Virus classification and support for different stakeholders

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Stakeholders in virus classification

- ICTV members!
- The wider virology community
  - Provides the framework for understanding virus relationships
  - Inference of the evolutionary basis for shared and divergent characteristics
  - Framework for understanding origins, zoonoses and adaptive evolution
- Educators
  - Stability in virus definitions and reference
- Clinicians, Veterinarians and Phytologists
  - Aetiological agents of infectious disease
  - Somewhat agnostic of the nature of the infectious agent (bacteria, fungi, virus, viroid)
  - Requires a clear reference to the infectious agent
- Regulators of international traffic, categorisation for biosecurity
  - Agents have to be unambiguously defined
  - Require clear inclusion and exclusion criteria for reference
  - Should use internationally recognised nomenclature

Species in Virology

- Classification of animals and plants
    - Species mark the finest division possible in phenotypes
    - Biological species principle (Mayr, 1942), interbreeding capability defines species membership
    - Fundamental to shared gene pools and organism evolution
    - The term is used, but must be defined differently for asexual organisms, including bacteria and viruses.

- Virus species

    "*A species is the lowest taxonomic level in the hierarchy approved by the ICTV. A species is a monophyletic group of MGEs whose properties can be distinguished from those of other species by multiple criteria*" – ICTV Rule 3.2 2023

- Criteria include phenotype and genetic relatedness:

    "*may include, but are not limited to, natural and experimental host range, cell and tissue tropism, pathogenicity, vector specificity, antigenicity, and the degree of relatedness of their genomes or genes*"

- Species have to be monophyletic

- No intention to specify a degree of genetic similarity in species assignment

- Phenotypic properties to define species and higher taxa are optional

Is the ICTV species level adequate and appropriate?

- One virus – one species
  - ✔ Original disease-based assignment
  - One species, one pathogen
  - Arboviruses, most plant viruses

Yellow fever virus – *Orthoflavivirus flavi*
Cowpea mosaic virus – *Comovirus vignae*

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  - More often found in sequence-based classifications
  - The identity of the species insufficiently describes the pathogen

Yellow fever virus – *Orthoflavivirus flavi*
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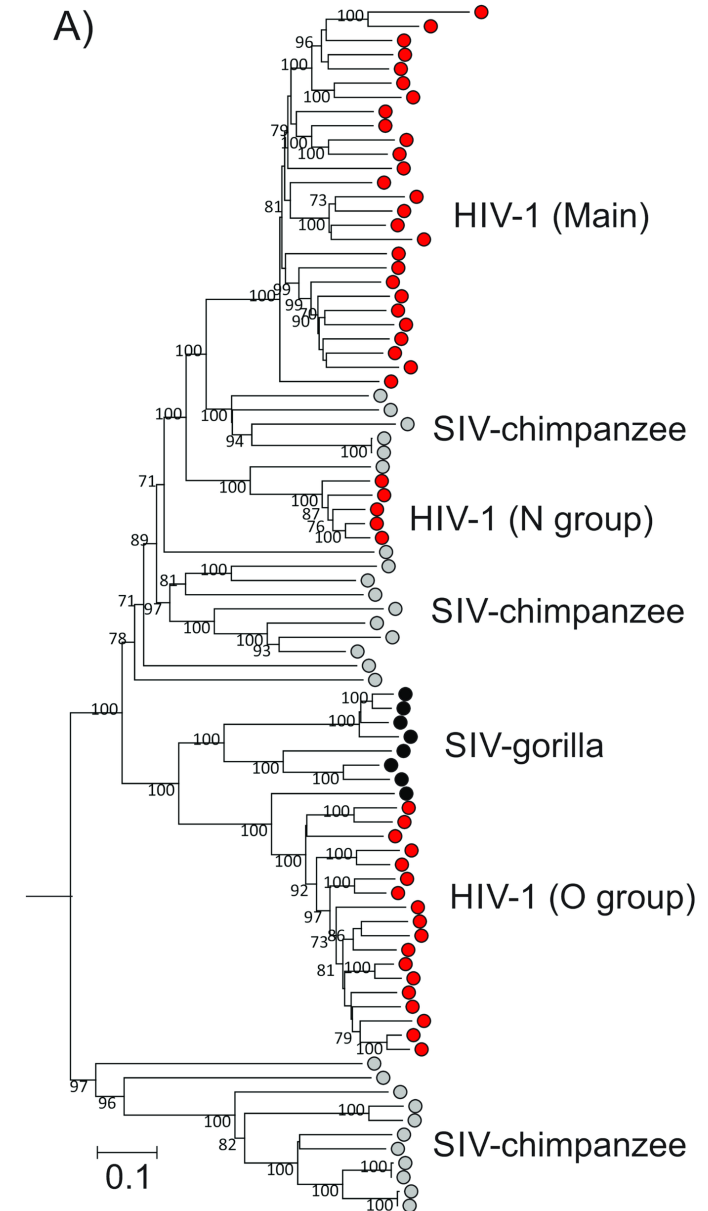
Coxsackievirus A20
Coxsackievirus A20
Poliovirus type 1
Poliovirus type 2 – *Enterovirus coxsackiepol*
Poliovirus type 3
Enterovirus C111 ....

