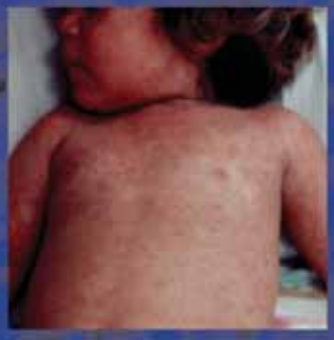
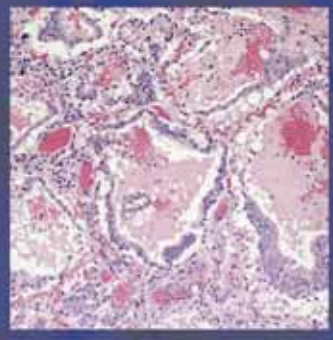
CLINICAL VIROLOGY

FOURTH EDITION



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DEDICATION

To our families—Eva, Sara, Matthew and Isabella; Kevin, Sarah, Christopher, Jennifer, and Katherine; Melissa, Dan, Gabi, Gretta, Grant, Geoff, Mary, Cotes, and Anderson—and to our many colleagues and friends, who have inspired and supported us throughout the years.

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Conflicts of Interest

Robert Atmar (chapter 49) has received research grant funding from and is a consultant to Takeda Vaccines, Inc.

Yuan Chang (chapter 26) holds patents that are assigned to his university on KSHV-related inventions.

Harry R. Dalton (chapter 50) has received travel and accommodation costs and consultancy fees from GlaxoSmithKline, Wantai, and Roche; travel, accommodation, and lecture fees from Merck, Gilead, and GFE Blut GmbH; and travel and accommodation fees from the Gates Foundation.

Mary K. Estes (chapter 49) is named as an inventor on patents related to cloning of the Norwalk virus genome and has served as a consultant to Takeda Vaccines, Inc.

Gao Shou-Jiang (chapter 26) holds patents that are assigned to his university on KSHV-related inventions.

Anne Gershon (chapter 22) has received service contracts (molecular VZV diagnosis for vaccine safety) and is a Merck ad hoc consultant and chair of the Data and Safety Monitoring Board (DSMB): GSK (on VZV) AAG

John Greenlee (chapter 28) receives honoraria as author and associate editor for Medlink and as chapter author for the Merck Manual. Dr. Greenlee's research is supported by the United States Department of Veterans Affairs.

Frederick G. Hayden (chapter 43) is a nonpaid consultant to multiple companies engaged in developing and/or marketing influenza antivirals and therapeutics. He receives personal compensation for service as SAB member on the University of Alabama NIAIAD-sponsored Antiviral Drug Discovery and Development Consortium, which is looking for novel influenza inhibitors. The University of Virginia has received honoraria payments since 2013 for Dr. Hayden's activities from Hologic (consulting), Singapore Institute of Infectious Diseases and Epidemiology (consulting), Gilead Sciences (DSMB), Sanofi-Pasteur (DSMB), and GSK (consulting).

Hans H. Hirsch (chapter 28) receives honoraria for scientific advisory boards from Chimerix Inc., Merck, and Oxford Immunotec; his research has been supported by unrestricted appointment grants of the University of Basel and by grants research from Chimerix Inc. and Novartis.

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Steven A. Locarinini (chapter 32) receives consulting fees (eg: advisory boards)—Gilead Sciences Inc. and Arrowhead Research Corp. and fees for non-CME services received directly from a commercial interest or their agent from Arrowhead Research Corp.

Patrick Moore (chapter 26) holds patents that are assigned to his university on KSHV-related inventions.

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Preface

Virology is currently one of the most dynamic areas of clinical medicine. Challenges related to novel viruses, changing epidemiologic patterns, new syndromes, unmet vaccine needs, antiviral drug resistance, and threats of bioterrorism are balanced against improved insights into viral pathogenesis, better diagnostic tools, novel immunization strategies, and an expanding array of antiviral agents. The demands on clinicians, public health workers, and laboratorians will continue to increase as will the opportunities for effective intervention. This text, now in its fourth edition, is designed to inform scientists and health care professionals about the medically relevant aspects of this rapidly evolving field.

