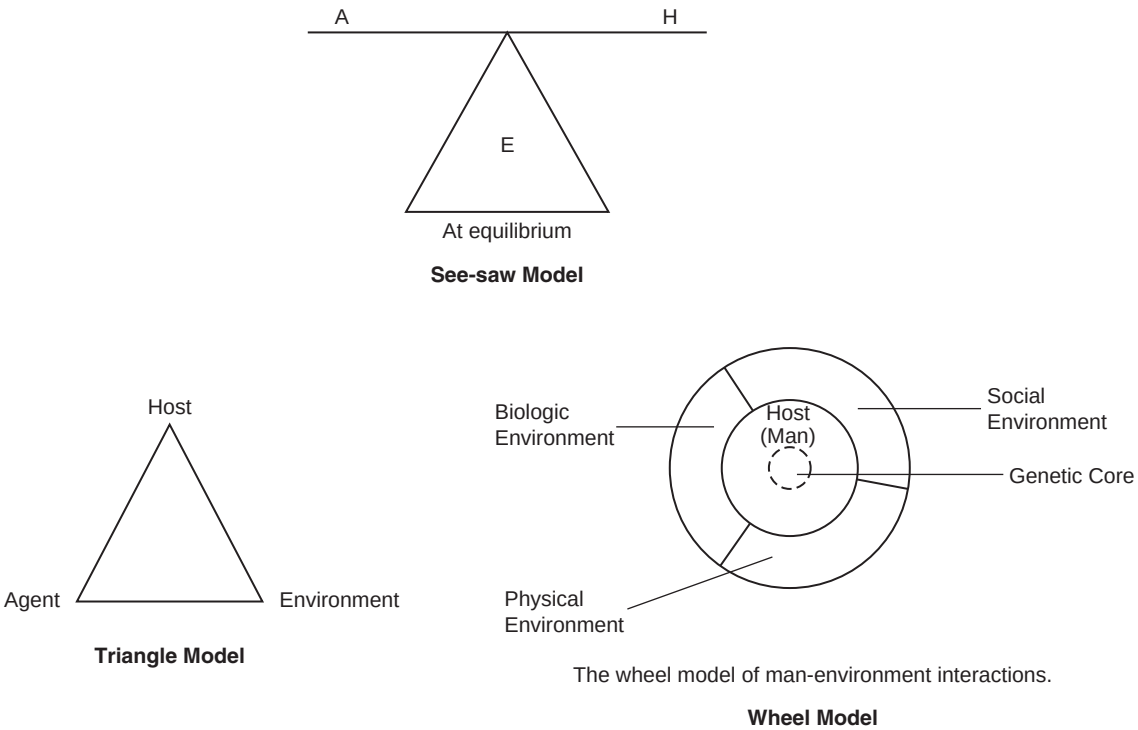

FIGURE 1-1 Models of interactions of agent, disease, and environment. (See-saw model from Fox JP, Elveback L, Gatewood L, et al. Herd immunity. *Am J Epidemiol* 1971;94:179–189, by permission of Oxford University Press. Triangle model and wheel model from Mausner JS, Kramer S, eds. *Mausner & Bahn epidemiology—an introductory text*. Philadelphia, PA: WB Saunders, 1985.)

triangle model, and the wheel model—have been frequently cited *(9,10)*. Each attempts to simply visualize the interplay between the three components.

INTERACTIONS OF AGENT, HOST, AND ENVIRONMENT

All outcome events (infection or disease) have multifactorial causes. For some infectious diseases, a single unique factor or agent is *necessary* and *sufficient* for the disease to appear. This is exemplified by measles or rabies. It is only *necessary* for the host to be exposed to and infected by an agent (the measles virus or the rabies virus) for that disease to develop. For other infectious diseases, the single factor of infectivity of the agent is *necessary* but not *sufficient* to cause disease in the host. *M. tuberculosis*, polio virus, hepatitis A, and many other agents *necessary* for specific disease in a human host infect without causing disease in a majority of cases. Within the hospital setting, exposure to a specific microorganism or colonization of an inpatient with an agent, such as vancomycin-resistant *enterococcus* (VRE) or *Staphylococcus aureus*, may be *necessary* but not *sufficient* to generate disease, which only develops through complex interactions between other contributory factors, such as age, state of debilitation, immune or nutritional status, device use, invasive procedures, antimicrobial usage, or susceptibility of the microorganism to available antimicrobials. The fact of the infection in these cases is not *sufficient* to produce disease in the host without the contribution of these latter elements in the host and the environment.

Agent

The agents causing healthcare-associated infectious diseases are microorganisms ranging in size and complexity from viruses and bacteria to protozoa and helminths. Bacteria, fungi, and certain viruses have been the agents most recognized and studied as causes of healthcare-associated infections *(11)*. For transmission to take place, the microorganism must remain viable in the environment until contact with the host has been sufficient to allow infection. Reservoirs that allow the agent to survive or multiply may be animate, as exemplified by healthcare worker carriage of staphylococci in the anterior nares or throat (12,*13–15*), or the inanimate environment, as demonstrated by *Pseudomonas* spp. colonization of sink areas, *Legionella* in hot or cold water supply systems *(16–19)*, *Clostridium difficile* spores on computer keyboards, or *Serratia marcescens* growing in contaminated soap or hand lotion preparations *(20–22)*.

Certain intrinsic and genetically determined properties of a microorganism are important for it to survive in the environment. These include the ability to resist the effects of heat, drying, ultraviolet light, or chemical agents, including antimicrobials; the ability to compete with other microorganisms; and the ability to independently multiply in the environment or to develop and multiply within another host or vector. Intrinsic agent factors important to the production of disease include infectivity, pathogenicity, virulence, the infecting dose, the agent's ability to produce toxins, its immunogenicity and ability to resist or overcome the human immune defense system, its ability to replicate only in certain types of cells, tissues, or hosts (vectors), its

ability to persist or cause chronic infection, and its interaction with other host mechanisms, including the ability to cause immunosuppression (e.g., HIV).

Once transferred to a host surface, the agent may multiply and colonize without invading or evoking a measurable host immune response *(23–25)*. The presence of an agent at surface sites in the host does not define the presence of an infection. Nonetheless, patients so colonized may act as the reservoir source of transmission to other patients *(26)*.

If infection takes place, a measurable immune response will develop in most hosts even if the infection is subclinical. The success of this process for the agent is increased in the nonimmune host and is most successful in the nonimmune, immunocompromised host. A microorganism's ability to infect another host vector (e.g., yellow fever virus in mosquitoes) or another nonhuman reservoir (e.g., yellow fever virus in the monkey) is important in the epidemiology of certain infectious diseases in world populations at large but plays little role in healthcare infection epidemiology.

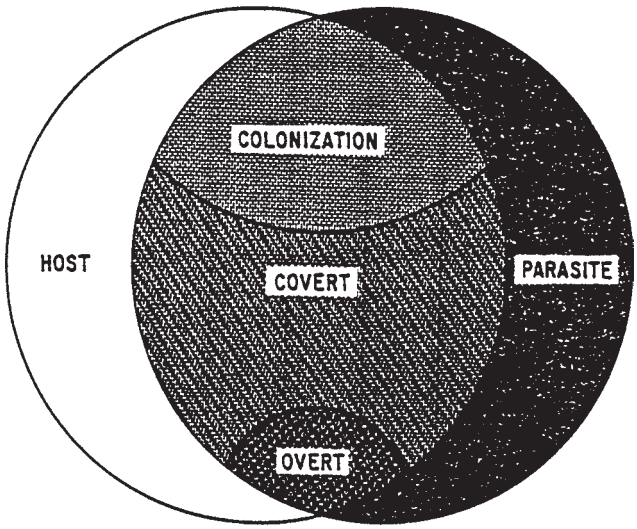

FIGURE 1-2 Venn diagram of agent–host interactions. An interaction between host and parasite may result in infection. Infection consists of colonization and an infectious disease. An infectious disease may be either covert (subclinical) or overt (symptomatic). (From Hoeprich PD, ed. *Infectious diseases*. Hagerstown, MD: Harper & Row, 1972:40.)

Host

Infection depends on exposure of a susceptible host to an infecting agent. Exposure of the susceptible host to such agents is influenced by age, behavior, family associations, occupation, socioeconomic level, travel, avocation, access to preventive healthcare, vaccination status, or hospitalization. Whether or not disease takes place in the infected host and the severity of disease when it appears depend not only on the intrinsic virulence factors of the agent but more importantly on the pathogenicity of the interactions between the agent and the host. The host immune defenses attempt to prevent infection. Thus, any reduction in host defenses may allow infection to take place with a smaller dose of microorganisms or at a body site that is not usually susceptible to infection. A combination of reductions in host defense characteristics and the requirements for an agent to cause infection are typical of the interactions that allow acquisition of opportunistic infections in immunocompromised patients. A commonly cited model indicating the potential interactions between agent and host and the relationships among colonization, infection, and clinical and subclinical disease is shown in Figure 1-2 *(27)*.

Host factors important to the development and severity of infection or disease may be categorized as intrinsic or extrinsic. Intrinsic factors include the age at infection; birth weight; sex; race; nutritional status *(28)*; comorbid conditions (including anatomic anomalies) and diseases; genetically determined immune status; immunosuppression associated with other infections, diseases, or therapy; vaccination or immunization status; previous experience with this or similar agents; and the psychological state of the host *(29)*. Colonization of the upper and lower respiratory tracts is more likely when the severity of illness increases in critically ill patients. This, along with other host impairments (e.g., reduced mucociliary clearance or changes in systemic pH), allows colonization to progress to invasive infection. Moreover, other clinical conditions may lead to an alteration in epithelial cell surface susceptibility to binding with bacteria, leading to enhanced colonization *(23–25)*. Extrinsic factors include invasive medical or surgical procedures; medical devices, such as intravenous catheters or mechanical ventilators; sexual practices and contraception; duration of antimicrobial therapy and hospitalization; and exposure to hospital personnel.

Environment

The environment provides the mutual background on which agent–host interactions take place and contains the factors that influence the spread of infection. Environmental factors include (a) physical factors such as climatic conditions of heat, cold, humidity, seasons, and surroundings (e.g., intensive care units, outpatient clinics, long-term care facilities, or water reservoirs); (b) biologic factors (e.g., intermediary hosts such as insect or snail vectors); and (c) social factors (e.g., socioeconomic status, sexual behavior, types of food and methods of preparation, and availability of adequate housing, potable water, adequate waste disposal and healthcare amenities). These environmental factors influence both the survival and the multiplication of infectious disease agents in their reservoirs and the behavior of the host in housing, occupation, and recreation that relate to exposure to pathogens. Food- and water-borne diseases flourish in warmer months because of better incubation temperatures for the multiplication of the agent and recreational exposures of the host, whereas respiratory agents appear to benefit from increased opportunities for airborne and droplet transmission in the closed and closer living environments of the winter. In US hospitals, the frequency of hospital-acquired *Acinetobacter* spp. infections is increasing in critical care units and has been shown to be seasonal in nature *(30)*. The seasonal variation in the incidence of this pathogen is thought to be due to changes in climate—summer weather increases the number of *Acinetobacter* spp. in the natural environment and transmission of this microorganism in the hospital environment during this season *(30)*.

Within healthcare settings, the components of the agent, host, and environment triad interact in a variety of ways to produce healthcare-associated infections. For example, the

intensive care unit is now considered the area of highest risk for the transmission of healthcare-associated pathogens in US hospitals (31). Moreover, methicillin-resistant *S. aureus* (MRSA), VRE, and ceftazidime-resistant *Pseudomonas aeruginosa* are endemic in many intensive care units in these hospitals (31). The emergence of vancomycin-resistant *S. aureus* in US institutions highlighted the unwelcome but inevitable reality that this pathogen may become endemic in acute care settings (32). A complex interaction of contributory factors, such as inadequate hand washing and infection control practices among healthcare workers, fluctuating staffing levels, an unexpected increase in patient census relative to staffing levels in the intensive care unit, or an unprecedented increase in the number of severely ill patients with multiple invasive devices, could all contribute to the acquisition of hospital infections caused by one of these endemic microorganisms *(33,34)*. Adding to the complexity of the process would be the unquantifiable mechanism of transmission of the agent from host to healthcare worker, healthcare worker to healthcare worker, and host to environment. Thus, acceptable measures for the prevention and control of healthcare-associated infection dictate that the healthcare epidemiologist looks at and analyzes the interrelationships among all components of the triad of agent, host, and environment (31).

It is well-known that the social environment is extremely significant in determining personal behavior that affects the direct transmission of agents, such as HIV via breast milk in regions of high HIV endemicity, gram-negative microorganisms via artificial nails worn by healthcare workers in US intensive care units *(35)*, and pathogens that cause sexually transmitted diseases. What must be understood to be equally relevant is the impact of other factors in the social environment, such as the distribution of and access to medical resources; the use of preventive services *(36–38)*; the enforcement of codes in food preparation, infection control practices, or occupational health practices; the extent of acceptance of breast-feeding for children *(39–41)*; and the acceptance of advice on the appropriate use of antimicrobials (*42–44*,45,*46*). Also, there must be an appreciation by patients, relatives, and healthcare workers alike that at-risk patients (e.g., those born very prematurely have severe congenital abnormalities, the very elderly, or those with premorbid end-stage cardiac or pulmonary disease), who have numerous indwelling medical invasive devices, or who have undergone multiple invasive procedures or surgical procedures would be particularly susceptible to healthcare-associated infections that are likely nonpreventable. There must be an informed and ethically sound willingness to reject the extraordinary application of medical technology, including the inappropriate or repeated use of resistance-inducing antimicrobials when clinical evidence and experience suggest that the condition of the sick patient is untreatable or irreversible.

Special Environments

Microenvironments, including military barracks, dormitories, day-care centers, chronic disease institutions, ambulatory surgery and dialysis centers, and acute care hospitals, provide special venues for agent–host interactions. Historically, epidemics in these institutional environments provided the experience that drove the development and acceptance of control measures, guidelines, and infection control programs. Acute care hospitals, especially those offering regional secondary and tertiary care, remain the dominant examples of these environments. Changing patterns of outpatient practice, home healthcare, and technical advances in medicine have resulted in increasingly severely diseased and injured populations being managed in acute care facilities. Data from CDC demonstrate that the changing healthcare environments in the United States are resulting in larger intensive care unit populations while there has been a general decrease in the number of general medical beds (31).

Special units for intensive medical or surgical care for extensive burns, trauma, transplantation, and cancer chemotherapy frequently house patients with increased susceptibility to infection (47). In these patients, reduced inocula of pathogens or commensals are required to cause infection, infection may take place at unusual sites, and usually nonpathogenic agents may cause serious disease and death. Frequent opportunistic infections in these patients require repeated, broad, and extended therapy with multiple antimicrobials, leading to increasingly resistant resident microbial populations (31,*46*).

