

SECTION B: Viruses

201 Classification of Human Viruses

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The virus family concept is fundamentally important in understanding the biologic classification of viruses.¹ By specifying the family to which a virus belongs, much can be inferred about its physical, chemical, and biologic properties and its evolutionary relationships and modes of gene expression.² Virus families are designated with the suffix *-viridae*.³ Families are distinguished largely on the basis of physiochemical properties, genome structure, size, morphology, and molecular processes.⁴ Table 201.1 lists some criteria that are used to differentiate human virus families.

The 26 virus families implicated in human disease⁵ are listed in Table 201.2. In some cases, humans serve as a reservoir for the viruses and the link to human disease is clear. In other cases, humans may be incidental hosts or the link to disease may be more tenuous.

Table 201.3 lists specific viruses within each family that are linked to human disease.

Facilitated by advances in molecular methods, the discovery of new viruses and more careful characterization of known viruses^{6,7} have resulted in frequent changes in family taxonomy. Examples of such changes include de novo creation of a virus family (e.g., Anelloviridae),⁸ splitting a new family off of an existing one (e.g., Hepeviridae from Caliciviridae),⁹ dividing a family into two new families (e.g., Papovaviridae into Papillomaviridae and Polyomaviridae),¹⁰ and uniting formerly separate families (e.g., incorporation of Toroviridae into Coronaviridae).^{11,12} Working groups¹³ within the International Committee on Taxonomy of Viruses (ICTV)¹⁴ have the responsibility of approving new names and making changes in classification. Figs. 201.1, 201.2, and 201.3

TABLE 201.1 Major Criteria for Classifying Human Virus Families

| Criterion | Basis of Classification |
|--|---|
| Type of genomic nucleic acid | DNA or RNA |
| Nucleic acid strandedness | ds, ss, partially ds |
| Sense of ss nucleic acid | +, -, – with ambisense |
| Capsid morphology | Icosahedral, helical, or complex |
| Envelope | Present or absent |
| Genome segmentation | Number of segments |
| Genomic structure | For example, type of RNA cap, location of structural genes or repeat sequences |
| Electron micrographic (EM) appearance | For example, bullet-shaped rhabdoviruses or star-shaped astroviruses |
| Size of virion and/or genome | For example, large-genome DNA viruses (e.g., poxviruses, herpesviruses) versus small-genome viruses (e.g., picornaviruses, parvoviruses, hepadnaviruses) |
| Nature of gene expression, including nature and number of mRNA transcripts | For example, use of genomic polyproteins (e.g., picornaviruses, flaviviruses); use of reverse transcriptase (e.g., retroviruses, hepadnaviruses); use of multiple 3' nested genes (e.g., coronaviruses); use of RNA ambisense coding (e.g., arenaviruses, bunyaviruses) |

ds, double stranded; ss, single stranded.

illustrate the relationships among human virus families in terms of key biologic criteria listed in Table 201.1.

Next-generation nucleic acid sequencing has facilitated rapid and massive screening of samples obtained from healthy individuals, patients, nonhuman organisms, and environmental sources, resulting in the ongoing discovery of numerous viruses.^{15,16} The clinical significance of most of these viruses has yet to be established. Advances in understanding the human microbiome are providing insights into the impact of microbial viruses in causing or modulating human disease. A well-characterized example is the role of *Vibrio cholerae* phage CTX ψ in producing the clinical symptoms of cholera.¹⁷

Families hierarchically are subdivided in a variety of ways, including into subfamilies (suffix *-virinae*), genera (suffix *-virus*), and species (suffix *-virus*).¹⁸ In the past, the conventions for naming species were somewhat arbitrary and varied from family to family. The ICTV has instituted a more uniform system. A virus species, as defined by van Regenmortel, is “a polythetic class of viruses that constitutes a replicating lineage and occupies a particular ecologic niche.”¹⁹ *Polythetic*

refers to the fact that viruses grouped within a species share many properties. Species criteria may include genetic structure, sequence homology, host range, tissue tropism, biologic reservoir, route of transmission, immunologic cross-reactivity, epidemiology, and pathogenicity.²⁰ With the advent of rapid nucleic acid sequencing, sequence homology has taken precedence over other species classification criteria.²¹

