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Addressing the zoonotic threat of merbecoviruses

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Merbecovirus is a subgenus of betacoronaviruses and exhibits high genetic diversity with a capacity for cross-species transmission. However, beyond Middle East respiratory syndrome coronavirus (MERS-CoV), our knowledge of the ecology and pathogenic potential of these viruses remains limited. Merbecoviruses were once thought to rely exclusively on dipeptidyl peptidase 4 for cell entry, but recent discoveries have revealed that several members can also engage with angiotensin-converting enzyme 2 or aminopeptidase N, expanding their receptor repertoire and potential host range. Here we summarize recent advances in understanding of the receptor usage of merbecoviruses and examine how these insights inform pandemic preparedness and risk assessment. We discuss the development of targeted diagnostics, broad-spectrum antivirals and vaccines, including pan-coronavirus strategies. Together, these advances provide a foundation for predictive surveillance and rational countermeasure design, enabling earlier detection and more effective containment of future merbecovirus spillover events before they escalate into epidemics.

The subgenus *Merbecovirus*, within the genus *Betacoronavirus* (*Coronaviridae* family), includes Middle East respiratory syndrome coronavirus (MERS-CoV) and poses a notable and continuous threat to human health. Whereas other betacoronaviruses—particularly severe acute respiratory syndrome coronavirus (SARS-CoV) and SARS-CoV-2 of the subgenus *Sarbecovirus*—have been studied intensely, important gaps remain in our understanding of merbecoviruses beyond MERS-CoV[1]. Recent reports of potential cross-species transmission events involving merbecoviruses, coupled with the identification of variants capable of utilizing receptors from diverse non-bat mammalian hosts, as well as emerging in vivo and in vitro data on their biological properties, underscore their potential threat to public health[2]. Therefore, we argue that research on the mechanisms of *Merbecovirus* adaptation and cross-species transmission, as well as preventive and therapeutic strategies, is of major importance. In this Review, we summarize recent insights into *Merbecovirus* biology derived from virus discovery and detailed molecular analysis, extending knowledge that has thus far been centred largely on MERS-CoV. The expanded understanding might serve as the groundwork for targeted vaccines, diagnostics and therapeutics, marking a transition from reactive outbreak responses to research that champions preparedness and predicts receptor shifts and potential host jumps before they occur.

Zoonotic potential of merbecoviruses

MERS-CoV was first identified in 2012 (Fig. 1a) and remains the only known *Merbecovirus* to cause disease in humans. As of February 2026, 2,647 laboratory-confirmed cases of MERS have been reported globally, including 959 deaths, resulting in a case fatality rate of 36% (ref. 3). MERS can range from mild illness, characterized by low-grade fever, a dry cough, a runny nose, a sore throat and muscle pain, to severe disease with progression to acute respiratory distress syndrome[4]. Approximately two-thirds of confirmed patients present with comorbidities[5]. Gastrointestinal and ocular symptoms may occasionally be the initial

