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Classification of Medically Important Viruses II: RNA Viruses

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The last issue of this newsletter (1) covered classification of DNA-containing animal viruses. Part II of this two-part article briefly discusses the classification of RNA-containing animal viruses. The chemical and morphologic properties of RNA-containing animal virus families are shown in Table 1.

Picornaviridae
The name picorna is an acronym derived from fast letters of poliovims, insensitivity to ether, coxsackievirus, orphan virus, rhinovirus, ribo-, nucleic, and acid; the double rr is contracted. Picornaviruses are small (20 to 30 nm), ether-resistant viruses containing ss-RNA. The RNA genome is positive-sense. It can serve as its own mRNA for protein translation and is infectious. The group of rhinoviruses and enteroviruses infect humans. Rhinoviruses are acid-labile whereas enteroviruses are acid-stable. With the use of highly specific typing sera, poliovims isolates can now be identified by type, county (or city), strain number, and year of isolation. For example, Pl/England/119/65 denotes a poliovims type 1, number 119, isolated in England in 1965. A new genus Heparnavirus, including hepatitis A (infectious hepatitis, jaundice) virus, has been added to the family Picornaviridae. Five genera have been described so far.

(i) Enterovirus—There are more than 72 members of the enterovirus genus that infect humans. The important ones are poliovims (types 1, 2, and 3), coxsackieviruses A (1 to 22, 24) and B (1 to 6), ECHO viruses (32 serotypes), new enteroviruses 68 to enterovirus 71, simian enteroviruses, and simian (18 serotypes), bovine (7 serotypes), and porcine (8 serotypes) enteroviruses.

(ii) Rhinovirus—human rhinoviruses (113 serotypes causing common colds), equine, and bovine rhinoviruses.

(iii) Cardiovirus—encephalomyocarditis virus of mice (EMC), mengovirus of mouse, and ME virus of mouse.

(iv) Aphthovirus—Foot and mouth disease (FMD) virus types O and A (now termed as aphthovirus O and A) was the first enterovirus isolated.

(v) Heparnavirus—hepatitis A virus (human enterovirus 72).

Caliciviridae
The family Caliciviridae is a newly described class of viruses that has been clearly separated from the Picornaviridae. The genus Calicivirus (from the Latin "calici," meaning cup-like) includes at least five distinct types that are found in the gastrointestinal tract of humans. The virion is similar to picornaviruses but slightly larger (37 nm). The genome is a single molecule of infectious, ss-RNA, positive-sense RNA with no lipid and no envelope. The Norwalk virus, a cause of acute gastroenteritis, has shown several similarities to calicivirus. Therefore, this agent has been classified as a probable calicivirus. There are a number of serotypes belonging to the single genus of family Caliciviridae:

Calcivirus—vesicular exanthema of swine virus (VESV), feline calicivirus (FCV) (formerly feline picornavirus), San Miguel sea lion virus (SMSV), and Norwalk virus.

Reoviridae
The members of the family reoviridae (Sigla: respiratory enteric orphan) are medium-sized (60 to 80 nm), nonenveloped, ether-resistant viruses containing segmented ds-RNA. Reoviruses of humans include rotaviruses, which are

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Have you ever tried to do antimicrobial susceptibility testing on an organism isolated from a cat, dog, or a rabbit? What method did you use and how did you interpret the results? The NCCLS has organized a new subcommittee to address the need for standardization of susceptibility testing of animal pathogens.

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an important cause of nonbacterial, acute, infantile gastroenteritis and have a distinctive wheel-shaped appearance. antigenically similar reoviruses infect many animals. Orbiviruses multiply both in arthropods and vertebrates and some have been considered as arboviruses. Reoviruses are not known to cause disease in humans although they have been found in the gastrointestinal tract of humans. Four genera have been described:

(i) Rotavirus—The genome has 11 segments. It includes human rotavirus, Nebraska calf diarrhea virus (NCDV), epizootic diarrhea of infant mice (EDIM), simian rotavirus (SA11), and bovine or ovine rotavirus (“O” agents).

(ii) Orbivirus—The genome has 10 segments. It includes bluetongue virus, Eugenangee virus, KemeroVo, African horse sickness virus, Colorado tick fever virus, and epizootic hemorrhagic disease virus of dear.