The current system of species classification does not always correspond to common usage or historical concepts of species. For example, the three immunologically distinct viruses targeted by the trivalent poliovirus vaccine are considered to be the same species: human enterovirus C.^{22,23} This species includes at least 23 additional serotypes with diverse clinical presentations, as well as circulating recombinant forms.²⁴ The practicality of distinguishing serotypes is emphasized by the eradication of wild poliovirus type 2 in 2000²⁵ and wild poliovirus type 3 in 2012.²⁶ Species can be subdivided further into groups, clades, types, subtypes, serotypes, variants, and isolates, depending on the family involved and the degree of similarity. Selected representatives

TABLE 201.2 Families of Viruses That Infect Humans

| Family Name | Derivation of Family Name | Genome | Segmentation | Capsid Morphology | Envelope |
|------------------------------------|------------------------------|-------------------------|---------------|-------------------|-----------|
| Adenoviridae | Gland | dsDNA | 1 | Icosahedral | Naked |
| Anelloviridae | Ring-shaped | ssDNA(-) ^f | 1 | Icosahedral | Naked |
| Arenaviridae | Sand | ssRNA(-) ^{g,h} | 2 | Helical | Enveloped |
| Astroviridae | Star | ssRNA(+) ⁱ | 1 | Icosahedral | Naked |
| Bornaviridae^a | Location in Germany | ssRNA(-) ^g | 1 | Helical | Enveloped |
| Bunyaviridae | Location in Uganda | ssRNA(-) ^{g,h} | 3 | Helical | Enveloped |
| Caliciviridae | Cup or chalice | ssRNA(+) ⁱ | 1 | Icosahedral | Naked |
| Coronaviridae^b | Crown | ssRNA(+) ⁱ | 1 | Helical | Enveloped |
| Filoviridae^a | Thread | ssRNA(-) ^g | 1 | Helical | Enveloped |
| Flaviviridae | Yellow | ssRNA(+) ⁱ | 1 | Icosahedral | Enveloped |
| Hepadnaviridae | Liver, DNA | Partially ssDNA | 1 | Icosahedral | Enveloped |
| Hepeviridae | Hepatitis E | ssRNA(+) ⁱ | 1 | Icosahedral | Naked |
| Herpesviridae^c | Creeping | dsDNA | 1 | Icosahedral | Enveloped |
| Orthomyxoviridae | True, slime or mucus | ssRNA(-) ^g | 6–8 | Helical | Enveloped |
| Papillomaviridae | Bumpy, tumor | dsDNA | 1 | Icosahedral | Naked |
| Paramyxoviridae^a | Alongside, slime or mucus | ssRNA(-) ^g | 1 | Helical | Enveloped |
| Parvoviridae | Little | ssDNA | 1 | Icosahedral | Naked |
| Picobirnaviridae | “Little”; “two”, RNA | dsRNA | 2 | Icosahedral | Naked |
| Picobirna | Little, two, RNA | dsRNA | 2 | Icosahedral | Naked |
| Picornaviridae^d | Little, RNA | ssRNA(+) ⁱ | 1 | Icosahedral | Naked |
| Pneumoviridae | “Lung” | ssRNA(-) ^g | 1 | Helical | Enveloped |
| Polyomaviridae | Many, tumor | dsDNA | 1 | Icosahedral | Naked |
| Poxviridae | Pustule | dsDNA | 1 | Complex | Varies |
| Reoviridae | Respiratory, enteric, orphan | dsRNA | 10–12 | Icosahedral | Naked |
| Retroviridae | Backward | ssRNA(+) ⁱ | 1 but diploid | Complex | Enveloped |
| Rhabdoviridae^a | Rod | ssRNA(-) ^g | 1 | Helical | Enveloped |
| Togaviridae | Cloak | ssRNA(+) ⁱ | 1 | Icosahedral | Enveloped |
| Delta^a | Fourth hepatitis group | ssRNA(-) ^g | 1 | Icosahedral | Enveloped |

^aMononegavirales.

^bNidovirales.

^cHerpesvirales.

^dPicornavirales.

^eFloating genus, which is not currently assigned to a viral family. It bears some similarities to viroid pathogens of plants.

^fssDNA(+) indicates the mRNA-coding strand.

^gssRNA(-) indicates the complement of the message-sense strand.

^hSome segments are ambisense.

ⁱssRNA(+) indicates a message-sense strand.

ds, double stranded; ss, single stranded.