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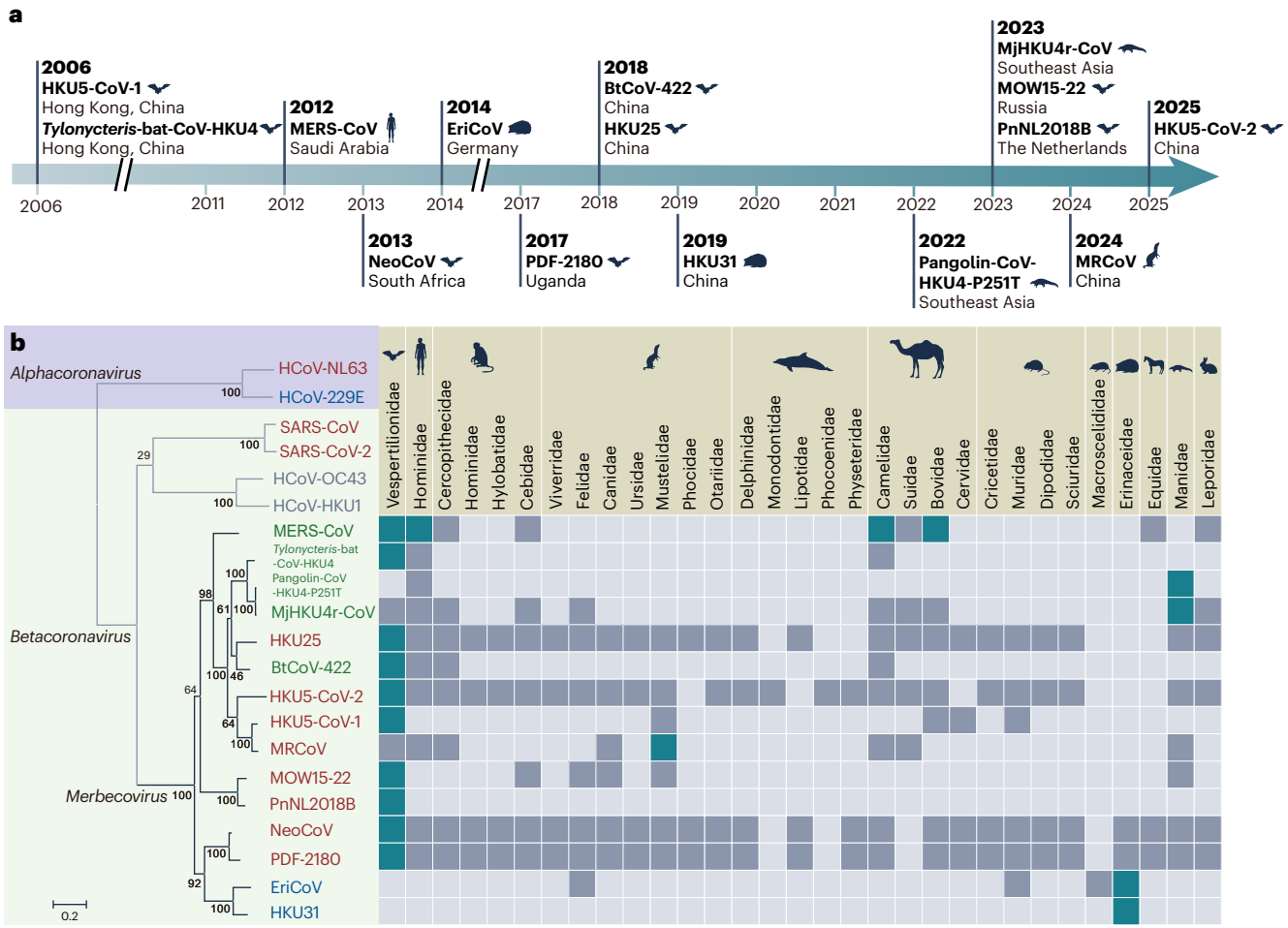

Fig. 1 | Discovery timeline, phylogenetic relationships, receptor usage and host range of merbecoviruses. a, Spatiotemporal distribution of representative merbecoviruses. The timeline shows the year of the first report, geographical origin and host species (depicted by icons) for each virus. **b**, Left: phylogenetic tree based on the representative amino acid sequences of spike proteins from merbecoviruses, with SARS-CoV-2 and other human coronaviruses included as outgroups. The scale bar indicates 0.2 amino acid substitutions per site and the numbers at the nodes denote bootstrap support values. Virus names are colour coded according to receptor usage (green, DPP4 binding; red, ACE2 binding; blue, APN binding; grey, other receptors). Right: host range of merbecoviruses across mammalian families. The top row lists families, from Vespertilionidae to Leporidae, with the icons above representing either confirmed hosts or representative species. For clarity, Hominidae is shown twice: once with a human icon to emphasize human relevance and once among the primates to represent non-human species. Cyan cells denote confirmed hosts; dark grey cells indicate potential hosts supported by in vitro experiments; and light grey cells indicate an absence of data on susceptibility. Icons created in BioRender; Jiang, Z. https://biorender.com/qo5nh3x (2024).

manifestations and neurological complications have been reported in severe cases[6]. Asymptomatic infections account for approximately 8% of cases globally, but reached up to 20.4% in the United Arab Emirates between September 2012 and June 2020[7].