The emergence or reemergence in this setting of pathogens resistant to all available antimicrobials is taking place, a situation that has not been present since the 1950s *(48)*. For example, in some institutions during the early 1990s, >80% of VRE isolates were documented as being resistant to all available antimicrobials *(49)*. Similarly, spiraling healthcare costs have been the major factor leading to the current shift toward managed care in the United States. The process has resulted in the downsizing of hospital workforces to cut costs and reduce patient charges. As a result, more severely ill patients are being managed or treated as outpatients or at home. For example, central venous catheters may be placed in the hospital, and kept *in situ* for long-term home infusion therapy. The trade-off is minimum exposure to the hospital environment with decreased costs to the patient. On the other hand, a patient with a central venous catheter in the home environment may be potentially at risk of bloodstream infections due to contamination of lines, dressing, and infusates in a care environment where infection control practices are not as well understood, practiced, or regulated.

INFECTION, COLONIZATION, AND SPECTRUM OF DISEASE

Infection is the successful transmission of a microorganism to a susceptible host, through a suitable portal of entry, with subsequent colonization, multiplication, and invasion. The source of a microorganism (the primary reservoir) may be animate (e.g., humans, mammals, reptiles, or arthropods) or inanimate (e.g., work surfaces, toys, false fingernails, toiletries, or soap). *Disease* is the overt damage done to a host as a result of its interaction with the infectious agent: it represents a clinically apparent response by or injury to the host after infection, with the affected person showing symptoms or physical signs that may be characteristic of infection with the invading pathogen. Thus, disease is the outcome of an infectious process, and

a *pathogen* is any microorganism with the capacity to cause disease in a specific host.

Unapparent or subclinical infection is a frequent occurrence where the infected person may not manifest any symptoms, signs, disability, or identifiable disease. For example, in patients who acquire *Salmonella typhi* infection (typhoid fever), a chronic infection of the gallbladder may develop with asymptomatic fecal excretion of the pathogen for years after the acute event. Patients in HIV-endemic countries may have *M. tuberculosis* bloodstream infections despite having normal chest radiographs and no symptoms or signs suggestive of underlying pulmonary disease *(50)*. Persons with subclinical infection are sometimes referred to as *carriers*. Subclinical infection may be recognized through laboratory testing of blood or other appropriate body material from the host. These tests may indicate evidence of an immune response to infection, the presence of antigens characteristic of the microorganism, abnormal cellular function in response to infection, or the presence of the microorganism itself.

Colonization is the presence of a microorganism in or on a host, with growth and multiplication, but without any overt clinical expression or detected immune reaction in the host at the time the microorganism is isolated. An infectious agent may establish itself as part of a patient's flora or may cause low-grade chronic disease after an acute infection. For example, 20% of healthy adults are persistent carriers of *S. aureus* in the anterior nares without any manifestation of clinical illness (*51*,52,*53*). However, under suitable conditions, patient populations colonized with *S. aureus* are at an increased risk of having infection and disease develop *(54–58)*. Once colonization or infection is established in a susceptible host, the agent may enter a silent or latent period during which there is no clinical or typical laboratory evidence of its presence. Thereafter, the host may manifest signs and symptoms of mild disease without disability, exhibit rapid or slow progression of disease, or progress to either temporary or chronic disability. Ultimately, the patient may die or have a complete recovery and return to health without sequelae.

The outcome of an infection is determined by the size of the *infecting dose*, the site of the infection, the vaccination status of the host, the speed and effectiveness of the host immune response, other intrinsic host factors (e.g., nutritional status), or promptness of instituting and effectiveness of the therapy. These factors together with intrinsic properties of a microorganism, such as its infectivity, pathogenicity, virulence, and incubation period, determine the course and progress of an infection, and manifestation of disease. *Infectivity* is the characteristic of the microorganism that indicates its ability to invade and multiply in a susceptible host to produce infection or disease; it is expressed as the proportion (i.e., the *attack rate*) of patients who become infected when exposed to an infectious agent. The basic measure of infectivity is the minimum number of infectious particles required to establish infection. Pathogens like polio or measles viruses have high infectivity.

The *pathogenicity* of an infectious agent is a measure of its ability to cause disease in a susceptible host. Thus, while the measles virus has a relatively high pathogenicity (i.e., few subclinical cases), the poliovirus has a low pathogenicity (i.e., most cases of polio are subclinical). The measure of pathogenicity is the proportion of infected persons with clinically apparent disease. The pathogenicity of an agent that is usually innocuous may be increased in a host with reduced defense mechanisms. For some agent–host interactions, the resultant disease is due to the effects of exaggerated or prolonged defense mechanisms of the host. The *virulence* of a microorganism is its intrinsic capability of infecting a host to produce disease. It follows that a pathogen might have varying degrees of virulence. Thus, although the nonencapsulated form of *Haemophilus influenzae* is a common inhabitant of the upper respiratory tract of healthy humans and causes localized infection without bacteremia (e.g., conjunctivitis or otitis media in children), the more virulent encapsulated type b form causes more invasive disease and is an important cause of meningitis or epiglottitis. If the disease is fatal, virulence can be measured with the case–fatality rate. For example, the rabies virus almost always produces fatal disease in humans and is therefore an extremely virulent agent.

The ability to diagnose an infection or disease depends on the degree to which typical symptoms and physical signs develop in patients, the appropriateness of diagnostic tests, and the sensitivity and specificity of these tests for the particular infecting agent. Whether an infecting agent produces clinical or subclinical infections depends on the agent and host factors, for example, age or immune status. Thus, *P. aeruginosa,* a ubiquitous pathogen that thrives in aquatic environments and vegetation, seldom causes disease in healthy humans. However, in debilitated, hospitalized patients, such as those with burns, critical care patients with multiple *in situ* invasive medical devices, or those who are on prolonged mechanical ventilation, this pathogen remains an important cause of ventilator-associated pneumonia in US hospitals *(59)*.

Certain agents may be associated with a variety of different syndromes that depend on age and vaccination status of the host, previous infection with the agent, and agent-related mechanisms that remain unclear. Thus, *Strongyloides* spp., a nematode that is endemic in many parts of the world, including Southeast Asia and some parts in the southeastern United States, can cause asymptomatic infection or be associated with several syndromes ranging from mild epigastric discomfort and chronic skin rashes to life-threatening hyperinfection that results in gram-negative bacteremia, pneumonia, and multisystem disease in immunosuppressed patients, including solid organ transplant recipients or patients with chronic airways disease who are steroid-dependent *(60–63)*. These differences in host–agent interactions underscore the difficulty in establishing causation and the importance of confirmatory laboratory evidence to precisely identify the causal agent associated with syndromes of infectious disease.

Once colonization or infection is established in a susceptible host, the agent may enter a silent or latent period during which there is no clinical or usual laboratory evidence of its presence. Thereafter, the host may manifest signs and symptoms of mild disease without disability, may have a rapid or slow progression of disease, or may progress to either temporary or chronic disability, or, ultimately, death. Alternatively, the patient may have a complete recovery and return to health without sequelae. In other instances, the entire process may be inapparent

or subclinical without evidence of disability or disease. Subclinical cases may be recognized through laboratory testing of blood or other body fluids of the host. These tests may indicate evidence of abnormal cellular function (abnormal liver function tests), the presence of an immune response to infection (antibody to hepatitis B virus core antigen), the presence of antigens characteristic of the microorganism (positive test for hepatitis B virus surface antigen), or the presence of the microorganism itself.

The ability to diagnose an infection or disease is obviously easier in clinical cases and much easier in severe clinical cases wherein the typical signs and symptoms of the disease are apparent and routine tests are diagnostic of the agent. The ratio of clinical to subclinical infections varies widely by agent and is influenced by certain host factors, such as age and immune status. Certain agents may be associated with a variety of different syndromes that depend on age and vaccination status of the host, previous infection with the agent, and agent-related mechanisms that remain unclear. Poliovirus is less likely to appear as a paralytic syndrome in children, and Coxsackie virus B infections may appear as myocarditis one year and more prominently as meningoencephalitis the next. Respiratory syncytial virus infections may appear as bronchiolitis in infants and as a common cold syndrome in their older caregivers. Since the ability to diagnose an infection or disease caused by a specific pathogen depends partly on the degree to which typical symptoms and physical signs develop in patients, variation in the clinical manifestation of disease underscores the difficulty in establishing causation, the importance of clinical awareness of syndromic variations of certain infections, and the importance of confirmatory laboratory evidence to precisely identify the causal agent associated with syndromes of disease outbreaks. Evans provides a detailed and excellent review of the principles and issues in establishing causation in infection and disease *(64)*.

MECHANISM OF SPREAD

Transmission

For infection to take place, microorganisms must be transferred from a reservoir to an acceptable entry site on a susceptible host in sufficient numbers (the infecting dose) for multiplication to occur. The infecting dose of a microorganism may depend in varying degrees on infectivity, pathogenicity, or virulence of the microorganism itself. The entire transmission process constitutes the *chain of infection*. Within the healthcare setting, the reservoir of an agent may include patients themselves, healthcare workers (e.g., nares or fingernails), tap water, soap dispensers, hand lotions, mechanical ventilators, intravascular devices, infusates, multidose vials, or various other seemingly innocuous elements in the environment.

Direct transmission from another host (healthy or ill) or from an environmental reservoir or surface by direct contact or direct large-droplet spread of infectious secretions is the simplest route of agent spread. Examples of direct-contact transmission routes include kissing (infectious mononucleosis), shaking hands (common cold [rhinovirus]), or other skin contact (e.g., contamination of a wound with staphylococci or *Enterococcus* spp. during trauma, surgical procedures, or dressing changes). Transmission of *Neisseria meningitidis*, group A streptococcus, or the respiratory syncytial virus (an important cause of respiratory infection in young children worldwide) by large respiratory droplets that travel only a few feet is regarded as a special case of direct-contact transmission.

Vertical transmission of infection from mother to fetus is another form of direct-contact transmission that may occur through the placenta during pregnancy (e.g., HIV, rubella virus, hepatitis B virus, or parvovirus), by direct contact of the infant with the birth canal during childbirth (group B streptococci), or via breast milk (HIV).

Indirect-contact transmission may occur via the hands of people, contaminated inanimate objects (fomites), various work surfaces, food, biological fluids (e.g., respiratory, salivary, gastrointestinal, or genital secretions, blood, urine, stool), invasive or shared medical devices, or through arthropod or animal vectors. Indirect-contact transmission is the most common mechanism of transfer of the microorganisms that cause healthcare-associated infections and commonly occurs via the hands of healthcare workers, their clothing, or instruments like stethoscopes or thermometers. Rapid dissemination of agents, such as respiratory syncytial virus or the influenza virus, may occur in day-care centers through salivary contamination of shared toys and games. *C. difficile* is an important diarrheal agent transmitted from patient to patient in acute care hospitals. Its transmission is abetted by its spore-forming ability to survive in the environment, and its selection and promotion in patients by the repeated and prolonged use of certain antimicrobials (65). Medical devices contaminated with blood-borne pathogens, including hepatitis B and C viruses, cytomegalovirus, and HIV, are sources of infection for both patients and medical care personnel in healthcare institutions *(66,67)*. Some viruses can remain viable for extended periods under suitable conditions. For example, Hepatitis B virus is relatively stable in the environment and remains viable in dried form for at least 7 days to 2 weeks on normal working surfaces at room temperature *(68)* This property has led to Hepatitis B virus transmission among dialysis patients through indirect contact via dialysis personnel or work surfaces in the dialysis unit *(69,70)*. Examples of other sources of healthcare-associated infections that occur through indirect contact include bacterial or viral contamination of musculoskeletal allograft tissues, intrinsic contamination of infusates or injectable medications, liquid soap, or contaminated medications prepared in the hospital pharmacy (*20*,*71*,72,*73–75*). The continuing presence of *Pseudomonas* spp. and other gram-negative rods in potable water supplies acts as an important reservoir for these agents and a readily available source for hand transmission to patients, especially the severely ill *(19,76)*.

Airborne transmission is another mechanism of indirect transfer of pathogens. Microorganisms transmitted by this method include droplet nuclei (1–10 μm) that remain suspended in air for long periods, spores, and shed microorganisms. The airborne transfer of droplet nuclei is the principal route of transmission of *M. tuberculosis*, varicella, or measles. The transmission of *Legionella* spp. through the

air in droplet nuclei from cooling tower emissions, and from environmental water sites, such as air-conditioning systems, central humidifiers, and respiratory humidification devices, is another important example of this type of spread (*77–79*,80,*81*). *C. difficile*–associated disease, the most common cause of healthcare-associated gastrointestinal infection in the United States, is frequently acquired through the transmission of spores via hospital work surfaces and the hands of healthcare workers (65,82). In fact, *C. difficile* may become endemic if its spores are propagated by air currents throughout an institution. Fungal spores can be an important cause of healthcare-associated infections. Spores of invasive fungi, such as *Aspergillus* spp., may be carried over long distances in hospitals to cause severe infections in immunosuppressed patients. The risk of spore contamination was highlighted by an outbreak of *Curvularia lunata* (a black fungus) among silicone breast implant recipients, who had undergone the breast augmentation procedures in an operating room that was erroneously maintained at negative pressure resulting in high spore counts in the operating room environment (operating rooms are supposed to be maintained at net positive pressures relative to adjacent areas). The surgeons had not implemented a closed system for inflating the breast prostheses with saline; instead, they had inflated the silicone prostheses using syringes filled with saline drawn up from a sterile bowl exposed to the ambient operating room environment. The end result was contamination of sterile saline in the open bowl with *C. lunata* spores, which were then injected inadvertently into the breast prostheses *(83)*. In some settings (e.g., burn units), staphylococci have been thought to spread on skin squamous cells that have been shed from patients or healthcare personnel. The importance of this mode of transmission, however, is not thought to be of great significance in other care settings. More recent data suggest that *S. aureus* is a common isolate in oropharyngeal cultures *(13)*. Although the epidemiologic implications of this finding remain uncharacterized, the ramification for infection control in healthcare facilities would be enormous if indeed the chain of infection for *S. aureus* includes oropharyngeal secretions or droplet nuclei. More recently, the emergence of extensively drug-resistant (XDR) strains of *M. tuberculosis* (i.e., strains resistant to practically all second-line agents) has again highlighted the importance of airborne transmission and the fact that the underlying reason for XDR emergence stems from poor general tuberculosis control and the subsequent development of multi-drug resistant (MDR)-tuberculosis (84,*85*).

Vector-borne transmission by arthropods or other insects is a form of indirect transmission, and may be mechanical or biologic. In mechanical vector-borne transmission, the agent does not multiply or undergo physiologic changes in the vector; in biologic vector-borne transmission, the agent is modified within the host before being transmitted. Although the potential for microorganism carriage by arthropods or other insect vectors has been described *(86,87)*, this type of transmission has not played any substantial role in the transmission of healthcare-associated infections in the United States. In tropical countries with endemic dengue, yellow fever, or malaria, vector-borne transmission is relatively more important, requiring screening of patients or other interventions, and preventive measures not ordinarily required for patients in colder climates.

Reservoirs

Humans are the primary reservoir for *Neisseria gonorrhoeae*, *S. typhi*, HIV, Hepatitis B and C viruses, or *Shigella* spp. Animals (zoonoses) harbor the rabies virus, *Yersinia pestis, Leptospira* spp., or *Brucella* spp. Environmental reservoirs include the soil (*Histoplasma capsulatum, Clostridium tetani*, and *Bacillus anthracis*) and water (*Legionella* spp., *P. aeruginosa, Serratia* spp., and *Cryptosporidium* spp.). In critical care units, reservoirs in ventilation circuits often harbor gram-negative pathogens, such as *P. aeruginosa, Serratia* spp., or *Acinetobacter* spp. For some infections, the interaction between host, agent, and environment might include an extrinsic life cycle of the agent outside of the human host. The interplay of such factors can add significant layers of epidemiological complexity in properly understanding the cause of an outbreak or in characterizing the chain of infection.