(iii) Reovirus—The genome has 10 segments. It includes mammalian reoviruses (three serotypes), and avian reoviruses (five serotypes).

(iv) Cypovirus—Cytoplasmic polyhedrosis group of insect viruses.

Birnaviridae

The members of this newly described family are nonenveloped medium-sized (60 nm) virions with bisegmented ds-RNA. There are no known human pathogens belonging to this family of viruses. There is only one genus:

Birnavirus—Infectious pancreatic necrosis virus of fish, infectious bursal disease virus of chickens.

Togaviridae

The name of this virus family is derived from Latin word “toga,” meaning gown (loose garment/envelope). Togaviruses include many of the viruses previously known as arboviruses (arthropod-borne) that are major human pathogens, as well as rubella virus. The virion are medium-sized (60 to 70 nm), enveloped, ether-sensitive with ss-RNA, positive-sense RNA. The virus particles mature by budding from the host cell plasma membrane. Five genera have been described:

(i) Alphavirus—formerly arbovirus group A, it includes about 20 mosquito-borne viruses, all serologically related. The genus also includes Chikungunya, Sindbis, Semliki Forest virus, western equine encephalitis (WEE), eastern equine encephalitis (EEE), Venezuelan equine encephalitis (VEE), Ross river virus, and O’Nyong-Nyong.

(ii) Rubivirus—rubella virus (German measles).

(iii) Pestivirus—bovine virus diarrhea (mucosal disease complex), hog cholera virus (murine swine fever), and Border disease virus.

(iv) Arterivirus—equine arteritis virus, simian hemorrhagic fever virus, Lelystad virus (porcine reproductive and respiratory syndrome virus), and VR2332.

(v) Unclassified—Riley’s lactate dehydrogenase-elevating virus (LDHV) of mice.

Flaviviridae

The members of this newly established family flaviviridae (from the Latin “flavus,” meaning yellow) include the viruses of the former genus Flavivirus of the Togaviridae family. The members of the family are enveloped viruses, slightly smaller than the Togaviruses (45 to 50 nm), containing ss, positive-sense RNA. The virion matures within cisternae of the endoplasmic reticulum in contrast to the alphaviruses that mature at the plasma membrane. This group of arboviruses includes yellow fever virus. Most members are transmitted by blood-sucking arthropods. Two genera, flavivirus and hepatitis C virus (HCV), have been described:

(i) Flavivirus—former arbovirus group B, about 50 viruses, all serologically related. It includes mosquito-borne viruses of yellow fever, West Nile fever, Japanese encephalitis, dengue (four serotypes), Murray valley encephalitis, Kunjin, St. Louis encephalitis, tick-borne viruses of Omsk hemorrhagic fever, and Russian spring-summer encephalitis.

(ii) Hepatitis C virus (HCV)—Recently described non-A, non-B hepatitis virus (NANBH) that is transmitted by blood transfusions or sexual contact is now called hepatitis C virus (HCV). This virus has properties similar to those of flavivirus.

Arenaviridae

The members of the family Arenaviridae (from the Latin “arenosus,” meaning sandy; appearance of the virus particle by electron microscopy) are enveloped spherical or pleomorphic viruses ranging in size from 50 to 300 nm. The genome is ss-RNA that is negative-sense; i.e., complementary to mRNA. The virions incorporate host cell ribosomes during maturation, which gives the particles a “sandy” appearance. Most members of this family are unique to tropical America (i.e., the Tacaribe complex). All arenaviruses pathogenic for humans cause chronic infections in rodents. Lassa fever virus of Africa is one example. Only one genus has been described:

Arenavirus—The type species is lymphocytic choriomeningitis viruses (LCM). This virus can establish persistent infections in mice and occasionally can cause aseptic meningitis in humans. Other members of the genus are the Lassa fever virus and members of the Tacaribe virus complex, including Junin virus (Argentine hemorrhagic fever), Machupo virus (Bolivian hemorrhagic fever), and Pichinde virus (nonpathogenic in humans). These viruses are highly contagious and fatal and are designated as “Biosafety level 4” pathogens.