MERS-CoV circulates endemically in dromedary camels (*Camelus dromedarius*)[8], where it remains prevalent[9]. Presumptive cross-species transmission to a variety of other species has also been documented[10] (Figs. 1b and 2). Human infections typically result from direct or indirect contact with infected camels. Other livestock, including cattle, goats, donkeys and sheep, have shown nucleic acid or serological evidence of MERS-CoV infection[11] (Supplementary Table 1), suggesting that these species may also serve as potential sources of infection in humans. Although human-to-human transmission accounts for a substantial proportion of MERS cases, it remains relatively inefficient and typically requires close contact. However, highly populated gatherings (such as the annual Hajj pilgrimage, which brings millions of individuals from nearly 180 countries to Saudi Arabia) and superspreading events (such as the nosocomial spread during the 2015 outbreak in South Korea[12]) highlight ongoing risks of large-scale transmission events and the continuous global public health threat posed by MERS-CoV[13].

The International Committee on Taxonomy of Viruses recognizes four species within the subgenus *Merbecovirus*. MERS-CoV belongs to the MERS-related coronaviruses (International Committee on Taxonomy of Viruses species *Betacoronavirus cameli*), which have been identified in several animal hosts. Three additional groups comprise the subgenus: *Tylonycteris* bat coronavirus HKU4 (*Betacoronavirus tylonycteridis*), *Pipistrellus* bat coronavirus HKU5 (*Betacoronavirus pipistrelli*) and Hedgehog coronavirus 1 (*Betacoronavirus erinacei*)[14] (Fig. 1b). Representative members of these groups have been detected in a range of mammals, including bats (*Tylonycteris pachypus*, *Pipistrellus abramus* and *Neoromicia capensis*), pangolins (*Manis javanica*), hedgehogs (*Erinaceus amurensis* and *Erinaceus europaeus*) and farmed minks (*Neogale vison*). *Tylonycteris*-bat-CoV-HKU4 was first identified in 2006 in lesser bamboo bats and later isolated in 2021, whereas related viruses such as MjHKU4r-CoV and pangolin-CoV-HKU4-P251T have been reported in pangolins[14–16]. Within the HKU5 group, mink respiratory coronavirus (MRCoV) was detected in farmed mink in 2024 and characterized in 2025 (refs. 2,17). In the Hedgehog coronavirus 1 group, HKU31 and *Erinaceus* coronavirus (EriCoV) have been identified in Amur and European hedgehogs, respectively[18–21]. Collectively, these

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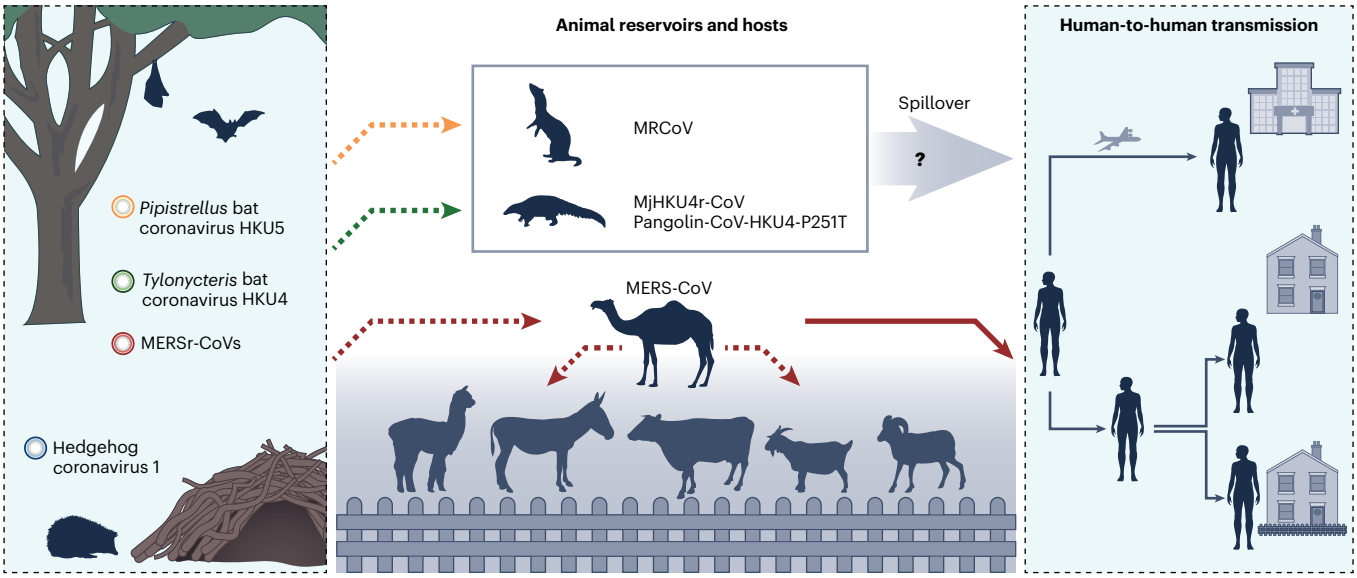