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- A recently zoonotic virus
  - Often clinically distinctive and important
  - Minimally different genetically from its animal source
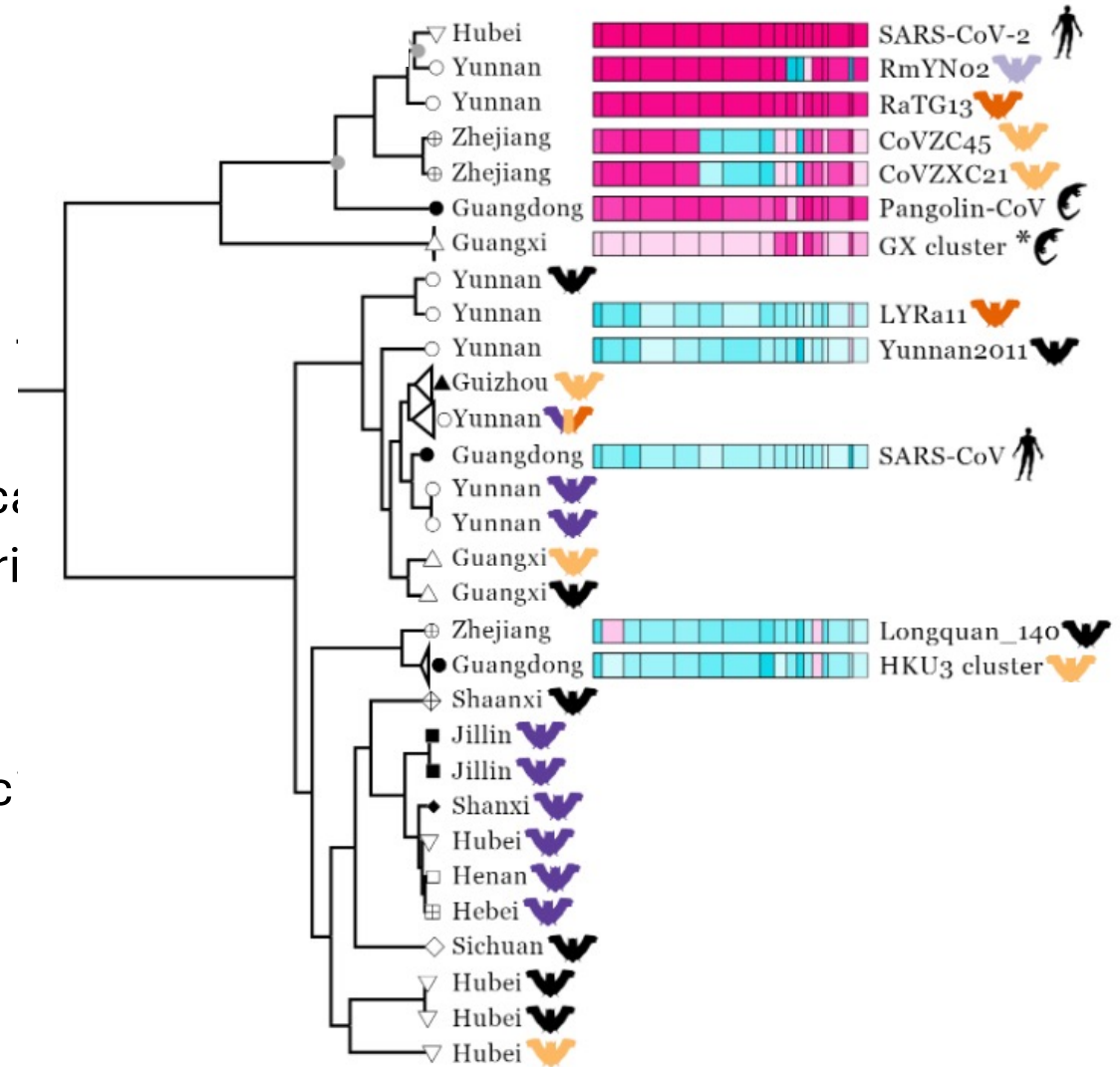
Taxonomy is only one way to classify viruses

- ## HIV-1 and HIV-2
  - Obvious clinical and regulatory *(eg.* biocontainment*)* importance of the term HIV-1
  - Can't be be represented as a species or below-species group

- ## SARS-CoV-2 and SARS-CoV
  - Lineages within a large clade of bat-infecting sarbecoviruses, collectively assigned to the species *Betacoronavirus pandemicum*

- ## Baltimore classification
  - Classifies viruses by replication mechanism and genome properties
  - Entirely incompatible with evolutionary origins and realm taxon assignments

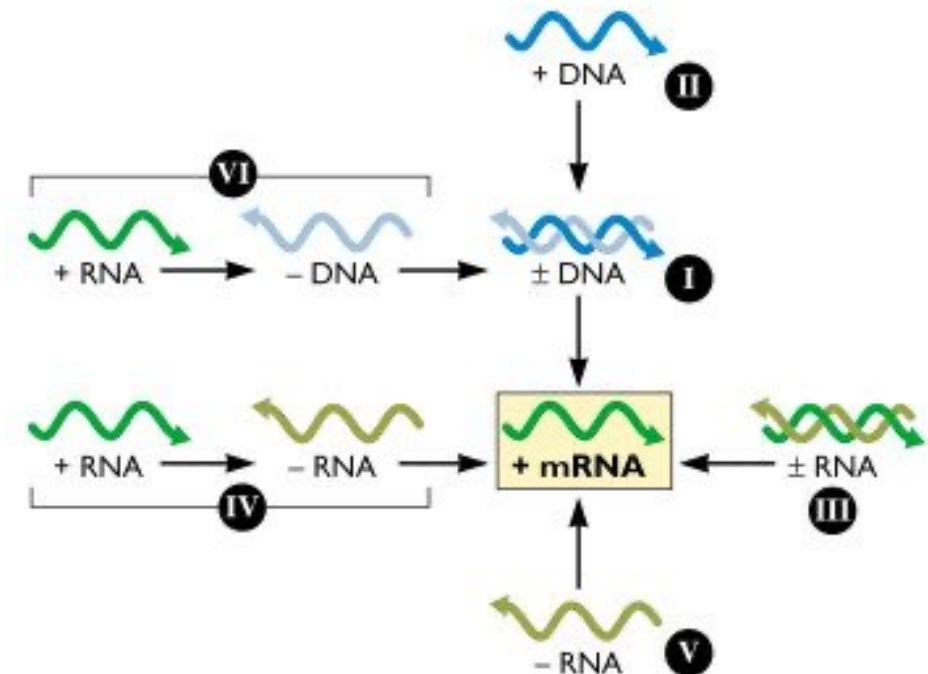 | | |
    |---|---|
    | I | *Adnaviria, Duplodnaviria, Varidnaviria, Monodnaviria* |
    | II | *Monodnaviria* |
    | III | *Riboviria* |
    | IV | *Riboviria* |
    | V | *Riboviria* |
    | VI | *Riboviria* |
    | ? | *Ribozyviria* |

