This form should be used for all taxonomic proposals. Please complete all those modules that are applicable (and then delete the unwanted sections). For guidance, see the notes written in blue and the separate document "Help with completing a taxonomic proposal"

Please try to keep related proposals within a single document; you can copy the modules to create more than one genus within a new family, for example.

MODULE 1: TITLE, AUTHORS, etc

Code assigned:	***2014.008a-hV***	(to be completed by ICTV officers)

Short title: New Classification Scheme for *Hepeviridae*
(e.g. 6 new species in the genus *Zetavirus*)

Modules attached (modules 1 and 9 are required)	**1** ☒	**2** ☒	**3** ☒	**4** ☐	**5** ☐
	6 ☐	**7** ☒	**8** ☒	**9** ☒	

Author(s) with e-mail address(es) of the proposer:

Michael A. Purdy (mup3@cdc.gov)
Donald B. Smith (donald.smith.mail@gmail.com)
Peter Simmonds (peter.simmonds@ed.ac.uk)
Suzanne U. Emerson (suzanne.emerson1@verizon.net)
Tim Harrison (T.Harrison@ucl.ac.uk)
Xiang-Jin Meng (xjmeng@vt.edu)
Hiroaki Okamoto (hokamoto@jichi.ac.jp)
Wim H. M. Van der Poel (Wim.vanderPoel@wur.nl)
Shahid Jameel (jameelshahid@gmail.com)

List the ICTV study group(s) that have seen this proposal:

A list of study groups and contacts is provided at http://www.ictvonline.org/subcommittees.asp . If in doubt, contact the appropriate subcommittee chair (fungal, invertebrate, plant, prokaryote or vertebrate viruses)	Hepeviridae Study Group

ICTV-EC or Study Group comments and response of the proposer:

The Hepeviridae Study Group helped to draft this proposal. See the attached manuscript.

Date first submitted to ICTV: June, 2014
Date of this revision (if different to above):

MODULE 2: **NEW SPECIES**

creating and naming one or more new species.

If more than one, they should be a group of related species belonging to the same genus. All new species must be placed in a higher taxon. This is usually a genus although it is also permissible for species to be "unassigned" within a subfamily or family. Wherever possible, provide sequence accession number(s) for one isolate of each new species proposed.

Code	***2014.008aV***	(assigned by ICTV officers)

To create one new species within:

Genus:	***Piscihepevirus* (new)**
Subfamily:	
Family:	***Hepeviridae***
Order:	

Fill in all that apply.

- If the higher taxon has yet to be created (in a later module, below) write "**(new)**" after its proposed name.
- If no genus is specified, enter "**unassigned**" in the genus box.

Name of new species:	**Representative isolate:**	**GenBank sequence accession number(s)**
Piscihepevirus A	Hennan Lake	HQ731075

Reasons to justify the creation and assignment of the new species:

- Explain how the proposed species differ(s) from all existing species.
    - If species demarcation criteria (see module 3) have previously been defined for the genus, **explain how the new species meet these criteria**.
    - If criteria for demarcating species need to be defined (because there will now be more than one species in the genus), please state the proposed criteria.
- Further material in support of this proposal may be presented in the Appendix, Module 9

This document includes a proposal to create two new genera within the family *Hepeviridae*, *Piscihepevirus* and *Orthohepevirus*. All known cutthroat trout virus isolates would be included as members of the species *Piscihepevirus A* within the genus *Piscihepevirus*. As sequences from most of the cutthroat trout virus isolates are only 262 nt in length, there is not enough information currently to delineate demarcation criteria for species within this genus.

MODULE 2: **NEW SPECIES**

creating and naming one or more new species.

If more than one, they should be a group of related species belonging to the same genus. All new species must be placed in a higher taxon. This is usually a genus although it is also permissible for species to be "unassigned" within a subfamily or family. Wherever possible, provide sequence accession number(s) for one isolate of each new species proposed.

Code	***2014.008bV***	(assigned by ICTV officers)

To create two new species within:

Genus:	***Hepevirus*** **(proposed name *Orthohepevirus*)**
Subfamily:	
Family:	***Hepeviridae***
Order:	

Fill in all that apply.
- If the higher taxon has yet to be created (in a later module, below) write "**(new)**" after its proposed name.
- If no genus is specified, enter "**unassigned**" in the genus box.