TABLE 201.3 Human Viral Infections Listed by Family^a

| Family Name | Representative Viruses ^b |
|------------------------------|--|
| Adenoviridae | Human adenovirus types 1 to 57 in seven species (human adenovirus species A to G) ^{28,29} |
| Anelloviridae ⁸ | Torque teno virus 1 (TTV1), ^c Torque teno mini virus 1, Torque teno midi virus 1 ²⁹ (type species for numerous viruses in 3 genera) |
| Arenaviridae | Lassa virus, lymphocytic choriomeningitis virus, Junin virus, Machupo virus, Guanarito virus, Sabiá virus, Whitewater Arroyo virus, ³⁰ Chapare virus, ³¹ Lujo virus |
| Astroviridae | Human astroviruses (eight serotypes) |
| Bornaviridae | Mammalian 1 bornavirus (formerly Borna disease virus [BDV]) ²⁹ |
| Bunyaviridae | California encephalitis virus, Sin Nombre virus, La Crosse virus, Hantaan virus, Muerto Canyon virus, Crimean-Congo hemorrhagic fever virus, Sandfly fever viruses, Rift Valley fever virus, Heartland virus, and many others |
| Caliciviridae | Noroviruses, sapoviruses |
| Coronaviridae | SARS coronavirus; MERS coronavirus ²⁹ ; human coronaviruses OC43, ³² 229E, NL63, ³³ and HKU1 ³⁴ ; human torovirus and other human enteric coronaviruses |
| Filoviridae | Ebola viruses (e.g., Zaire ebolavirus, Bundibugyo ebolavirus, Reston ebolavirus, Sudan ebolavirus, Tai Forest ebolavirus), ²⁹ Marburg virus |
| Flaviviridae | Genus <i>Alphavirus</i> : dengue virus, yellow fever virus, Japanese encephalitis virus, West Nile virus, Murray Valley encephalitis virus, Kyasanur encephalitis virus, tick-borne encephalitis virus, Zika virus, and others Genus <i>Hepacivirus</i> : hepatitis C virus (HCV) Genus <i>Pegivirus</i> ^d : GB virus-C ^e (GBV-C) (formerly hepatitis G virus [HGV]) ³⁵ |
| Hepadnaviridae | Hepatitis B virus (HBV) |
| Hepeviridae ⁹ | Hepatitis E virus (HEV) |
| Herpesviridae | Herpes simplex virus type 1, herpes simplex virus type 2, varicella-zoster virus, cytomegalovirus, Epstein-Barr virus, human herpesvirus 6, human herpesvirus 7, human herpesvirus 8 (i.e., Kaposi sarcoma-associated herpesvirus), herpes simian B virus |
| Orthomyxoviridae | Influenza A virus (e.g. subtype H1N1), influenza B virus, influenza C virus, Thogoto virus, Dhori virus, ³⁶ Bourbon virus |
| Papillomaviridae | Human papilloma virus (>150 types with various degrees of oncogenicity) ³⁷ |
| Paramyxoviridae | Measles (rubeola) virus, mumps virus, parainfluenza viruses, Hendra virus, Nipah virus, Menangle virus ³⁸ |
| Parvoviridae | Human parvovirus B19, human bocavirus, ³⁹ adeno-associated viruses ^{5,6} |
| Picobirnaviridae | Human picobirnavirus |
| Picornaviridae ⁴⁰ | Genus <i>Enterovirus</i> : human rhinoviruses (>100 serotypes), enteroviruses (>100 serotypes, including poliovirus 1–3, coxsackievirus A and B, echoviruses, and other human enteroviruses) Genus <i>Hepatovirus</i> : hepatitis A virus (HAV) Genus <i>Parechovirus</i> : human parechoviruses Genus <i>Kobuvirus</i> : Aichi virus Genus <i>Cosavirus</i> : human cosaviruses ⁴¹ Genus <i>Cardiovirus</i> : Vilyuisk human encephalomyelitis virus, Saffold viruses ⁴² Genus <i>Salivirus</i> : human klassevirus, ⁴³ salivirus A Genus <i>Senecavirus</i> : Seneca Valley virus ^d Unassigned: Syr-Darya Valley fever virus |
| Pneumoviridae | Respiratory syncytial virus, human metapneumoviruses |
| Polyomaviridae | JC virus, BK virus, KI virus, WU virus, Merkel cell polyomavirus, lymphotropic polyomavirus, human polyomavirus 6, human polyomavirus 7, trichodysplasia spinulosa-associated polyomavirus, human polyomavirus 9 ^{44,45} |
| Poxviridae | Molluscum contagiosum virus, variola (smallpox) virus, monkeypox virus, vaccinia virus, orf virus, pseudocowpox virus, Tanapox virus, Yaba monkey tumor virus ⁴⁶ |
| Reoviridae | Human rotavirus, Colorado tick fever virus, human reovirus, ^c Kemerovo virus |
| Retroviridae | Human immunodeficiency viruses types 1 and 2, human T-lymphocyte lymphotropic viruses, ⁴⁷ xenotropic murine leukemia virus-related virus, ⁹ human endogenous retroviruses (HERVs), simian foamy virus |
| Rhabdoviridae | Rabies virus, vesicular stomatitis virus, Australian bat lyssavirus, Duvenhage virus, Mokola virus |
| Togaviridae | Rubella virus; Chikungunya virus; eastern equine, western equine, and Venezuelan equine encephalitis viruses; Ross River, Sindbis, and Semliki Forest viruses |
| Delta ^h | Hepatitis delta virus ⁹ (HDV) |