Subspecies and other below-species classification

- All biological codes have one or more, optional below-species ranks
  - Zoological classification allows Latinised trinomials
    Common and West African Chimpanzees: *Pan troglodytes troglodytes, P. t. verus*
  - More flexible and extensive in botany, with additional categories such as varieties
Subspecies:	*Poa secunda* subsp. *juncifolia*
Varieties	*Acanthocalycium klimpelianum* var. *macranthum*
Cultivars	*Pinus nigra* 'Arnold Sentinel'
Two lower ranks	*P. edulis* f. *flavicarpa* 'FB200'
  - Assignments are made independently of the biological species principle (but grey areas)

- The ICTV does not classify virus below the species rank
  - Assignments are formally unrecorded by the ICTV
  - Consensus on definitions, nomenclature made in the wider virology community
  - Establishing a consensus in the community and disseminating information
  - Many conflicting and outdated classification schemes

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  - **Arbitrariness of the species level assignment level**
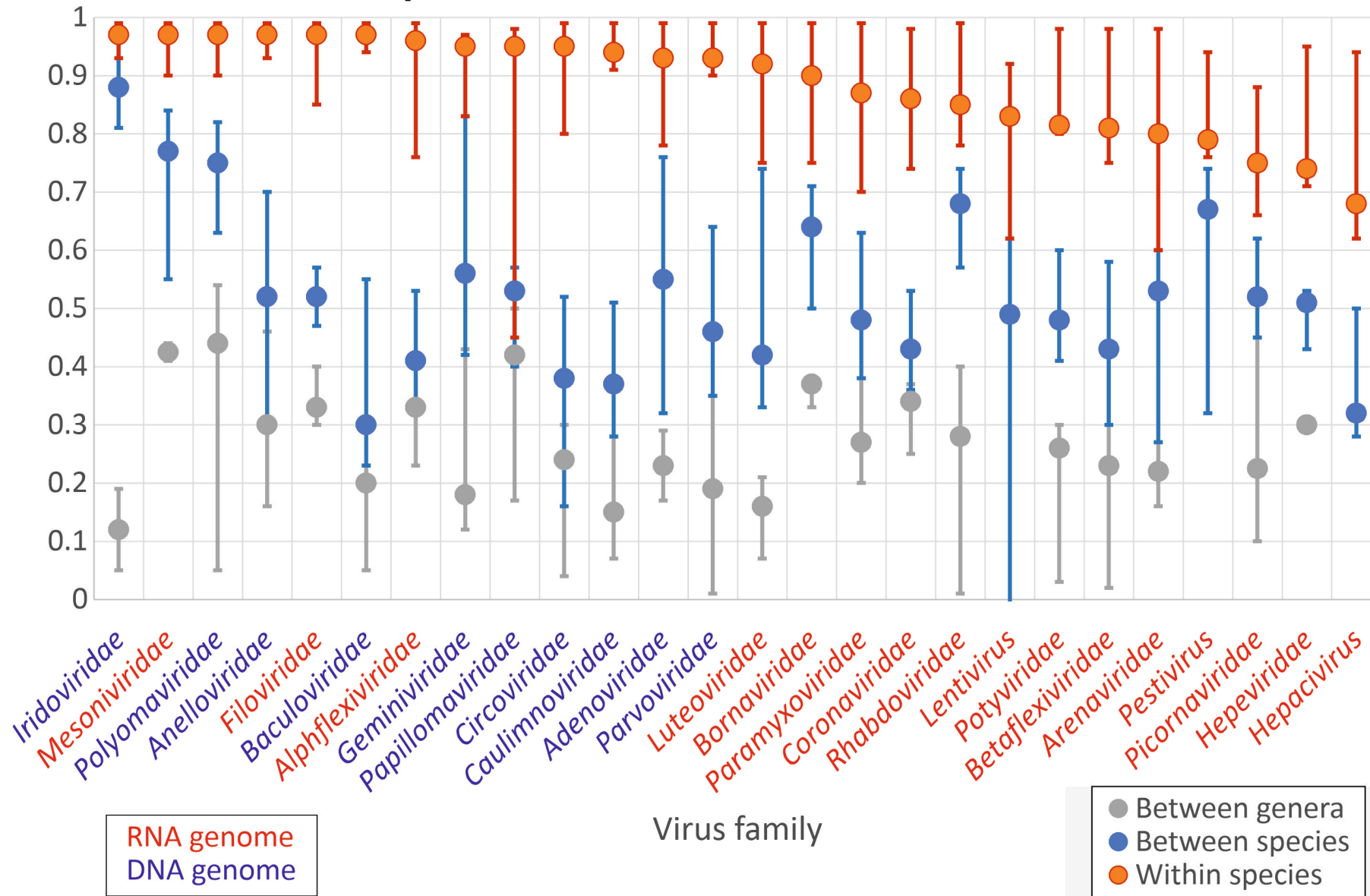
Genetic correlates of species-level classification