Name of new species:	**Representative isolate:**	**GenBank sequence accession number(s)**
Orthohepevirus C	R63	GU345042
Orthohepevirus D	BatHEV/BS7/GE/2009	JQ001749

Reasons to justify the creation and assignment of the new species:

- Explain how the proposed species differ(s) from all existing species.
    - If species demarcation criteria (see module 3) have previously been defined for the genus, **explain how the new species meet these criteria**.
    - If criteria for demarcating species need to be defined (because there will now be more than one species in the genus), please state the proposed criteria.
- Further material in support of this proposal may be presented in the Appendix, Module 9

In the past decade the number of hosts known to be infected by *Hepeviridae* has expanded dramatically, as has the diversity of virus variants characterized to date. This has necessitated a major restructuring of the current classification scheme for this family. Evidence is presented in section 2014.008eV and the appendix for the creation of two genera in this family. One genus would include all known sequences of cutthroat trout virus (comprising isolates from trout and other fish species) and the other would include all known *Hepeviridae* variants that infect avians and mammals. The species in the genus *Orthohepevirus* are described here. Demarcation criteria are based on phylogenetic analyses of hepatitis E virus sequences (see Module 3). Viral sequence variants of a particular species form a well-defined phylogenetic grouping and have amino acid sequence p-distances of less than 0.3 to the defined type species in certain subgenomic regions (see attached manuscript in the appendix). Avian sequences are not segregated into a new genus because the amino acid sequence p-distances between avian sequences and representatives of *Orthohepevirus* species *A*, *C* and *D* in three different subgenomic regions are all are less than 0.55 (figures 1, 2 and 3). *Orthohepevirus A* includes all viral variants known to infect humans (presently known as genotypes 1-4) as well as further variants infecting camels and wild boars. Additional hosts for these viruses include swine, deer, rabbits, rats, and mongooses. *Orthohepevirus B* includes all variants known to infect avians.

Orthohepevirus C includes most variants that infect rats and all variants known to infect ferrets. *Orthohepevirus D* includes all variants known to infect bats. It should be noted that rats may be infected with both *Orthohepevirus A* and *Orthohepevirus C* (Johne et al., 2010; Kanai et al., 2012; Lack et al., 2013).

MODULE 3: **NEW GENUS**

creating a new genus

Ideally, a genus should be placed within a higher taxon.

Code	***2014.008cV***	(assigned by ICTV officers)

To create a new genus within:

Subfamily:	
Family:	***Hepeviridae***
Order:	

Fill in all that apply.

- If the higher taxon has yet to be created (in a later module, below) write “**(new)**” after its proposed name.
- If no family is specified, enter “**unassigned**” in the family box

naming a new genus

Code	***2014.008dV***	(assigned by ICTV officers)

To name the new genus: *Piscihepevirus*

Assigning the type species and other species to a new genus

Code	***2014.008eV***	(assigned by ICTV officers)

To designate the following as the type species of the new genus

Piscihepevirus A	Every genus must have a type species. This should be a well characterized species although not necessarily the first to be discovered

The new genus will also contain any other new species created and assigned to it (Module 2) and any that are being moved from elsewhere (Module 7b). **Please enter here the TOTAL number of species (including the type species) that the genus will contain:**

1.

Reasons to justify the creation of a new genus:

Additional material in support of this proposal may be presented in the Appendix, Module 9