Fig. 2 | Cross-species transmission of merbecoviruses. Schematic of *Merbecovirus* cross-species transmission. The coloured circular icons denote the four *Merbecovirus* groups: *Pipistrellus* bat coronavirus HKU5 (orange), *Tylonycteris* bat CoV HKU4 (green), MERS-related coronaviruses (MERSr-CoVs; red) and Hedgehog coronavirus 1 (blue). The coloured arrows indicate transmission events from original hosts to other species. Dashed and solid arrows indicate proposed cross-species transmissions and pathways that have resulted in confirmed human infections, respectively. Icons created in BioRender; Jiang, Z. https://biorender.com/qo5nh3x (2024).

and other findings illustrate the broad host diversity and geographical spread of *Merbecovirus* species (Fig. 1a).

Bats are regarded as the principal natural reservoirs of coronaviruses, including most merbecoviruses (Supplementary Table 1). Although some bat coronaviruses are predicted to have the intrinsic capacity to infect humans[22], zoonotic transmission typically requires adaptation via an intermediate host[23]. Documented cross-species transmission within the HKU4 and HKU5 groups underscores the adaptability of these viruses and their potential for host switching. Pangolin-CoV-HKU4-P251T probably originated from bat-to-pangolin transmission and serological evidence indicates that MjHKU4r-CoV, another bat-derived virus, circulates in pangolins, demonstrating successful adaptation to a non-bat host[14,15]. These examples highlight the ongoing expansion of phylogenetically diverse merbecoviruses into mammalian hosts that have closer contact with humans than their ancestral bat reservoirs, reinforcing concerns about future zoonotic emergence (Figs. 1a and 2).

Characterizing the ecological and molecular factors that facilitate cross-species transmission is critical for assessing zoonotic risk[24]. Identifying merbecoviruses with the potential to infect humans in wildlife and domestic animals, and elucidating the viral determinants of host adaptation, will clarify the pathways that enable interspecies transmission[25]. Enhanced surveillance is therefore required to detect genomic alterations of concern, allowing the early identification of emerging *Merbecovirus* lineages and variants—particularly recombinant viruses—before they acquire the capacity for sustained human transmission[26].

Advances in understanding *Merbecovirus* infection mechanisms

Understanding how merbecoviruses adapt to infect a new host is central to assessing their zoonotic potential. Functional studies now rely heavily on improved virus isolation and reverse genetics systems (Box 1), which together enable detailed analysis of receptor usage, viral replication, host range and pathogenicity. Although many aspects of infection can be modelled using specialized tools, such as pseudoviruses or recombinant spike proteins, studies using authentic viruses and their genetically modified derivatives can provide confirmation of functional relevance and allow in vitro analysis of viral evolution and adaptation. Such experimental approaches are valuable for identifying molecular determinants of host adaptation and informing assessments of cross-species transmission risk, provided they are conducted under appropriate containment conditions. Depending on the experimental design, some studies may also require case-by-case risk–benefit assessment, regulatory oversight and stringent biosafety safeguards.