Clinical Virology has two major sections. The first addresses infections and syndromes related to particular organ systems, as well as the fundamentals of modern medical virology, including immune responses and vaccinology, diagnostics, and antivirals. The second provides agent-specific chapters that detail the virology, epidemiology, pathogenesis, clinical manifestations, laboratory diagnosis, and prevention and treatment of important viral pathogens. In a multiauthored text like *Clinical Virology,* the selection of authors is key. The senior authors for individual chapters were chosen because of their internationally recognized expertise and active involvement in their respective fields. In addition, common templates for the syndrome-specific and separately for the agent-specific chapters allow the reader to readily access material. Since publication of the third edition in 2009, all of the chapters have been extensively revised to incorporate new information and relevant citations. The timeliness and presentation of the fourth edition have been enhanced by publication of chapters online as they have become available and by the increased numbers and incorporation of color figures into the text. New chapters on Bornaviruses and Anelloviruses have been added, and the rapidly expanding field of antiviral drugs demanded dividing the subject into four chapters.

We have been particularly fortunate in receiving invaluable help from our administrative assistants, Mayra Rodriguez, Dunia Ritchey, and Lisa Cook. In addition, we express our appreciation for the enthusiastic professional support provided by Christine Charlip, Lauren Luethy, and Larry Klein of ASM Press.

DOUGLAS D. RICHMAN
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Important Notice (Please Read)

This book is intended for qualified medical professionals who are aware that medical knowledge is constantly changing. As new information becomes available, changes in treatment, diagnostic procedures, equipment, and the use of drugs and biologicals become necessary. The editors, authors, and publisher have, as far as it possible, taken care to ensure that the information is up-to-date but cannot guarantee that it is.

Consequently, readers are strongly advised to confirm that the information, especially with regard to drug usage, complies with the latest legislation and standards of practice. The authors, editors, and publisher make no warranty, expressed or implied, that the information in this book is accurate or appropriate or represents the standard of care for any particular facility or environment or any individual's personal situation.

Introduction

DOUGLAS D. RICHMAN, RICHARD J. WHITLEY, AND FREDERICK G. HAYDEN

1

Clinical virology incorporates a spectrum of disciplines and information ranging from the x-ray crystallographic structure of viral proteins to the global socioeconomic impact of disease. Clinical virology is the domain of molecular biologists, geneticists, pharmacologists, microbiologists, vaccinologists, immunologists, practitioners of public health, epidemiologists, and clinicians, including both pediatric and adult health care providers. It encompasses events impacting history that range from pandemics and Jennerian vaccination to the identification of new pathogens, mechanisms of disease, and modern countermeasures like antiretrovirals. For example, since the previous edition of this text, sequencing techniques from human specimens have led to the identification of numerous new members of several virus families, including polyomaviruses, orthomyxoviruses, and bunyaviruses (1–3). New viral pathogens have emerged or been recognized, including a camel-associated coronavirus causing the SARS-like Middle East respiratory syndrome, the tick-borne zoonotic orthomyxovirus (Bourbon virus) (2), the bunyaviruses (severe fever with thrombocytopenia virus) (3) and Heartland virus (4, 5), and newly emerged avian and swine influenza viruses causing zoonotic infections (H7N9, H5N6, H6N1, H10N8, H3N2v) (6–10). A bornavirus, belonging to a virus family known to cause disease in animals but with an unproven role in human disease, has been isolated in a cluster of encephalitis cases (11). Well-recognized pathogens like Chikungunya and Zika viruses have spread geographically to cause major outbreaks in the Western Hemisphere (12, 13). The political and social consequences of vaccine denialism have delayed the eradication of polio and measles globally and resulted in re-emerging outbreaks of measles in Europe and North America. Most dramatically, the pattern of relatively limited, albeit lethal, outbreaks of Ebola virus in central Africa over the past 40 years changed in 2014 with the West African outbreak that caused over 28,000 infections leading to over 11,000 fatalities, including more than 500 health care workers, before coming under apparent control in 2016 (http://www.who.int/csr/disease/ebola/en/).