Cutthroat trout virus exhibits the characteristic three overlapping open reading frame (ORF) genome arrangement seen among avian and mammalian members of the family *Hepeviridae*. Additionally, motifs characteristic for methyltransferase, papain-like protease, macro domain, helicase and replicase are found in the cutthroat virus ORF1. However, amino acid sequence similarities between cutthroat virus and the avian and mammalian members of the family are only 26-27% (ORF1), 18-21% (ORF2) and 13-16% (ORF3). In contrast, these similarities are 42-49% (ORF1), 42-55% (ORF2) and 20-29% (ORF3) between avian and mammalian *Hepeviridae*. MotifScan was used to identify clearly homologous subgenomic regions. Three regions were identified; methyltransferase (ORF1-28 to 389 aa), helicase (ORF1-971 to 1185 aa), replicase (ORF1-1249 to 1671 aa; reference sequence M73218). Each region was aligned and maximum-likelihood phylogenetic trees were generated (figure 1; see the attached manuscript for supporting details). Branch lengths of these trees demonstrate that cutthroat trout virus is substantially divergent from other members of *Hepeviridae*. Pairwise distances among these subgenomic amino acid sequences form non-overlapping distributions (figure 2), with the greatest p-distances (> 0.55) observed in comparisons between cutthroat trout virus and other *Hepevirus* variants. Additionally, cutthroat trout virus has a different genome organization from members of the *Orthohepevirus* genus. While the three partially overlapping ORF genome structure is maintained, ORF3 is displaced to the middle of ORF2, rather than overlapping the 5'-end of ORF2 as seen in avian and mammalian HEVs.

Origin of the new genus name:

All previous *Hepeviridae* host species have been either avians or mammals. In 2011 cutthroat trout virus, isolated from trout in 1988 (Hedrick et al., 1991) was identified as belonging to the family *Hepeviridae* (Batts et al., 2011). All known variants only infect fish, and only have 13-27% amino acid sequence similarity in ORF1, ORF2 or ORF3 with avian and mammalian variants.

Reasons to justify the choice of type species:

HQ731075 was the first full-length sequence of this viral variant to be published.

Species demarcation criteria in the new genus:

If there will be more than one species in the new genus, list the criteria being used for species demarcation and explain how the proposed members meet these criteria.

At present all known cutthroat trout virus sequences appear to belong to a single species (*Piscihepevirus A*). Because most of the known isolates of this virus are represented by sequences that are only 262 nt in length, there is a need to await the characterization of further full-length genome sequences before species demarcation criteria can be developed.

MODULE 7: **REMOVE and MOVE**

Use this module whenever an existing taxon needs to be removed:

- *Either* to abolish a taxon entirely (when only part (a) needs to be completed)
- *Or* to move a taxon and re-assign it e.g. when a species is moved from one genus to another (when BOTH parts (a) and (b) should be completed)

Part (a) taxon/taxa to be removed or moved

Code	***2014.008fV***	(assigned by ICTV officers)

To remove the following taxon (or taxa) from their present position:

Avian hepatitis E virus **(proposed name *Orthohepevirus B*)**

The present taxonomic position of these taxon/taxa:

Genus:	***Unassigned***	Fill in all that apply.
Subfamily:		
Family:	***Hepeviridae***	
Order:		

If the taxon/taxa are to be abolished (i.e. not reassigned to another taxon) write "yes" in the box on the right	

Reasons to justify the removal:
Explain why the taxon (or taxa) should be removed

Please refer to 2014.008gV

Part (b) re-assign to a higher taxon

Code	***2014.008gV***	(assigned by ICTV officers)

To re-assign the taxon (or taxa) listed in Part (a) as follows:

Genus:	***Hepevirus*** **(proposed name *Orthohepevirus)***	Fill in all that apply. • If the higher taxon has yet to be created write "**(new)**" after its proposed name and complete relevant module to create it. If no genus is specified, enter "**unassigned**" in the genus box.
Subfamily:		
Family:	***Hepeviridae***	
Order:		

Reasons to justify the re-assignment:

- If it is proposed to re-assign species to an existing genus, please explain how the proposed species differ(s) from all existing species.
    - If species demarcation criteria (see module 3) have previously been defined for the genus, explain how the new species meet these criteria.
    - If criteria for demarcating species need to be defined (because there will now be more than one species in the genus), please state the proposed criteria.
- Provide accession numbers for genomic sequences
- Further material in support of this proposal may be presented in the Appendix, Module 9

With the recognition of cutthroat trout virus as a member of the *Hepeviridae* family, and the divergence of cutthroat trout virus with respect to other members of the family, an expansion of the genus *Hepevirus* (proposed name *Orthohepevirus*) to include two both species *Hepatitis E virus* (proposed name *Orthohepevirus A*) and *Avian hepatitis E virus* (proposed name *Orthohepevirus B*) is suggested.