Entry strategies

On the surface of coronavirus virions, spike proteins assemble into trimers. Each monomer contains an S1/S2 junction that separates the receptor-binding S1 subunit from the membrane-fusion S2 subunit. In certain merbecoviruses, including MERS-CoV, this site can be cleaved by furin during virion maturation, a feature thought to enhance transmissibility. In other contexts, cleavage at the S1/S2 site occurs after virus attachment to a susceptible host cell and is mediated by host proteases such as transmembrane protease serine 2 or cathepsins. The S2 subunit, which is relatively conserved among betacoronaviruses, subsequently undergoes further proteolytic activation at the S2′ site by the same proteases, enabling fusion of the viral envelope with the host cell membrane[27] (Fig. 3a).

MERS-CoV was the first *Merbecovirus* shown to utilize the human cell-surface enzyme dipeptidyl peptidase 4 (DPP4) as an entry receptor. Other merbecoviruses with similar spike protein and receptor-binding domain (RBD) sequences, such as BtCoV-422 and HKU4, also utilize DPP4 for cell entry[28,29] (Fig. 3b). Structural analyses have identified key molecular adaptations that enable DPP4-using merbecoviruses to engage the human receptor[30]. Recent studies have demonstrated that several bat-origin merbecoviruses have independently evolved to use the cell-surface protein angiotensin-converting enzyme 2 (ACE2) instead of DPP4. These viruses comprise members of the MERS-related coronavirus group, including NeoCoV and PDF-2180, which emerged in Africa[31], MOW15-22 and PnNL2018B from Europe[32] and HKU25-related viruses from Eurasia[33], as well as multiple representatives of the HKU5 group: the prototypic HKU5 (HKU5-CoV lineage 1 (HKU5-CoV-1))[34], HKU5-CoV-2 (ref. 35) and MRCoV[17]. Strikingly, despite this receptor shift, the three-dimensional RBD structures of

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BOX 1

Advances in *Merbecovirus* isolation and recombinant virus generation

Numerous genetically diverse merbecoviruses have been identified through broad coronavirus screening and metagenomic sequencing. However, functional characterization is often limited by the inability to recover replication-competent isolates, creating a major bottleneck for pathogenesis studies and countermeasure evaluation. Conventional cell lines used for coronavirus isolation are largely ineffective for bat-derived merbecoviruses. Current isolation strategies therefore exploit knowledge of viral entry receptors—DPP4, ACE2 and APN (Supplementary Table 1)—and have successfully recovered viruses from the HKU5 group by overexpressing DPP4 or ACE2 receptors from susceptible bat species in various cell lines[107]. A recently developed customized viral receptor strategy further overcomes these limitations by grafting viral receptor-binding domains onto artificial scaffolds, thereby enabling receptor-mediated cell entry independent of the natural receptor. This approach has been successfully used to isolate an ACE2-using HKU5 strain from bat samples[108] and represents a versatile new platform for virus isolation. Additionally, organoid models, particularly bat-derived organoid systems, have substantially improved the recovery of previously difficult-to-culture bat-borne viruses[109] and may facilitate the successful isolation of further *Merbecovirus* members.

An alternative to direct virus isolation is the generation of recombinant viruses from complete viral genome sequences. Recent advances, including yeast-based transformation-associated recombination (TAR) cloning and other equally efficient reverse-genetics systems, have accelerated this process: the construction of complementary DNA clones suitable for infectious virus rescue can now be completed in about one week[110]. In the TAR approach, yeast cells are co-transformed with a linearized *Escherichia coli* or *Saccharomyces cerevisiae* shuttle vector and overlapping DNA fragments spanning the entire viral genome. Homologous recombination in yeast efficiently assembles these fragments into a full-length viral complementary DNA clone within the vector backbone. The assembled genome is recovered as a circular plasmid, amplified in *E. coli* and transfected into mammalian cells to rescue a recombinant virus. TAR cloning also simplifies mutagenesis and enables the insertion of reporter or heterologous genes by incorporating modified DNA fragments during assembly. However, the increasing accessibility of reverse-genetics systems, particularly when combined with AI-driven design and generative modelling of spike protein structures, raises legitimate dual-use concerns, including the potential synthesis of novel or recombinant viral variants. It is therefore critical to avoid gain-of-function experiments that could inadvertently generate viruses with enhanced virulence or transmissibility, and to strengthen ethical oversight and governance surrounding the creation of novel viral constructs[111,112].

