

Review

Highly adaptive *Phenuiviridae* with great biomedical importance

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Abstract

The newly established virus family *Phenuiviridae* in *Bunyavirales* harbors viruses infecting three kingdoms of host organisms (animals, plants, and fungi), which is rare in known virus families. Many phenuiviruses are arboviruses and replicate in two distinct hosts (e.g., insects and humans or rice). Multiple phenuiviruses, such as *Dabie bandavirus*, *Rift Valley fever phlebovirus*, and *Rice stripe tenuivirus*, are highly pathogenic to humans, animals, or plants. They impose heavy global burdens on human health, livestock industry, and agriculture and are research hotspots. In recent years the taxonomy of *Phenuiviridae* has been expanded greatly, and researches on phenuiviruses have made significant progress. With these advances, this review drew a novel panorama regarding the biomedical significance, distribution, morphology, genomics, taxonomy, evolution, replication, transmission, pathogenesis, and control of phenuiviruses, to aid researchers in various fields to recognize this highly adaptive and very important virus family.

Keywords

arbovirus; evolution; genome; host; pathogenesis; *Phenuiviridae*

1. Introduction

The virus family *Phenuiviridae* in the order *Bunyavirales* was established in 2017 [1]. Of all the 185 known virus families listed by the International Committee on Taxonomy of Viruses, only *Phenuiviridae* and *Reoviridae* harbor viruses infecting three kingdoms of host organisms (animals, plants, and fungi) [2, 3]. Besides adaptation to extremely diverse hosts, many phenuiviruses have evolved delicate strategies to infect and circulate between two distinct types of hosts (e.g., ticks and humans or rice) [1, 4-6]. Moreover, as elucidated in **Section 2**, multiple phenuiviruses are highly pathogenic to humans, animals, or plants. They impose heavy global burdens on human health, the livestock industry, and agriculture. Of them, Rift Valley fever (RVF) and severe fever with thrombocytopenia syndrome (SFTS) caused by phenuiviruses were prioritized by the World Health Organization as two of the eleven infectious diseases with an urgent need for accelerated research [7].

To date, many reviews regarding one or several important phenuiviruses have been published [8, 9], but *Phenuiviridae* remains elusive because no comprehensive reviews on phenuiviruses at the family level have been published. Moreover, many novel species and some novel genera of *Phenuiviridae* have been identified [1, 4, 5, 10], and research targeting various aspects of this important virus family has made significant progress. Therefore, many expressions concerning this family have been outdated or incomplete. For instance, it is incorrect to claim severe fever with thrombocytopenia syndrome virus (SFTSV) belongs to the genus *Phlebovirus* in *Phenuiviridae* [9]. With these advances, this review drew a novel panorama regarding the biomedical significance, distribution, morphology, genomics, replication, taxonomy, evolution, pathogenesis, and control of phenuiviruses to aid researchers in various fields to recognize this important virus family.

2. Biomedical significance of phenuiviruses

The phenuivirus of *Dabie bandavirus*, usually termed SFTSV, was first reported in 2011 [11]. In recent years, over 1000 SFTS cases have been confirmed annually in China [12]. Human SFTS cases have also been identified in South Korea, Japan, and Vietnam [13-16]. Clinical symptoms include high fever, thrombocytopenia, leukopenia, lymphadenopathy, gastrointestinal disorders, hemorrhagic manifestations (hematuria, hematochezia, and/or hemoptysis), encephalitis-associated neurologic symptoms (lethargy, muscular tremors, convulsions, and coma), and multiple-organ dysfunction, with the incubation period of 7–14 days and mortality rates of 6–27% [12, 14]. Asymptomatic SFTS infections were also

reported. Most fatal SFTS cases occur in patients >50 years of age, while all age groups are susceptible to SFTSV infection. Humans and domestic or wild animals can be readily infected with SFTSV during the blood-feeding of virus-carrying ticks.

The phenuivirus of *Heartland virus* (HRTV) shares the same genus with SFTSV. HRTV was first isolated in 2009 from two patients in the USA [17], and both patients were hospitalized for acute onset of febrile illness with fatigue, anorexia, diarrhea, leukopenia, and thrombocytopenia and reported multiple tick exposures in the days before their illness. HRTV-specific antibodies have been detected in wild animals in 13 eastern and central states. A targeted survey identified 16 patients with acute HRTV disease in seven states with illness onset from April to September. Most reported fatigue, anorexia, nausea, headache, confusion, arthralgia, or myalgia, and 14 cases were hospitalized with two fatalities [18].

The phenuivirus *Bhanja bandavirus* is tick-borne and has been found in Asia, Africa, and Europe [19]. It infects humans, sheep, goats, cattle, hedgehogs, and squirrels. It causes encephalitis in young ruminants and conjunctivitis or meningoencephalitis in humans with the symptoms of headache, photophobia, vomiting, and paresis [20].

The phenuivirus of *Rift Valley fever phlebovirus* (RVFV) causes the mosquito-borne zoonosis of RVF that was first described in Kenya in 1930 [8]. RVF has been endemic throughout multiple African countries and the Arabian Peninsula [21, 22]. RVFV primarily infects domestic sheep, goats, and cattle, causing high mortality rates among young animals and "abortion storms", in which nearly all infected pregnant animals abort pregnancies [23]. Human infections with RVFV result in various clinical symptoms, including fever, headache, backache, vertigo, anorexia, photophobia, miscarriage in pregnant women, and life-threatening hemorrhagic diatheses [24]. Around 1–2 % of human infections result in severe disease, often with high mortality levels [21, 25-27]. The disease may last several days to a month. Some patients show a reduction of symptoms on the third day and recrudescence 1–3 days later. Outbreaks appeared regularly from the 1950s and started outside Africa after 2000. RVF has led to thousands of human deaths and millions of animal deaths in Africa [28]. It is a heavy burden to human health and the livestock industry in the Arabian Peninsula. African buffalo and giraffes are susceptible to RVFV.

The phenuivirus of *Toscana phlebovirus* (TOSV) is prevalent in the countries surrounding the Mediterranean [29]. TOSV has diverged into three distinct lineages roughly corresponding to three overlapping regions. TOSV is found in both the male and female sand flies and can be sexually transmitted between adults and transovarially transmitted to larvae.

TOSV infection is prevalent in dogs and other domestic animals [30]. Seroprevalence among humans is around 10–24%, occasionally reaching 40% within the endemic regions. Although mild TOSV infection cases are generally self-limiting febrile illnesses, TOSV causes sporadic severe meningitis, meningoencephalitis, and other neuroinvasive diseases, such as Guillain-Barré syndrome, hydrocephalus, myositis, fasciitis, polymyeloradiculopathy, deafness, and facial paralysis [31]. Most symptomatic infections show headaches, fever, nausea, vomiting, neck rigidity/pain, and leg stiffness. Most TOSV cases recover without permanent sequelae.

Some other phenuiviruses in the genus *Phlebovirus* can also infect humans. For instance, *Sicilian phlebovirus* (i.e., sandfly fever Sicilian virus) and *Naples phlebovirus* (i.e., sandfly fever Naples virus) transmitted by sandflies are responsible for most clinically described "sandfly fever" [30]. Both viruses are endemic in the Mediterranean region and western and central Asia, and their distribution extends into the European continent, northern Africa, and as far east as China [32]. Symptoms of these infections are clinically similar and often described as 3-day-fever characterized by abrupt onset of fever, headache, muscular pain, photophobia, and nausea. The phenuivirus *Punta Toro phlebovirus* (PTV) identified in Panama is also transmitted by sandflies and causes an acute febrile illness lasting 2–5 days [33]. Although a 35% seroprevalence has been reported in Panama, little is understood about the distribution of this virus. The phenuiviruses *Cocle phlebovirus*, and *Chagres phlebovirus* were identified from febrile humans also in Panama [33]. The phenuivirus *Buenaventura phlebovirus* was identified from a febrile human in Colombia. The phenuiviruses *Candiru phlebovirus* and *Alenquer phlebovirus* were identified from febrile humans in Brazil, and phenuiviruses *Echarate phlebovirus* and *Maldonado phlebovirus* were identified from febrile humans in Peru [34]. The human febrile illness caused by these phleboviruses is usually nonspecific and self-limited. Moreover, these phleboviruses can also infect domestic animals (e.g., dogs and cats) and various wild animals.