^aExamples listed correspond to common usage and do not necessarily comply with the official International Committee on Taxonomy of Viruses (ICTV) designations of virus species.

^bSome zoonoses are included.

^cOrphan virus for which a link to human disease has not been determined.

^dProposed genus name.

^eSatellite virus requiring coinfection with heterologous virus for replication.

^fPorcine virus being used clinically in humans as an oncolytic agent.⁴⁸

^gPossible laboratory contaminant.

^hFloating genus, which is not currently assigned to a viral family. It bears some similarities to viroid pathogens of plants.

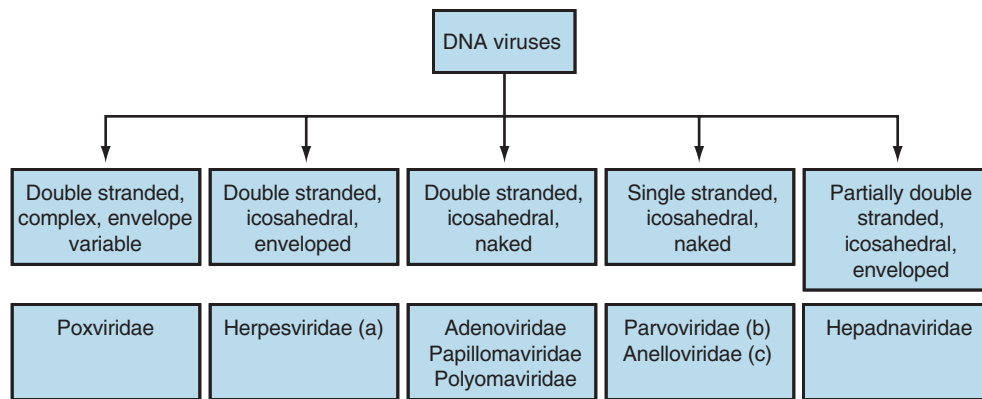


FIGURE 201.1 Organizational chart of the eight human virus families with DNA genomes. The chart groups virus families using the strandedness of the viral genome, the structure of the capsid, and the presence or absence of an envelope. All of these viruses are nonsegmented. Like retroviruses, hepadnaviruses contain reverse transcriptase. One family of viruses has been assigned to the Herpesvirales (a) order of viruses. Parvoviruses (b) vary in the percentage of positive- and negative-sense single-stranded DNA (ssDNA) genomes that are packaged, depending on the genus. Anelloviruses (c) package negative-sense ssDNA genomes; this strand is transcribed into mRNA.