INCUBATION PERIOD AND COMMUNICABILITY

The *incubation period* is the time between exposure to an infectious agent and the first appearance of evidence of disease in a susceptible host. The incubation period of a pathogen usually is typical for that class of microorganisms and may be helpful in diagnosing unknown illness or making a decision regarding further diagnostic testing. The first portion of the incubation period after colonization and infection of a person is frequently a silent period, called the *latent period*. During this time, there is no obvious host response, and evidence of the presence of the infecting agent may not be measurable or discernible. Measurable early immune responses in the host may appear shortly before the first signs and symptoms of disease, marking the end of the latent period. Incubation periods for a microorganism may vary by route of pathogen inoculation, and the infecting dose. For example, brucellosis may be contracted through direct contact with blood or infected organic material, ingestion of raw dairy products, or through airborne transmission in a laboratory or abattoir; these various modes of transmission result in an incubation period for brucellosis that is highly variable, ranging from 5 days to several months. Incubation periods for other common microorganisms are as follows: 1 to 4 days for the rhinovirus (the common cold) or influenza virus; 5 to 7 days for herpes simplex virus; 7 to 14 days for polio virus; 6 to 21 days for measles virus; 10 to 21 days for chickenpox virus; 20 to 50 days for hepatitis A virus and the rabies virus; and 80 to 100 days for hepatitis B virus.

The *communicable period* is the time in the natural history of an infection during which transmission may take place. Generally, microorganisms that multiply rapidly and produce local infections are associated with short incubation periods. For example, enterotoxin-producing *S. aureus* undergoes such rapid multiplication in unrefrigerated food that symptoms of food poisoning may become manifest within 1 to 6 hours of ingestion of the contaminated meal. Microorganisms that cause disease that depend on

hematogenous spread or multiplication in distant organs tend to have longer incubation periods. HIV antibodies are generally detectable 1 to 3 months after the initial exposure, whereas the HIV-infected person might remain asymptomatic for years. Cytomegalovirus, a blood-borne pathogen that frequently causes posttransplant or post-transfusion infection, generally causes illness 3 to 8 weeks after initial exposure.

OUTBREAKS, EPIDEMICS, AND EPIDEMIC INVESTIGATION

An infectious disease outbreak or epidemic is defined as an increase in the occurrence of infection or disease above the baseline or background rate, in a given area in a specific patient population. Epidemics may originate from a common source or be propagated from person to person. Common source epidemics appear when susceptible persons have mutual exposure to the same agent in the same time period. If the exposure to an infectious agent happens at a single event at a single time and place, such as at a church dinner, it is called a *point source epidemic*. When this happens, the affected (exposed) patients usually have a similar incubation period, and the average time from the onset of first symptoms back to the initial, common exposure event is the natural incubation period of the agent. If the agent is known, its identified incubation period helps to define the time of the common event. For example, onset of symptoms of food poisoning caused by *S. aureus* usually occurs within 1 to 6 hours; symptoms due to *Shigella* spp. usually occur within 24 to 48 hours. If exposure to an infecting agent is continuous, as in a hospital room with an air-conditioner contaminated with *Legionella* spp., episodes of *Legionella* pneumonia among hospital inpatients may appear sequentially. Sewage from a treatment plant seeping into a water supply is another example of continuous source exposure in which a persistent increase above an expected level extends beyond a single incubation period.

Propagated epidemics occur when serial direct or indirect transmission of a microorganism occurs from susceptible host to susceptible host (e.g., person-to-person spread of *Malassezia pachydermatis*, a microorganism with a short incubation *(88)*), or it may occur at a more leisurely pace as in transmission of an agent from a carrier to a susceptible individual (e.g., transmission of *Nocardia farcinica* from the hands of a colonized healthcare worker to a surgical site *(89)*). Thus, investigation of an epidemic requires a prioritized and systematic approach to the gathering and analysis of data with careful attention to epidemiologic and clinical detail and correct interpretation of microbiological and other laboratory information.

Investigating an Epidemic

The first and most critical step in an outbreak investigation is ascertaining that an epidemic does indeed exist. This step assumes some previous information on the usual or endemic rate of occurrence of the infection or disease under study. When there is a perceived increase in the occurrence of an infection without reference to a baseline level, the aggregation of case-patients is classified as a *cluster*. Many clinical microbiology laboratories that serve large teaching hospitals or other healthcare institutions maintain computerized, retrospective line listings of infection or colonization caused by pathogens that are endemic in the institution. Such line listings are readily available on request and enable documentation of endemic infection rates.

The first hint of an outbreak or an unusual cluster of infections may be the appearance of a microorganism from epidemiologically related sources noticed by the clinician, infection control team, pharmacy, or laboratory personnel. The microbiology laboratory has been likened to an early warning, laboratory-based surveillance system for the detection of outbreaks *(11,90)*. For example, laboratory technologists might be the first to suspect the presence of an outbreak of healthcare-associated infections by being alert and noting in a line listing the existence of an unusual cluster of isolates of a particular morphology, species, or antimicrobial susceptibility profile. End-of-the-day scrutiny of routine line listings of microorganisms growing in cultures by a staff microbiologist might herald the presence of a cluster of infections or antimicrobial-resistant microorganisms in a specific hospital inpatient service that would have otherwise been overlooked or missed by the clinician or healthcare epidemiologist. Or perception by an astute pharmacist of overprescribing of antimicrobials for infections caused by an unusual microorganism could be a lead to ascertainment of a putative cluster or outbreak.

Computerized laboratory records, line listings, and culture reports that have been retrospectively archived constitute an invaluable source of site-specific, baseline data on endemic infection rates with which to compare current perceived increases in infection rates for various patient populations in a facility. If a comparison of epidemic and preepidemic infection rates suggests the presence of an outbreak, the clinical microbiology personnel on the team conducting the outbreak investigation must then ensure that all isolates and relevant specimens from patients associated with the putative outbreak are saved for culture or other analyses that might become necessary later on in the investigation. Thus, the initial investigation and characterization of outbreaks or clusters of infection must necessarily involve the laboratory *(91)*.

To determine the existence of an outbreak, one must understand the etiology of the infection or disease. If the syndrome is unrecognized, a consensus case definition or criteria for the condition must be formed. This case definition must be fulfilled for each event that is judged to be associated with the epidemic. The case definition may include a medical sign or symptom; a syndrome; an abnormal laboratory test (e.g., a raised white blood cell count); the isolation of an etiological agent (e.g., positive blood cultures for bacteremia); or one of the serologic tests, such as those for serum immunoglobulin levels (e.g., immunoglobulin M group), that suggest acute or recent infection. The case definition for epidemics of unknown etiology might include combinations of clinical and laboratory parameters. Depending on the data available at the onset of an investigation, a case definition may include classification of the ill as (a) definite cases, (b) probable cases, or (c) possible cases.

Case definitions of healthcare-associated infections usually involve clinical, epidemiologic, and laboratory parameters and delineate the patients (*person*) who have specific symptoms or syndromic features, the period (*time*) during which the symptoms began or were recognized, the location (*place*) of the problem, and the infecting agent and anatomic site of infection (*what*). If the case definition is microorganism-based, a careful review of the existing microbiology records usually is all that is needed to identify case-patients and determine numerator and denominator data for the calculation of comparable rates. After a case definition has been formulated, the outbreak investigators must identify and ascertain case-patients. This step may be accomplished by calling hospitals, clinics, health departments, physicians' offices, schools, or workplaces, or careful examination of patients' medical, surgical, or laboratory records, patient census listings, administrative staffing records, death certificates, or existing surveillance data, such as frequency of medical device or antimicrobial use. Laboratory records play a vital role in this undertaking by providing confirmatory data on pathogen identification, site of infection, antimicrobial susceptibility testing profiles (antibiograms), or microorganism biochemical profiles (biotype number).

In industry, annual product reviews analyze the assorted quality parameters that intersect with a given product, such as reviewing the number of laboratory deviations, the number of confirmed batch failures, or the number of manufacturing/testing changes. If available, such data are helpful in investigations of national or international outbreaks, such as those associated with widespread distribution of an intrinsically contaminated drug, device, or other product. Within healthcare systems, comparable quality systems are found largely in clinical laboratories. For example, in the microbiology laboratory, quality reviews similar to those performed in the pharmaceutical industry include systematic analyses of batch failures of reagents; monitoring culture media quality and variability of set incubation temperatures for incubators; quality assurance checks of antimicrobial-impregnated disks and adherence to standards set by the Clinical and Laboratory Standards Institute for antimicrobial susceptibility testing; regular assessments of the ability of microbiology personnel to accurately identify or characterize "unknown" isolates from the American Type Culture Collection; or weekly checks of the optical density cutoff points for spectrophotometers used in serological testing. Data from these reviews are indispensable for outbreak investigations, especially when an outbreak is linked epidemiologically to practices and procedures in the laboratory (see Chapter 9).

When an infection outbreak is recognized only by the presence of a cluster of patients with a specific syndrome, idiosyncratic clinical features, or pyrogenic reactions, and the case definition contains only clinical or epidemiologic parameters, initial cultures of relevant body sites may be negative. In these instances, it is vital that the laboratory be involved in all subsequent decision making in the outbreak investigation, particularly regarding the types of cultures, specimens, serologic tests, or assays that should be considered to assist in determining the source or cause of the outbreak. Such additional investigations may include testing large volumes of dialysis fluid or water for endotoxin, performing specialized serologic tests for *Salmonella* spp., or molecular genotyping. These indispensable roles of the laboratory underscore the interdependency of epidemiology and laboratory disciplines during the investigation of an outbreak where the suspected pathogen is absent or not initially apparent, and the direction of the subsequent investigation may require specialized laboratory tests or assays that become obvious only after an epidemiologic evaluation (see Chapter 95).

After case ascertainment, the next steps are to prepare a line listing of the patients who meet the case definition and construct an *epidemic curve* by plotting the number of cases (*y*-axis) over time (*x*-axis), and identify on a geographic map the location of the cases. The line listing should contain the basic demographic data and characteristics that are relevant to the outbreak, and should include the features of the outbreak in terms of person, place, and time that were established by the case definition.

Critical variables in an outbreak investigation include the following: (a) When did the exposure take place? (b) When did the disease begin? (c) What was the incubation period for the disease? If any two of these are known, the third can be calculated. The epidemic curve can graphically suggest the temporal relationship between acquisition of infection or disease and index case, the existence of a common source, the incubation period of an infectious agent, or the mode of transmission. In addition, the epidemic curve can be used to determine the probable period of exposure to a source: first look-up the average, median, and range of the relevant incubation period of the suspected infection in question. This information can be obtained from a recognized reference source (e.g., the *Control of Communicable Diseases Manual (7)*. The median incubation period is the time when 50% of case-patients would have acquired the infection. A rapid assessment would be to count back the average incubation period from the median case-patient and the minimum incubation period from the earliest case-patient. There are limitations in extrapolating inferences from an epidemic curve. For example, the curve might not have a "classic" shape, especially if the outbreak is small. Moreover, an observed shape may be consistent with more than one interpretation; intermittent exposures to a common source may look like person-to-person exposure, or the incubation period may remain unknown.

With an initial count of the cases completed, one can determine the rates of infection and illness in the population by age group, birth weight, gender, ethnic origin, religious affiliation, socioeconomic status, water supply, food ingestion, device use, treatment regimens, or other factors that appear to be historically associated with the individuals infected. On the basis of this preliminary analysis, a hypothesis is generated to identify the high-risk population. One may consider conducting a case–control epidemiologic study to compare ill persons (case-patients) with randomly selected persons who have remained well (control group) to identify exposures significantly associated with cases. The contrast between cases and controls is then determined by calculation of the odds ratios and

confidence intervals for each exposure. Alternatively, one may conduct a cohort study in which attack rates are compared through calculation of relative risks and confidence intervals for persons exposed and not exposed to a specific risk factor. Not all case-patients can be expected to fit the hypothesis because a background rate of endemic infections or disease must be assumed for many infectious agents (e.g., *Enterococcus* spp. in healthcare facilities). Using the hypothesis, one searches for additional case-patients, both to increase the numbers for statistical study and to include persons with mild or subclinical disease, who might otherwise escape evaluation.

With the additional findings, the data are analyzed and an interpretation of the events is prepared. If the hypothesis is supported, it is confirmed in a final report; if not, the data are reviewed for alternative hypotheses, and another round of testing and analyses is begun. On the basis of the analyses and the supported hypothesis, intervention and follow-up programs are outlined, including both short-term and long-term control measures. Finally, the findings are reported formally to local and regional authorities, public health agencies, and medical and public groups, indicating the nature of the outbreak and recommendations for future prevention and control.

The Role of Epidemiology and Microbiology in the Investigation of Outbreaks

Traditionally, the most important function of the microbiology laboratory during outbreak investigations has been to accurately identify outbreak pathogens, to conduct relevant antimicrobial susceptibility testing, and to determine the clonality (similarity) of outbreak pathogens based on whatever phenotypic or genotypic typing methods are available to the laboratory. These functions now encompass all stages of outbreak investigations. There are two different approaches to an investigation of infectious disease outbreaks: (i) to conduct extensive culture surveys to identify the source of the outbreak (*laboratory-based investigation*) or (ii) to conduct an epidemiologic investigation with subsequent epidemiology-directed environmental or personnel cultures or assays (epidemiologic investigation with laboratory confirmation). Experience from CDC suggests that the former "shot-gunning" approach creates much superfluous work and may be counterproductive, because risk factors or environmental reservoirs that are epidemiologically relevant could potentially be missed altogether, or the wrong source identified *(92)*. Initial culture surveys of the environment or personnel without a prior epidemiologic investigation may appear to identify or "implicate" the causal agent or person, but also may represent secondary contamination or colonization rather than the true source. This may result in erroneous recommendations or interventions, or inappropriate actions against staff members who are not in any way epidemiologically associated with disease transmission. Other published data from CDC suggest that an epidemiology-directed approach is generally more accurate and less costly for identifying the source and mode of transmission of outbreak pathogens *(93,94)*.

In many CDC outbreak investigations, subsequent laboratory studies have indeed confirmed the epidemiologic findings *(93–95)*; moreover, there have been occasions when the investigators of an outbreak have had to draw conclusions solely on the epidemiologic findings without laboratory confirmation, because relevant microbiological specimens often are discarded before the decision to conduct a formal investigation is made *(74,75)*. Random culture surveys of personnel, products, or the environment without a prior epidemiologic investigation may be misdirected, expensive, unsustainable, or costly in terms of human and laboratory resources and should not be performed before comparative epidemiologic studies are completed.