On the positive side, the development of new diagnostic technologies has provided dramatic advances for the detection of new pathogens and the diagnosis and management of virus infections in the clinic. Human "virome" projects based on high-throughput serologic screening, sequencing, and other technologies have documented the frequent but individually unique patterns of infection that we have with these microbes (14–16). Since the previous edition we have seen the revolutionary impact of combination antiviral therapy for HIV, with approximately 15 million people under treatment globally in 2015, followed by the development of 8- to 12-week interferon-free regimens for hepatitis C, with cure rates of over 95%. Modified viruses have become therapeutic tools in treating some forms of malignancy (e.g., herpes simplex virus for glioblastoma) (17, 18). In addition, promising new antiviral drugs and vaccines are in development for many other virus infections. The editors hope that the fascinating breadth and importance of the subject of clinical virology will be conveyed by this text. In this fourth edition, the editors have attempted to update and expand upon the information in the previous edition, while making the content more accessible with Internet-based technology.

A few words about nomenclature are necessary. Students (among others) are plagued by virus classification. Historically, classification reflected the information available from general descriptive biology. Viruses were thus classified by host (e.g., plant, insect, murine, avian), by disease or target organ (e.g., respiratory, hepatitis, enteric), or by vector (e.g., arboviruses). These classifications were often overlapping and inconsistent. Molecular biology now permits us to classify viruses by genetic sequence and biophysical structure, which can be quantitative and evolutionarily meaningful. Table 1, which shows the taxonomy of human viruses, is derived from the comprehensive Ninth Report of the International Committee on Taxonomy of Viruses (19).

The list in Table 1 represents viruses known to infect humans. Many of the agents are primarily animal viruses that accidentally infect humans: herpesvirus B, rabies, the Arenoviridae, the Filoviridae, the Bunyaviridae, and many arthropod-borne viruses. The role of intraspecies transmission of viruses is becoming increasingly appreciated. Although its contribution to zoonotic infections like H5N1 and antigenic shift of influenza A virus is well documented, the role of intraspecies transmission is a major consideration in the "emerging" diseases caused by Sin Nombre virus and related hantaviruses, Nipah virus, Ebola virus, arenavirus, hemorrhagic fevers, variant bovine spongiform encephalopathy, and most importantly, the human immunodeficiency viruses.

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TABLE 1 Taxonomy of human viruses

Family	Subfamily	Type species or example	Morphology	Envelope	Chapter
	Genus				
DNA viruses					
dsDNA viruses					
Poxviridae			Pleomorphic	+	19
	Chordopoxvirinae				
	Orthopoxvirus	Vaccinia virus, variola			
	Parapoxvirus	Orf virus			
	Molluscipoxvirus	Molluscum contagiosum virus			
	Yatapoxvirus	Yaba monkey tumor virus			
Herpesviridae			Icosahedral	+	
	Alphaherpesvirinae				
	Simplexvirus	Human herpesvirus 1 and 2			20
		Cercopithecine herpesvirus 1 (herpesvirus B)			21
	Varicellovirus	Human herpesvirus 3			22
	Betaherpesvirinae				
	Cytomegalovirus	Human herpesvirus 5			23
	Roseolovirus	Human herpesvirus 6 and 7			24
	Gammaherpesvirinae				
	Lymphocryptovirus	Human herpesvirus 4			25
	Rhadinovirus	Human herpesvirus 8			26
Adenoviridae	*Mastadenovirus*	Human adenoviruses	Icosahedral	–	27
Polyomaviridae	*Polyomavirus*	JC virus	Icosahedral	–	28
Papillomaviridae	*Papillomavirus*	Human papillomaviruses	Icosahedral	–	29
ssDNA viruses					
Parvoviridae			Icosahedral	–	
	Parvovirinae				30
	Erythrovirus	B19 virus			
	Dependovirus	Adeno-associated virus 2[a]			
	Bocavirus	Human bocavirus			
Anelloviridae	*Alphatorquevirus*	Torque teno virus[a]	Icosahedral	–	31
DNA and RNA reverse transcribing viruses					
Hepadnaviridae	*Orthohepadnavirus*	Hepatitis B virus	Icosahedral with envelope	+	32
Retroviridae			Spherical	+	