The phenuivirus of *Rice stripe tenuivirus* (RSV) causes one of rice's most destructive viral diseases, which leads to a 30–40% reduction in rice yield in affected regions [35]. It is widely distributed throughout East Asia, especially in China, Japan, and Korea. Over 80% of the rice fields in Eastern China and Korea are affected by this disease annually [36]. RSV is transmitted by the small brown plant-hopper (*Laodelphax striatellus* Fallén). RSV-infected plants display chlorosis, weakness, necrosis in leaves, abnormal growth, and even complete grain yield loss. RSV also harms other staple crops, such as wheat, barley, maize, oat, and foxtail millet [34]. RSV can also infect *Arabidopsis* [35, 37].

The phenuivirus of *Rice grassy stunt tenuivirus* (RGSV) shares the same genus with RSV and causes a severe viral disease of rice. RGSV is widely distributed in the Philippines, Thailand, Vietnam, China, and India. Infected rice plants show pronounced stunting with short, erect, mottling, and narrow leaves that are pale green or pale yellow. The phenuivirus of *Rice hoja blanca tenuivirus* and its vector *Tagosodes orizicolus* (Muir) can cause up to 100% yield loss in Latin American rice fields [38]. This virus is present only in the Americas. The phenuivirus of *Maize stripe tenuivirus* is widely distributed, affecting maize worldwide, sorghum in India, and itchgrass in the USA [39].

Besides the above pathogenic phenuiviruses, some other phenuiviruses are also pathogenic to humans, animals, or plants. For example, *Guertu bandavirus* can infect humans, as suggested by serological evidence and cell culture [40]. Infection of *Tacheng uukuvirus* (i.e., Tacheng tick virus 2) in a febrile human was reported in 2021 [41]. *Human tanzavirus* was identified from a human with fever, headache, back pain, and pollakiuria in 2019 in Tanzania [42]. Infection of *Gouleako goukovirus* with severe symptoms in swine in South Korea was reported in 2013. In many countries, Apple rubodvirus 1 and 2 are associated with apple rubbery wood disease, reducing fruit yield by up to 30% in apples and 50% in pear [3]. *Citrus coguvirus* is associated with a severe citrus disease, the graft-transmissible citrus concave gum-blind pocket, reported over 80 years ago. Infected citrus trees show deeply depressed trunk concavities frequently associated with leaf chlorotic flecking. Two unclassified members in the genus *Citrus*, *Watermelon crinkle leaf-associated virus 1* and *Watermelon crinkle leaf-associated virus 2*, are associated with mosaic and curling leaves of watermelons.

3. Morphology and genomics of phenuiviruses

Many phenuiviruses are icosahedral spheres with a diameter of 80–160 nm [43], except plant-infecting and fungi-infecting phenuiviruses that are symmetric filamentous spirals (**Figure 1**). Virions of one RVFV strain had a 95 ± 9 nm diameter with a volume of $\sim 2.3 \times 10^5$ nm³ [44]. Most regular virions of RVFV have highly dense protrusions on their surface, forming an icosahedral lattice (T= 12 triangulation, which is likely unique to viruses in *Bunyavirales*). The heterodimers of the glycoproteins, Gn and Gc, of RVFV, form 122 capsomers (12 pentons each composed of five Gn/Gc heterodimers and 110 hexons each composed of six Gn/Gc heterodimers), namely the dense protrusions on the virus icosahedral surface, which extend ~ 96 Å above the viral lipid envelope.

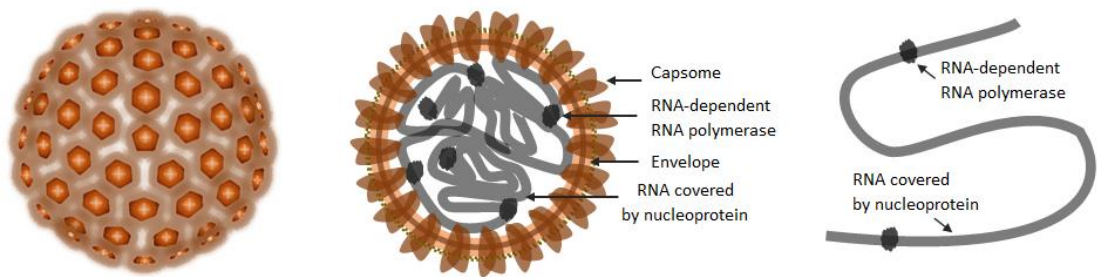


Figure 1. Morphology of phenuiviruses. The icosahedral exterior (left) and interior (middle) of many vertebrate-infecting phenuiviruses are distinct from the filamentous spiral virion (right) of many plant-infecting phenuiviruses.

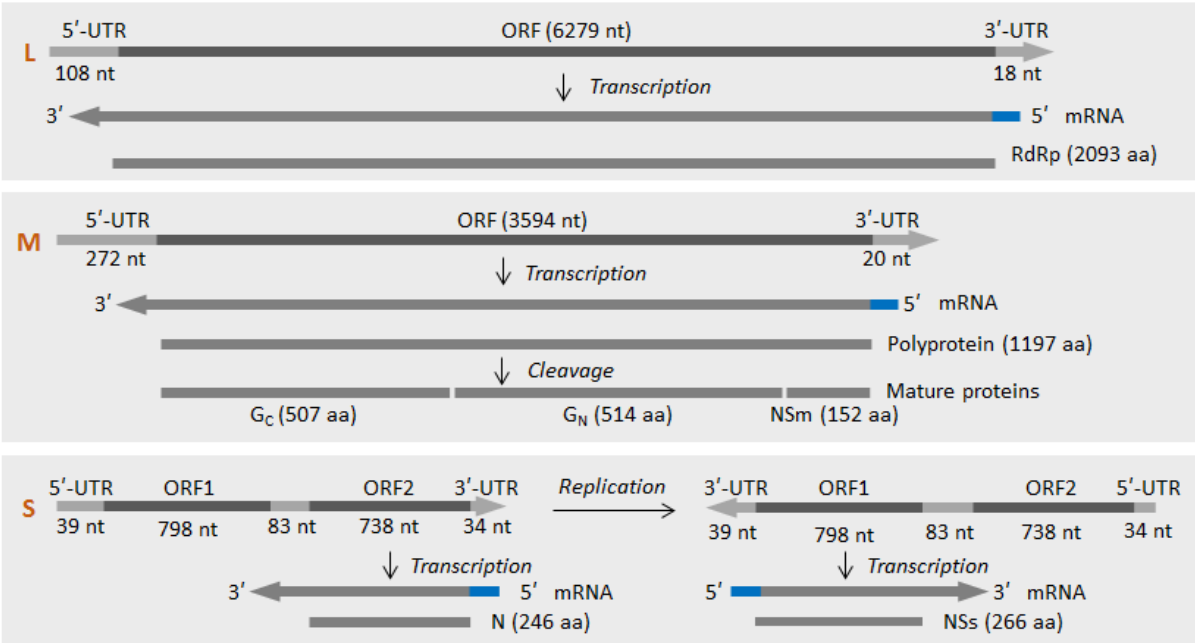


Figure 2. The three genomic RNA segments (L, M, and S) of a Rift Valley fever virus (RVFV) and their encoding proteins. These sequences were reported previously [45]. ORF: open reading frame. UTR: untranslated region. Blue lines represent the 5'-methylated cap and some nucleotides transferred from host cell mRNAs to the viral mRNAs. Translation of the M segment may initiate at different starting codons. Lines are not drawn to scale.