The change from the current name of *Hepevirus* to *Orthohepevirus* for avian and mammalian HEVs is used to make it clear that not all members of *Hepeviridae* belong to the same genus. This proposal suggests the existence of two genera in the *Hepeviridae* family.

Species demarcation criteria in the expanded genus *Hepevirus* (proposed name *Orthohepevirus*):

If there will be more than one species in the new genus, list the criteria being used for species demarcation and explain how the proposed members meet these criteria.

Species within *Orthohepevirus* cluster into four distinct clades supported by >95% of bootstrap replicates (Figure 1) and share amino acid sequence similarities of 42-49% (ORF1), 42-55% (ORF2) and 20-29% (ORF3) with p-distances of < 0.55 in three homologous regions (Figure 2). It is proposed that these clades correspond to four species. Their designations are; *Orthohepevirus A, Orthohepevirus B, Orthohepevirus C, Orthohepevirus D*.

Orthohepevirus A includes all viruses known to infect humans, swine, deer, boar, rabbits, camels and mongooses as well as a minority of variants infecting rats. *Orthohepevirus B* includes all viruses known to infect avians. *Orthohepevirus C* includes most viruses known to infect rats and all those known to infect ferrets, and *Orthohepevirus D* includes all viruses known to infect bats. The designations chosen were selected for two reasons. First, they will not be compromised by current or future discoveries on the extent of host range. For example, based on partial genome sequences, *Orthohepevirus C* variants have been isolated from *Rattus* and *Bandicota* species (Li et al., 2013), which are members of the order *Rodentia*, from Asian musk shrews (Guan et al., 2013), which are members of order *Soricomorpha*, and from ferrets (Raj et al., 2012) and mink (Krog et al., 2013), which are members of the order *Carnivora*. Wider screening may reveal wider host ranges than presently recognized. Second, rats may be infected with variants from *Orthohepevirus A* and *Orthohepevirus C* (Johne et al., 2010; Kanai et al., 2012; Lack et al., 2013). Thus naming an *Orthohepevirus* species after a specific host could lead to confusion.

MODULE 8: **NON-STANDARD**

Template for any proposal not covered by modules 2-7. This includes proposals to change the name of existing taxa (but note that stability of nomenclature is encouraged wherever possible).

non-standard proposal

Code	***2014.008hV***	(assigned by ICTV officers)

Title of proposal: (i) Change the name of the genus *Hepevirus* to *Orthohepevirus.* (ii) Change the name of the species *Hepatitis E virus* to *Orthohepevirus A.* (iii) Change the name of the species *Avian hepatitis E virus* to *Orthohepevirus B.*

Text of proposal:

With the recognition of cutthroat trout virus as a member of the *Hepeviridae* family, and the divergence of cutthroat trout virus with respect to other members of the family, a restructuring of *Hepeviridae* to include two genera is suggested. The change from the current usage of *Hepevirus* to *Orthohepevirus* for avian and mammalian HEVs and *Piscihepevirus* for trout HEVs is used. If the suggestion for splitting known HEV sequences into two genera is acceptable, the genus name *Hepevirus* should be changed to *Orthohepevirus* to make it clear that not all members of *Hepeviridae* belong to the same genus.

The constituent species of the genus *Hepevirus* will be moved to the new genus *Orthohepevirus*. The species *Hepatitis E virus* will be renamed *Orthohepevirus A*, and the species *Avian hepatitis E virus* will be renamed *Orthohepevirus B.*

The renaming of the genus *Hepevirus* as *Orthohepevirus* and the species *Hepatitis E virus* as *Orthohepevirus A* does not change the current taxonomic relationship between *Hepevirus* and *Hepatitis E virus*.

MODULE 9: **APPENDIX**: supporting material

additional material in support of this proposal

References:

Batts, W., et al. (2011). "A novel member of the family Hepeviridae from cutthroat trout (Oncorhynchus clarkii)." Virus Res **158**(1-2): 116-123.

Guan, D., et al. (2013). "Asian musk shrew as a reservoir of rat hepatitis E virus, China." Emerg Infect Dis **19**(8): 1341-1343.

Hedrick, R. P., et al. (1991). "A Small RNA Virus Isolated from Salmonid Fishes in California, USA." Can J Fish Aquat Sci **48**(1): 99-104.

