Genetic diversity, recombination dynamics, and global evolution of rabbit haemorrhagic disease virus (RHDV GI.1-GI.2): implications for epidemiology, host range, and control strategies

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Abstract. Rabbit haemorrhagic disease virus (RHDV; *Lagovirus europaeus* GI.1-GI.2) exhibits extensive genetic diversity driven primarily by recombination, rapid capsid evolution, and cross-species transmission. This mini-review synthesizes current knowledge on the genetic classification, recombination mechanisms, phylogeography, and epidemiological consequences of RHDV diversification. Phylogenetic analyses distinguish pathogenic genotypes GI.1 and GI.2 from benign rabbit caliciviruses (GI.3-GI.4), with GI.2 emerging as the dominant global lineage. Recombination at the RdRp-VP60 junction is identified as the principal evolutionary mechanism, generating mosaic genomes that combine non-structural and structural gene segments from distinct parental strains. Notably, all characterized GI.2 variants are recombinant, often incorporating non-structural genes from benign or classical strains, which significantly enhances viral fitness, transmission, and adaptability. Global phylogeographic data reveal frequent transcontinental spread and rapid strain replacement, with GI.2 displacing earlier genotypes in multiple regions. This genetic plasticity is closely associated with expanded host range, increased pathogenic variability, and the ability to infect multiple lagomorph species and younger animals. Furthermore, emerging recombinant strains demonstrate the capacity to evade pre-existing immunity, posing challenges for vaccine efficacy and disease control. Overall, RHDV represents a highly dynamic viral system in which recombination and selection jointly shape evolutionary trajectories, necessitating continuous surveillance and adaptive management strategies.

Key Words: rabbit haemorrhagic disease virus, RHDV2, Lagovirus europaeus, genetic diversity, recombination, phylogeography, viral evolution, host range expansion, vaccine escape, epidemiology.

Introduction. Rabbit haemorrhagic disease virus (RHDV, Lagovirus europaeus GI.1-GI.2) shows remarkable genetic diversity driven largely by recombination, rapid evolution of the capsid gene, and host jumps between rabbits and hares (Nas 2020; Capucci et al 2022). This diversity has major epidemiological consequences, including replacement of classical strains, expansion of host range, vaccine escape, and complex global spread patterns (Ramsey et al 2020; Taggart et al 2022; Sun et al 2024).

The aim of this mini-review is to provide a comprehensive analysis of the genetic diversity and evolutionary mechanisms of Rabbit haemorrhagic disease virus, with particular emphasis on the role of recombination in shaping viral fitness, host range, and global dissemination. Additionally, the review seeks to evaluate the epidemiological and immunological implications of emerging recombinant strains and to highlight the challenges they pose for disease control and vaccine development.

Genetic diversity and classification of RHDV. RHDV belongs to lagoviruses genogroup GI, with pathogenic genotypes GI.1 (classical RHDV and variants GI.1a-d) and GI.2 (RHDV2/b), and benign genotypes GI.3-GI.4 (RCVs) (Tokarz-Deptuła et al 2024; Shah et al 2023). Full-genome phylogenies place all lagoviruses into four main clades (GI.1, GI.2, RCV, HaCV/EBHSV), with GI.1 and GI.2 further subdivided into multiple sub-clades, reflecting substantial amino-acid drift across ORF1 and ORF2 (Shah et al 2023). Historical sequencing of "old" Portuguese RHDV identified a novel non-structural lineage recombining with G1 structural genes, revealing undersampled diversity even in early outbreaks (Lopes et al 2017). A comprehensive review of global GI.2 detections from 2010-2023 documents widespread genetic heterogeneity, including numerous recombinant lineages and regional variants (Asín et al 2024).

Recombination as the main driver of diversity. Recombination hotspots at the conserved RdRp-VP60 junction separate non-structural (NS) and structural (S) coding regions and repeatedly generate mosaic genomes (Lopes et al 2015; Lopes et al 2017; Abrantes et al 2020; Mahar et al 2021). Full-genome analyses show that all characterized GI.2 strains are recombinants, typically with benign GI.3 or GI.4 (or GI.1a/b) NS genes and GI.2 structural genes (Lopes et al 2015; Abrantes et al 2020; Ben Chehida et al 2021). Multiple recombination events were documented in RHDVb/GI.2 between 1994-2014, always retaining the GI.2 capsid while swapping NS regions from benign or classical pathogenic strains (Lopes et al 2015). In Australia, at least six independent GI.4P-GI.2 recombinants emerged within two years and rapidly displaced parental GI.2 despite nearly identical VP60, implicating NS genes as major determinants of epidemiological fitness (Mahar et al 2021). Similar GI.1aP-GI.2 recombinants in China and GI.3P-GI.2 variants in Tunisia and other regions further expand GI.2 genomic diversity and virulence profiles (Ben Chehida et al 2021; Li et al 2023; Hu et al 2025). Recombination can also cross genogroup boundaries: German hares carried viruses with GI.2 structural genes and EBHSV (GII.1) NS genes, dramatically increasing potential lagovirus variability (Szillat et al 2020), and an RHDV2 strain in European hare carried NS genes from an unidentified hare lagovirus and GI.2 structural genes, showing that NS origin can restrict host range and create evolutionary dead-ends (Cavadini et al 2023).