Table 1. Hosts and genomic structures of the 20 genera in *Phenuiviridae*

Genus	Representative species	Hosts	Segments and encoded proteins are given in parentheses
<i>Beidivirus</i>	<i>Dipteran beidivirus</i>	Dipteran insects	L(RdRp) M(Gn-Gc) S(N)
<i>Phasivirus</i>	<i>Badu phasivirus</i>	Mosquitos, flies	L(RdRp) M(Gn-Gc) S(N)
<i>Goukovirus</i>	<i>Gouleako goukovirus</i>	Mosquitos, pigs?	L(RdRp) M(Gn-Gc) S(N)
<i>Hudivirus</i>	<i>Dipteran hudivirus</i>	Dipteran insects	L(RdRp) M(Gn-Gc) S(N)
<i>Hudovirus</i>	<i>Lepidopteran hudovirus</i>	Lepidoptera	L(RdRp) M(Gn-Gc) S(N)
<i>Pidchovirus</i>	<i>Pidgey pidchovirus</i>	Moths	L(RdRp) M(Gn-Gc) S(N)
<i>Tanzavirus</i>	<i>Human tanzavirus</i>	Unknown vector, humans	L(RdRp) M(Gn-Gc) S(N)
<i>Bandavirus</i>	<i>Dabie bandavirus</i>	Ticks, humans, other vertebrates	L(RdRp) M(Gn-Gc) S(<u>NSs</u> -N)
<i>Mobuvirus</i>	<i>Mothra mobuvirus</i>	Moths and Mosquitos	L(RdRp) M(NSm-Gn-Gc) S(<u>NSs</u> -N)
<i>Phlebovirus</i>	<i>Rift Valley fever phlebovirus</i>	Dipteran insects (esp. sandflies)	L(RdRp) M(NSm-Gn-Gc) S(<u>NSs</u> -N)
<i>Ixovirus</i>	<i>Norway ixovirus</i>	Ticks	L(RdRp) M(?) S(N)
<i>Uukuvirus</i>	<i>Pacific coast uukuvirus</i>	Ticks-borne, vertebrates	L(RdRp) M(Gn-Gc) S(N)
<i>Uukuvirus</i>	<i>Uukuniemi uukuvirus</i>	Ticks-borne, vertebrates	L(RdRp) M(Gn-Gc) S(<u>NSs</u> -N)
<i>Horwuvirus</i>	<i>Horsefly horwuvirus</i>	Mosquitos, horseflies, gadflies	L(RdRp) M(Gn-Gc) S1(N) S2(NSs)
<i>Wenrivirus</i>	<i>Shrimp wenrivirus</i>	Shrimps	L(RdRp) M(Gn-Gc) S1(N) S2(NSs)
<i>Entovirus</i>	<i>Entoleuca entovirus</i>	Fungi (Entoleuca)	L(RdRp) M(<u>MP</u> -N)
<i>Lentinivirus</i>	<i>Lentinula lentinivirus</i>	Fungi (shiitake mushroom)	L(RdRp) M(<u>MP</u> -N)
<i>Coguvirus</i>	<i>Citrus coguvirus</i>	Plants (grapevine, watermelon)	L(RdRp) M(<u>MP</u> -N)
<i>Coguvirus</i>	<i>Grapevine coguvirus</i>	Plants (grapevine)	L(RdRp) M(MP) S(N)
<i>Laulavirus</i>	<i>Laurel Lake laulavirus</i>	Plants (grapevine), ticks?	L(RdRp) M(MP) S(N)
<i>Rubodvirus</i>	<i>Apple rubodvirus 1</i>	Plants (apple tree and grapevine)	L(RdRp) M(MP) S(N)
<i>Tenuivirus</i>	<i>Rice stripe tenuivirus</i>	Planthoppers and gramineous crops	4–8 segments encoding RdRp, MP, N, and other proteins, as detailed previously [39]

Note: the question marks in this table suggest the relevant information is unavailable or questionable; RdRp: RNA dependent RNA polymerase; Gn-Gc: two glycoproteins; NSm and NSs: two nonstructural proteins; N: nucleocapsid protein; MP: movement protein; those proteins given with underlines are encoded in the positive sense, and all other proteins are encoded in the negative sense.

Most plant-infecting phenuiviruses are usually symmetric filamentous spirals. For instance, virions of tenuiviruses are filamentous spirals, 3–10 nm wide and 500–2100 nm long, and look like strings of beads [39, 46]. Coguvirus particles are elongated flexuous spirals, 200–300 nm long and 6 nm wide [47, 48]. The morphology of fungi-infecting phenuiviruses remains unknown, but from the fact that they are similar to plant-infecting phenuiviruses in genomics (**Table 1**), virions of fungi-infecting phenuiviruses are possibly filamentous spirals.

Phenuiviruses have 2–8 single-stranded RNA genomic segments, totally composed of around 10 000–25 000 nucleotides [39]. The numbers and functions of proteins encoded by phenuivirid genomes are different among genera and species (**Table 1**).

Many vertebrate-infecting phenuiviruses (e.g., RVFV) have three genomic segments which encode at least four structural proteins (**Figure 2**). The longest (L) segment of genomic RNA encodes an RNA-dependent RNA polymerase (RdRp), responsible for the replication and transcription of viral genomic RNA. RdRp of phenuiviruses also has endonuclease functions [49]. The medium (M) segment encodes a precursor polypeptide, cleaved by host signal peptidase into two envelope glycoproteins, Gn and Gc. Gn and Gc are responsible for virion binding to the target cells and penetrating the cytosol, assembling in cytosols, and they constitute tropism restriction factors. They are also the targets for neutralizing antibodies, making them key targets for vaccine development [49]. Both Gn and Gc contain N-glycosylation sites [50].

The small (S) segment encodes the nucleocapsid protein (N) that encapsulates the genomic RNA. RdRp, N, and genomic RNA constitute the viral ribonucleoproteins (RNPs). The S segment of some phenuiviruses also encodes a nonstructural protein, NSs, which impacts interferon production in host cells and viral virulence [39, 51]. Unlike some tick-borne phenuiviruses (e.g., SFTSV), some dipteran-borne phenuiviruses (e.g., RVFV) encode another nonstructural protein, NSm, before the coding region of Gn in the M segment. NSm interacts with the outer mitochondrial membrane [52]. NSm regulates the p38 mitogen-activated protein kinase stress response and has an anti-apoptotic role, which is important for the infectivity of the phenuiviruses in dipteran insects [53]. For many phenuiviruses, the viral L and M segments are in the negative sense, while the viral S segment is in double senses for

encoding proteins (**Figure 2**). For all ambisense genomic segments of phenuiviruses, there is an untranslated intergenic region in a stable hairpin structure between the two open reading frames encoded in two senses.

Fungi-infecting phenuiviruses are distinct from those of vertebrate-infecting phenuiviruses in genomics [2, 54]. Their genomes consist of two single-stranded RNA segments. The longer segment encodes RdRp negatively, and the shorter segment encodes movement protein (MP) and nucleocapsid protein (N) in the positive and negative senses. The functions of MP will be given below.

Plant-infecting phenuiviruses are distinct from vertebrate-infecting phenuiviruses and similar to fungi-infecting phenuiviruses in genomics (**Table 1**). Their genomes consist of 2–8 single-stranded RNA segments [39]. For instance, the genome of RSV consists of four single-stranded RNA segments, RNA1–RNA4, that encode seven proteins. RNA1 is the longest and encodes RdRp in the negative sense. RNA2–RNA4 are ambisense, and each encodes two ORFs separated by an untranslated intergenic region. The proteins encoded by these three segments in the positive sense are termed p2–p4, and the proteins encoded by these three segments in the negative sense are termed pc2–pc4. pc2 is a glycoprotein precursor involved in insect vector transmission. p2 is a nonstructural protein participating in RNA silencing suppression and systemic movement. pc3 is a nucleocapsid (N) protein that tightly encapsulates the genome RNA. p3 is a non-structural protein that functions as a robust viral suppressor of RNA. pc4 is a movement protein (MP) that accumulates to high levels in RSV-infected plants and plays a role in RSV pathogenicity [55]. p4 is a disease-specific protein whose expression is associated with the severity of RSV symptoms [56]. MP of fungi-infecting phenuiviruses and plant-infecting phenuiviruses is vital for them to spread from infected cells to neighboring cells [39, 57, 58]

Terminal sequences of phenuivirus genomic segments are conserved and complementary, likely in a genus-specific manner [39, 47, 48]. For phleboviruses, they are 5'-ACACAAAG.....CUUUGUGU-3'. These conserved and complementary terminal sequences enable base pairing and form a stable panhandle structure involved in transcription, replication, encapsulation, and packaging of the viral RNAs [39, 59].

4. Taxonomy of phenuiviruses

The families and genera in *Bunyavirales* are classified as per their phylogenetical relationships in their RdRp genes, namely that all the families in *Bunyavirales* form distinct branches in the phylogenetic tree of *Bunyavirales*, and all the genera in each of the families form distinct branches in the phylogenetical tree of the family, as per their RdRp gene sequences. Species in *Phenuiviridae* are also classified as per their phylogenetic relationships in their RdRp genes, which are usually consistent with their host distribution, number of segments, and conserved sequences at genomic RNA termini [60]. In recent years, species demarcation of some genera in *Phenuiviridae* has been based on the identity of the RdRp sequence. For instance, species of the genus *Phlebovirus* are currently discriminated by <95% identity of the amino-acid sequences of RdRp [60].