- When in Rome.....
  - PASC* – Pairwise similarity comparisons
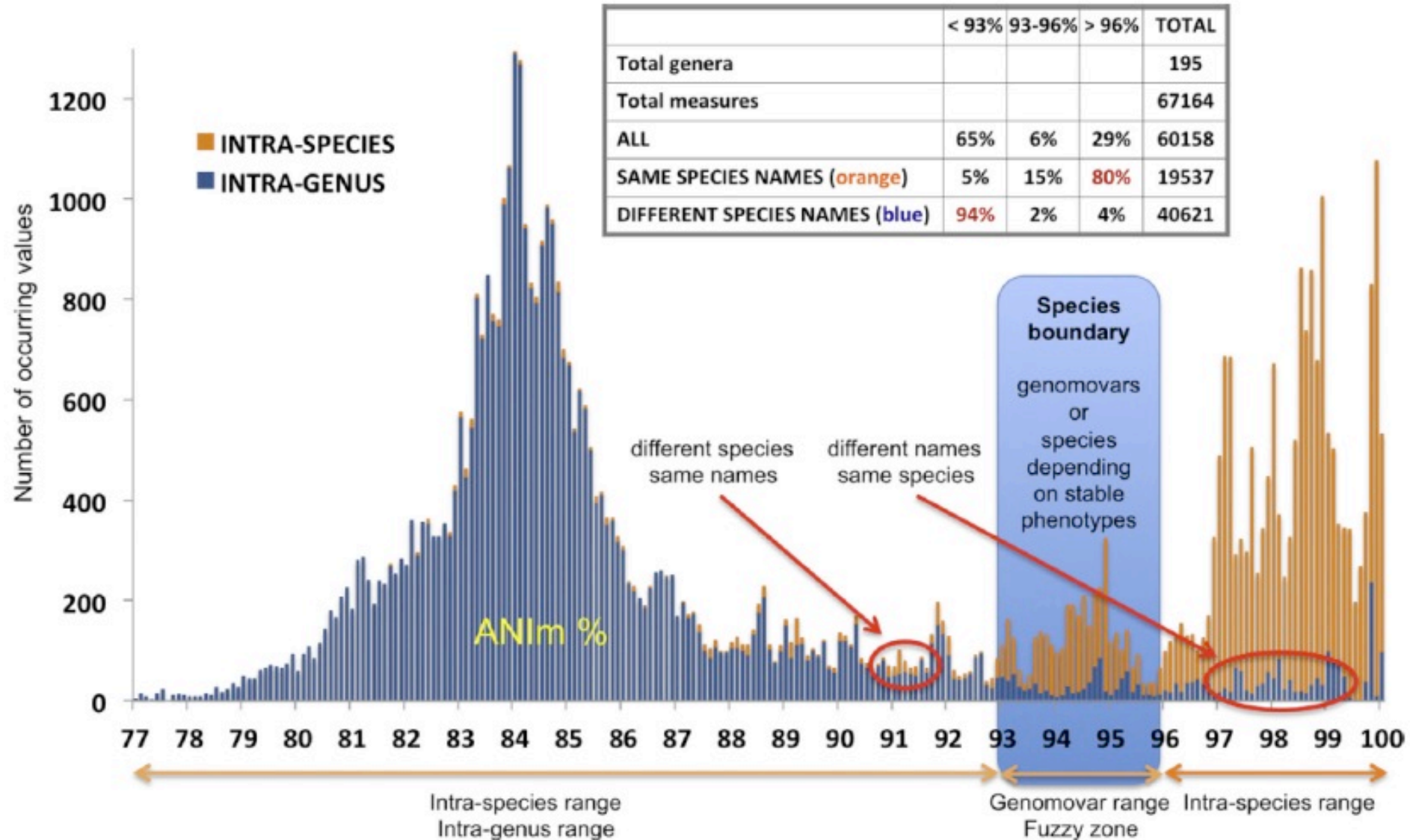 - Systematic calculation of pairwise distances between species and genera