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| Virus family   | Capsid symmetry | Virion: | Ether sensitivity | Site of capsid assembly | Site of nucleocapsid envelopment | No. of capsomeres | Mol. wt. of nucleic acid in virion (x 10) | Physical type of nucleic acid | No. of genes (approx.) | Ribonucleoprotein helix diameter (nm) | Virion diameter (nm) |
|---------------|----------------|---------|-------------------|-------------------------|----------------------------------|-------------------|----------------------------------------|-------------------------------|-------------------------------|-------------------------------|----------------------|
| Picomaviridae | Icosahedral    | Naked   | Resistant         | Cytoplasm               |                                  | 32                | 2.3–2.8 ss                             | 4–6                           |                               | 20–30                         | 20–30     |
| Caliciviridae | Icosahedral    | Naked   | Resistant         | Cytoplasm               |                                  | 32                | 2.6 ss                                 | 4–6                           |                               | 35–39                         | 35–39     |
| Reoviridae    | Icosahedral    | Naked   | Resistant         | Cytoplasm               |                                  | 32                | 12–15 ds segmented                     | 10–12                         |                               | 60–80                         | 60–80     |
| Togaviridae   | Icosahedral    | Enveloped| Sensitive         | Cytoplasm               | Surface membrane                  | 32?               | 4 ss                                    | 10                            |                               | 50–70                         | 50–70     |
| Flaviviridae  | Unknown or complex | Enveloped | Sensitive     | Cytoplasm               | Intracytoplasmic membrane        | 4                 | ss                                      | 10                            |                               | 45–50                         | 45–50     |
| Arenaviridae  | Unknown or complex | Enveloped | Sensitive     | Cytoplasm               | Surface membrane                  | 3–5               | ss segmented                           | 10                            |                               | 50–300                        | 50–300    |
| Coronaviridae | Unknown or complex | Enveloped | Sensitive     | Cytoplasm               | Intracytoplasmic membrane        | 7                 | ss                                      | 30                            | 11–13                         | 80–160                        | 80–160    |
| Retroviridae  | Unknown or complex | Enveloped | Sensitive     | Cytoplasm               | Surface membrane                  | 7–10              | ss diploid                             | 4                             |                               | –100                          | –100      |
| Bunyaviridae  | Helical        | Enveloped| Sensitive     | Cytoplasm               | Intracytoplasmic membrane        | 6–15              | ss segmented                           | >3                            | 10–12                         | 90–100                        | 90–100    |
| Orthomyxoviri-| Helical        | Enveloped| Sensitive     | Cytoplasm               | Surface membrane                  | 5                 | ss segmented                           | 10                            | 9–15                          | 80–120                        | 80–120    |
| dae            |               |         |                  |                         |                                  |                   |                                        |                               |                               |                               |          |
| Paramyxoviri-| Helical        | Enveloped| Sensitive     | Cytoplasm               | Surface membrane                  | 5–7               | ss                                      | >10                           | 18                            | 150–300                       | 150–300   |
| dae            |               |         |                  |                         |                                  |                   |                                        |                               |                               |                               |          |
| Rhabdoviridae | Helical        | Enveloped| Sensitive     | Cytoplasm               | Surface membrane                  | 4                 | ss                                      | 5                             | 18                            | 75 x 180                       | 75 x 180  |

* ss = single-stranded; ds = double-stranded.
Retroviridae

The retroviruses (from the Latin "retro," meaning backwards; reverse transcribes RNA to DNA) are enveloped viruses (90 to 120 nm) whose genome contains duplicate copies of high molecular weight, ss-RNA of the same polarity as viral mRNA. The virion contains a reverse transcriptase (RNA-DNA). The virus is replicated from an integrated "provirus" DNA copy in infected cells. The association of acquired immunodeficiency syndrome (AIDS) with retroviruses has been well recognized. Three subfamilies of Retroviridae have been described.

(i) Oncovirinae (from the Greek "oncos," meaning tumor)—a large group, including members causing leukemias or sarcomas of animals and humans, some transduce cellular oncogenes. Mouse mammary tumor virus, human T-lymphotropic virus (HTLV-1, HTLV-2, HTLV-5), and Rous sarcoma virus (chickens).

(ii) Lentivirinae (from the Latin "lentus," meaning slow)—slow disease onset, cytolytic, nononcogenic, cause neurological disorders. Human immunodeficiency virus (HIV-1, HIV-2), visna/maedi virus group (sheep), and caprine arthritis/encephalitis virus (goats).