Bunyavirales covered nine families, including the one *Phenuiviridae* to accommodate the previous genera of *Phenuivirus*, *Goukovirus*, *Phasivirus*, and *Tenuivirus* in 2017 [1]. After that, many novel species of viruses were identified in recent years with high throughput sequencing and bioinformatics technologies. Consequently, in 2021, *Bunyavirales* harbored 12 families [5], and *Phenuiviridae* harbored the following 20 genera (**Table 1**), 133 species (**Figure 3**), and some unclassified viruses.

(1) ***Bandavirus***, previously belonging to *Phlebovirus* [40], currently consists of eight tick-borne species. Four of them, SFTSV, HRTV, *Guertu bandavirus*, and *Bhanja bandavirus*, can infect humans.

(2) ***Beidivirus***, first identified in 2016 in China [61], currently covers only one species of dipteran viruses, *Dipteran Beidivirus*.

(3) ***Goukovirus***, first identified in 2011 in Cote d'Ivoire [62], currently covers three species of mosquito viruses: *Gouleako goukovirus*, *Cumuto goukovirus*, *Yichang insect goukovirus*. Surprisingly, it was reported in 2013 that infection of *Gouleako goukovirus* in swine in South Korea was prevalent and associated with severe swine diseases [63], but this finding has not been supported by other studies after that [64].

(4) ***Hudivirus***, first identified in 2016 in China [61], currently covers one species of dipteran viruses, *Dipteran hudivirus*.

(5) ***Hudovirus***, first identified in 2016 in China [61], currently covers one species of lepidopteran viruses, *Lepidopteran hudovirus*.

(6) ***Ixovirus***, first identified in 2014 in North America [65], currently covers two species of tick-borne viruses, *Norway ixovirus* and *Scapularis ixovirus*, whose genomes have not been fully sequenced.

(7) **Mobuvirus**, first identified in 2016 in the USA [66], currently covers two species of arthropods (mosquito and moth) viruses, *Mothra mobuvirus* and *Narangue mobuvirus*.

(8) **Phasivirus**, first identified in 2012 in China [10], currently covers seven species of arthropod (e.g., mosquitos, flies) viruses, such as *Dipteran phasivirus*, distributed at least in Asia, Australia, and South America [67].

(9) **Phlebovirus**, the largest genus in *Phenuiviridae*, and currently covers 63 species of viruses circulating in arthropods (particularly sandflies) and mammals. Its members RVFV, TOSV, *Sicilian phlebovirus* (i.e., sandfly fever Sicilian virus), *Naples phlebovirus* (i.e., sandfly fever Naples virus) frequently cause human infections. *Punta Toro phlebovirus*, *Cocle phlebovirus*, *Buenaventura phlebovirus*, *Echarate phlebovirus*, *Alenquer phlebovirus*, *Maldonado phlebovirus*, *Cocle phlebovirus*, *Candiru phlebovirus*, and *Chagres phlebovirus* were also identified from febrile humans, but they likely circulated only in the Americas [33, 34, 68]. RVFV also causes illness in domestic and wild animals [69].

(10) **Pidchovirus**, first identified in 2016 in the USA [66], currently covers two species of moth viruses, *Pidgey pidchovirus*, and *Coleopteran pidchovirus*.

(11) **Tanzavirus**, first identified in 2019 in Tanzania [42], currently covers one species, *Human tanzavirus*, identified from a human with fever, headache, back pain, and pollakiuria. This virus likely does not encode NSs and NSm.

(12) **Uukuvirus**, first identified in 1960 in Finland, currently covers 17 species of tick-borne viruses. Uukuviruses are non-pathogenic to humans, but a patient infected with *Tacheng uukuvirus* (i.e., Tacheng tick virus 2) was reported recently [41]. Genomic segments of some uukuviruses (e.g., *Dabieshan uukuvirus*, *Tacheng uukuvirus*, and *Lihan uukuvirus*) have not been fully sequenced. Some uukuviruses, such as *Uukuniemi uukuvirus* (UUKV), *Murre uukuvirus*, and *Grand Arbaud uukuvirus*, encode NSs. Some uukuviruses include *Tacheng uukuvirus*, *Lihan uukuvirus*, *Pacific coast uukuvirus* (previously termed *Pacific coast tick phlebovirus*), and *American dog uukuvirus* (previously termed *American dog tick phlebovirus*), do not encode NSs.

(13) **Horwuvirus**, first identified in 2015 [10], currently covers *Horsefly horwuvirus* and *Kimberley horwuvirus* that circulate in mosquitos and gadflies at least in China and Australia [10, 70]. Unlike the above genera with three genomic segments, this genus has four segments encoding RdRp, Gn/Gc, N, and a non-structural protein, respectively (**Table 1**).

(14) **Wenrivirus**, identified in 2015 in China [71], currently covers one species of prawn viruses, *Shrimp wenrivirus*. Like horwuviruses, genomes of wenriviruses contain four segments (**Table 1**) [71].

(15) **Entovirus**, first identified in the fungi family *Xylariaceae Ascomycota* in 2018 in Spain [2], currently covers one species of fungi viruses, *Entoleuca entovirus*.

(16) **Lentinivirus**, first identified in 2019 in Japan [54], currently covers one species of fungi viruses, *Lentinula lentinivirus*, which infects the shiitake mushroom (*Lentinula edodes*). Like *Entovirus*, the genome of *Lentinivirus* has two segments (**Table 1**).

(17) **Coguvirus**, first reported in 2018 [48], currently covers three species and two unclassified species. Its member *Citrus coguvirus* is associated with the severe citrus disease, the graft-transmissible citrus concave gum-blind pocket. Its unclassified members, *Watermelon crinkle leaf-associated virus 1* and *Watermelon crinkle leaf-associated virus 2*, are associated with mosaic and curling leaves of watermelons and first identified in China in recent years. Genomes of coguviruses are bipartite, except for Grapevine coguvirus whose genome is tripartite (**Table 1**).

(18) **Laulavirus**, first identified in 2017 in the USA [72], currently covers three plant viruses *Grapevine laulavirus 2*, *Grapevine laulavirus 3*, and *Grapevine laulavirus 4* [73], and a tick virus, *Laurel Lake laulavirus*. *Laurel Lake laulavirus* did not encode the proteins of Gn and Gc but encoded a movement protein. It is hence a typical plant-infecting phenuivirus that could infect and be transmitted by ticks.

(19) **Rubodvirus**, first identified in 2018 in Canada [74], currently covers four species of plant viruses, *Apple rubodvirus 1*, *Apple rubodvirus 2*, *Grapevine rubodvirus 1*, and *Grapevine rubodvirus 2*. They have been identified in America, China, Canada, Germany, and Argentina [75]. The first two viruses are associated with diseases in apple and pear trees [3].

(20) **Tenuivirus**, first identified in 1993 in Colombia [3], currently covers nine species of plant viruses, such as RSV, RGSV, *European wheat striate mosaic tenuivirus*, *Maize stripe tenuivirus*, and *Melon tenuivirus*. They can replicate in the leaves of rice, maize, sorghum, and other relevant gramineous and relevant vector planthoppers. They cause important crop diseases [76, 77]. Genomes of tenuiviruses have 4–8 segments, including three or more ambisense segments. Their virions are branched or thin filamentous spirals.

5. Evolution of phenuiviruses

Phenuiviruses are highly successful in evolution because they infect three kingdoms of host organisms, and many of them can replicate alternatively in two distinct kingdoms of hosts. However, the evolution of phenuiviruses has seldom been studied systematically at the family level. It is tough to obtain evidence to ascertain when phenuiviruses originated, although it has been suggested that the last common ancestor of bunyaviruses, including phenuiviruses, might be an invertebrate virus (e.g., an insect-infecting virus) [78]. The origin of certain taxa of phenuiviruses has been estimated. For instance, a spatiotemporal analysis placed Middle-East as the geographic origin of the most recent common ancestor of some phleboviruses circulating in Europe and suggested that these phleboviruses possibly originated around 225 years ago [79].