	Deltaretrovirus	HTLV 1 and 2			33
	Lentivirus	Human immunodeficiency viruses 1 and 2			34
	Spumavirus	Spumavirus (foamy virus)[a]			
RNA viruses					
dsRNA viruses					
Reoviridae			Icosahedral	–	
	Orthoreovirus	Reovirus 3[a]			
	Orbivirus	Kemerovo viruses			35
	Coltivirus	Colorado tick fever virus			35
	Seadornavirus	Banna virus			35
	Rotavirus	Human rotavirus			36
Negative-stranded ssRNA viruses					
Paramyxoviridae			Spherical	+	
	Paramyxovirinae				
	Respirovirus	Human parainfluenza viruses			37
	Morbillivirus	Measles virus			38
	Rubulavirus	Mumps virus			39
	Henipavirus	Nipah virus			40
	Pneumoniavirinae				
	Pneumovirus	Human respiratory syncytial virus			37
	Metapneumovirus	Human metapneumovirus			37
Rhabdoviridae			Bacilliform	+	41
	Vesiculovirus	Vesicular stomatitis virus			
	Lyssavirus	Rabies virus			
Filoviridae	*Filovirus*	Ebola virus	Bacilliform	+	42
Orthomyxoviridae			Spherical	+	43
	Influenzavirus A	Influenza A virus			
	Influenzavirus B	Influenza B virus			
	Influenzavirus C	Influenza C virus			
Bornaviridae	*Bornavirus*	Borna disease virus	Spherical	+	57
Bunyaviridae			Amorphic	+	44
	Orthobunyavirus	Bunyamwera virus, LaCrosse virus			
	Hantavirus	Hantaan virus, Sin Nombre virus			
	Nairovirus	Congo-Crimean hemorrhagic fever virus			
	Phlebovirus	Rift Valley fever virus			
Arenaviridae	*Arenavirus*	Lymphocytic choriomeningitis virus	Spherical	+	45

(*Continued on next page*)

TABLE 1 Taxonomy of human viruses (*Continued*)

Family	Subfamily	Type species or example	Morphology	Envelope	Chapter
Positive-stranded ssRNA viruses					
Picornaviridae			Icosahedral	–	
	Enterovirus	Polioviruses			46
	Rhinovirus	Human rhinoviruses			47
	Hepatovirus	Hepatitis A virus			48
Caliciviridae	*Calicivirus*	Norwalk virus	Icosahedral	–	49
Hepeviridae	*Hepevirus*	Hepatitis E virus	Icosahedral	-	50
Astroviridae	*Mamastrovirus*	Human astrovirus 1	Icosahedral	–	51
Coronaviridae	*Coronavirus*	Human coronavirus	Pleomorphic	+	52
Flaviviridae			Spherical	+	
	Flavivirus	Yellow fever virus			53
	Hepacivirus	Hepatitis C virus			54
Togaviridae			Spherical	+	
	Alphavirus	Western equine encephalitis virus			55
	Rubivirus	Rubella virus			56
Subviral agents: satellites, viroids, and agents of spongiform encephalopathies					
Subviral agents					
Satellites (single-stranded RNA)	*Deltavirus*	Hepatitis delta (D) virus	Spherical	+	58
Prion protein agents		Creutzfeld-Jakob agent	?	–	59

[a]Human virus with no recognized human disease.

Although not a documented risk, the theoretical threats of organ transplants from primates and pigs prompted a section on xenotransplantation in the chapter on transplantation. In addition, a number of human viruses have not been recognized to cause human disease, including spumaretroviruses, reoviruses, anelloviruses, and the adeno-associated parvoviruses. The text does not elaborate on these viruses in detail, but the editors did elect to include a chapter on Torque teno virus and related anelloviruses, despite any proven disease association, because of their remarkably high prevalence in human populations globally and the remarkably high titers achieved in blood. We have also added a new chapter on bornaviruses, which may represent either a newly recognized zoonosis or an emerging infection.

In order to provide a comprehensive yet concise treatment of the diverse agents and diseases associated with human viral infections, the editors have chosen to organize the textbook into two major sections. The first provides information regarding broad topics in virology, including immune responses, vaccinology, laboratory diagnosis, and principles of antiviral therapy, and detailed considerations of important organ system manifestations and syndromes caused by viral infections. The second section provides overviews of specific etiologic agents and discusses their biology, epidemiology, pathogenesis of disease causation, clinical manifestations, laboratory diagnosis, and management. We have attempted to ensure that the basic elements are covered for each of the viruses of interest, but it is the authors of each of these chapters that have done the real work and to whom we owe our gratitude and thanks.