(iii) Spumavirinae (from the Latin "spuma," meaning foam)—foamy viruses of humans, not oncogenic, cause no clinical disease but characteristic vacuolated "foamy" cytopathology.

Orthomyxoviridae

The members of the orthomyxoviridae (from the Greek "orthos," meaning straight, true; and Greek "myxa," meaning mucus; affinity for mucins, glycoprotein cell surfaces) family are medium-sized, 80 to 120 nm enveloped viruses containing a segmented ss-RNA, negative-sense RNA genome. Particles are either round or filamentous. As part of their surface, orthomyxoviruses have projections that contain hemagglutinin or neuraminidase activities. The internal nucleoprotein helix measures 9 to 15 nm, and the RNA is made up of eight segments. During replication, the nucleocapsid is assembled in the nucleus, whereas the hemagglutinin and neuraminidase accumulate in the cytoplasm. The virus matures by budding at the cell membrane. All orthomyxoviruses are influenza viruses that infect humans or animals. The segmented nature of the viral genome permits ready genetic reassortment when two influenza viruses infect the same cell; this explains the high rate of natural variation among influenza viruses. The influenza A virus has two specific surface antigens; hemagglutinin (H) and neuraminidase (N). There are 12 subtypes of H (H1 to H12) and nine subtypes of N (N1 to N9). There are two genera of orthomyxoviruses: (i) Influenzavirus—type A (human, equine, and swine), type B, and swine plague; (ii) Influenzavirus C (only one strain) causes mild respiratory disease (7).

Paramyxoviridae

The members of the family Paramyxoviridae (from the Greek "para," by side of; hemagglutinin and neuraminidase activities on the same polypeptide spike on the envelope) are similar to but larger (150 to 300 nm) than orthomyxoviruses. Both the nucleocapsid and the hemagglutinin are formed in the cytoplasm. Those infecting humans include mumps, measles, parainfluenza virus, and respiratory syncytial virus. In contrast to influenza viruses, paramyxoviruses are genetically stable. Three genera of paramyxoviruses have been described:

(i) Paramyxovirus—parainfluenza type 1, 2, and 3 viruses of humans, parainfluenza virus of several animal species, mumps virus, Newcastle disease virus, Yucaipa, and other avian parainfluenza viruses.

(ii) Morbillivirus—measles, canine distemper, and rinderpest.

(iii) Pneumovirus—respiratory syncytial virus (RSV) of humans and cattle, and pneumonia virus of mice.

Rhabdoviridae

The members of family Rhabdoviridae (from the Greek "rhabdos," meaning rod) are enveloped virion resembling a bullet, flat at one end and round at the other, measuring about 75 x 180 nm. The envelope has 10 nm spikes. The genome is ss, nonsegmented, negative-sense RNA. Particles are formed by budding from the cell membrane. The most lethal rabies virus belongs to this group. Two genera are described:

(i) Vesiculovirus (from the Latin "vesicula," meaning blister)—Vesicular stomatitis virus (VSV) with a wide host range and Chandipura virus.

(ii) Lyssavirus (from the Greek "lyssa," meaning rage; rabies)—rabies.

Filoviridae

The members of the family Filoviridae (from the Latin "filum," meaning thread) are highly infectious, enveloped, pleomorphic virions. The diameter of the virion is 80 nm in diameter and has varying lengths ranging from 130 nm to 14,000 nm. The genome is negative-sense, ss-RNA. These viruses resemble rhabdoviruses in some aspects but have been grouped as a separate family on the basis of properties significantly different from those of established families. Replication occurs in the cytoplasm; assembly occurs by budding from the cell membrane. Only one genus has been established: Filovirus—including Marburg virus, a simian virus that is highly pathogenic for humans, and Ebola virus. Both these viruses cause hemorrhagic fever and are highly infectious.

Coronaviridae

The members of the family Coronaviridae (from the Latin "corona," meaning crown; petal-shaped or club-shaped) are enveloped, 80 to 160 nm particles containing an unsegmented genome of ss-RNA; the nucleocapsid is probably helical, 11 to 13 nm in diameter. They resemble orthomyxoviruses, but coronaviruses have petal-shaped surface projections arranged in a fringe like a solar corona. Coronavirus nucleocapsids develop in the cytoplasm and mature by budding into cytoplasmic vesicles. Human coronaviruses have been isolated from patients with acute upper respiratory tract infections. Coronavirus of animals readily establish persistent infections. Only one genus has been described in this family: Coronavirus—members include avian infectious bronchitis virus, mouse hepatitis virus.