Phenuiviruses employ multiple mechanisms to change their genomic sequences to adapt to various hosts or ecosystems. First, they can add, delete, re-assort, and recombine certain genomic segments or genes through horizontal gene transfer (HGT) mode, which is sometimes termed the modular genome evolution process [54, 80], or horizontal virus transfer (HVT) [39]. HGT is superior to HVT in terminology, as HGT is a more widely accepted

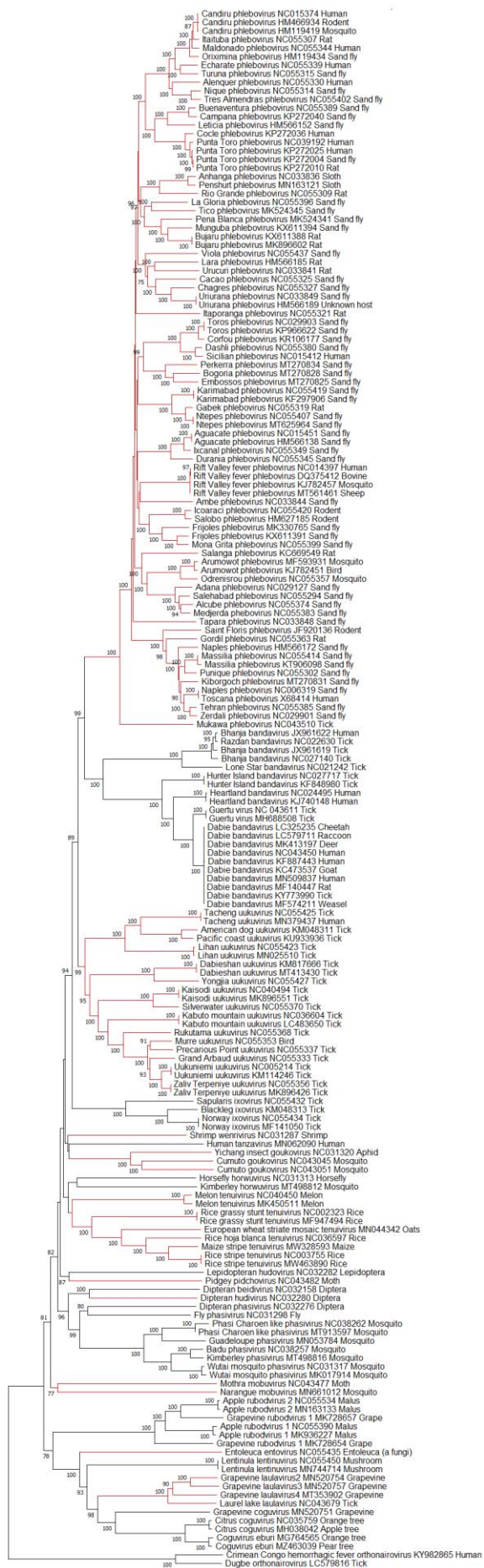


Figure 3. Phylogenetic relationships among genera and species in *Phenuiviridae*. The relationships were calculated using the Software Mega 7.0 with the amino acid sequences of the viral RdRp gene, the Neighbor-joining method, and the Poisson model. Rates among sites were set uniform, and gaps were treated as pairwise deletion. Bootstrap values were calculated in 1000 replicates. Viruses were designated using their species names, their sequence accession numbers in GenBank, and their hosts. Genera were differentiated alternately with red branches. Two nairoviruses were employed as the outgroup.

concept in evolutionary biology [81, 82], and HVT indicates one approach for HGT. HGT leads to the fact that many phenuiviruses have different genomic segments and genes combinations, as given in **Table 1**. These combinations likely aid relevant phenuiviruses to fit different hosts. For instance, the MP gene is more helpful for plant-infecting phenuiviruses than for vertebrate-infecting phenuiviruses, and NSm aids some phenuiviruses to replicate in dipteran insects. Genes for HGT of phenuiviruses may be from phenuiviruses, host RNAs, and other parasites co-infecting the same host [82]. HGT of phenuiviruses adds difficulty in the phylogenetic analysis [6], and the taxonomy of phenuiviruses has to be based solely on the phylogenetic relationships of the viral RdRp gene. For instance, *Citrus cogusvirus* was classified into *Phenuiviridae* based on its RdRp gene sequence, although this virus clustered with the genus *Ophiovirus* in *Aspiviridae*, as per its M genomic segment sequence [48].

Reassortment events of SFTSV, RVFV, and other phenuiviruses have been reported [6, 77, 83-86]. Many genomic reassortment events in phenuiviruses were involved with homologous L and S segments and heterologous M segments [6], which possibly resulted from the fact that RdRp encoded by the L segments interacts more closely with N encoded by the S segments than with the envelope proteins encoded by the M segments. Family-level phylogenetical analysis suggested that re-assortment of the genomic segment is important for forming *Phenuiviridae* and other families in the order *Bunyavirales* [87].

The evolution of some phenuiviruses changed one or more negative-sense segments into ambisense segments. For instance, two negative-sense genomic segments of coguviruses encoding the viral MP gene and N gene respectively likely evolved into one genomic segment encoding the viral MP gene and N gene at two senses (**Table 1**), which could be attributed to recombination in the host cytosol between the viral strand of one genomic segment and the complementary strand of another genomic strand [74].

Genomic recombination of phenuiviruses has been reported, although recombination is possibly rare in negative-sense RNA viruses [88]. For instance, the M segments of some SFTSVs were recombined from two prevailing SFTSV lineages, and this recombination can induce an antigenic shift of the virus [89].

Insertion, deletion, and substitutions of nucleotides are relatively frequent in phenuivirid genomic RNAs [48, 89]. Accumulation of these mutations leads to different genotypes of phenuiviruses that are associated with geographic distribution and migration of insect vectors

[59, 90]. Insertion and deletion of nucleotides occur more frequently in the intergenic regions and the 5' or 3' noncoding regions of RSVs [91].

RSV replicating in vector insects may enrich 15- and 16-nt extensions in the 3'-termini of the viral RNA segments. These extensions were gradually eliminated in the host plant (rice), indicating that variations in the 3'-termini of viral genomes may result from different selections in insects and plants [92].

6. Replication of phenuiviruses

It largely remains unknown how phenuiviruses replicate in their host cells, except for some phenuiviruses, e.g., SFTSV, RVFV, TOSV, and UUKV, in mammalian cells [93]. Their replication involves attachment and internalization to host cells, transportation to endosomes, transfusing and penetrating the cytosol, genomic transcription, translation, replication, virion assembly, and virion release [94] (**Figure 4**), as detailed below.

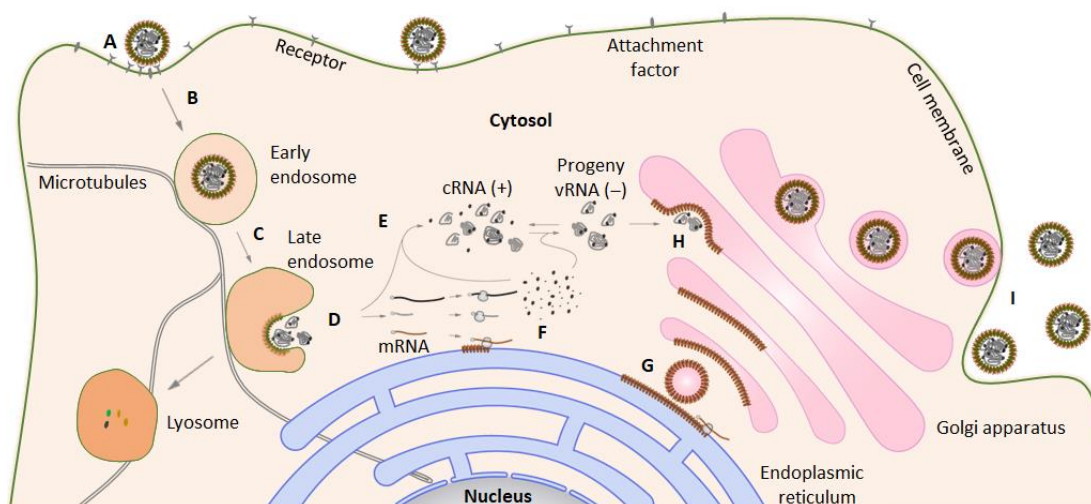


Figure 4. Replication cycle of many phenuiviruses. **A:** cellular attachment of phenuiviruses through interaction between viral glycoproteins and host cell receptors and attachment factors; **B:** internalization of phenuiviruses; **C:** trafficking of phenuiviruses from the cell's periphery into the center of the cytosol via endosomes along microtubules; **D:** fusion of the viral envelope and the endosome membrane and release of the viral genome into the cytoplasm; **E:** replication of the viral RNA (vRNA) into complementary RNA (cRNA) followed by replication of cRNA into vRNA and formation of progeny RNP; **F:** transcription of vRNA into mRNA followed by viral proteins translation, and process of viral glycoproteins on endoplasmic reticulum; **G:** transfer of viral glycoproteins from the endoplasmic reticulum

to Golgi apparatus via vesicles; **H**: assembly of virions on the membrane of Golgi apparatuses; **I**: release of virions through exocytosis.