Johne, R., et al. (2010). "Detection of a novel hepatitis E-like virus in faeces of wild rats using a nested broad-spectrum RT-PCR." J Gen Virol **91**(3): 750-758.

Kanai, Y., et al. (2012). "Hepatitis E virus in Norway rats (Rattus norvegicus) captured around a pig farm." BMC Res Notes **5**: 4.

Lack, J. B., et al. (2012). "Hepatitis E Virus Genotype 3 in Wild Rats, United States." Emerg Infect Dis **18**(8): 1268-1273.

Li, W., et al. (2013). "High prevalence of rat hepatitis E virus in wild rats in China." Vet Microbiol **165**(3-4): 275-280.

Raj, V. S., et al. (2012). "Novel Hepatitis E Virus in Ferrets, the Netherlands." Emerg Infect Dis **18**(8): 1369-1370.

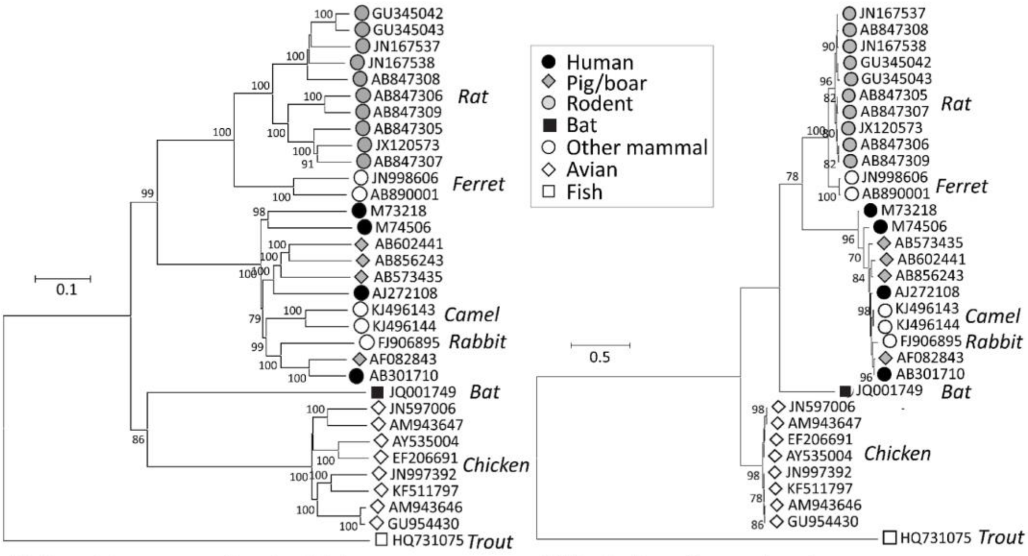
Smith, D. B., et al. (2013). "Genetic variability and the classification of hepatitis E virus." J Virol **87**(8): 4161-4169.

Annex:

Include as much information as necessary to support the proposal, including diagrams comparing the old and new taxonomic orders. The use of Figures and Tables is strongly recommended but direct pasting of content from publications will require permission from the copyright holder together with appropriate acknowledgement as this proposal will be placed on a public web site. For phylogenetic analysis, try to provide a tree where branch length is related to genetic distance.