Bunyaviridae

The name of this family is derived from Bunyamwera, a location in
Uganda, Africa, where the type species of virus was isolated. This is the largest virus family of the vertebrates with more than 225 members. The virion is a spherical, 90 to 100 nm particle that replicates in the cytoplasm and acquires an envelope by budding into the Golgi apparatus. The genome is made up of a triple-segmented, ss, negative-sense RNA. The majority of these viruses are transmitted to vertebrates by arthropods (arboviruses). Hantaviruses, a cause of hemorrhagic fevers and nephropathy, are transmitted to humans by rodents. The Bunyaviridae have five genera:

(i) Bunyavirus—includes all former arbovirus group C viruses. 145 viruses, mosquito-transmitted; California encephalitis group including La Crosse, Lumbo, and Snowshoe hare virus, Bunyamwera supergroup.

(ii) Phlebovirus—sandfly (Phlebotomus) fever, Rift Valley fever. These are predominantly sandfly-borne viruses.

(iii) Nairovirus—tick-transmitted; Crimean-Congo hemorrhagic fever (CCHF—two serotypes), Nairobi sheep disease.

(iv) Hantavirus—Hantaan virus is the type species of this newly established Hantavirus genus. Other viruses of this genus are Lee virus, Seoul virus, Tchoupitoulas virus, Girard Point virus, Sapporo rat virus, Prospect Hill virus, Puuimal virus, and Thottapalayam. The name Muerto canyon virus (MCV) has been proposed for the etiologic agent for Hantavirus pulmonary syndrome (HPS). Initially, this virus was named as Four Corners strain after the regions of New Mexico, Utah, Arizona, and Colorado where the first cases occurred. The newly described MCV strain differs from other known hantaviruses. Its effects are more rapid and more lethal and it destroys the lungs rather than the kidneys.

(v) Uukuvirus—Uukuneimi and related viruses of birds and mammals.

Unclassified viruses
A virus is a set of genes, either DNA or RNA, packaged in a protein-containing coat. The extracellular infectious virus particle is called a virion. There are certain viruses that have insufficient information to permit classification. Recently, unconventional virus-like forms of life have been discovered that have entirely different properties. These forms have been termed as viroids and prions. The term “viroids” has been introduced for a new class of subviral agents characterized by the apparent absence of an extracellular dormant phase (virion) and by a genome much smaller than those of known viruses. Viroids are infectious, low molecular weight circular RNA molecules that lack protein shells (capsid) and are resistant to heat and organic solvents but sensitive to nucleases and are responsible for a variety of plant diseases. The name “prions” has been proposed for another new class of proteinaceous infectious particles that lack any detectable nucleic acid. Prions are resistant to heat, UV rays, and nucleases, but are sensitive to proteases and they seem to be nonimmunogenic.

These are transmissible infectious agents responsible for some viral diseases with very long incubation periods (up to 30 years in humans), including neurodegenerative disorders such as kuru; Creutzfeldt-Jakob disease (CJD) (small particles probably 4 to 6 nm in diameter; Gerstmann-Straussler-Scheinker disease (GSS); the animal diseases scrapie of sheep and goats, bovine spongiform encephalopathy, chronic wasting diseases of mule deer and elk, and transmissible mink encephalopathy. This group of agents is also known as the chronic infectious neuropathic agents (CHINA viruses).

Delta hepatitis or hepatitis D virus (HDV) is a defective satellite of hepatitis B virus, requiring the presence of hepatitis B virus for its replication and assembly. The virion is 35 to 37 nm in diameter and consists of an envelope made of HBsAg surrounding a structure containing delta antigen. The infections caused by this agent may be acute or chronic.

Recently, a 32- to 42-nm spherical non-A, non-B hepatitis virus (NANBHIV) that is responsible for waterborne epidemics in developing countries, has been named as hepatitis E virus (HEV). On the basis of physicochemical characterization and morphological properties, HEV resembles calicivirus (2), but genomic analysis indicates similarities to Alphavirus (5, 10). Further characterization is needed for the final taxonomic classification.