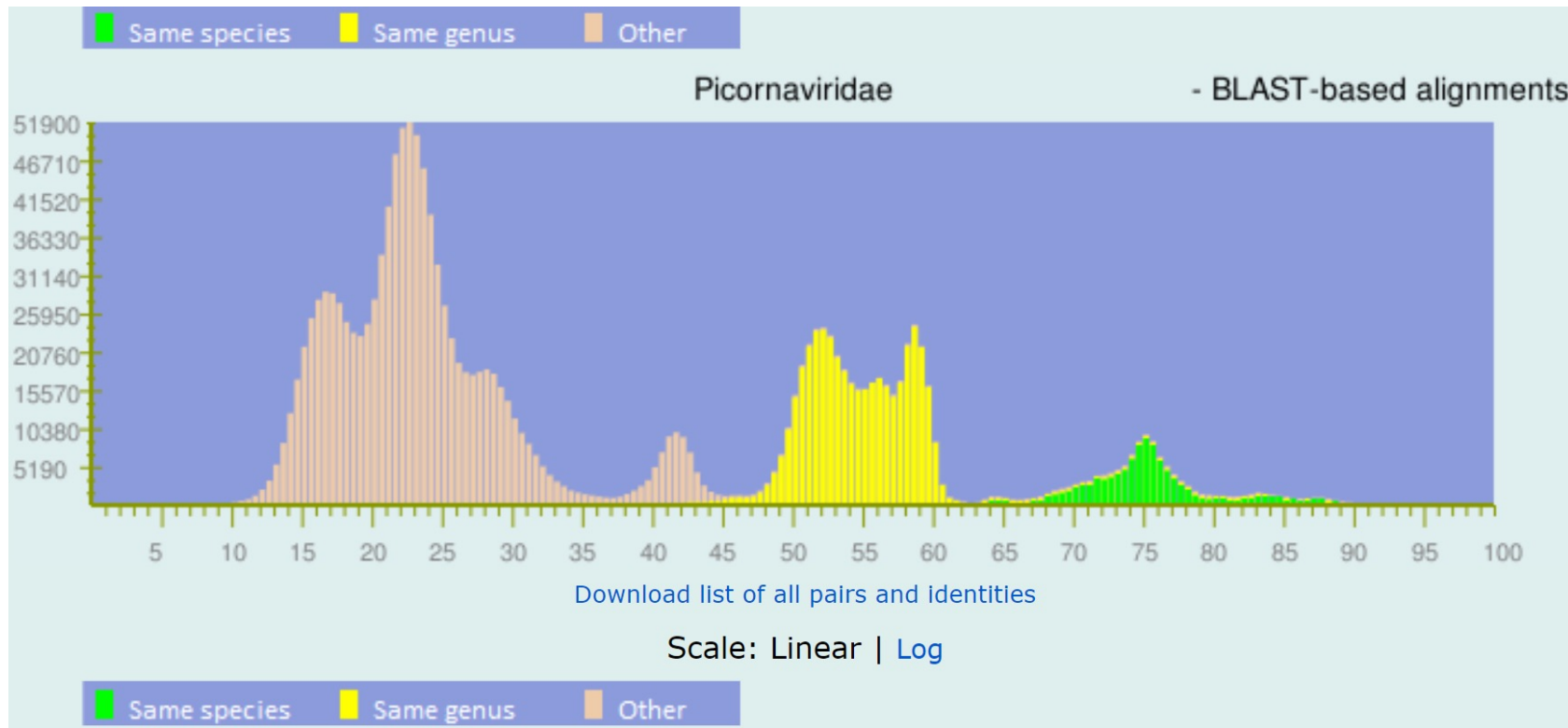
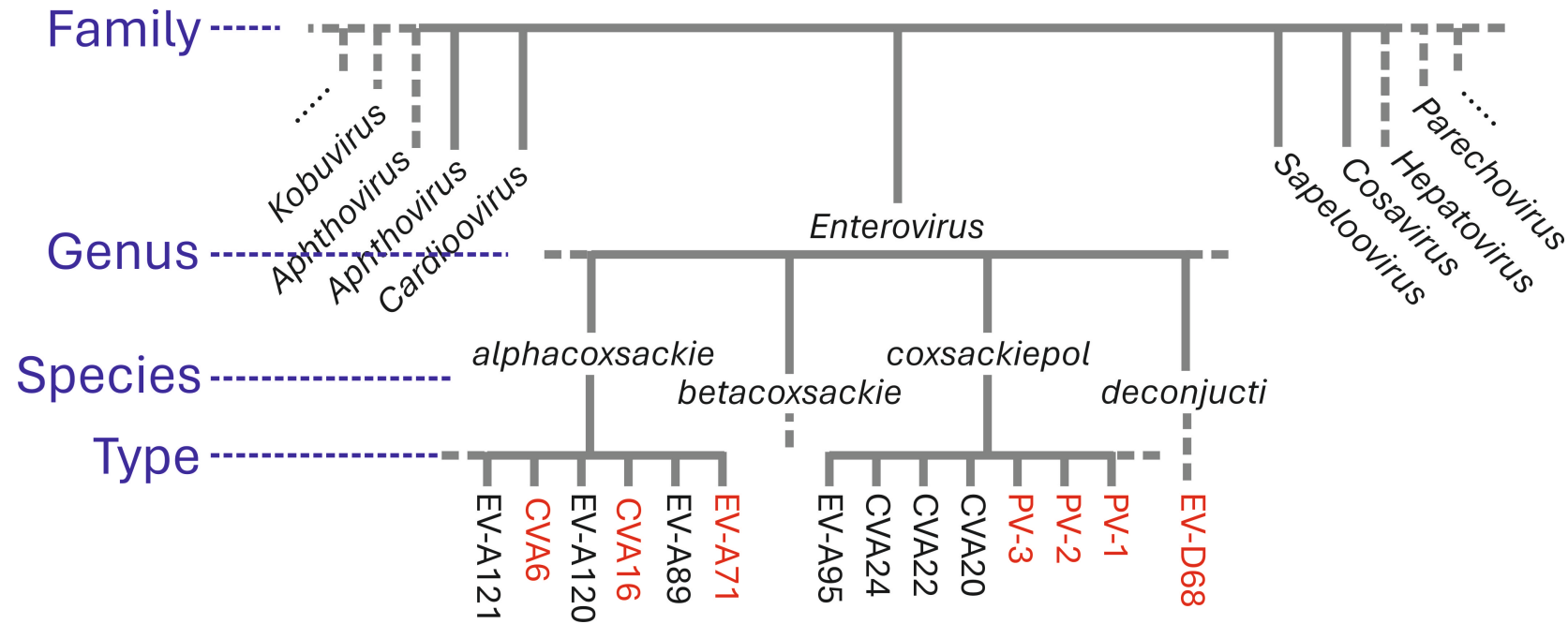Pairwise similarity ranges of species and genus ranks in representative virus families