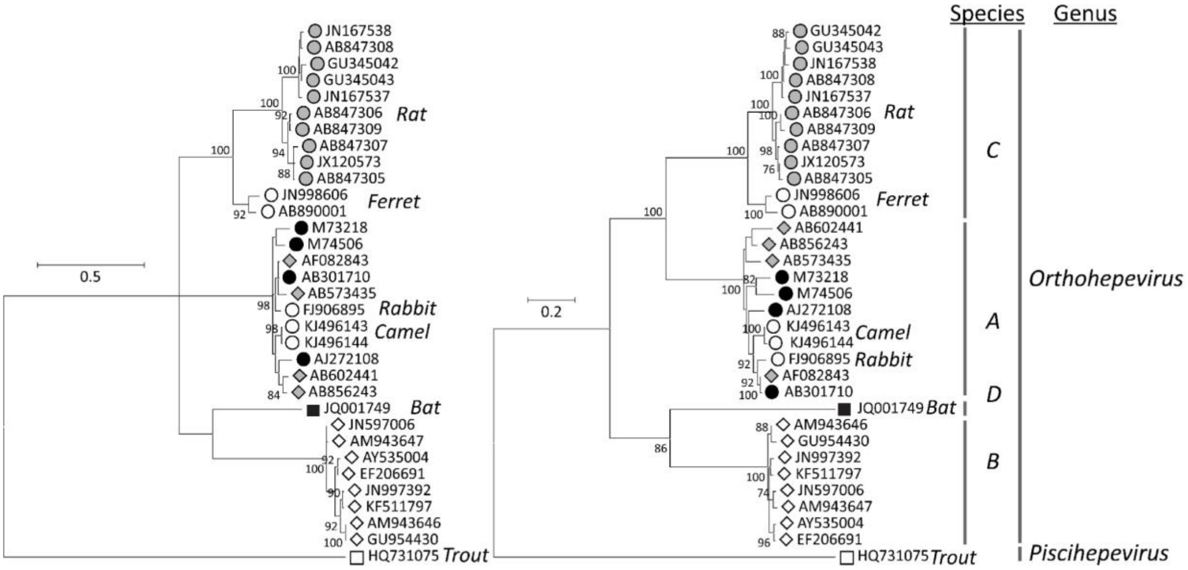
Additional supporting information is contained in the attached manuscript. Smith, D.B., Simmonds, P., Jameel, S., Harrison, T.J., Meng, X.-J., Okamoto, H., Van der Poel, W.H.M., Purdy, M.A., 2014. Consensus Proposals for Classification of the Family Hepeviridae. J Gen Virol 95, 2223-2232.

Fig. 1 Phylogenetic analysis of members of the family *Hepeviridae*. (A) Neighbour-joining tree of p-distances among aligned complete genome sequences. Bootstrap support for individual branches is indicated. (B) Maximum likelihood tree for amino acid sequences in methyltransferase domain (ORF1-28 to ORF1-389) (C) helicase domain (ORF1-971-ORF1-1185) (D) RNA-dependent RNA polymerase domain (OR1-1249-1671) (E) Proposed classification. Maximum likelihood trees were computed using the LG model with a gamma distribution of evolutionary rates among sites with some invariant sites. Branches supported by >70% of bootstrap replicates are indicated.



A) Complete genome (nucleotide)

B) Methyltransferase domain



C) Helicase domain

D) RNA polymerase domain

E) Proposed Classification

Fig. 2 Frequency distribution of distances among sequences of members of the family *Hepeviridae*. Histograms show the frequency of amino acid sequence p-distances among amino acid sequences of the methyltransferase (ORF1 -28 to ORF1-389, blue line), helicase (ORF1-971 to ORF1-1185, green line) and RdRP (ORF1-1249 to ORF1-1671, red line) domains. The methyltransferase and helicase distance frequencies are shifted by 160 and 80 respectively in order to improve legibility. Solid boxes – range of inter-generic distances; open box - range of inter-specific distances.