Table 1

Representative recombination types and host associations in RHDV/GI.2

Genomic pattern (NS/S)	*Typical host(s) and context*	*References from literature*
GI.3P-GI.2 or GI.4P-GI.2	Wild/domestic rabbits, Africa, Europe, Australia; highly fit epidemic lineages	Abrantes et al 2020; Ben Chehida et al 2021; Mahar et al 2021; Shah et al 2023; Asín et al 2024
GI.1aP-GI.2	Domestic rabbits in China; increased virulence and vaccine breakthrough	Li et al 2023; Hu et al 2025
GI.2P-GII.1 (GI.2 S / GII.1 NS)	Hares in Germany; inter-genogroup recombination	Szillat et al 2020
GII.?P-GI.2 (hare NS / GI.2 S)	European hare in Italy; non-infectious for rabbits, no spread	Cavadini et al 2023

Summarized by Consensus 2026.

Global phylogeography and strain turnover. Phylogeographic analyses over 1988-2021 show four main clades with frequent long-distance movement and multiple introductions between continents. GI.2 outbreak strains in the USA link to Canadian and German viruses, while Australian RHDV connect to USA-Germany haplotypes, illustrating repeated transcontinental jumps (Shah et al 2023). In Africa, Tunisian GI.2 strains are GI.3P-GI.2, likely introduced from Europe, with evidence for multiple independent

introductions across the continent (Ben Chehida et al 2021). Singapore's 2020 outbreak strain is a GI.2 S / GI.4 NS recombinant closely related to recent Australian variants, implying recent transboundary spread of a recombinant lineage (Koh et al 2023). In Germany, full genomes from 2013-2020 show near-complete replacement of GI.1 by GI.2, with rare persistence of GI.1 and novel GI.2/GI.1b and GI.2/EBHSV recombinants (Szillat et al 2020). Similarly, in Australia GI.2 replaced GI.1 and earlier variants as the dominant strain within 18 months of its arrival, spreading continent-wide and spilling over repeatedly into hares (Mahar et al 2017). In Portugal, surveillance from 2013-2016 found only GI.2 in wild rabbits, with about one-third seropositive, indicating widespread endemic circulation and complete displacement of GI.1 in sampled populations (Rouco et al 2018).

Host range expansion, pathogenicity and immune/ecological implications. Genetic diversification, particularly in GI.2, is tightly linked to expanded host range and altered age and species susceptibility. GI.2 causes disease not only in domestic and wild European rabbits but also in multiple hare species, young rabbits, and even some wild ruminants, contrasting with the rabbit-restricted primary disease caused by GI.1/GI.1a (Asín et al 2024; Tokarz-Deptuła et al 2024). Infection of captive mountain hares in Germany by a GI.2 strain related to rabbit viruses confirms that prior recombination events facilitated efficient cross-species transmission (Buehler et al 2020). Global reviews emphasize GI.2 detection in many lagomorph genera and occasional non-lagomorph hosts, raising concerns about ongoing host range expansion as the virus encounters new communities and benign caliciviruses with which it can recombine (Asín et al 2024).

At the within-species level, recombinant GI.1 strains can induce distinct innate and humoral immune responses compared with non-recombinant GI.1a, implying that each recombinant must be evaluated individually for immunopathogenesis and potential vaccine performance (Bębnowska et al 2023). In China, GI.1aP-GI.2 recombinants displayed moderately enhanced virulence and caused disease in rabbits vaccinated against parental GI.2, demonstrating that new genomic combinations can undermine existing immunity and that rapid molecular evolution complicates control strategies (Li et al 2023; Hu et al 2025). A newly detected Chinese GI.2 variant with GI.1a-like NS genes and capsid closely related to North American GI.2 caused high mortality (70-80%) and required development of a homologous VP60 virus-like particle vaccine, underlining the need to update vaccines to match emergent recombinant variants (Hu et al 2025). In Poland, simultaneous field epidemics caused independently by co-circulating GI.1a and GI.2 strains in a small geographic area showed that coexistence of genotypes does not necessarily force immediate new recombination, suggesting distinct evolutionary paths and niche partitioning among genetic forms (Fitzner et al 2025). However, intensive surveillance in Australia revealed that, when recombination does occur, new GI.2 recombinants can quickly outcompete parental strains, even without major capsid changes, pointing to NS-gene-driven differences in replication or transmission that boost epidemiological fitness (Mahar et al 2017; Mahar et al 2021).

Conclusions. Rabbit haemorrhagic disease virus represents a highly dynamic pathogen whose evolution is primarily driven by recombination between non-structural and structural genomic regions. This process generates genetically diverse mosaic viruses, particularly within the globally dominant GI.2 genotype.

Recombination plays a central role in shaping epidemiological fitness, with increasing evidence that non-structural genes significantly influence viral replication, transmission, and adaptability, challenging the traditional capsid-focused perspective. The rapid global spread and repeated replacement of GI.1 by GI.2 highlight the virus's capacity for transcontinental dissemination and continuous emergence of novel variants. In parallel, genetic diversification is closely linked to host range expansion, enabling infection of multiple lagomorph species and younger animals.

The emergence of recombinant strains with potential vaccine escape underscores the need for continuous genomic surveillance and adaptive vaccine strategies. Overall, effective control of RHDV requires integrated approaches combining molecular epidemiology, evolutionary analysis, and flexible disease management.

Conflict of interest. The authors declare that there is no conflict of interest.

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*** Consensus, 2026 An AI-powered search engine for research. Available at https://consensus.app. Accessed at: February 2026.

Received: 02 March 2026. Accepted: 04 April 2026. Published online: 19 April 2026.
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How to cite this article:
Cîmpean A., Dăescu A. M., Grabán Z. A., 2026 Genetic diversity, recombination dynamics, and global evolution of rabbit haemorrhagic disease virus (RHDV GI.1-GI.2): implications for epidemiology, host range, and control strategies. Rabbit Gen 16(1):21-25.