Better defined thresholds for bacterial species

R. Rosselló-Móra, R. Amann / Systematic and Applied Microbiology 38 (2015) 209–216

|	< 93%	93-96%	> 96%	TOTAL
Total genera				195
Total measures				67164
ALL	65%	6%	29%	60158
SAME SPECIES NAMES (orange)	5%	15%	80%	19537
DIFFERENT SPECIES NAMES (blue)	94%	2%	4%	40621

Consequences of the species level demarcation

- No defined level of genetic divergence that might define species and below-species classification levels
  - Within-species divergence of hepaciviruses is less that between-species divergence of *Iridoviridae, Mesoniviridae, Polyomaviridae* and *Rhabdoviridae*
  - Reflects historical frameworks for defining and identifying species based on distinguishable disease phenotypes
- The ICTV has no formal role in the definition of nomenclature of viruses below the species level, despite its arbitrariness

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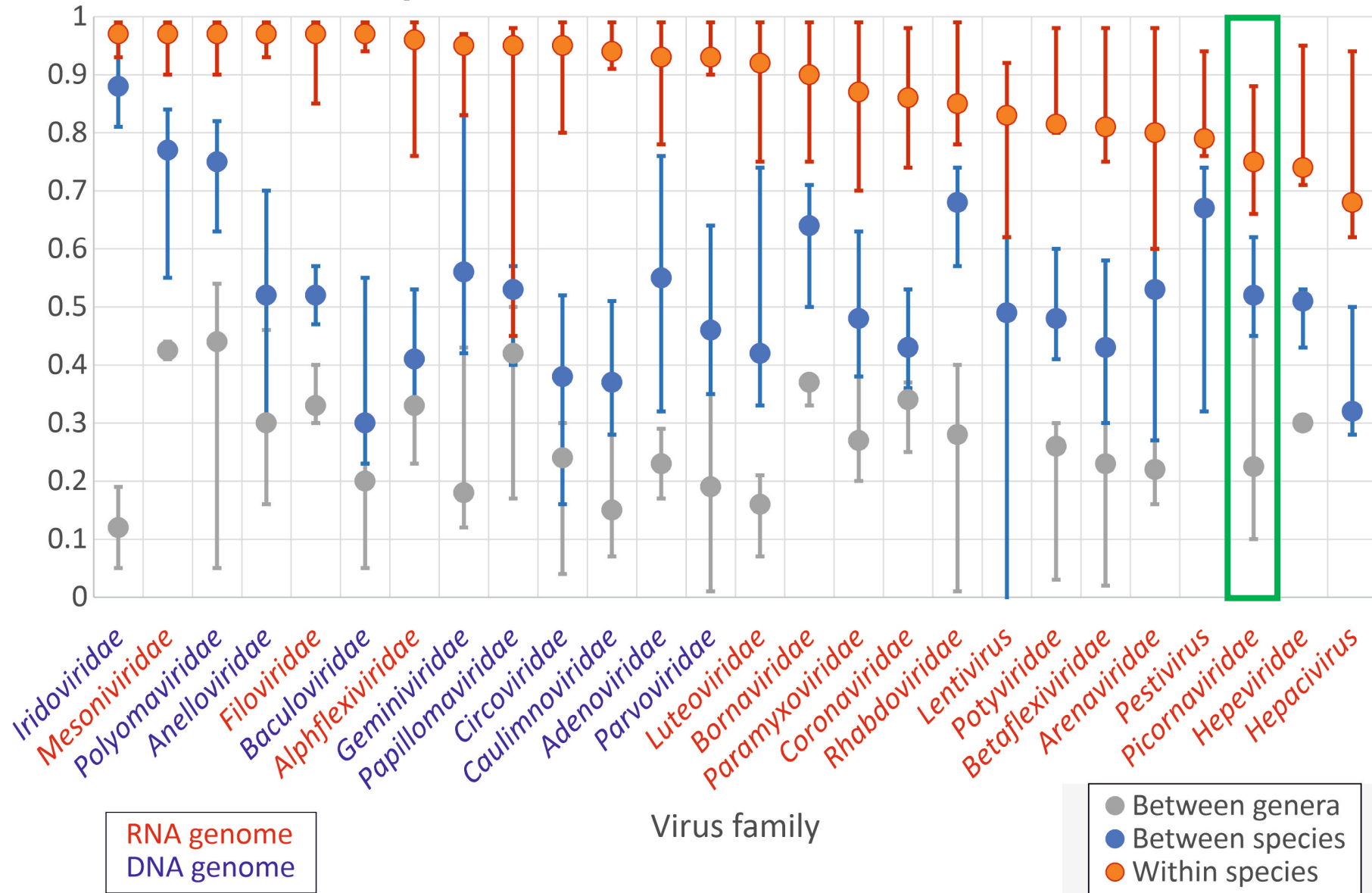
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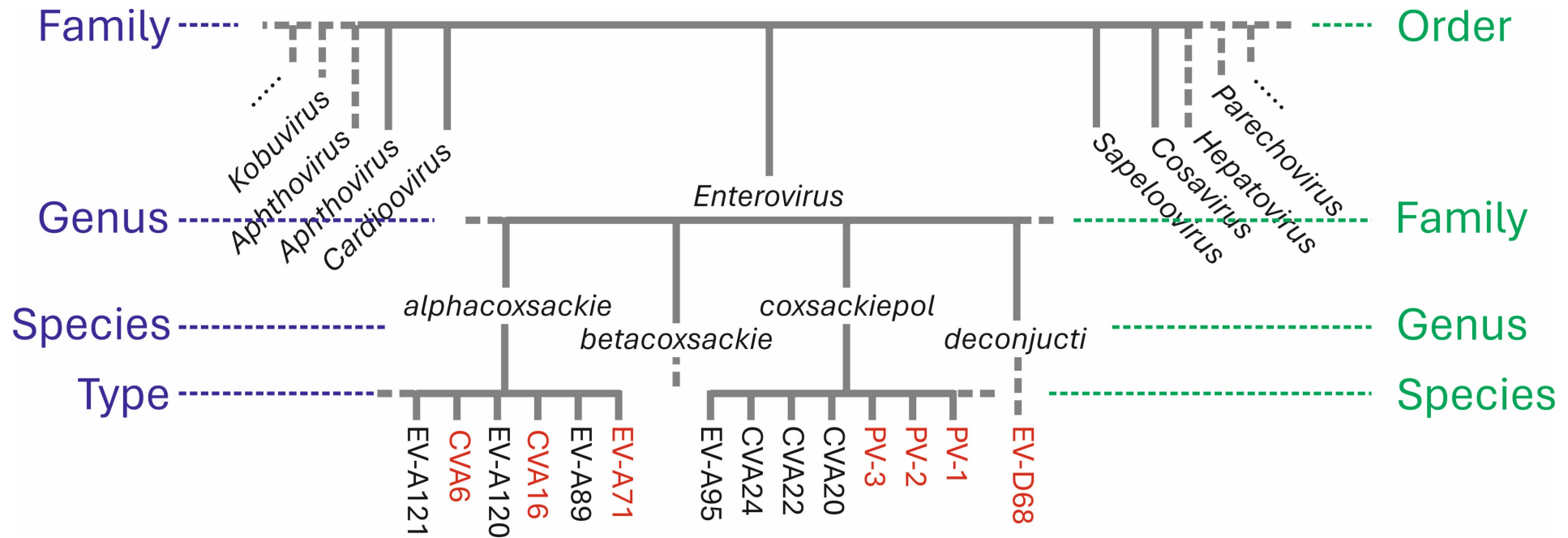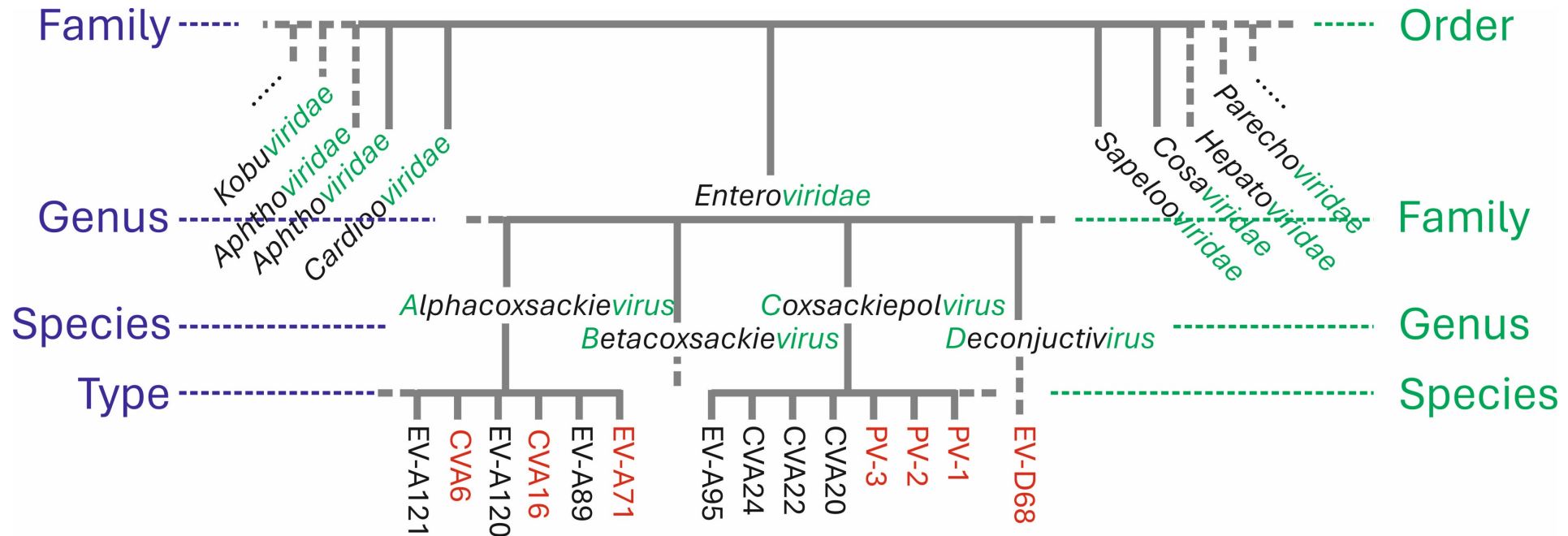
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A UK Regulatory Document