Epidemiologic principles are particularly important when addressing the issue of intrinsic microbial contamination of a product within an industrial plant. Intrinsic contamination of a normally sterile product may be detected in-house through quality assurance surveillance, such as end-product sampling, or it may manifest as a common-source outbreak of local, national, or international proportions *(73)*. If a pharmaceutical product is suspected to be associated with an infectious disease outbreak, integration of epidemiology and microbiology remains vital to conducting a successful outbreak investigation (the principles have been described earlier). Such an approach has been used to successfully investigate a nationwide outbreak of sterile peritonitis due to intrinsic endotoxin contamination of peritoneal dialysis solution from a single manufacturer, infections among recipients of contaminated allograft tissues, and fungal infection of saline-filled silicone breast implants *(83,96)*.

Epidemiologic methods are used to investigate and relate causal factors to an outbreak and are essential for understanding the mechanisms of infection acquisition and transmission, determining risk factors, and directing the application and practice of clinical microbiology methods. The information from epidemiologic and descriptive studies may provide important clues regarding the causes of or risk factors associated with infections, and may be used to generate causal hypotheses.

To test a hypothesis, one may attempt to identify the high-risk population and design appropriate microbiologic studies and culture surveys. Thus, the laboratory service must be able and prepared to collect relevant specimens through liaison with the epidemiologist, culture or process these specimens using reproducible, quality-controlled methods, and disseminate the information back to other outbreak coinvestigators in a timely manner.

In summary, the following issues must be considered when interpreting environmental culture data: (a) surfaces by themselves do not transmit disease; transmission from surfaces is more likely mediated by personnel who might not have maintained scrupulous aseptic conditions resulting in cross contamination of patient care items; (b) for environmental sampling, there are no benchmarks or standards to compare data generated from different culture methods; and (c) epidemiology is essential for interpreting environmental cultures—just because a pathogen is isolated from an environmental culture does not necessarily mean that there is a problem. The classic steps in the recommended investigation of an epidemic are outlined in Table 1-1.

TABLE 1-1

Steps in Investigating an Epidemic

- Confirm the existence of an epidemic
- Establish a case definition that reflects time, place, and person
- Ascertain cases and create a line listing
- Create an epidemic curve
- Determine the extent and characteristics of cases by rapid survey
- Formulate a working hypothesis
- Test the hypothesis through epidemiologic studies
- Initiate appropriate microbiology or other laboratory studies that are directed by the epidemiologic data
- Analyze all cases for interpretation
- Reassess hypothesis if not proven and initiate additional studies where warranted
- Draw conclusions and inferences from investigation
- Communicate with relevant personnel and recommend appropriate control and preventive measures (exit interviews and preliminary report)
- Continue postoutbreak surveillance for new cases
- Reevaluate control measures
- Prepare a formal written report and disseminate findings in a published manuscript

PREVENTION AND CONTROL

Measures for the prevention and control of communicable diseases are directed at various links in the *chain of infection*. These include interventions to (a) eliminate or contain the reservoirs of infectious agents or curtail the persistence (endemicity) of a microorganism in a specific setting; (b) interrupt the transmission of infectious agents; or (c) protect the host against infection and disease. This approach calls for a detailed knowledge of the epidemiology of infectious diseases in a variety of settings or environments.

Modifying Environmental Reservoirs

Interventions chosen to modify a reservoir depend on whether the reservoir is *animate* or *inanimate*. *Quarantine*, the restriction of movement of individuals who have been exposed to a potentially transmissible agent for the entire incubation period of the infection, is now rarely used to control human disease in healthcare settings and has been replaced, largely, by active surveillance of exposed individuals in acute care hospitals or long-term care facilities. Animate reservoirs (i.e., carriers) include healthcare personnel who are colonized with potential pathogens in their nares or hands, relatives (or pets) who visit patients in intensive care units, or patients known to be colonized or infected with a particular healthcare pathogen and are moved from one unit to another within a given institution, or are transferred from one hospital to another. Since disease is often subclinical, it may be difficult to recognize and separate silent carriers from susceptible persons.

Treatment of humans to eradicate their carriage of transmissible pathogens that are typically found in healthcare settings has had variable success. For example, treatment to eradicate VRE often yields mixed results *(97–99)*; whereas, there has been limited success in the eradication of MRSA among hospital inpatients (100,*101–103*) and in the community (*104*). There are no compelling data that show an association between eradication of gram-negative carriage among patients or healthcare personnel and reduced rates of transmission. Thus, removal of an individual healthcare worker, known to be a reservoir for a potentially transmissible pathogen, from a healthcare setting (e.g., bone marrow unit or surgical intensive care unit) with susceptible patients might be the only control or preventive option. Human carriers of transmissible pathogens may be isolated from susceptible individuals, who are not colonized or infected, for the duration of their stay at the institution or for as long as they harbor the microorganism (*105*,106). Finally, ethical issues arise when the decision is made to expose asymptomatic carriers or colonized but well persons to medical therapy that might have serious side effects, or render them susceptible to adverse events, such as healthcare-associated infections, disease, or undue morbidity.

In healthcare settings, reservoirs of a transmissible pathogen might be limited solely to the inanimate environment. Thus, appropriate control measures might include removing contaminated fruit, flowers, intravenous infusates, hand lotions, toys, white coats, stethoscopes, or other objects deemed to be potential reservoirs; appropriate handling of sewage and medical waste per published guidelines; ensuring that scrupulous aseptic techniques are maintained during invasive procedures or line insertion; or destroying the agent in the environmental niche (e.g., work surfaces in an intensive care unit, medicine preparation areas, or moisture reservoirs in mechanical ventilators) by chemical or physical means. In some healthcare settings, such as medical or intensive care units, microorganisms, such as VRE or *C. difficile*, may remain endemic or persistent despite identification and appropriate treatment or elimination of reservoirs. Such persistence may require periodic enhanced environmental cleaning of the concerned unit to curtail the endemicity of the pathogen (107). The importance of modifying environmental reservoirs for the control and prevention of infectious disease is sustained by the fact that much of the reduction in disease and death from infectious diseases in the industrialized world during the 20th century has been attributed to purification of potable water by filtration and chlorination, improvements in the cooking, processing, and inspection of food, and advancements in housing, nutrition, and sanitary disposal of human waste (*108*).

Interrupting Transmission

Many of the features of interventions necessary for interrupting the transmission of infection are identical to those included in the interventions necessary for modifying inanimate environmental reservoirs discussed above. The most important addition to these has been in the behavioral changes necessary to support improvements in the area of personal hygiene, specifically in the washing of hands between tasks in the preparation of food, caring for children, and caring for the sick (*109,110,*111). In the control of healthcare-associated infections, the use of appropri-

ate barriers, including the use of gloves, gowns, and eye protection, has been emphasized to prevent the transmission of blood-borne pathogens (e.g., HIV and hepatitis B) between patients and healthcare workers, as has the use of high-filtration masks for protection from respiratory transmission of influenza or tuberculosis (*105*,106). Although one of the key measures for the prevention and control of healthcare-associated infections remains the routine washing of hands before, between, and after patient contacts in healthcare settings, compliance or adherence to hand washing protocols among healthcare professionals—a behavioral attribute—remains wanting *(112)*; this is not surprising since as far back as 1996, Goldmann et al. found that National Guidelines seldom are studied thoroughly by physicians, and, if they are read, they rarely are incorporated into everyday practice *(46)*. Compounding the problem is the growing body of evidence that hand hygiene is but one factor in the complex interplay of host, agent, and the environment that facilitates transmission.

For a microorganism like VRE, transmission is enabled by one or more of the following factors: (a) the degree of hand hygiene among healthcare personnel; (b) the inherent properties of the microorganism that enable it to remain viable *days to weeks* on dry, inert environmental surfaces, coats, or ties; (c) the proportion of patients in the unit of concern who are colonized with VRE; (d) the proportion of patients who are inherently susceptible to infection; (e) selective pressure of vancomycin use in the unit; and (f) adherence to prevention efforts among healthcare personnel. Given the above, it follows that complete adherence to a strict hand hygiene policy alone will not necessarily preclude intrahospital transmission of VRE.

One method commonly used to interrupt transmission of pathogens in healthcare settings is the isolation of patients known to be colonized or infected with a particular pathogen in a separate area so as to reduce the probability of transmission of infection to other patients. This method may include allocation of these cohorted patients to specific healthcare workers to avoid transmission of the pathogen by the healthcare workers themselves.

Protecting the Host

The risk of acquisition and transmission of infectious diseases among patient populations in healthcare settings is better characterized if the patients' immune status or immune response is known. Immunization is the most effective method of individual and community protection against epidemic diseases, and can be active or passive. Through active immunization, smallpox, one of the major global communicable diseases, was eradicated *(113–115)*. Although polio has been eliminated from large areas, including all of the Americas (80), and indigenous transmission of wild poliovirus types 1 and 3 infection has been interrupted in all but four countries worldwide (Afghanistan, India, Nigeria, and Pakistan), there were still 1,655 cases reported in 2008 *(116)*. The occurrences of other childhood diseases have been substantially reduced, including diphtheria, pertussis, tetanus, measles, mumps, rubella, and infections of *H. influenzae* type B *(36,117,118)*. Since one of the main goals of epidemiology is to identify subgroups in the patient population that are at high risk for infection and disease, a knowledge of the vaccination status of patients is essential for the prevention of infection or disease. Institutional immunization programs have been recommended as part of the occupational health services of healthcare facilities for some time, but compliance for all healthcare workers has only recently come under mandate. Evaluation of patients for immunization during hospital admission is another program widely recommended but incompletely implemented. The residual endemic problems and periodic outbreaks of these vaccine-preventable diseases in both populations at large and in healthcare institutions have been largely the result of failure of the delivery programs for the vaccines. These have been due to poor funding, poor prioritization of the programs, the lack of political will, and the lack of organization of the vaccine effort—not to failure of the vaccine to immunize *(38)*.

Passive immunization with hyperimmune or standard immunoglobulins is another intervention valuable in a small group of diseases, including certain genetic and acquired immunodeficiency diseases, primary antibody-deficiency disorders, hypogammaglobulinemia in chronic lymphocytic leukemia, measles, hepatitis A, varicella-zoster, hepatitis B, and HIV infections in children *(36)*. Hyperimmune globulin preparations are obtained from blood plasma donor pools preselected for high antibody content against a specific antigen (e.g., hepatitis B immune globulin, varicella-zoster immune globulin, cytomegalovirus immune globulin, and respiratory syncytial virus immune globulin). Although active searches have been carried out for other kinds of immunomodulating agents (e.g., interferons and cytokines) and biologics that heighten host immune function and protect the host from infection or disease, there are no data that indicate such treatment modalities play any significant role in the prevention and control of healthcare-associated infections.

Administering antimicrobials to ensure the presence of an anti-infective agent at the site of a potential infection is a more recent addition to the control programs protecting the host. The use of a single dose or short course of preoperative antimicrobials to reduce the probability of infection with agents commonly seen following certain procedures has become a standard part of surgical practice *(119)*.

Profound cellular and humoral immunosuppression may ensue in patients following chemotherapy or radiotherapy of certain malignancies, or may be a consequence of the primary disease process. Therapy-related immunosuppression occurs during or following bone marrow transplantation or may be a sequelae of therapeutic regimens used to prevent rejection of transplanted organs. The use of local and systemic anti-infectives in these patients has either prevented infection or mitigated the duration and severity of infection, leading to reduced morbidity and mortality, and improved outcomes *(120–123)*. The use of preprocedure (e.g., surgery or dental) antimicrobial prophylaxis in individuals with a history of rheumatic heart disease is also a standard recommendation to prevent bacterial endocarditis *(124–126)*. Unfortunately, one of the side effects of repeated short courses of antimicrobials has been the appearance of significant resistance to these agents among pathogens associated with healthcare-associated infections (31,*127*,*128*). This problem has been aggravated by overprescribing of antimicrobials for nonbacterial infection by some practitioners, over-the-counter

sale of antimicrobials in many parts of the world, and the use of subtherapeutic doses of growth promoters in animal husbandry in the United States and other countries (*129–131*,132).

HEALTHCARE-ASSOCIATED INFECTIONS AND INFECTIOUS DISEASES

Inherent in the measures for the prevention and control of healthcare-associated infections is the ongoing education of healthcare workers in infection control practices and procedures through guidelines published by CDC *(133,134)*, and the implementation of surveillance measures to detect changes in the incidence or prevalence rates of infections caused by microorganisms commonly associated with healthcare-associated infections. The acute care hospital (inpatient, outpatient, and intensive care unit) settings and long-term care and home healthcare facilities provide special settings for the interaction of the agents of infection and patients and healthcare workers. The ongoing study of the basic epidemiologic features of agent–host interactions in these environments has led to recommendations for wide application of, and extensive testing of, surveillance, prevention, and control programs, which have proven highly successful. Descriptions of the special features of the investigations and interventions of these programs are the topics of the chapters to follow.

Despite falls in overall rates of healthcare-associated infections involving the bloodstream, respiratory tract, surgical wounds, and urinary tract, rates of infections caused by *antimicrobial-resistant* pathogens have been increasing across the United States. Thus, control of antimicrobial resistance in the 2000s remains inextricably linked to the control of transmission of healthcare-associated, *antimicrobial-resistant* pathogens and the infections they cause. The seriousness of the problem was underscored in an editorial by Muto, who made the point that "for as long as CDC has measured the prevalence of hospital-acquired infections caused by multidrug-resistant microorganisms, it has been increasing" *(135)*. The myriad of articles in the medical literature has in effect helped explain this failure since much of the data originated in facilities that had implemented untried control programs or had already instituted considerably ineffective programs.

Acute care hospital (inpatient, outpatient, and intensive care unit) settings, free standing medical and surgical centers, long-term care facilities, and the home provide special settings for the interaction of the agents of infection and hosts (i.e., patients, relatives, and healthcare workers alike). The ongoing study of the basic epidemiologic features of agent–host interactions in these environments has led to evidence-based recommendations for healthcare-associated infections surveillance, and prevention and control programs, which have proved highly successful. For example, the Society for Healthcare Epidemiology of America (SHEA) has established evidence-based guidelines to control the spread of MRSA and VRE in acute care settings (136). The tenets of the SHEA guidelines are based on identification and containment of spread through (a) active surveillance cultures to identify the reservoir for spread; (b) routine hand hygiene; (c) barrier precautions for patients known or suspected to be colonized or infected with epidemiologically important antimicrobial-resistant pathogens, such as MRSA or VRE; (d) implementation of an antimicrobial stewardship program; and (e) decolonization or suppression of colonized patients (136). Numerous reports presented at the SHEA annual meetings over the past 5 years have repeatedly shown control of endemic or epidemic MRSA and VRE infections through implementation of the SHEA guidelines. There is now growing evidence that active surveillance cultures do indeed reduce the incidence rates of MRSA and VRE infections and that programs described in the SHEA guidelines are effective and cost-beneficial (137,*138*,*139*). Many other studies have since established that identification of patients colonized with MRSA or VRE on admission to hospital for critical care may enhance implementation of interventions to decrease infection (*140*).

Despite all of the resources put into surveillance activities for healthcare-associated infections in facilities throughout the nation, there remain several obstacles that hinder progress in the control of these infections. These include (a) substantial variation in surveillance activities from one medical center to another and in the collection, aggregation, and use of surveillance data; (b) lack of designated staff healthcare epidemiologists to proactively aggregate, manage, and analyze surveillance data, and apply the results effectively; (c) failure of healthcare facilities to use effective control measures or inconsistent implementation of such measures (e.g., surveillance cultures not being performed as recommended); (d) lack of commitment and prescience among healthcare providers and administrative personnel alike in appreciating the fact that the initial outlay of financial resources that is necessary for employing healthcare epidemiologists and infection preventionists and executing surveillance activities and preventive measures could actually result in improved patient outcomes and substantial savings.