Cellular attachment of phenuiviruses is mediated via the binding of viral glycoproteins to host cell receptors essential for virus entry. The attachment can be aided by certain attachment factors that are dispensable for virus entry [95]. A few receptors of phenuiviruses have been found in humans and other vertebrates, but none in arthropods or plants. Dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin (DC-SIGN) on dendritic cells, macrophages, megakaryocytes, some B-cells, and platelets is the receptor of PTV, RVFV, TOSV, and UUKV [96, 97]. Liver-specific intercellular adhesion molecule-3-grabbing non-integrin (L-SIGN) is likely the attachment factor of these phenuiviruses, heparan sulfate is likely the attachment factor of RVFV and TOSV [98], and nonmuscle myosin heavy chain type IIA is likely the attachment factor of SFTSV [99].

Internalization of phenuiviruses after cellular attachment involves diverse pathways and various cellular factors in a pH-dependent fashion. Some phenuiviruses likely aggregate their receptors at the site of contact, thus generating a receptor-enriched microdomain at the plasma membrane [95]. After that, virions are internalized via caveolin-mediated endocytosis (as for RVFV) [100], the clathrin-mediated endocytosis (as for SFTSV) [101], or the clathrin-independent endocytosis (as for UUKV) [102]. One phenuivirus may employ two or more internalization pathways. For instance, RVFV can employ caveolin-mediated endocytosis and caveolin-independent micropinocytosis [93]. Ribonuclease kappa promotes the internalization of some phenuiviruses [103].

Internalization of SFTSV into host cells requires recruiting clathrin onto the cell membrane to form clathrin-coated pits that further pinch off from the plasma membrane to form discrete vesicles [101]. These vesicles become Rab5+ early endosomes that travel from the cell's periphery towards the nucleus along the intracellular microtubules [102]. During the trafficking, early endosomes exchange various materials with their outside and become more acidic, and early endosomes (pH ~6.0) become late endosomes (pH ~5.5) and lysosomes (pH ~4.5) [104]. A phenuivirus can bind to and enter its mammalian host cell within 30 s and then travel in endosomes for dozens of minutes. In late endosomes, the viral glycoprotein Gc, as a class II membrane fusion protein, mediates the fusion of the viral envelope with the endosomal membrane [50]. This step is triggered by the acidification of late endosomes, which changes the conformation of Gn and thus releases Gc from the control of Gn.

The fusion of viral and endosomal membranes releases the viral RNP complexes into the cytoplasm for replication and transcription of the viral genome. Before replication initiation, the 3' and 5' ends of the genomic RNA (vRNA) are sequestered at different sites of the RdRp protein. Upon initiation, the 3' end of the vRNA is translocated into the RdRp chamber. As elongation proceeds, the vRNA disengages from the N protein. The newly synthesized 5' end and complementary RNA (cRNA) bind to newly produced RdRp and are encapsulated into RNPs with newly produced N proteins. Upon termination, template 5' and 3' ends rebind to their specific sites at the RdRp, and the packaging of the progeny complementary RNP is completed [105]. The synthesized cRNA is then employed as the template to synthesize vRNA by viral RdRp in the same way.

The cytoplasmic tail of phlebovirus Gc proteins is short (e.g., only five amino acid residues for UUKV), while the cytoplasmic tail of Gn is much longer (e.g., 81 amino acid residues for UUKV) [50]. The extended length is associated with additional biological functions: the Gn cytoplasmic tail contains the Golgi localization signal and initiates the budding process and packaging RNPs into virus particles [93].

Transcription of phenuivirid genomes begins with a cap-snatching mechanism, in which host mRNAs are cleaved at a position close to the 5' cap by RdRp [106]. The short capped fragments (10–25 nucleotides long) snatched from the host mRNA are used as primers for viral mRNA transcription, as observed for many other viruses with a single negative-sense RNA genome [106]. After snatching the capped primers, phenuiviruses may use a "prime-and-realign" strategy for transcription initiation. Phenuivirid genomic RNAs do not contain a poly(U) sequence that directs the generation of a poly(A) tail in viral mRNA, so their transcription terminates at termination signal sequences in untranslated regions, which is different from that of many other RNA viruses that terminate their transcription at the short poly(U) stretches. Hence the messenger RNAs of phenuiviruses do not have poly(A) tails.

Viral proteins are translated by ribosomes, and viral precursor glycoproteins are cleaved into Gn and Gc by signal peptidase at the endoplasmic reticulum, where Gn and Gc are decorated with *N*-linked glycans and form heterodimers. The two chaperones, calnexin, and binding immunoglobulin protein, are required to correct Gn and Gc folding [50]. Similarly, protein-disulfide-isomerase catalyzes the folding of Gn and Gc by aiding the formation of disulfide bonds. After that, the Gn/Gc heterodimers are exported via vesicles from the endoplasmic reticulum to the Golgi apparatus, where virions are assembled. Calreticulin

prevents misfolded Gn and Gc from being exported from the endoplasmic reticulum to the Golgi apparatus [50]. The viral nucleocapsid protein and the viral polymerase are synthesized in the cytoplasm, where they form RNP complexes, together with newly produced genomic RNA. Correctly folded Gn/Gc heterodimers are transported into the lipid bilayer membrane of the Golgi apparatus, where they associate with and package RNP complexes via the cytoplasmic tails of Gn during the intracellular budding process [107]. After the budding of new virus particles from the Golgi, virus-containing vesicles are transported to the plasma membrane, where the virions are released via exocytosis [50]. Some phenuiviruses (e.g., SFTSV) may be efficiently delivered to neighboring uninfected cells through extracellular vesicles in receptor-independent exocytosis machinery [93].

Enveloped vertebrate-infecting phenuiviruses enter arthropod cells through interaction between virus surface glycoproteins and host cellular factors. They then replicate in a way similar to the process depicted in **Figure 3** [108]. Like vertebrate-infecting phenuiviruses, the glycoprotein precursor pc2 encoded by the second segment of RSV is cleaved into pc2-N and pc2-C, which are functional homologs of Gn and Gc, but they are nonstructural. pc2-N and pc2-C are required for RSV entrance into the planthopper midgut cells [109]. They interact with RSV RNPs, and pc2-N binds to an unknown receptor. The binding leads to endocytosis followed by internalization of the RNPs/ pc2-N/ pc2-C complexes into early and late endosomes [109]. Under an acidic condition inside the late endosomes, pc2-C undergoes a conformation change that triggers cell membrane fusion, which releases RSV/pc2-N complexes into the cytosol [109]. Another report suggests that the non-structural protein NS4 (p4) of RSV is also associated with RSV's RNPs and forms inclusion bodies that interact with the microvilli of the host midgut epithelium. NS4 hence aids the virus to enter host cells in midgut visceral muscles, alimentary tract, salivary glands, and reproductive system via microvilli formed by actin [108]. Interaction between virus nucleocapsid protein and certain vector proteins, such as the cuticular protein CPR1 and the lipid transport protein vitellogenin, also aids RSV to enter vector cells [46, 110]. CPR1 binds to RNPs of RSV in the insect, stabilizes the virus in the hemolymph, and aids the virus to move to the salivary tissues [110]. Hemocyte-produced vitellogenin binds to RNPs of RSV, and this aids RSV to invade oocytes through the vitellogenin transportation route, which is critical for vertical transmission of RSV [110].