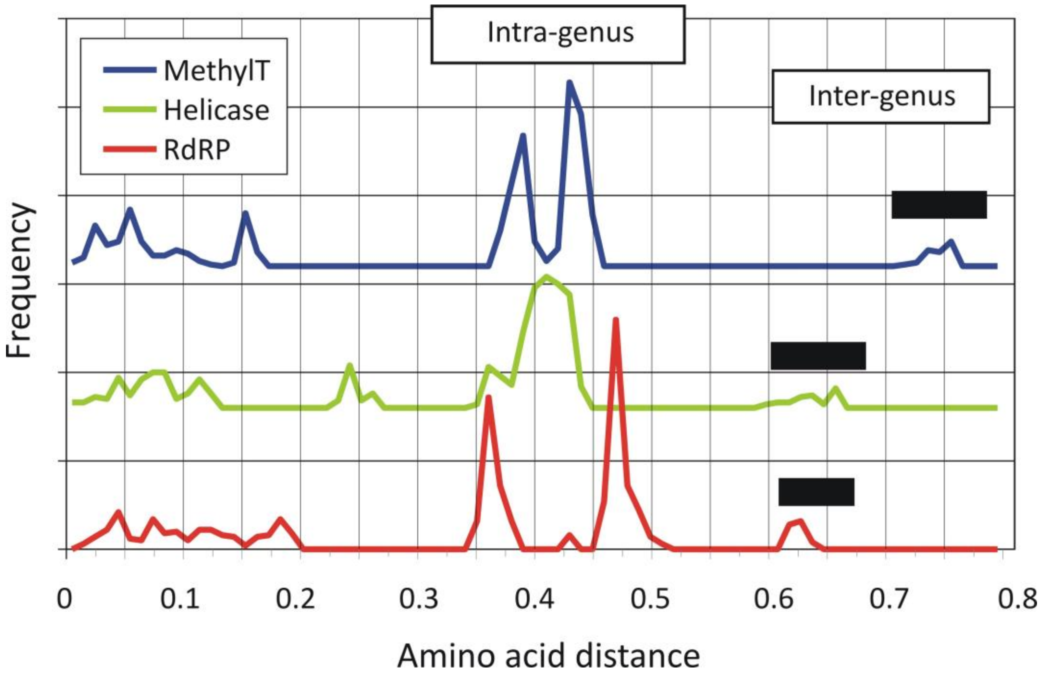
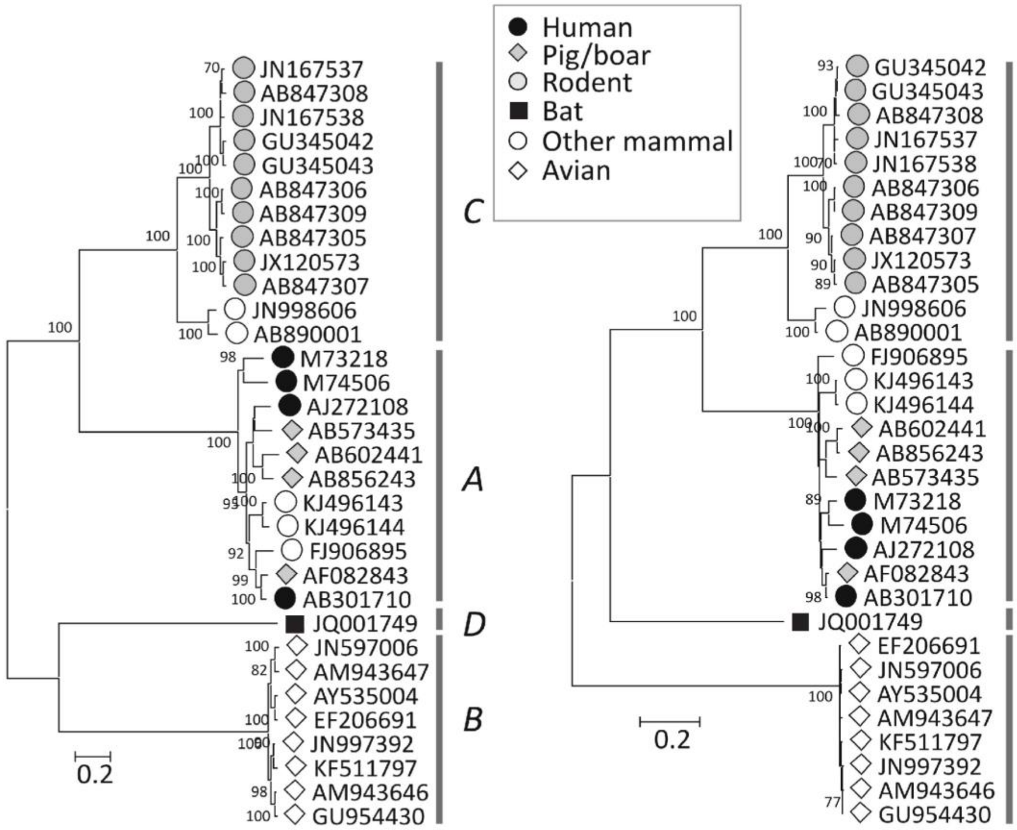
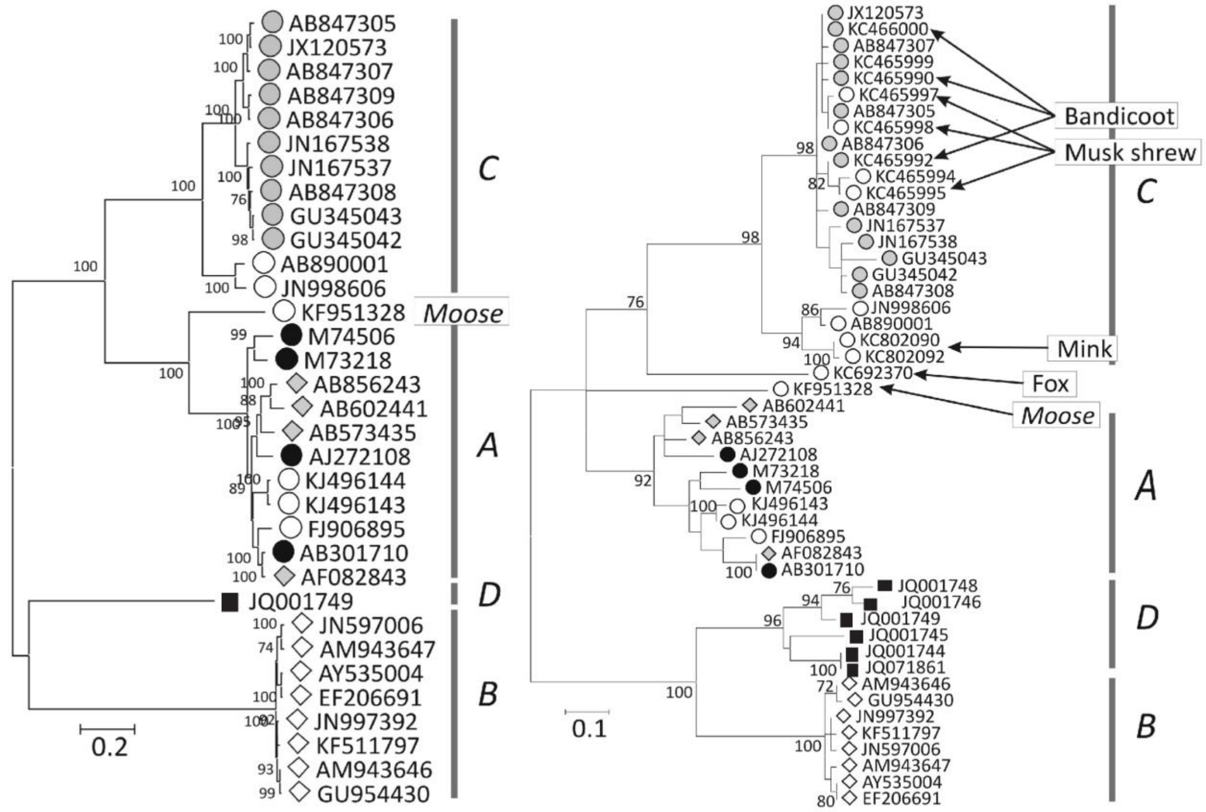


Fig. 3 Phylogenetic analyses of members of the genus *Orthohepevirus*. Maximum likelihood tree for amino acid sequences in (A) ORF1 and (B) ORF2 (C) ORF1-779 to the end of ORF2 with the addition of KF951328 from moose, (D) ORF1-1420 to ORF1-1505 with the addition of sequences from mink, fox, greater bandicoot, Asian musk shrew and bat. Maximum likelihood trees were produced using the LG model with a gamma distribution of evolutionary rates among sites with some invariant sites. Branches supported by >70% of bootstrap replicates are indicated.



A) ORF1

B) ORF2



C) ORF1(779-end) + ORF2

D) ORF1 (1420-1505)

DISCLAIMER

This information is distributed solely for the purpose of pre-dissemination peer review under applicable information quality guidelines. It has not been formally disseminated by the Centers for Disease Control and Prevention/Agency for Toxic Substances and Disease Registry. It does not represent and should not be construed to represent any agency determination or policy. Use of trade names is for identification only and does not imply endorsement by the U.S. Department of Health and Human Services, the Public Health Service, or the Centers for Disease Control and Prevention. The conclusions in this document are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention. The authors declare that they have no conflict of interest.