In conclusion, epidemiologic methods can enhance and strengthen evidence-based infection prevention and control through the design and conduct of studies to ascertain risk factors for infection and disease, establish the appropriateness of laboratory testing (e.g., the clinical significance of positive blood cultures), or determine best outcome correlates. In addition, familiarity with infectious diseases epidemiology enables characterization of community or healthcare-associated infections, the pathogens that cause these infections and their respective antimicrobial susceptibility profiles, and risk factors that cause (or are associated with) infection. Such data allow cost-effective patient care in hospitals with adequate resources, and enable development of logical, evidence-based preventive policies that could be applied to hospitals without sophisticated epidemiologic or laboratory support. Finally, the integration of epidemiologic and microbiologic principles is necessary for the development of robust surveillance systems for tracking emerging infections and antimicrobial resistance, for the effective conduct of infection control activities and outbreak investigations, and for informed clinical and public health decision making, research, and management practices.

REFERENCES

6. Weinstein MP, Towns ML, Quartey SM, et al. The clinical significance of positive blood cultures in the 1990s: a prospective comprehensive evaluation of the microbiology, epidemiology, and outcome of bacteremia and fungemia in adults. *Clin Infect Dis* 1997;24:584–602.
12. Sivaraman K, Venkataraman N, Cole AM. *Staphylococcus aureus* nasal carriage and its contributing factors. *Future Microbiol* 2009;4:999–1008.
31. Archibald L, Phillips L, Monnet D, et al. Antimicrobial resistance in isolates from inpatients and outpatients in the United States: increasing importance of the intensive care unit. *Clin Infect Dis* 1997;24:211–215.
32. Centers for Disease Control and Prevention. *Staphylococcus aureus* resistant to vancomycin–United States, 2002. *MMWR Morb Mortal Wkly Rep* 2002;51:565–567.
45. Goldmann DA, Huskins WC. Control of nosocomial antimicrobial-resistant bacteria: a strategic priority for hospitals worldwide. *Clin Infect Dis* 1997;24(suppl 1):S139–S145.
47. Pittet D, Harbarth S. The intensive care unit: part A. Healthcare-associated infection epidemiology, risk factors, surveillance, engineering, and administrative infection control practices, and impact. In: Jarvis WR, ed. *Bennett & Brachman's hospital infections*. 5th ed. Philadelphia, PA: Lippincott Williams & Wilkins, 2007:373–393.
52. Kluytmans JA, Wertheim HF. Nasal carriage of *Staphylococcus aureus* and prevention of nosocomial infections. *Infection* 2005;33:3–8.
65. Johnson S, Gerding DN. *Clostridium difficile*–associated diarrhea. *Clin Infect Dis* 1998;26:1027–1034.
72. Kainer MA, Linden JV, Whaley DN, et al. Clostridium infections associated with musculoskeletal-tissue allografts. *N Engl J Med* 2004;350:2564–2571.
80. Lin YS, Stout JE, Yu VL, et al. Disinfection of water distribution systems for Legionella. *Semin Respir Infect* 1998;13:147–159.
82. Archibald LK, Banerjee SN, Jarvis WR. Secular trends in hospital-acquired *Clostridium difficile* disease in the United States, 1987–2001. *J Infect Dis* 2004;189:1585–1589.
84. Centers for Disease Control and Prevention. Emergence of *Mycobacterium tuberculosis* with extensive resistance to second-line drugs–worldwide, 2000–2004. *Morb Mortal Wkly Rep* 2006;55:301–305.
100. Vos MC, Behrendt MD, Melles DC, et al. 5 years of experience implementing a methicillin-resistant *Staphylococcus aureus* search and destroy policy at the largest university medical center in the Netherlands. *Infect Control Hosp Epidemiol* 2009;30:977–984.
106. Siegel JD, Rhinehart E, Jackson M, et al. 2007 guideline for isolation precautions: preventing transmission of infectious agents in health care settings. *Am J Infect Control* 2007;35:S65–S164.
107. Byers KE, Durbin LJ, Simonton BM, et al. Disinfection of hospital rooms contaminated with vancomycin-resistant *Enterococcus faecium. Infect Control Hosp Epidemiol* 1998;19:261–264.
111. Boyce JM, Pittet D. Guideline for Hand Hygiene in Health-Care Settings: recommendations of the Healthcare Infection Control Practices Advisory Committee and the HICPAC/SHEA/APIC/IDSA Hand Hygiene Task Force. *Infect Control Hosp Epidemiol* 2002;23:S3–S40.
132. Levy SB, Marshall B. Antibacterial resistance worldwide: causes, challenges and responses. *Nat Med* 2004;10:S122–S129.
136. Muto CA, Jernigan J, Ostrowsky BE, et al. SHEA guideline for preventing transmission of multidrug-resistant strains of *Staphylococcus aureus* or *Enterococcus* in healthcare settings. *Infect Control Hosp Epidemiol* 2006;24:362–386.
137. Ostrowsky BE, Trick WE, Sohn AH, et al. Control of vancomycin-resistant enterococcus in health care facilities in a region. *N Engl J Med* 2001;344:1427–1433.

CHAPTER 2

Modern Quantitative Epidemiology in the Healthcare Setting

Jerome I. Tokars[1]

I often say that when you can measure what you are speaking about, and express it in numbers, you know something about it; but when you cannot express it in numbers, your knowledge is of a meager and unsatisfactory kind; it may be the beginning of knowledge, but you have scarcely, in your thoughts, advanced to the stage of Science, whatever the matter may be. *Lord Kelvin*

The job of the hospital epidemiologist is an intensely political one, into which we can occasionally interject some science. *Jonathan Freeman*

This chapter is about quantitative epidemiology, a term without a formal definition. However, epidemiology can be defined as "the study of the distribution and determinants of health-related states or events in specified populations, and the application of this study to control of health problems" *(1)*. "Distribution" refers to rates of disease overall and in various subgroups; for example, what percent of patients having cardiac surgery develop a surgical site infection? Assembling such rates requires an important series of steps, including determining which diseases are important, how they should be defined, and by what practical means they can be measured. "Study of … determinants of health-related states," or risk factors for disease, is the part of the definition closest to quantitative epidemiology. For example, what determines whether one patient gets a surgical site infection while another does not, or why the infection rate is higher at one hospital than at another? "Application of this study to control of health problems" is the all-important final step, requiring wisdom, judgment, and political savvy. Given the difficulty of this final step, we should at least be sure that we have done the best possible job at quantitative epidemiology, that is, of analyzing and presenting the data needed for decision making.

In one sense, epidemiology is merely "quantified common sense." For example, the simple observation that "our infection rate is higher than theirs because our patients are sicker than theirs" describes what epidemiologists call confounding. Confounding bedevils a variety of activities in healthcare epidemiology, including the comparisons of disease rates among hospitals that underlie interhospital comparisons (benchmarking) and quality assurance programs. Simply comparing crude infection or death rates among hospitals, without accounting for factors such as severity of illness, leads to obviously incorrect conclusions. While the concept of confounding may be intuitive, there is considerable complexity in application of the methods of quantitative epidemiology to deal with confounding.

It is difficult to determine the boundary between quantitative epidemiology and a related discipline, statistics. Many healthcare epidemiologists have taken introductory statistics courses, but such entry-level courses are becoming less and less adequate with each passing year. A study of articles in a prominent medical journal showed substantial increases in the use of advanced methods such as multiple regression (from 5% of articles in 1978–1979 to 51% of articles in 2004–2005), survival methods (from 11% to 61%), and power analyses (from 3% to 39%) *(2)*. In 2004 to 2005, 79% of the articles used methods beyond the scope of introductory statistics courses. Greater knowledge of quantitative epidemiology/statistics is needed both to interpret the infection control literature and to practice healthcare epidemiology.

HISTORY OF EPIDEMIOLOGY

A famous early example of applied epidemiology is the work of Dr. John Snow, a physician in London during the cholera epidemic of 1855 (3). At that time, the germ theory of disease had not been accepted and the pathogen causing cholera, Vibrio cholerae, was unknown. Whereas the prevailing view during this period was that disease was caused by a miasm or cloud, Snow inferred from epidemiologic evidence that cholera was a water-borne illness. He constructed a spot map of cholera cases and noted a cluster of cases near a water pump on London's Broad Street, the so-called Broad Street pump. This early use of a spot map to find the putative cause of an outbreak is an example of descriptive epidemiology. He also

[1]The findings and conclusions in this report are those of the author and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

performed several analytic studies, noting that the rate of cholera was higher for people who obtained water from more polluted areas of the Thames. His well-known intervention was to remove the handle from the Broad Street pump, thereby preventing the use of this contaminated water, after which cases of cholera in the vicinity were said to have decreased. This example illustrates that epidemiologists can define the mechanism of disease spread and institute control measures before the agent causing disease is discovered. More recent examples of this power of epidemiology include Legionnaires' disease and human immunodeficiency virus disease; for both diseases, the mechanism of spread and means of prevention were inferred by epidemiologists before the microbe was discovered in the laboratory.

DESCRIPTIVE VERSUS ANALYTIC EPIDEMIOLOGY

In descriptive epidemiology, we describe characteristics of the cases and generate hypotheses. The line list of cases, case series, epidemic curves, and spot maps are examples. In analytic epidemiology, we use comparison groups, calculate statistics, and test hypotheses. Many outbreaks and other problems in healthcare epidemiology can be solved by thoughtful examination of descriptive data without the use of analytic epidemiology. However, the increasingly complex nature of healthcare and associated illness demands that we have a firm grounding in analytic or quantitative epidemiology, which is the main focus of this chapter.

MEASURES OF FREQUENCY

Proportions (synonyms are *probability*, *risk*, and *percentage*) are the simplest way to represent how often something occurs. A proportion is the ratio of a part to the whole; that is, the numerator of the ratio is included in the denominator. The proportion with disease is the number of people who get the disease divided by the total number at risk for the disease; that is, proportion ill = number ill/(number ill + number well). The probability of pulling an ace from a deck of cards is 4/52 = 7.7%. Proportions can be represented by a fraction (e.g., 0.077) or a percentage (e.g., 7.7%) and can range from 0 to 1.0 or from 0% to 100%. Proportions cannot be >1.0 or 100% since, using proportions, each entry in the denominator can have at most one entry in the numerator. A proportion is unitless, because the numerator and denominator have the same units. The proportion is the measure of frequency used in cohort studies and to calculate the relative risk.

Odds represent the ratio of a part to the remainder or the probability that an event will occur divided by the probability that it will not occur. Unlike in proportions, the numerator of the ratio is not included in the denominator. The odds of a disease occurring equal the number of people with the disease divided by the number without the disease; that is, odds of illness = number ill/number well. The odds of pulling an ace from a deck of cards are 4/48 = 8.3%. Note that the odds of illness are always higher than a corresponding proportion ill, because the denominator is smaller for odds. Odds are unitless and have bounds of zero to infinity. Odds are used in case–control studies and to calculate the odds ratio.

A rate, in contrast to proportions and odds, has different units of measure in the numerator and denominator, as in 55 miles/hour or 20 healthcare-associated infections/1,000 observed patient-days. A rate can have any value from zero to infinity. Rates are used in incidence density analyses.

Common Usage

The proportion ill, especially in outbreaks, is often called an "attack rate," although strictly speaking it is a misnomer to refer to a proportion as a rate. This chapter follows common usage in using the following terms interchangeably with proportion ill: percent ill, attack rate, and rate of illness.

Cumulative Incidence Versus Incidence Density

In a cumulative incidence study, time at risk is not taken into account; the denominator is the total number of persons at risk, and the proportion with disease (or proportion with potential risk factors for disease) is calculated. The cohort and case–control studies presented in the following section are examples of cumulative incidence. In an incidence density study, time at risk is accounted for; the denominator is person-time at risk and a rate of illness (e.g., infections per 1,000 patient-days) is calculated. This type of study is considered later in this chapter.

BASIC STUDY DESIGN

There are three types of analytic study: cohort, case–control, and cross-sectional. The goal of analytic epidemiologic studies is to discover a statistical association between cases of disease and possible causes of disease, called *exposures*. A first step in any such study is the careful definition of terms used, especially defining what clinical and laboratory characteristics are required to indicate a case of disease.

The Cohort Study and Relative Risk

Prospective Cohort Study There are several subtypes of cohort study, but all have certain common features and are analyzed the same way. In the prospective cohort study, we identify a group of subjects (e.g., persons or patients) who do not have the disease of interest. Then, we determine which subjects have some potential risk factor (exposure) for disease. We follow the subjects forward in time to see which subjects develop disease. The purpose is to determine whether disease is more common in those with the exposure ("exposed") than in those without the exposure ("nonexposed"). Those who develop disease are called "cases," and those who do not develop disease are "noncases" or "controls."

A classic example of a prospective cohort study is the Framingham study of cardiovascular disease, which began in 1948 (3). Framingham is a city about 20 miles from Boston with a population of about 300,000, which was considered to be representative of the US population. A random sample of 5,127 men and women, age 30 to 60 years and without evidence of cardiovascular disease, was enrolled in 1948. At each subject's enrollment, researchers recorded gender and the presence or absence of many exposures, including smoking, obesity, high blood pressure, high cholesterol, low level of physical activity, and family history of cardiovascular disease. This cohort was then followed forward in time by examining the subjects every 2 years and daily checking of the only local hospital for admissions for cardiovascular disease.

Note several features of this study. The study was truly prospective in that it was started before the subjects developed disease. Subjects were followed over many years and monitored to determine if disease occurred, that is, if they became "cases." This is an incidence study, in which only new cases of disease were counted (because persons with cardiovascular disease in 1948 were not eligible for enrollment). In an incidence study, it is necessary to specify the study period, that is, how long the subjects were allowed to be at risk before we looked to see whether they had developed disease.

The Framingham study allowed investigators to determine risk factors for a number of cardiovascular disease outcomes, such as anginal chest pain, myocardial infarction (heart attack), death due to myocardial infarction, and stroke. One finding of this study was that smokers had a higher rate of myocardial infarction than nonsmokers. An advantage of this study design is that it is very flexible, in that the effect of many different exposures on many different outcome variables can be determined. The disadvantages are the time, effort, and cost required.

Relative Risk Performing hospital surveillance for surgical site infections (SSIs) is an example of a prospective cohort study. Assume that during one year at hospital X, 100 patients had a certain operative procedure. Of these, 40 were wound class 2 to 3 and 60 were class 0 to 1. Note that wound class was determined before it was known which patients were going to develop SSI; this makes it a prospective cohort study. A subgroup or sample of patients was not selected; that is, the entire group was studied. When the patients were followed forward in time, the following was found: of 40 patients with class 2 to 3 procedures, 10 developed SSI; of 60 patients with class 0 to 1 procedures, 3 developed SSI.