Replication of phenuiviruses of plants and fungi is not well known [39]. These viruses likely enter the cytosol of plant or fungi cells due to mechanical wounds, such as those caused

by grafting or insect sucking [48]. After that, viral RNPs start to disseminate, followed by the transcription, replication, and translation of the viral genomic RNAs under the aids of multiple host factors. Then the virions are assembled, and mature virions begin to infect neighboring cells. The nonstructural protein MP (pc4) of RSV accumulates close to the cell walls of infected rice leaves and aids intercellular trafficking of newly replicated viruses via plasmodesmata. The viral MPs form some tubules, which transiently dilate the openings of plasmodesmata to facilitate the cell-to-cell movement of virions [111, 112]. The viral MPs can also bind to the viral RNA and interact with several host proteins for its function. Hosts have evolved various mechanisms, such as the innate immune responses of ticks, the innate and acquired immune responses of mammals, and RNA silencing of plants and fungi, to inhibit replication of viruses [9, 39, 113-115]. Meanwhile, viruses have mechanisms to avoid these inhibition mechanisms of hosts [46, 116, 117]

7. Transmission of phenuiviruses

Many aspects of transmission of phenuiviruses remain unknown, except for some phenuiviruses of great biomedical significance. In brief, many phenuiviruses are mainly transmitted from arthropods to arthropods of the same taxon (e.g., tick-to-tick, mosquito-to-mosquito, or sandfly-to-sandfly), and from arthropods of certain taxa to vertebrate animals or plants of certain taxa, and vice versa (**Figure 5**). Transmission of some phenuiviruses from infected vertebrates, including humans, to vertebrates, is also possible.

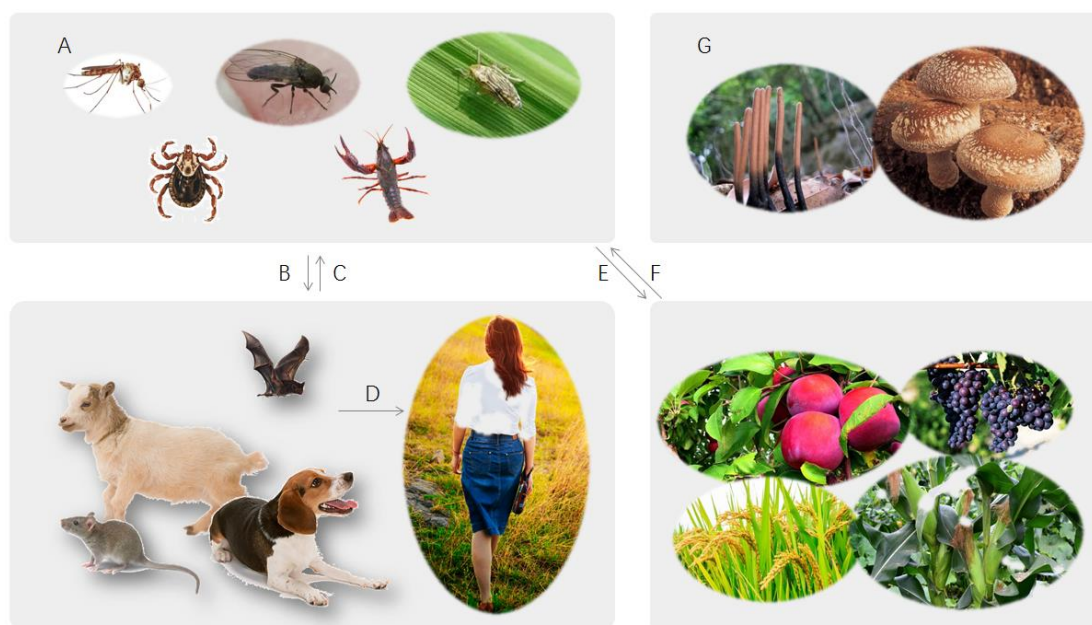


Figure 5. Typical transmission routes of phenuiviruses. **A:** many phenuiviruses replicate and spread in certain arthropods; **B:** many phenuiviruses in arthropods are transmitted to and replicate in vertebrates including humans; **C:** many phenuiviruses in vertebrates are transmitted to and replicate in arthropods; **D:** some phenuiviruses in vertebrates are transmitted to and replicate in humans; **E:** many phenuiviruses in arthropods are transmitted to and replicate in plants; **F:** Many phenuiviruses in plants are transmitted to and replicate in arthropods; **G:** Some phenuiviruses replicate in and are transmitted to certain species of fungi.

SFTSV is maintained in nature by either a tick-to-tick cycle (via transovarial or transstadial transmission) or a tick-to-mammal cycle [12, 118-121]. Ticks serve not only as vectors but also as reservoirs of SFTSV. *Haemaphysalis longicornis* acts as the main transmission vector of SFTSV, although the SFTSV RNA has been identified in several other species of ticks [122]. SFTSV has been detected in various domestic and wild animals, but these vertebrate animals do not develop significant viremia and long viremic periods, suggesting that these animals, like infected humans, are likely accidental hosts [123, 124]. While the primary infection route to humans is through infected tick bites, human-to-human and animal-to-human transmission cases have been reported [125, 126].

Amblyomma americanum ticks are the vector for HRTV, and they are widely distributed across the eastern and central United States [17, 127]. Serologic surveys of mammals and birds subsequently detected HRTV-specific neutralizing antibodies in a variety of mammals, including raccoons and white-tailed deer, suggesting that various medium- and large-sized mammals may serve as hosts, but experimental infection of mice, rabbits, hamsters, chickens, raccoons, goats, and deer with HRTV failed to produce detectable viremia [127].

RVFV is maintained through vertical transovarial transmission in mosquitos between epidemics [128]. RVFV can infect a broad range of arthropods, including midges, sandflies, and ticks. Nevertheless, transmission by arthropods other than mosquitoes is likely only mechanical. RVFV has been detected in over 50 mosquito species in endemic regions [129], predominantly within *Aedes* and *Culex*'s genera. RVFV could survive between epizootics via the vectors of *Aedes* mosquito eggs, which can withstand desiccation and remain viable for several years. Wild ungulates and livestock can also harbor low-level infection. Mosquitoes can also transmit RVFV to wild ungulates, such as African buffalos, giraffes, black rhinos, impalas, and African elephants. During heavy rains, a surge in mosquito populations likely

leads to increased infection of livestock, and viral amplification between numerous vector species and ruminants occurs, which usually further leads to increased human cases and deaths. Human infection can occur via mosquito bites, or more commonly, contact with infected animal tissue and fluid, particularly when humans slaughter animals [8]. Humans are likely dead-end hosts with minimal involvement in viral amplification.

RGSV, RSV, and other plant-infecting phenuiviruses are transmitted horizontally by delphacid planthoppers. Many of them (e.g., RSV) are also vertically transmitted by viruliferous females to their offspring. Unlike RSV, RGSV is not transmitted via eggs [39]. RGSV is transmitted by the brown planthopper *Nilaparvata lugens* and two other *Nilaparvata* species, and RSV is transmitted by the small brown planthopper *Laodelphax striatellus*. RGSV naturally infects only rice and the vector *N. lugens*. In the tropics, RGSV and *N. lugens* are generally endemic in rice-planting areas. In cooler areas, *N. lugens* migrates annually during the monsoon season from the tropics. When the incidence of RGSV is high, the rice crop also suffers direct damage from the feeding of *N. lugens*, and usually in addition from rice ragged stunt virus, which is also transmitted by *N. lugens*. Rice cultivars with resistance to *N. lugens* have been planted widely in Asia, and the incidence of RGSV is low to nonexistent in these resistant cultivars [130]. However, new biotypes of *N. lugens* can overcome the resistance and feed in these cultivars [131].

RGSV and RSV infect the midgut epithelium of planthoppers, spread into visceral muscle tissues, disseminate in the hemolymph and other organs, and then move to the salivary glands, from which the viruses can be transmitted to a new plant host [46]. Planthoppers can transmit tenuiviruses to new plant hosts 4–31 days after obtaining the viruses from infected plants [46]. RGSV replicates in the principal and accessory salivary glands, but not in neural tissues and ovarioles, whereas RSV replicates in both the ovarioles and the principal salivary glands, but not in the accessory salivary glands.

Some phenuiviruses employ arthropods, and some other phenuiviruses employ vertebrates or plants as their amplifying and reservoir hosts. Rodents and bats could be amplifying hosts of some phenuiviruses pathogenic to humans, such as SFTSV and RVFV [132-134].

Because many phenuiviruses of biomedical significance are transmitted by arthropods, their infections in humans, domestic animals, or crops are more prevalent in certain seasons and certain regions [39].