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Section I

Viral Syndromes and General Principles

Respiratory Infections

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2

Respiratory viral infections have a major impact on health. Acute respiratory illnesses, largely caused by viruses, are the most common illness experienced by otherwise healthy adults and children. Data from the United States, collected in the 1992 National Health Interview Survey, suggest that such illnesses are experienced at a rate of 85.6 illnesses per 100 persons per year and account for 54% of all acute conditions exclusive of injuries (1). A total of 44% of these illnesses require medical attention and result in 287 days of restricted activity, 94.4 days lost from work, and 182 days lost from school per 100 persons per year. The morbidity of acute respiratory disease in the family setting is significant. The Tecumseh study, a family-based surveillance study of respiratory illness, estimated that approximately one-quarter of respiratory illnesses result in consultation with a physician (2). Illness rates for all acute respiratory conditions are highest in young children, and children below the age of 9 have been estimated to experience between five and nine respiratory illnesses per year (3).

Mortality due to acute viral respiratory infection in otherwise healthy individuals in economically developed countries is rare, with the exception of epidemic influenza and possibly respiratory syncytial virus. However, acute respiratory infection is a major cause of childhood mortality in low- and middle-income countries (4), and it is estimated that 4.5 million children under 5 years of age die annually from acute respiratory infection. Viruses are estimated to play a contributing role in approximately 20% to 30% of these deaths (4). In response, the World Health Organization has undertaken a major new initiative, the Battle against Respiratory Viruses (or BRaVe) to foster research on these pathogens (5).

Both RNA and DNA viruses are responsible for these infections, producing clinical syndromes ranging in severity from merely uncomfortable to life threatening. Each of these viruses may be responsible for different clinical syndromes depending on the age and immune status of the host. Furthermore, each of the respiratory syndromes associated with viral infection may be caused by a variety of specific viral pathogens (Table 1; also see Table 1 in Chapter 52). This chapter describes the clinical syndromes of respiratory virus infection, the spectrum of viruses associated with these syndromes, and the pathophysiology of these illnesses. Specific features of the virology and pathophysiology of disease induced by individual viral agents are described in greater detail in each of the virus-specific chapters.

SEASONAL PATTERNS OF RESPIRATORY VIRUS INFECTION

Many of the viruses associated with acute respiratory disease display significant seasonal variation in incidence (Fig. 1). Although the exact seasonal arrival of each virus in the community cannot be predicted with precision, certain generalizations are useful diagnostically and in planning control strategies. For example, both influenza and respiratory syncytial virus epidemics occur predominantly in the winter months, with a peak prevalence in January to March in the northern hemisphere. Although the periods of peak incidence for these two viruses usually do not coincide, there is often overlap between the two seasons. Parainfluenza virus type 3 (PIV-3) infections show a predominance in the spring, while types 1 and 2 (PIV-1 and PIV-2) cause outbreaks in the fall to early winter. Rhinoviruses may be isolated throughout the year, with increases in frequency in the spring and fall. The peak prevalence of enteroviral isolations is in late summer and early fall, while adenoviruses are isolated at roughly equal rates throughout the year. The herpesviruses do not show significant seasonal variation in incidence, except for varicella, which occurs throughout the year, but more commonly in late winter and early spring.

COMMON COLDS

Clinical Features and Syndrome Definition

Common colds are familiar to most adults and are usually self-diagnosed. Most observers consider colds to include symptoms of rhinitis with variable degrees of pharyngitis; the predominant associated symptoms include nasal stuffiness, sneezing, runny nose, and sore throat. Patients often report chills, but significant fever is unusual. Cough and hoarseness are variably present and may be more frequent in the elderly (6). Headache and mild malaise may occur. Although a multitude of viruses may be associated with this syndrome, the pattern of symptoms associated with colds does not appear to vary significantly among agents. Physical findings are nonspecific and most commonly include nasal discharge and

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