The Approved List
of biological agents

Advisory Committee on Dangerous Pathogens

Family **Picornaviridae**		
Order **Picornavirales**		
Genus **Cardiovirus**		
Cardiovirus B (Saffold virus)	2	
Genus **Cosavirus**		
Cosavirus A	2	
Genus **Enterovirus**		
Enterovirus D, Human Enterovirus type 70	2	Synonyms: Coxsackievirus CA24 (A24); Enterovirus 70
Human Enterovirus A also known as Coxsackieviruses (A)	2	
Enterovirus B (which includes the sub-species Echoviruses and the coxsackieviruses)	2	
Human enterovirus C type 1 (also known as Poliovirus)	2	Poliovirus Vaccine available
Human enterovirus C type 2 (also known as Poliovirus)	3	
Human enterovirus C type 3 (also known as Poliovirus)	2	

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Enterovirus A

The species **Enterovirus A** (formerly named *Human enterovirus A*) consists of 25 (sero)types: coxsackievirus A2 (CVA2), CVA3, CVA4, CVA5, CVA6, CVA7, CVA8, CVA10, CVA12, CVA14, CVA16, enterovirus A71 (EV-A71), EV-A76, EV-A89, EV-A90, EV-A91, EV-A92, EV-A114, EV-A119, EV-A120, EV-A121, EV-A122 (formerly SV19), EV-A123 (formerly SV43), EV-A124 (formerly SV46) and EV-125 (formerly BA13).