Cohort study data are commonly presented in a 2×2 table format. The general form of the 2×2 table is shown in Table 2-1, and the 2×2 table for this SSI example is shown below. Notice that the columns denote whether disease (SSI) was present and the rows whether exposure (wound class 2–3) was present. In this example, exposed means being class 2 to 3 and nonexposed means being class 0 to 1. In the 2×2 table below, the total number of cases is 13, total noncases is 87, total exposed is 40, total nonexposed is 60, and total patients is 100.

TABLE 2-1

The 2 × 2 Table and Associated Formulas

Exposure	Disease: Yes	Disease: No	
Yes	a	b	$a + b = h_1$
No	c	d	$c + d = h_2$
	$a + c = v_1$	$b + d = v_2$	N

Exposed cases = a
Exposed noncases = b
Nonexposed cases = c
Nonexposed noncases = d
Total cases = $a + c = v_1$
Total noncases = $b + d = v_2$
Total exposed = $a + b = h_1$
Total nonexposed = $c + d = h_2$
Total subjects = $a + b + c + d = n$

$$\text{Relative risk} = \frac{\%\text{ ill exposed}}{\%\text{ ill nonexposed}} = \frac{a/(a+b)}{c/(c+d)}$$

$$\text{Odds ratio} = \frac{ad}{bc}$$

Expected values (where "ea" denotes "the expected value of cell a")
ea = $h_1 v_1 / n$
eb = $h_1 v_2 / n$
ec = $h_2 v_1 / n$
ed = $h_2 v_2 / n$

$$\text{chi-square} = \frac{(a-\text{ea})^2}{\text{ea}} + \frac{(b-\text{eb})^2}{\text{eb}} + \frac{(c-\text{ec})^2}{\text{ec}} + \frac{(d-\text{ed}^2)}{\text{ed}}$$

Alternate "calculator" formula: chi-square = $(ad - bc)^2(n - 1)/(a + b)(c + d)(a + c)(b + d)$

Disease: Surgical Site Infection

Exposure	Yes	No	
Class 2–3	10	30	40
Class 0–1	3	57	60
	13	87	100

In the exposed group, the proportion ill = 10/40 = 0.25 or 25%. In the nonexposed group, the proportion ill = 3/60 = 0.05 or 5%. We compare the frequency of disease in the exposed versus nonexposed groups by calculating the relative risk (often called risk ratio). The relative risk of 5.0 means that patients in wound class 2 to 3 were five times more likely to develop SSI than were patients in wound class 0 to 1.

$$\text{Relative risk} = \frac{\%\text{ ill exposed}}{\%\text{ ill nonexposed}} = \frac{\%\text{ ill class } 2-3}{\%\text{ ill class } 0-1} = \frac{a/(a+b)}{c/(c+d)} = \frac{25}{5} = 5.0$$

Retrospective Cohort Study A retrospective cohort study is started after disease has developed. A study period

(start date and stop date) is decided upon. Using patient records, we look back in time to identify a group (cohort) of subjects that did not have the disease at the start time. We then use patient records to determine whether each cohort member had a certain exposure. Again using patient records, we determine which cohort members developed disease during the study period. Finally, we calculate the percent with disease in those with the exposure and those without the exposure and compare the two.

The following is an example of a retrospective cohort study based on the SSI example above. Hospital X noted that the overall SSI rate of 13% was higher than in previous years. We want to determine whether a new surgeon (surgeon A) was responsible for the increase. The prospective surveillance system did not routinely record the surgeon performing each procedure, so we pull the records from each procedure and record whether or not surgeon A was involved. We find that surgeon A operated on 20 patients,3 of whom later developed SSI. Among the 80 other patients, 10 developed SSI. The percent ill in the exposed group (surgeon A) = 3/20 = 15%. The percent ill for other surgeons (nonexposed) = 10/80 = 12.5%. The relative risk = 15%/12.5% = 1.2.

The interpretation is that patients operated on by surgeon A were 1.2 times (or 20%) more likely to develop disease than patients operated on by other surgeons. Factors to consider in deciding whether surgeon A is truly a cause of the problem are presented below (see Interpretation of Data, Including Statistical Significance and Causal Inference).

To review, this was a retrospective cohort study, since data on the exposure were collected from patient records after we knew which patients had developed SSI. The retrospective nature of data collection is sometimes irrelevant and sometimes a problem. For certain types of data, such as length of hospital stay or death, retrospective data collection will be as good as prospective. However, determining other factors, such as which ancillary personnel treated a given patient, may be difficult to do after the fact, and retrospective studies using such data may be less valid.

Observational Versus Experimental Studies Epidemiologic studies are generally observational; that is, the investigator collects data but does not intervene in patient care. Patients, physicians, nurses, and random processes all play a part in determining exposures in the hospital. The goal of observational studies is to simulate the results of an experimental study (see Quasi-Experimental Studies)

In an experimental study, a group (cohort) of subjects is identified and the investigator assigns some of them to receive treatment A (exposed) and the remainder to receive an alternate treatment B (nonexposed). The patients are followed forward in time, the cases of disease are recorded, and the rates of illness and relative risk are calculated as usual. The experimental study is a special type of a prospective cohort study where the two exposure groups are assigned by the investigator.

Cohort Studies With Subjects Selected Based on Exposure In this type of cohort study, subjects are selected based on exposure. We select two subgroups: one that is exposed and one that is nonexposed. Both groups are followed forward in time to see how many develop disease. Consider the SSI example and surgeon A above. We study all 20 patients operated on by surgeon A (exposed); of the 80 patients operated on by other surgeons, we randomly select 40 (nonexposed). Thus, only 60 patients of the original group of 100 are included in this study.

Note that this is a type of cohort study, not a case–control study. In a case–control study, the subjects are chosen based on whether or not they have disease. In this study, subjects were chosen based on whether or not they had exposure.

The disadvantage of this type of cohort study, where the subjects are selected based on exposure, is that only one exposure (i.e., the exposure that you selected subjects on) can be studied. However, this type of study is very useful for studying an uncommon exposure. In the SSI surveillance example used above, consider the situation if there had been 500 surgical procedures, and surgeon A had performed only 20 of them. If you performed a cohort study of the entire group, you would have to review 500 charts, which would waste time and effort. Instead, you could perform a cohort study of the 20 procedures performed by surgeon A (exposed), and 40 randomly selected procedures performed by other surgeons (nonexposed). The second alternative would be much more efficient.

Cohort Studies—Summary Cohort studies can be prospective or retrospective, observational or experimental. They usually include a whole group of subjects, but studying two subgroups selected based on exposure is also possible. The 2×2 table layout and calculations are the same for all types of cohort studies. All have in common that subjects are chosen without regard to whether they develop disease.

The Case–Control Study and Odds Ratio

In a case–control study, we choose subjects for study based on whether they have disease. Since we have to know which subjects developed disease before we select them, case–control studies are always retrospective. We usually study those with disease (cases) and choose a sample of those without disease (controls). We usually study one to four controls per case. The more controls, the greater the chance of finding statistically significant results. However, there is little additional benefit from studying more than four controls per case. Controls are usually randomly selected from subjects present during the study period who did not have disease.

Example: Case–Control Study of Surgical Site Infections This is the same example presented in the section on cohort study and relative risk. At hospital X, 100 patients had a certain operative procedure, 40 class 2 to 3 (exposed) and 60 class 0 to 1 (nonexposed), and 13 developed SSI. To perform a case–control study, we select the 13 patients with SSI (cases) and also study 26 patients who had surgical procedures but did not have SSI (controls). We studied two controls per case, but could have studied fewer or more controls. The controls were randomly chosen from all patients who had the surgical procedure under study but did not develop SSI. From their

medical records, we find which of the subjects had class 2 to 3 procedures and which had class 0 to 1 procedures. Our data showed that, of 13 cases, 10 had class 2 to 3 procedures. Of 26 noncases, 9 had class 2 to 3 procedures. The 2×2 table for this example is as follows:

Disease: Surgical Site Infection

		Yes	No	
Exposure	Class 2–3	10	9	
	Class 0–1	3	15	
		13	26	39

In a case–control study, we cannot determine the percent ill in the exposed or nonexposed groups, or the relative risk. In this example, note that the percent ill among class 2 to 3 is NOT = 10/(10 + 9) = 52.6%. However, we can validly calculate the percent of cases that were exposed, 10/13=76.9%, and the percent of noncases that were exposed, 9/26 = 34.6%. Note that the cases were much more likely to have the exposure than were the controls. Most importantly, we can calculate the odds ratio (also called the relative odds; Table 2-1) as follows:

$$\text{Odds ratio} = \frac{ad}{bc} = \frac{10 \times 15}{9 \times 3} = \frac{150}{27} = 5.6$$

We can interpret the odds ratio as an estimate of the relative risk. Using the case–control method, we estimated that patients in class 2 to 3 were 5.6 times more likely to develop SSI than were patients in class 0 to 1. Note that the odds ratio is similar to, but slightly higher than, the relative risk (5.0) we calculated previously. If the frequency of disease is not too high, that is, is less than approximately 10%, the odds ratio is a good approximation of the relative risk.

The meanings of the letters (i.e., *a*, *b*, *c*, and *d*) used to represent the 2×2 table cells are different in cohort versus case–control studies (Table 2-1). For example, in a cohort study, *a* denotes the number of cases of disease among exposed persons; in a case–control study, *a* denotes the number exposed among a group of cases. Although this distinction may not be clear to the novice, it will suffice to keep in mind that in a case–control study, it is not valid to calculate percent ill or relative risk, but it is valid to calculate an odds ratio.

A more in-depth explanation of the odds ratio is as follows. In a case–control study, we actually measure the odds of exposure among those with disease and the odds of exposure among those without disease. The ratio of these two odds is the exposure odds ratio; if equal to 2.0, this would be interpreted as "the odds of exposure are twice as high in those with disease versus those without disease." However, the exposure odds ratio is not a very useful quantity. Fortunately, it can be proven mathematically that the exposure odds ratio equals the disease odds ratio. Therefore, using our example of 2.0, we can say that the odds of disease are twice as high in those exposed versus those not exposed, which is closer to being useful. Finally, we use the odds ratio as an approximation of the relative risk (where the frequency of disease is not too high) and say simply that those with exposure are twice as likely to get disease.

Selection of Controls Selection of controls is the critical design issue for a case–control study. Controls should represent the source population from which the cases came; represent persons who, if they had developed disease, would have been a case in the study; and be selected independently of exposure *(4)*. It is always appropriate to seek advice when selecting controls, and may be worthwhile to select two control groups to compare the results obtained with each.

An example of incorrect selection of controls is provided by a case–control study of coffee and pancreatic cancer (3,5). The cases were patients with pancreatic cancer, and controls were selected from other inpatients admitted by the cases' physicians but without pancreatic cancer. The finding was that cases were more likely to have had the exposure (coffee drinking) than the controls, which translated into a significant association between coffee drinking and pancreatic cancer. The problem was that the controls were not selected from the source population of the cases (cases did not arise from hospital inpatients) and thus were not representative of noncases. The physicians admitting patients with cancer of the pancreas were likely to admit other patients with gastrointestinal illness; these control patients were less likely to be coffee drinkers than the general population, possibly because they had diseases that prompted them to avoid coffee. A better control group might have been healthy persons of similar age group to the cases.

More contemporary examples of problematic control selection are studies of the association between vancomycin receipt and vancomycin resistance (6). Cases are often hospitalized patients who are culture positive for vancomycin-resistant enterococci. Controls have often been selected from patients who were culture positive for vancomycin-sensitive enterococci. Using this control group, case-patients will be more likely to have received vancomycin than the controls, resulting in a significant association and elevated odds ratio. The problem is that controls were not representative of the source population and were less likely to have received vancomycin than other patients, since vancomycin would have suppressed or eliminated vancomycin-sensitive microorganisms. Better control groups would be hospital patients similar in age and severity of illness to the cases.

A potential problem is that hospital patients without a positive culture may include some patients who had the microorganism but were not cultured. Inclusion of these patients as controls would bias the odds ratio to 1.0 (null result). An alternative method is to limit controls to those with at least one clinical culture performed. However, this may not be preferable since it results in selection of sicker controls ("severity of illness bias") and also biases the odds ratio toward 1.0 *(7)*. Another way to look at this issue of potential "contamination" of the control group with unrecognized cases is as follows: in a study design called the case-cohort study, cases are compared with subjects chosen from all patients (i.e., from both cases and noncases); then, the *ad*/*bc* statistic equals the relative risk rather than the odds ratio; therefore, inadvertent inclusion of noncases in the control group when performing a case–control study may "bias" the odds ratio toward the relative risk and thus be advantageous.

Comparison of Cohort Versus Case–Control Studies

Cohort studies may be prospective or retrospective, but case–control studies are always retrospective. A major advantage of cohort studies is that we can calculate the percent ill and the relative risk. Cohort studies are less subject to bias than case–control studies. The potential disadvantages of cohort studies are that they are more time-consuming and expensive and may require study of a large group to collect information on a small number of cases.

Prospective cohort studies are the premier type of observational study. They provide the strongest evidence; are less subject to bias in collecting exposure data, since exposure is recorded before the subjects develop disease; and are flexible in that it is possible to study many exposures and diseases. The disadvantage is that it may be necessary to follow subjects over a long period of time to determine whether they develop disease.

The advantages of the case–control study are that we can determine risk factors while studying a relatively small group of patients; we can study as many risk factors as desired; and case–control studies are usually quicker, easier, and cheaper than cohort studies. The disadvantages are that the percent ill and relative risk are not determined; only one disease can be studied at a time; and the selection of controls can be subtle and introduces the chance of error. Deciding which is the most appropriate control group for a particular study is a matter of opinion about which even well-trained epidemiologists may disagree.

Cross-Sectional or Prevalence Study

A third type of study (besides cohort and case–control) includes only subjects who are present in a locality at one point in time. Exposure and disease are ascertained at the same time. Depending on the way the subjects were selected, a cross-sectional study may be analyzed as a cohort study or a case–control study.

A cross-sectional study is clearly not an incidence study, which would include as cases only those free of disease at the start of the study and who develop disease during the study period. However, if an entire group present at one point in time is studied, the results can be analyzed in a 2×2 table similar to that used for cohort studies. The formula used to calculate a relative risk in a cohort study would yield a prevalence ratio in a cross-sectional study. If the group present at one point in time is sampled as in a case–control study (i.e., the cases and a random selection of noncases are studied), then the odds ratio formula could be used to calculate a prevalence odds ratio.

Incidence Versus Prevalence

Incidence includes only new cases of disease with onset during a study period; the denominator is the number of subjects without disease at the beginning of the study period. Incidence measures the rate at which people without the disease develop the disease during a specified period of time; it is used to study disease etiology (risk).

Prevalence includes both new and old cases that are present at one time and place, measuring the proportion of people who are ill. The commonest measure of prevalence is point prevalence, which is the proportion of individuals who are ill at one point in time. Point prevalence is a unitless proportion. A different measure of prevalence, period prevalence, is the proportion of persons present during a time period with disease. Period prevalence has been criticized as an undefined mixture of both prevalent and incident cases without quantitative use, but is occasionally seen.

Prevalence studies are the ideal way to measure disease burden and plan for needed resources. For example, if we wanted to know how many isolation rooms would be needed for patients with resistant microorganisms, we would want to know average prevalence, that is, the total number of patients with recognized drug-resistant microorganisms of either new or old onset in the hospital at any given time.