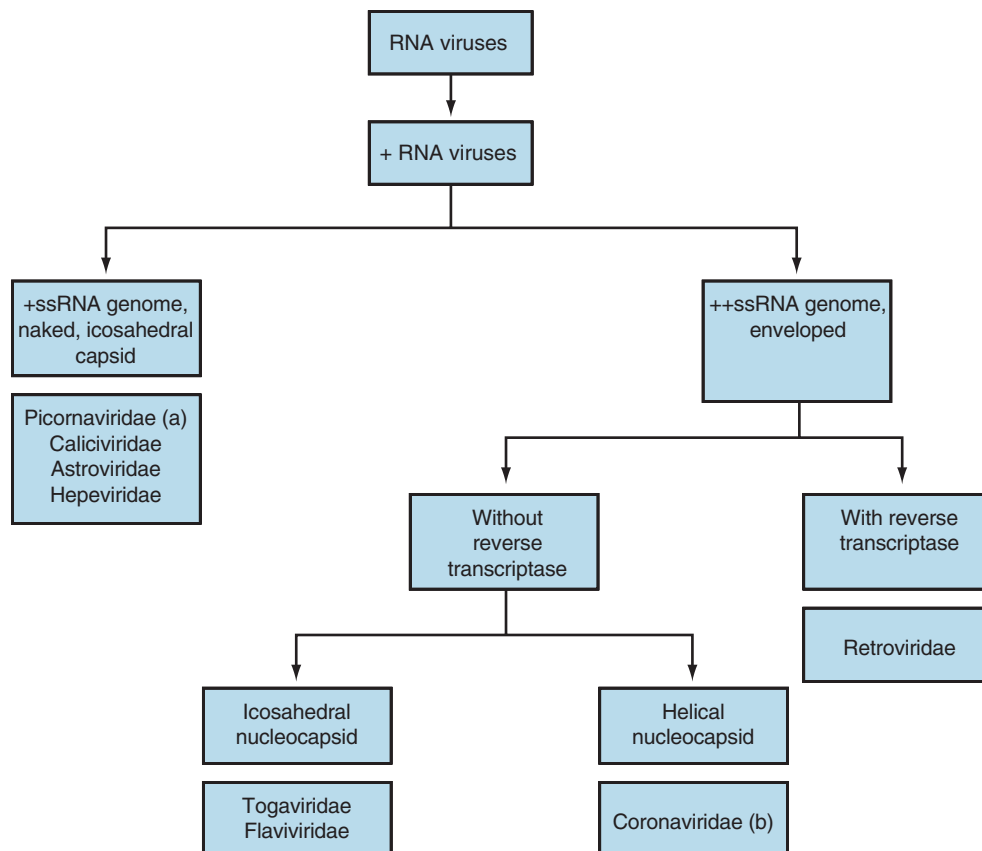
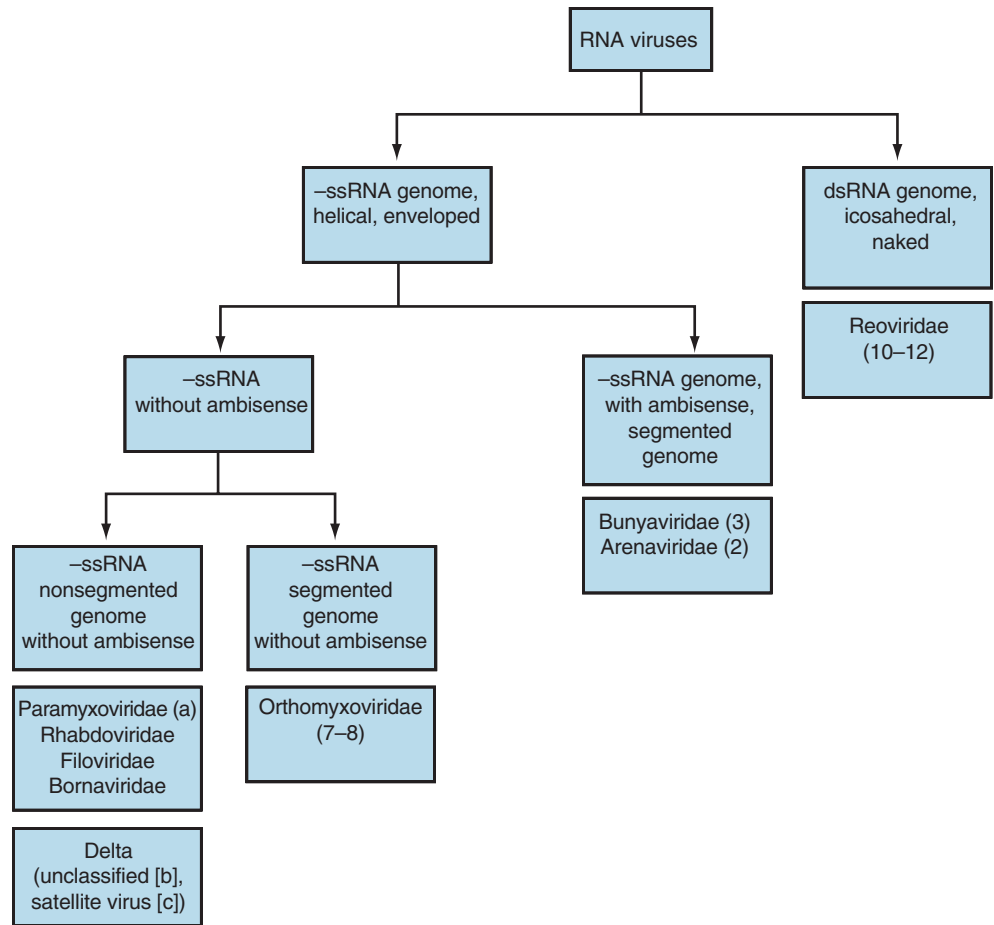