Serotype	Prototype strain	Accession no.	Known hosts*	Sequence reference
CVA2	Fleetwood	AY421760	*Homo sapiens*	Oberste *et al.*, 2004
CVA3	Olson	AY421761	*Homo sapiens*	Oberste *et al.*, 2004
CVA4	High Point	AY421762	*Homo sapiens*	Oberste *et al.*, 2004
CVA5	Swartz	AY421763	*Homo sapiens*	Oberste *et al.*, 2004
CVA6	Gdula	AY421764	*Homo sapiens*	Oberste *et al.*, 2004
CVA7	Parker	AY421765	*Homo sapiens*	Oberste *et al.*, 2004
CVA8	Donovan	AY421766	*Homo sapiens*	Oberste *et al.*, 2004
CVA10	Kowalik	AY421767	*Homo sapiens*	Oberste *et al.*, 2004
CVA12	Texas-12	AY421768	*Homo sapiens*	Oberste *et al.*, 2004
CVA14	G-14	AY421769	*Homo sapiens*	Oberste *et al.*, 2004
CVA16	G-10	U05876	*Homo sapiens*	Poyry *et al.*, 1994
EV-A71	BrCr	U22521	*Homo sapiens*	Brown & Pallansch, 1995
EV-A76	FRA91-10369	AY697458	*Homo sapiens*	Oberste *et al.*, 2005a
EV-A89	BAN00-10359	AY697459	*Homo sapiens*	Oberste *et al.*, 2005a
EV-A90	BAN99-10399	AY697460	*Homo sapiens*	Oberste *et al.*, 2005a
EV-A91	BAN00-10406	AY697461	*Homo sapiens*	Oberste *et al.*, 2005a
EV-A92	USA/GA99-RJg-7	EF667344	*Macaca mulatta; Macaca nemestrina; Cercocebus atys*	Oberste *et al.*, 2008
EV-A114	V13-0285/IND/2013	KU355876	*Homo sapiens*	Deshpande *et al.*, 2016
EV-A119	hu/09C13CMR	KC787153	*Homo sapiens; Gorilla gorilla; Pan troglodytes*	Ayukekbong *et al.*, 2013
EV-A120	MAD-2741-11	LK021688	*Homo sapiens*	Razafindratsimandresy *et al.*, 2014
EV-A121	V13-0682/IND/2013	KU355877	*Homo sapiens*	Deshpande *et al.*, 2016
EV-A122	SV19-M19s	AF326754	*Macaca fascicularis; Macaca mulatta; Macaca nemestrina*	Oberste *et al*, 2007
EV-A123	SV43-OM112t	AF326761	*Macaca fascicularis*	Oberste *et al*, 2007
EV-A124	SV46-OM22	AF326764	*Macaca mulatta; Macaca nemestrina*	Oberste *et al*, 2007
EV-A125	BA13	AF326750	*Papio cynocephalus*	Oberste *et al*, 2007

*, *Gorilla gorilla*, gorilla; *Pan troglodytes*, chimpanzee; *Homo sapiens*, man; *Macaca mulatta*, rhesus macaque; *Macaca nemestrina*, pigtail macaque; *Macaca fascicularis*, long tailed or crab eating macaque; *Cercocebus atys*, sooty mangabey; *Papio cynocephalus*, yellow baboon.
Download all of the above publically available sequences (EMBL: ascii; fasta).

Enterovirus A receptors

Nishimura, Y. and Shimizu, H. (2012). Cellular receptors for human enterovirus species A. Front. Microbiol. 3:105. Epub 2012 Mar 27.

Is there a case for below-species taxa of viruses?

- Can existing classifications be adopted as the basis for taxon names?
- Use the flexibility of ICBN code (or an approximation) that uses designators

  Enterovirus coxsackipol type 'poliovirus 2'

  Orthobunyavirus bunyamweraense ssp. 'Bunyamwera virus'

  Betacoronavirus pandemicum isolate 'SARS Coronavirus 2'

- Assignments would be based on stakeholder need
- Provides the authority and permanence of an established taxonomic framework
  - Established through community-based taxonomy proposals
  - Formal and coordinated oversight and standardisation of criteria and nomenclature
  - Recording in the Master Species List
  - Information provided in standardised form to INSDC databases
- Publication record, attribution and access to taxonomy additions and changes

Summary and questions

- A virus taxonomy serves a very wide community of scientists, clinician and regulators

- A taxonomy based on evolutionary relationships cannot reproduce all categories needed for clinical and regulatory purposes
    - The classification may be below the species level
    - The category may not be monophyletic or defined without reference to genomic relatedness

- The lack of a subspecies rank is one of several exceptions in virus taxonomy compared to the three other codes

- There is a degree of arbitrariness in where the species level is set in terms of sequence identities and biological properties

- There should be a re-examination of whether this could be reviewed with options to:
    - Re-classify species more consistently at a genomic level (95% ANI?) – this would be difficult for the virus community and may cut across useful categories
    - Extend taxonomy below species where required and justified – relatively straightforward