The name Toroviridae has been proposed for the undescribed doughnut-shaped, ss-RNA viruses associated with diarrhea in horses (Breda virus) and calves (Breda virus). RNA-containing Borna disease virus causes an encephalomyelitis of horses and sheep. These are not fully characterized and are unclassified.

Astrovirus has been visualized by electron microscopy in fecal specimens from humans, calves, dogs, swine, ducks, turkeys, and lambs. At present five antigenically distinct groups of human astrovirus have been described. The virions are spherical, 27 to 32 nm in diameter, and have a characteristic star-shaped appearance. Their genome consists of ss RNA about the same size as that of picornaviruses.

Arboviruses
Arboviruses (Sigla: arthropod-borne) do not belong to a virus family. These are the viruses that are pathogenic for humans and are arthropod-transmitted. All of these viruses (>350) have a complex cycle involving arthropods as vectors that transmit the viruses to vertebrate hosts by their bite. Virus replication does not seem to harm the infected arthropod. Arboviruses infect humans, mammals, birds, and snakes and use mosquitoes and ticks as vectors. Human pathogens include dengue, yellow fever, encephalitis viruses, and others. Arboviruses belong to several virus families, including Togaviridae, Flaviviridae, Bunyaviridae, Rhabdoviridae, Arenaviridae, and Reoviridae.

The information on the taxonomic classification of medically important animal viruses is very helpful in microbiological diagnostic laboratories, in medicine, in teaching, in research, and in veterinary medicine. It is the continuous work of the members of the ICTV who gathered this information over a long period of time that has improved our understanding of viral diseases. With the existing knowledge, the diagnosis of most viral diseases is much simplified either by isolating the viruses in culture, or by serological or immunological tests, or molecular biology approaches.
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Editorial

Veterinary Antimicrobial Susceptibility Testing Coming of Age

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Clinical microbiology laboratories in hospitals, clinics, or private settings are accustomed to handling bacterial pathogens from humans, conducting standardized antimicrobial susceptibility testing (AST), and reporting results to physicians. On the other hand, veterinary AST (VAST) is conducted by a variety of laboratories ranging from the large state-of-the-art (university, state, or private) to a practitioner’s back office; all without accepted guidelines or standards. It has been the custom for the more proficient laboratories to follow the existing National Committee for Laboratory Standards (NCCLS) standards, but each may use different modifications of these procedures to accommodate the fastidious pathogens associated with veterinary bacteriology. In addition to the discrepancies of media and methods, the only source of interpretive criteria for determining the susceptibility of veterinary pathogens has been developed using human pathogens, pharmacokinetics, and clinical trials. These extrapolated criteria have led to some confusion when veterinary laboratory results are applied in actual clinical veterinary practice.

To address this situation the NCCLS Area Committee on Microbiology has recently formed a subcommittee (NCCLS Subcommittee on Veterinary Antimicrobial Susceptibility Testing) to address the unique needs of laboratories and clinicians dealing with antimicrobial susceptibility testing of bacteria from cattle, swine, poultry, horses, dogs, and lactating dairy cattle.

The subcommittee was formed in 1993 and comprises representatives from the animal health industry, university laboratory diagnosticians, test equipment manufacturers, government regulatory officials, veterinarians, and members of the human use AST committee. The VAST subcommittee is charged with the task of developing standards for the performance of AST and rational interpretive criteria for specific antibiotics and animal species, and assisting government and animal health industry regulatory groups in developing the testing criteria for new as well as for existing antimicrobial agents.

The first step taken by the subcommittee was to develop methodological standards for VAST. It was decided to use the current NCCLS documents for easily grown aerobic pathogens such as gram-negative organisms (e.g., pasturellaee, enterics) and gram-positive organisms (e.g., staphylococci and streptococci) as a starting point in developing a tentative document of specific veterinary standards (1, 2). In addition, current working groups are addressing standardization of media and conditions for the growth of fastidious pathogens such as Actinobacillus pleuropneumoniae (swine respiratory pathogen) and Haemophilus somnus (cattle pathogen). Anaerobic microorganisms, mycobacteria, mycoplasma, spirochetes, and agents of minor disease concern have been intentionally excluded at this time. Quality control organisms and antimicrobial agents used in both human and veterinary medicine are accepted by the subcommittee (e.g., penicillins, erythromycin, tetracycline, tested with American Type Culture Collection strains);