Prevalence can also be used as a simple, quick, and dirty way to measure disease frequency and risk factors, but such estimates may be biased by length of stay. It is often said that prevalence equals incidence *times* duration. That is, prevalence is higher if either incidence is higher or if the duration of the illness is longer. In hospital studies, prevalence is greatly influenced by length of stay and mortality. For example, assuming that ascertainment of vancomycin-resistant enterococci is stable, the prevalence of vancomycin-resistant enterococci in a hospital may decrease because of an effective prevention program, or because patients with this microorganism are being discharged sooner or dying more commonly than had been the case previously.

Point prevalence and incidence density are mathematically linked; in a steady-state or dynamic population, one can be derived from the other. Prevalence can be derived from incidence density and distributions of durations of disease, and incidence density may be derived from prevalence and distributions of durations to date of disease *(8–11)*.

INTERPRETATION OF DATA, INCLUDING STATISTICAL SIGNIFICANCE AND CAUSAL INFERENCE

Measures of Size of Effect and their Interpretation

The relative risk and the odds ratio measure the size of effect, that is, the magnitude of the association between an exposure and a disease. A relative risk of 1.3 shows a modest association, whereas a value of 20 shows a large association. In general, odds ratios are interpreted in the same manner as relative risks.

Because the relative risk = percent ill exposed/percent ill nonexposed, the relative risk can fall into three categories. First, if the two percents are approximately equal, the relative risk is approximately 1.0; this is a null result showing no association between exposure and disease. Second, if the percent ill is higher in the exposed group, the relative risk is >1.0; exposure is apparently associated with disease, is a risk factor for disease, and may be a cause of disease. Third, if the percent ill is higher in those without exposure,

the relative risk is <1.0; exposure is again apparently associated with disease, but in this instance the exposure prevents disease. An example of a preventive exposure is vaccine use; persons who are "exposed" to the vaccine have a lower rate of disease than those not exposed, leading to a relative risk <1.0. Interpretation of odds ratios as equal to, greater than, or less than 1.0 is similar. To intelligently interpret relative risks and odds ratios, we must in addition understand statistical significance and the distinction between association and causation (presented below).

Relative risks can be interpreted as a percent increase or decrease. For example, a relative risk of 1.5 could be interpreted in two ways: disease is 1.5 times more likely in exposed than in nonexposed, or disease is 50% more likely in exposed than in nonexposed. Similarly, a protective relative risk of 0.6 could be interpreted in two ways: illness was 0.6 times as likely in exposed than in nonexposed, or illness was 40% less likely in the exposed group.

Statistical Significance and *p* Values

For a given group and time period, an association between exposure and disease might occur due to chance alone. For example, suppose that over many years the rate of SSI at hospital A is the same as that of other hospitals. However, during a given quarter, the rate at hospital A may be higher or lower than average by chance alone. To tell us the probability that the SSI rate at hospital A differed from the rate at other hospitals due to chance alone, we commonly use two measures of statistical significance, the *p* value and the confidence interval.

The *p* value measures the probability that a given result, or one more extreme, could have happened by chance alone if there was no association between exposure and diseases. Because computer packages calculate *p* values automatically, it is more important to know how to interpret than to calculate them. *P* values range from >0 to 1.0. By convention, a *p* value ≤.05 indicates statistical significance. This means that there is a ≤5% or ≤1/20 chance that the result we found (or one more extreme) could have occurred by chance alone; exposure is associated with disease. Another way of stating this is that we are 95% certain that this observed difference did not arise by chance alone. If the *p* value is >.05, the result is not considered statistically significant and could well have happened by chance alone; we do not have evidence that exposure is associated with disease.

The .05 cutoff was not chosen for any particular reason but now is very commonly used. There is not a meaningful difference between *p* values of .04 and .06; although the latter would not usually be considered statistically significant, in fact there is only a 6% chance that such a result could have occurred by chance alone. The adoption of the arbitrary .05 standard has its unfortunate aspects and is subject to interpretation after considering all of the sources of bias described below. Some published manuscripts describe interesting or important studies where the *p* value did not reach .05, thus allowing readers to make their own determinations of biologic importance.

Small epidemics, or epidemics that are stopped before there are sufficient cases to demonstrate statistical significance at the .05 level, may be biologically very important, so epidemiologists who work with observational data in hospitals should not consider statistical *p* values to be of primary interest. Biologic importance and size of effect are much more compelling than *p* values in the face of an ongoing problem in a hospital.

In biostatistical terms, significance testing can be viewed as follows. We assume the null hypothesis that there is no true difference in rate of illness between the exposed and nonexposed groups. We then compute the *p* value, that is, probability of the results (or results more extreme) under the null hypothesis. If the *p* value is low, then apparently the null hypothesis was wrong, and we reject the null hypothesis and embrace the alternative hypothesis, namely, that there is a true difference between exposed and nonexposed (see Chapter 3).

Type I Versus Type II Error The *p* value required for statistical significance is commonly called the chance of type I error. This means that if we conclude that hospital A has a high (or low) rate of illness based on a *p* value of .05, there is a 5% chance that we are drawing this conclusion in error. The type I error then indicates the chance of concluding that a difference in rates exists when in fact there is no true difference. Type II error measures the opposite problem—that there really is a difference between the two rates but we erroneously conclude that they are the same. The power of a study (discussed below) = 1—the probability of type II error.

Methods of Calculating p Values *P* values for 2×2 tables may be calculated by the chi-square or Fisher exact methods. The chi-square *p* value is valid when an expected value (Table 2-1) is not <5; if an expected value is <5, the Fisher exact results should be used. Computer packages commonly calculate expected values and print out a suggestion to use the Fisher exact *p* value if appropriate. In addition to a simple or uncorrected chi-square value, computer packages may compute a continuity corrected (or Yates corrected) value. The formula for continuity correction involves subtracting 0.5 from each cell in the 2×2 table. There are usually not great differences among these chi-square values, and many authorities suggest using the simple or uncorrected value.

The calculation of chi-square value does not differ depending on whether data are from a cohort, case–control, or cross-sectional study. However, the computation of chi-square value is different for incidence density data. Calculation of chi-square value is shown in Table 2-1 and Question 3 in Appendix 1 at the end of this chapter. Later in this chapter we suggest some shareware programs that perform these calculations. When one has the value for chi-square, one can determine the *p* value by looking it up in a table or by using a statistical program. In Excel, the CHIDIST function calculates the *p* value for a given chi-square value and number of degrees of freedom.

P values may be one-tailed or two-tailed. Two-tailed *p* values are usually twice as great as one-tailed values. A two-tailed *p* value assumes that the rate in the exposed group could have been either higher or lower than in the unexposed group due to chance alone. A one-tailed value recognizes only one of these two possibilities. For example, suppose that a study showed rates of illness significantly lower among those exposed to a putative toxin

than among those not exposed; if the intent had been to conclude that the "toxin" might actually be protective, we should use a two-tailed test; however, if the intent had been to consider such a finding to be spurious and probably due to chance alone and conclude that the toxin has no effect, then we should use a one-tailed test. Although there is no uniform agreement as to whether one- or two-tailed results should be used, the majority of authors use two-tailed *p* values. This suggests that, for uniformity and ease of comparison among studies, two-tailed *p* values should be the standard.

One-tailed tests are standard for noninferiority studies, which are becoming more common in the literature. An example is a trial of whether hepatitis A vaccine is inferior to the standard method, immune globulin, for postexposure prophylaxis *(12)*. Hepatitis rates were 4.4% among those vaccinated and 3.3% among those receiving immune globulin (relative risk = 1.35, two-tailed confidence interval = 0.7–2.67, one-tailed upper confidence limit = 2.40). Since the one-tailed upper confidence limit did not overlap a predetermined relative risk of 3.0, the authors concluded that the vaccine was noninferior. If the rate of hepatitis A had been lower among those receiving vaccine than immune globulin, the authors would have dismissed the finding and not concluded that the vaccine was better. Given this intent, a one-tailed test was appropriate for this study, as it is for other noninferiority trials.

Confidence Intervals

The second way to judge statistical significance is the confidence interval for a relative risk or odds ratio. The confidence interval combines the concepts of size of effect (relative risk) and strength of association (*p* value). A 95% confidence interval means that, roughly speaking, we are 95% sure that the true relative risk lies between the upper and lower confidence interval limits. For example, assume that a study showed a relative risk of 5.0 with a 95% confidence interval of 1.47 to 17.05. Our best guess is that the relative risk is 5.0, which seems quite high, but we are 95% sure that it lies between 1.47 and 17.05. This is much more informative than simply reporting the probability of our results under the null hypothesis (*p* value). An additional benefit of the confidence interval is humility; a wide interval points out the uncertainty in our results.

If a 95% confidence interval does not cross 1.0, the result is statistically significant at the .05 level. Remembering the formula for the relative risk, a relative risk >1.0 with a 95% confidence interval excluding 1.0 means that we are 95% sure that the rate of illness in the exposed group is greater than the rate of illness in the nonexposed group.

Causal Inference: Association Versus Causation

A statistical association between an exposure and a disease does not necessarily mean that the exposure caused the disease. Sir Bradford Hill first described a set of logical criteria by which associations could be judged for potential causality. Fulfillment of Hill's criteria does not guarantee that an association is causal, but failure to meet these criteria generally excludes the possibility of causality. These criteria have changed somewhat over time, but here is a version appropriate for healthcare epidemiology:

1. Size of effect can be estimated by the relative risk. Large effects are more likely to be causal than small effects. The magnitude of a credible relative risk must depend on the magnitude of the potential sources of bias. Generally, a relative risk >2.0 or <0.5 in a well-done study is difficult to ignore.
2. Strength of association can be measured by the *p* value. A relatively weak association can more easily be the result of random or systematic error. A *p* value near .05 would be considered a weak association. The same information is better presented by the statement that a relative risk 95% confidence bound near 1.0 would be evidence of a weak association.
3. Consistency: A particular effect should be reproducible in different populations and settings.
4. Temporality: The cause must precede the effect.
5. Biologic gradient: There should be a dose–response effect. More exposure should lead to more outcome.
6. Plausibility of the biologic model: There should be a reasonable biologic model to explain the apparent association. This includes Hill's criteria of coherence, experimental evidence, and analogy.

ERRORS IN EPIDEMIOLOGIC STUDIES

Epidemiologic studies, even observational studies, involve people and are usually expensive. Therefore, the practical goal is to design a study that requires the least resources yet will provide a good-enough answer to a question. Since the perfect epidemiologic study will never be done, every epidemiologist has to be an expert on sources of error in measurement. For every question or every study, one must review the potential sources of error, estimate their likely direction and magnitude, and then decide what overall effect these distortions might have on the result of the study.

It is worthwhile to distinguish random variation, random error, and systematic error. Random variation is the statistical phenomenon of variability due to chance alone, and is sometimes called background or noise. If we were measuring SSIs, the true underlying SSI rate would vary each month according to many factors, including the mix of surgeons and patients involved; assuming hypothetically that these factors could be held stable, the SSI rate would still vary each month because of chance alone (i.e., random variation). On the other hand, random and systematic *errors* are produced by inaccuracies in finding or recording data. Random error would occur if we incorrectly measure the SSI rate to be higher than it actually is during some months and lower than it actually is in other months; over many months, these random errors in measurement balance each other and the average value would be correct. Systematic error would occur if we consistently measured the SSI rate as higher or lower than the true rate, and an average over many months would be wrong; systematic error is also called *bias*. We define validity as getting the right answer, or alternately as a lack of bias.

A related concept is *precision,* which may be functionally defined as the width of the confidence interval. A narrow

confidence interval indicates high precision; that is, we are confident that the true value is within a narrow range. A confidence interval is narrower when both random variation and random error are low and vice versa. A larger sample size leads to a narrower confidence interval and greater precision. Precision may also be improved by modifying the study design to increase the statistical efficiency by which information is obtained from a given number of study subjects.

Selection Bias or Berkson's Bias

Selection bias occurs when inappropriate subjects are chosen for a study. An example is a study of mortality rates in patients with versus without bacteremia. The problem is that blood cultures are selectively obtained from patients who appear septic, and thus mildly ill patients who may have unrecognized bacteremia are not included as cases. Therefore, cases are not representative of all patients with bacteremia. Including only the sicker cases leads to an overestimate of the mortality associated with bacteremia. Other examples of selection bias are given in the section on selection of controls for case–control study. Selection bias cannot be corrected by data analysis techniques. In traditional surveillance, however, where no selection of subjects occurs, selection bias is not usually a problem.

Misclassification or Information Bias

After subjects are chosen, errors in classification of exposure or outcome are called *misclassification*. For example, suppose that one is comparing postsurgical infections between thoracic and general surgeons. In this hypothetical hospital, the thoracic surgeons do routine urine cultures for all patients with urinary catheters, sputum cultures for all intubated patients, and vascular catheter tip cultures when catheters are removed. However, the general surgeons obtain cultures only when they feel it is necessary. A comparison of infection rates shows higher infection rates for the thoracic surgeons when all that has really happened is that infection status has been misclassified.

Misclassification may be differential or nondifferential. Differential misclassification means that, in a case–control study, exposure is incorrectly determined to a differing extent among those with versus without disease or, in a cohort study, that disease is incorrectly determined to a differing extent among those with versus without exposure. Differential misclassification may bias the calculated relative risk away from the null value of 1.0, making the relative risk either falsely high (for risk factors with relative risk >1.0) or falsely low (for protective factors with relative risk <1.0). Conversely, nondifferential misclassification would mean that exposure was recorded incorrectly to a similar extent for those with and without disease, or disease was recorded incorrectly to a similar extent in those with and without exposure. This type of misclassification biases the relative risk toward the null value of 1.0.

Note that mere low sensitivity does not mean that data are not useful. The reliability of data primarily depends on how consistent the sensitivity remains in the data collection. National data on sexually transmitted diseases and food-borne illnesses such as salmonella gastroenteritis have a consistent sensitivity of around 0.01 or 1%, but these data remain useful because the sensitivity has been relatively constant at that level over time, so that secular increases or decreases are evident. Data with higher levels of sensitivity but greater variability are actually less reliable in making valid comparisons. Benchmarking comparisons among facilities should be attempted only when a practitioner has some measure of the comparative sensitivities of data from different populations.

A Broader View of Bias

Bias can be more generally defined as a systematic deviation from the truth: any trend in the collection, analysis, interpretation, publication, or review of data that can lead to conclusions that are systematically different from the truth *(13)*. In the analysis phase of a study, if one has a strong preconceived idea of what the answer should be, then a biased analysis and interpretation of the data may result. If one keeps analyzing and reanalyzing data with a view to finding something statistically significant to publish, eventually a satisfactory result will be found. This has been expressed as "If you torture data enough, it will confess to anything." Publication bias results when studies that show a statistically significant difference between study groups are published, whereas other studies of the same topic that did not show such a difference remain unpublished.