FIGURE 201.2 Organizational chart of the eight human virus families with positive-sense (+) RNA (i.e., mRNA-like) genomes. The chart groups virus families using the presence or absence of an envelope, the presence of reverse transcriptase, and the structure of the capsid. All of these viruses have a single-stranded (ss), nonsegmented viral genome. One family of viruses (a) has been assigned to the Picornavirales order of viruses. Another family of viruses (b) has been assigned to the Nidovirales order of viruses.

FIGURE 201.3 Organizational chart of the remaining eight human RNA virus families, including the negative (–) single-stranded (ss) (i.e., complementary to message sense) and double-stranded (ds) RNA viruses. The chart groups the families using the structure of the genome, presence or absence of an envelope, and the presence or absence of ambisense gene expression. For segmented viruses, the number of genome segments is listed in parentheses. One group of virus families (a) is assigned to the Mononegavirales (i.e., monosegmented and negative-stranded) order of viruses. The unclassified or floating genus (b) is not currently assigned to a viral family. It bears some similarities to viroid pathogens of plants. Satellite virus (c) refers to the fact that hepatitis D virus (HDV) depends on HBV, a genomically unrelated virus, for its successful replication.



BOX 201.1 Common Routes of Virus Transmission to Humans

Respiratory route (i.e., droplet, aerosol, and respiratory secretions on the hands and elsewhere; oral exchange): influenza virus, varicella-zoster virus, human rhinovirus, human adenovirus, respiratory syncytial virus, parainfluenza virus, metapneumovirus
 Fecal-oral route: polioviruses, coxsackieviruses, hepatitis A virus, rotavirus, astrovirus, norovirus
 Direct contact: human papillomavirus (HPV), molluscum contagiosum, herpes simplex virus type 1 (HSV-1)
 Sexual: human immunodeficiency virus type 1 (HIV-1), human T-lymphotropic virus type 1 (HTLV-1), hepatitis B virus (HBV), human papillomavirus types 16 and 18 (HPV-16, HPV18), HSV-2
 Urine-associated: cytomegalovirus (CMV)
 Parenteral route (i.e., blood and blood products, transplantation, tattooing, and scarification): HIV-1, HBV, hepatitis C virus (HCV)
 Animal bite: rabies virus, Duvenhage virus

Vertical route (e.g., germline, intrauterine, perinatal, human milk): HIV-1, HTLV-1, germline transmission of endogenous retroviruses
 Arthropod-borne route (e.g., mosquitos, ticks, sandflies): Japanese encephalitis virus, West Nile virus, dengue virus, yellow fever virus, Zika virus, chikungunya virus, and many others
 Rodent-associated transmission: Lassa fever virus, sin nombre, and other hanta viruses (e.g., Hantaan virus, Seoul virus, and Puumala virus)
 Bat-associated transmission: rabies virus, Nipah virus, Ebola virus, severe acute respiratory syndrome coronavirus (SARS CoV)
 Monkey-associated transmission: herpes B virus, monkeypox virus, orf virus
 Other zoonotic associations (e.g., cows, sheep): orf virus, cowpox virus

called *type viruses* may be used to illustrate the properties of a particular taxon.

A number of virus families are assigned to higher-level orders, which are designated with the suffix *-virales*. Examples are Herpesvirales, Mononegavirales, Picornavirales, and Nidovirales.²⁷ They are indicated by footnotes in Table 201.2. Most families are unassigned to orders.

In addition to biologic classification, viruses often are categorized according to their clinical presentation (i.e., syndromic classification), epidemiology, or mode of transmission. Box 201.1 lists the major routes of transmission for human diseases, with representative examples of viruses transmitted by each route.

Understanding virus classification can lead to important generalizations regarding the prevention and treatment of viral infection and insights into the distribution and evolution of viruses. In addition,

insights from viral taxonomy play key roles in preventing and staunching the spread of viral disease at the population level.

All references are available online at www.expertconsult.com.

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