Some grapevine phenuiviruses are transmitted through graft [47]. Fungi phenuiviruses are possibly transmitted horizontally in the same species or among similar species of fungi [2]. The involvement of arthropods in the transmission of these mycoviruses remains unknown.

8. Pathogenesis of phenuiviruses

Different pathogenic phenuiviruses have different mechanisms of pathogenesis, as shown below with the examples of several pathogenic phenuiviruses.

After SFTSV enters a human body via tick biting, it replicates in dendritic cells and macrophages, mainly at the biting site. Then the virus enters lymph nodes nearby and replicates in immune cells, such as B-cells and macrophages. Replication of SFTSV impairs host immune responses and leads to viremia, which further aids the virus to replicate in more host cells, particularly in the spleen. After that, SFTSV infection causes thrombocytopenia, bleeding in the gastrointestinal tract, abdomen, and lungs, liver necrosis, cytokine storm, and severe inflammatory responses [14, 135]. Thrombocytopenia likely results from clearance of SFTSV-bound platelets by macrophages and increased consumption of peripheral platelets due to virus-induced disseminated intravascular coagulation and endothelial damage [14]. The cytokine storm is characterized by the hyperproduction of proinflammatory cytokines and chemokines in response to the virus replication, causing severe pathological changes and multiorgan dysfunction [136].

SFTSV RNAs are typical pathogen-associated molecular patterns, which could be specifically identified by pattern recognition receptors, including RIG-I-like-receptors (RLRs) [117]. RLRs can be activated by binding to short (<300 base pairs) dsRNA with a 5'triphosphate that is formed during SFTSV infection [137, 138]. Activated RLRs recruit the mitochondria outer membrane protein, MAVS, and mediate downstream signaling cascade activation, leading to phosphorylation and nuclear translocation of interferon-regulatory factors and NF- κ B. They also induce the production of type I interferon that binds to the interferon- α/β receptor and mediates the activation of STAT1 and STAT2 heterodimers, and transcriptional activation of IFN-stimulated genes are important in the host innate immune system against viral infection [139].

In host cells, SFTSV NSs forms inclusion bodies that capture multiple host immune molecules, such as RIG-I, STAT1, and STAT2 [135, 140, 141]. Hence SFTSV NSs aids the virus to evade the host innate immune response and serve as a critical virulence molecule

[117]. RVFV is similar to SFTSV in pathogenesis [117, 142], and deletion of the NSs gene greatly attenuates RVFV [39, 51].

In recent years, substantial advances on the pathogenesis of a few plant-infecting phenuiviruses (e.g., RSV and RGSV) have been achieved [116, 143]. RSV invades plants when small brown planthoppers suck them. Infection at the seedling stage causes severe leaf damage and systemic symptoms, frequently leading to rice death. After the invasion, RSV immediately moves to meristems (e.g., apical domes and leaf primordia) at the base of the seedling, multiplies there, and spreads systemically along with active cell division [144].

Symptoms of plants infected with phenuiviruses likely result from the hijacking of important plant functions, such as host cell replication and translation machinery, host cytoskeleton, ion homeostasis, and hormone homeostasis, by viral components [116]. For instance, the CBL–CIPK Ca^{2+} signaling network involved in the regulation of ion homeostasis is changed by the p5 protein of RGSV, which decreases potassium content and causes symptoms of potassium deficiency [143]. RSV infection can suppress jasmonic acid-mediated resistance via hijacking the brassinosteroid signaling pathway in rice [145]. RGSV infection can activate some genes associated with tillering and involve the inactivation of gibberellic acid and indole-3-acetic acid, which may cause the excess of tillering and the stunting of infected plants [146]. The RGSV protein p3 induces an E3 ubiquitin ligase that triggers ubiquitin–proteasome-mediated degradation of one subunit of plant-specific RNA polymerase IV, which is necessary for RNA-directed DNA methylation [147]. Virus-derived small interfering RNA in infected *Nicotiana benthamiana* can influence eIF4A mRNA regulation, causing leaf twisting and stunting [148]. Expression of some genes related to chloroplast is substantially suppressed by infection of RGSV and RSV, which often causes photosynthesis defects and chlorotic symptoms [56, 146, 148-150].

9. Control of pathogenic phenuiviruses

The control of pathogenic phenuiviruses relies on systematic surveillance, correct diagnosis, and proper interventions [14, 28]. Symptoms and epidemiological information are useful for the preliminary diagnosis of some phenuivirid diseases. However, confirmation of phenuivirid diseases should be based on symptoms, epidemiological information, and correct detection of the nucleic acids, proteins, and/or antibodies specific to relevant phenuiviruses [28, 151-153].

There are currently no specific therapeutics or vaccines to combat human infections of SFTSV, HTRV, RVFV, and other phenuiviruses. Ferret and other animal models of some human phenuivirid diseases have been developed, which are valuable in developing therapeutics and preventive measures [14, 154]. Live-attenuated virus-based, viral vector-based, and DNA-based vaccines for SFTS, which are expected to be used for humans and companion dogs and cats, have been under investigation, and their efficacy has been confirmed using animal models [155], but none of them have entered clinical trials.

RVFV vaccines have been used in animals in endemic regions, and human RVFV vaccines have entered clinical trials [156, 157]. Inactivated RVF candidate vaccine requires three doses and the live-attenuated MP-12 candidate vaccine requires only one dose to induce protective immunity [157]. An adenovirus-vector RVF vaccine is also under clinical trials, and two other live-attenuated RVF vaccines, RVFV-4s and DDVax, have been under preclinical research [28].

Control of severe plant diseases caused by phenuiviruses, e.g., RSV and RGSV, mainly relies on pesticides to control their vector plant-hoppers. Pesticides are also widely employed to reduce arthropods to control various human and animal arboviruses, including phenuiviruses. However, pesticides are costly and harmful to humans and animals and heavily pollute the environment [145]. Breeding of virus-resistant cultivars is an economical, effective, and environment-friendly measure for controlling severe viral plant diseases [145, 158]. One RSV-resistance gene in the rice genome, *STVII*, has been identified [36]. This gene encodes a sulfotransferase catalyzing the conversion of salicylic acid to sulphonated salicylic acid. Another gene, *Stvb-i*, is also highly associated with RSV resistance, and rice varieties harboring *Stvb-i* have shown stable resistance for over 50 years in paddy fields of Japan [144]. However, virus mutants can resume virulence in cultivars introgressed with natural resistance genes [39, 159]. The expression of various viral genes has proven effective in preventing or reducing infection by plant viruses through RNA interference (RNAi), also termed RNA silencing [160].

Control of arthropod vectors is important and challenging for controlling arthropod-borne arboviruses, including some pathogenic phenuiviruses worldwide [161]. For mosquitoes, researches focus on genetically modified vectors, eave tubes, attractive toxic sugar baits, and biocontrol agents; for ticks, researches focus on repellents, acaricides, and behavior-based control tools [162]. Anti-tick vaccines that could be used in humans or animals targeting pathogen transmission are under investigation [162].

10. Discussion

From the panorama of phenuiviruses depicted above, phenuiviruses are highly adaptive with great significance in the health of humans, animals, and plants. In recent years, the taxonomy of *Phenuiviridae* has been expanded and revised rapidly, and research targeting various aspects of this important virus family has made significant progress. Meanwhile, many aspects of this family need further investigation. For instance, the phenuiviruses identified could be only a small portion of the phenuiviruses circulating on the earth.

In the coming years, many research advances of *Phenuiviridae* can be envisaged. More novel genera or species in *Phenuiviridae* will be discovered, particularly from novel regions or host species, like reported recently novel phenuiviruses from grass, nematodes, and bats [71, 163-165]. Some genomic segments of important known phenuiviruses (e.g., *Tacheng uukuvirus*, *Dipteran beidivirus*, *Laurel Lake laulavirus*, and some tenuiviruses) shall be sequenced or parsed [61]. The taxonomy of *Phenuiviridae* shall be further expanded and revised frequently, structures and functions of genes of more phenuiviruses shall be revealed, and more evolutionary features of phenuiviruses shall be inferred. The mechanisms about the replication and trans-species infection of more phenuiviruses shall be further investigated. The biomedical importance and pathogenesis of more phenuiviruses shall be clarified through target surveillance, and molecular studies and more vaccines and other measures for the control of highly pathogenic phenuiviruses shall be evaluated. The panorama depicted in this review can be a useful reference for these explorations.

Data availability

Data of this review are provided by relevant references and are available upon request to the corresponding author through email.

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