Inaccuracy of Hospital Surveillance

Errors in routine hospital surveillance for healthcare-associated infections could result in either reporting of spurious episodes of infection or lack of reporting of true infections. In practice, the latter problem is much more common. Patients with true healthcare-associated infections escape detection because (a) not all relevant data are present in the medical record or laboratory reports; (b) the data collector may overlook relevant data; and (c) the physician did not order appropriate tests to detect the infection. Estimates of the loss of sensitivity due to (a) and (b) above are shown in Table 2-2. In this table, all sensitivities are related to a composite standard, including data from multiple independent surveys of the medical record, bedside examination, and microbiology laboratory records.

The effect of point (c) above was measured in the Study of the Efficacy of Nosocomial Infection Control (SENIC) (14,*15*). The overall culturing rate, which was the proportion of patients with signs or symptoms of any infection that had at least one appropriate culture done, was 32% in 1970 and 40% in 1975 to 1976 (14). The proportion of febrile patients from whom at least one appropriate culture was obtained was 28% in 1970 and 45% in 1975 (14). These measures varied substantially from 5% to 95% by hospital type and region of the country. Patients in academic hospitals in the northeast United States had the highest likelihood of being appropriately cultured. It follows that patients in such hospitals were more likely to have a healthcare-associated infection documented. For urinary tract infections, pneumonias, and bacteremias, the lack of availability of objective data was a major determinant of observed rates of infection *(15)*.

The National Nosocomial Infections Surveillance (NNIS) system, now replaced by the National Healthcare Safety Network (NHSN), conducted a study of the accuracy of reporting healthcare-associated infection rates in intensive care unit patients (16). The sensitivity in this study was greatly improved over that found in the SENIC

TABLE 2-2

Sensitivities of Methods of Case-Finding for Healthcare-Associated Infections Quantifying Only Omissions from Limited Data Sources and Errors by Surveyors

Method	*Study (Reference)*	*Sensitivity*
Reference standard: Duplicate surveys + Record review + Bedside examination + Laboratory tests		
	UVA, BCH, CDC (23)[a]	1.00
Single survey: Record review + Bedside examination + Laboratory tests		
	BCH	0.98
Physician self-reports	CHIP (23)[a]	0.14–0.34
Micro laboratory reports	CHIP (23)[a]	0.33–0.65
Micro laboratory reports	UK *(82)*	0.71
Kardex clues (50% sample)	UVA (23)[a]	0.69–0.85
Record review (100% sample)	UVA (23)[a]	0.90
Kardex clues	UK *(82)*	0.49
Ward Ilaison	UK *(82)*	0.58
ICD-9 coded dx	BCH (22)	0.02–0.35
ICD-9 coded dx	Yale *(83)*	0.57
SENIC pilot record review	CDC *(84)*	0.66–0.80
SENIC project record review	CDC *(85)*	0.05–0.95
NNIS	CDC (16)	0.30–0.85

Note: The effects of failure of physicians to evaluate patients with suspicious clinical episodes were not included in these measures. These data do not include losses from unresolved clinical episodes.
[a]Some of these results have previously been summarized in Freeman and McGowan (23).
UVA, University of Virginia; BCH, Boston City Hospital; CDC, Centers for Disease Control and Prevention; CHIP, Community Hospital Infection Protocol; UK, United Kingdom; Yale, Yale University; NNIS, National Nosocomial Infections Surveillance; SENIC, Study of the Efficacy of Nosocomial Infection Control.
(Adapted from Freeman J, McGowan JE Jr. Methodologic issues in hospital epidemiology. I. Rates, case finding, and interpretation. *Rev Infect Dis* 1981;3:658–667.)

project, as the NNIS hospitals correctly reported the majority of infections that occurred. Still of concern, however, was the continuing wide range in the sensitivity that varied from 30% to 85%, depending on the site of infection. In this study, substantial numbers of healthcare-associated infections were missed by prospective monitoring and a different large group was missed by retrospective chart review.

The implications of these findings for benchmarking rates among hospitals are obvious. There is a disincentive for physicians and hospitals to self-report healthcare-associated infections, and this leads to the paradox that hospitals that do the worst job of collecting data and documenting infections report the lowest rates.

External Validity (Generalizability)

The sections above on bias and errors concern internal validity; that is, are we measuring correctly within the population we selected? External validity or generalizability asks the question, are our results applicable in other settings? Generalizability is always a matter of opinion. A lack of bias does not guarantee generalizability. A perfectly done epidemiologic study may or may not be generalizable to a larger population.

Epidemiologists frequently choose to study unrepresentative samples of subjects in order to answer a scientific question cleanly, cheaply, practically, or safely. Although not widely generalizable, a study result may be scientifically sound for the population on which the study was performed. In a randomized trial, for example, potential study subjects and their physicians must determine that it is safe for the study subjects to accept any of the study treatments before they can be randomized. Patients who have a contraindication to one of the treatments cannot be included in the study on the chance that they might be randomized to the contraindicated treatment. Thus, many treatable patients must ordinarily be excluded from randomized trials, rendering the sample of patients on whom the trial is actually performed highly unrepresentative of the population as a whole *(17)*. This lack of representativeness does not indicate that the study is epidemiologically biased, but it may limit the generalizability of the study result to a larger population.

The Collaborative Antibiotic Prophylaxis Efficacy Research Study (CAPERS) of antibiotic prophylaxis for clean (herniorrhaphy and breast) surgery used both experimental and observational components *(18,19)*. In the experimental component, 1,218 patients were randomized to receive or not receive prophylaxis; patients were not included in this study if they or their physicians did not provide consent. In the observational component, 3,202 other patients received prophylaxis at the discretion of their surgeons. Both components showed that about half of the SSIs were prevented by antibiotic prophylaxis. In this particular instance, the result of the randomized trial turned out to be generalizable to the larger group, but this need not have been so.

ACCOUNTING FOR TIME AT RISK

Because many healthcare-associated infections are related to time at risk, and because average lengths of hospital stay are decreasing, state-of-the-art studies must use methods that account for time at risk. Studies of mortality present a similar challenge: we all have one death per lifetime, and that is unavoidable, but it matters very much just when that death occurs. Methods used to account for time at risk include incidence density methods and survival analysis.

Incidence Density

Incidence density studies are a type of cohort study where the denominator is the total person-time at risk for all subjects, rather than the number of subjects. Commonly used denominators in healthcare-related incidence density studies are patient-days (vascular or urinary), catheter-days, and ventilator-days. Of the four most commonly studied healthcare-associated infections, three are device-related and are best studied using incidence density methods: catheter-associated bloodstream infections (BSIs), ventilator-associated pneumonias, and catheter-associated urinary tract infections (20).

Only one of the four (SSI) is best studied using cumulative incidence methods; that is, the denominator is the number of surgical procedures.

If the event being studied is an infection, then incidence density is the number of infections in a specified quantity of person-time in the population at risk. The population at risk is composed of all those who have not yet suffered an infection. After a patient acquires an infection, that patient would be withdrawn from the population at risk. All hospital days for each patient who never acquired an infection would be included in the pool of days at risk, but for a patient who became infected only those hospital-days before the onset of the infection would be included.

Incidence density is the instantaneous rate of change or what used to be called the force of morbidity. For convenience in healthcare epidemiology, healthcare-associated infection rates are usually expressed as the number of events in 1,000 hospital-days, because this usually produces a small single- or double-digit number, but we could have used seconds or years.

The basic value of this measure can be seen when comparing healthcare-associated infection rates in two groups with large differences in time at risk, for example, in short-stay patients versus long-stay patients, or infection rates with peripheral venous catheters versus implanted ports. By contrast, if one looks at events that come from a point source, such as eating vanilla ice cream at a church supper, or events that are not time related, like acquiring tuberculosis during bronchoscopy with a contaminated bronchoscope, the attack rate or cumulative incidence is an excellent measure of incidence. SSIs are usually thought of as having a point source—the operation; therefore, cumulative incidence methods are adequate for studies of SSI.

An incidence density rate = total events/total time at risk for an event. If we have an exposed and nonexposed group, then we define the rate ratio = rate ill in exposed/rate ill in nonexposed. The rate ratio is a measure of the size of effect analogous to the relative risk used in cumulative incidence studies. Rate ratios are sometimes called incidence density ratios, relative risks, or risk ratios. Rate ratios are interpreted in a similar manner to relative risks; a rate ratio of 2 means that disease incidence was twice as great in the exposed group than in the nonexposed group. Note that the units for the denominators of incidence density divide out, so that you will find the same incidence density ratio no matter whether you use time units of seconds or millennia. *P* values for the rate ratio may be calculated by a chi-square or binomial exact method.

Multiple Events in a Single Patient

Standard statistical tests assume that each observation in a data set is independent, having no linkage with other observations. A corollary is that each subject in a study should contribute at most one event to a data set; that is, we should study only first events in an individual. If this rule is not followed, the calculated confidence intervals and *p* values may not be valid. However, it is well-known that a subset of patients will have multiple episodes of infection and other adverse outcomes. Also, patients with a first event are more likely to suffer a second (*21*,*22*,23,24,*25*). For quantitative analyses, these nonindependent events cannot simply be summed. The biologic and statistical import of 5 infections per 100 discharges would be entirely different depending on whether it represented five sequential infections in a single patient or five first infections in 5 different patients.

Furthermore, a first healthcare-associated infection becomes a risk factor for a second, and risk factors for multiple infections are different from the risk factors for a first infection. The simplest way to cope with multiple incident events in the same individual is to restrict quantitative analyses to first events. A second method is to stratify by number of previous infections, for example, study the effect of exposures on risk of first infection, then on risk of second infection, and so on. These individual strata would then be combined into a summary relative risk. However, this method also violates the independence rule for conventional data analyses. A third alternative is to use statistical methods designed for longitudinal or correlated data. This type of analysis is technically complex (see Longitudinal Analysis and Repeated Measures, below).

Survival Analysis

Survival analysis is a second method for accounting for time at risk (3). Survival analysis usually consists of the familiar Kaplan–Meier plot, where at time zero survival begins at 1.0 or 100% and gradually falls off as subjects are followed forward in time. Survival can literally mean not dying, or it can mean remaining free of infection or whatever outcome variable is being studied. The opposite of survival is termed "failure," which again may either mean death or onset of another adverse event. An extremely useful feature of survival analysis is that it can make use of subjects who are lost to follow-up or die of a disease other than that of interest; these subjects are called "censored" since we don't know if they would have failed if we had been able to follow them for a longer period of time.

Statistical packages automatically plot survival curves for two or more groups and calculate a *p* value for the difference between the two groups. Median survival (the follow-up time when the probability of survival is 0.5 or 50%) is often reported. The Kaplan–Meier plot represents a univariable analysis. Multivariable survival analysis is accomplished via regression models, the most common of which is the Cox model (discussed below).

CONFOUNDING AND EFFECT MODIFICATION

Confounding

Confounding can be defined as "a situation in which a measure of the effect of an exposure on risk is distorted because of the association of the exposure with other factor(s) that influence the outcome under study" *(1)*. An intuitive example given in the chapter introduction was "our infection rate is higher than theirs because our patients are sicker than theirs." We can set up an experimental study to measure the effect of only one exposure at a time, but in observational studies where several exposures may act jointly to produce disease, we often need to use statistical techniques to tease out the independent effect of any one exposure.

TABLE 2-3

Sample Data: Simple and Stratified Analyses

a. Numbers of Patients Total and Infected, Hospitals A vs. B

	High-Risk Patients		*Low-Risk Patients*		
Hospital	*Total*	*Number Infected*	*Total*	*Number Infected*	*Overall Infection Rate*
A	900	90	100	1	91/1,000 = 9.1%
B	100	10	900	9	19/1,000 = 1.9%

b. Simple (Crude) Analysis: Effect of Hospital

Hospital (Exposure$_1$)	*Total Patients*	*No. (%) Infections*	*Relative Risk*
A	1,000	91 (9.1)	4.8
B	1,000	19 (1.9)	—

c. Stratified Analysis: Effect of Hospital Stratified by Patient Risk

Patient Risk (Exposure$_2$)	*Hospital (Exposure$_1$)*	*Total Patients*	*No. (%) Infections*	*Relative Risk*
High	A	900	90 (10)	$RR_1 = 1.0$
High	B	100	10 (10)	—
Low	A	100	1 (1)	$RR_2 = 1.0$
Low	B	900	9 (1)	—

Note: Mantel–Haenszel summary relative risk (RR_{MH}) = 1.0.

Example of Confounding by Severity of Illness Let's hypothetically assume that we were studying healthcare-associated infections at two hospitals, A and B. In our simplified example, there are two types of patients: high-risk patients who have a 10% risk of disease per hospitalization and low-risk patients who have a 1% risk. During a time period, hospitals A and B both admit 1,000 patients, but hospital A admits 900 high-risk and 100 low-risk patients, whereas hospital B admits 100 high-risk and 900 low-risk patients. Using hospital A as the exposed group, the relative risk is 9.1/1.9 = 4.8; that is, the risk of infection after admission to hospital A was 4.8 times higher than after admission to hospital B (Table 2-3).

This is an example of confounding. We are primarily interested in the relationship between one exposure (hospital A, which we shall denote as exposure$_1$) and disease. However, the effect of a second exposure (high- vs. low-risk patient, denoted by exposure$_2$) confuses or confounds our ability to measure the effect of exposure$_1$. This occurs because of an unequal mix of exposure$_2$ among the exposure$_1$ groups (high-risk patients comprise 90% of hospital A admissions but only 10% of hospital B admissions).

Stratified Analysis Stratification is an important method to detect and control for confounding. First, we compute a simple or crude relative risk by our usual 2 × 2 table methods (Table 2-3b). Second, we perform a stratified analysis: we calculate two relative risks (RRs), designated RR_1 and RR_2. In the above example of hospitals A and B, RR_1 measures the effect of hospital A among high-risk patients and RR_2 the effect of hospital A among low-risk patients (Table 2-3c). In this example, both RR_1 and RR_2 are equal to 1.0. Third, with the help of a statistical program, we compute a Mantel–Haenszel summary relative risk (RR_{MH}), which is a weighted average of RR_1 and RR_2. In this example, the RR_{MH} was also 1.0 (i.e., null result), indicating that there was no association between hospital and infection after adjusting for patient risk.

There was an obvious case-mix difference between hospitals A and B. The RR_{MH} is our prediction of what the crude relative risk would have been if there had not been a case-mix difference between the hospitals. Calculating an RR_{MH} is a way of adjusting for a potential confounding exposure, and thus the RR_{MH} is a type of adjusted relative risk. Other methods of calculating an adjusted relative risk include indirect standardization and regression modeling (these methods are presented later in this chapter).

Calculation of Mantel–Haenszel Relative Risk and Odds Ratio If there are i strata, the four cells of the 2 × 2 table are designated a_i, b_i, c_i, and d_i; the total number of subjects in each stratum is $n_i = a_i + b_i + c_i + d_i$; and $\sum$ indicates the sum over all i strata:

$$\text{Mantel–Haenszel summary relative risk} = \frac{\sum a_i(c_i + d_i)/n_i}{\sum c_i(a_i + b_i)/n_i}$$

$$\text{Mantel–Haenszel summary odds ratio} = \frac{\sum (a_i d_i)/n_i}{\sum (b_i c_i)/n_i}$$

Recognizing Confounding The following is a simple functional definition of confounding: if the adjusted relative risk differs to a meaningful extent from the crude relative risk, then confounding is present. There is no statistical test or firm guide for how great the difference must be.