these viruses remain nearly identical to that of MERS-CoV. In addition, the RBDs of these ACE2-using merbecoviruses exhibit several markedly different receptor-binding modes (Fig. 3b), engaging different amino acid residues on the ACE2 surface. In some cases, their binding footprints (contacted amino acid residues on the receptor surface) closely resemble that of SARS-CoV-2 (refs. 17,32). Notably, ACE2 utilization constitutes a key molecular determinant for the high transmissibility and ongoing adaptation of SARS-CoV-2, whose circulating variants consistently maintain a high affinity for ACE2, thereby contributing to recurrent global waves of infection. These findings illustrate how different coronavirus lineages can independently evolve to exploit the same host receptor through distinct structural solutions. Indeed, even phylogenetically distant coronaviruses can converge on ACE2 as a shared entry receptor, serving not only the subgenera *Sarbecovirus* and *Merbecovirus* but also the more evolutionarily distant HCoV-NL63 (which causes the common cold in humans; subgenus *Setracovirus*; genus *Alphacoronavirus*)[36–38] (Fig. 1b).

ACE2 sequences show marked diversity among bat species and some closely resemble those of non-bat mammals, potentially facilitating cross-species transmission. Consequently, the specificity for ACE2 orthologues, and therefore probably the host range, varies substantially among merbecoviruses. For example, MOW15-22 and PnNL2018B display a narrow tropism, using ACE2 exclusively from *Pipistrellus* bats. In contrast, viruses such as HKU5-CoV-2 and MRCoV, whose RBD footprints overlap with those of ACE2-using sarbecoviruses and HCoV-NL63, exhibit broader host ranges and bind ACE2 from various bat species as well as multiple non-bat mammals (Supplementary Table 1). Importantly, adaptation to ACE2 from new hosts can occur through minimal genetic changes: two amino acid substitutions in the RBD of a bat HKU5-CoV-1 variant enable efficient use of mink ACE2 (ref. 17), whereas a single substitution in the RBD of HKU5-CoV-1 or NeoCoV confers binding to human ACE2 (refs. 31,39). Similarly, mutations in the spike protein of *Tylonycteris*-bat-CoV-HKU4 enhance its affinity for human DPP4 and promote entry into human cells (Supplementary Table 1).

Beyond DPP4 and ACE2, a third receptor has recently been proposed. In two preprints that have not yet been peer reviewed, aminopeptidase N (APN) was reported to function as a putative entry receptor for most known members of Hedgehog coronavirus 1, which circulate widely in hedgehog populations. If confirmed, these findings would complete the receptor profile of the subgenus *Merbecovirus*[40,41]. Although APN is a well-established receptor for several alpha- and deltacoronaviruses[42,43], EriCoV would represent the first *Betacoronavirus* reported to exploit APN (Fig. 1b). Structural analyses have revealed a unique RBD–APN interface, distinct from other APN-binding coronaviruses, suggesting that coronaviruses have repeatedly and independently evolved to use APN as an entry receptor, as has also been observed for ACE2. Importantly, the interaction is highly species specific: among 30 mammalian APN orthologues tested, only four—from hedgehogs, cats, rats and elephant shrews—supported viral entry. Comparative sequence analyses identified key determinants of host restriction, particularly the presence of *N*-glycans at or near the RBD-binding site in many species, including humans, which sterically block virus binding. This strong species barrier minimizes the immediate zoonotic risk of EriCoV to humans. Nevertheless, the possibility of adaptation and spillover to potentially susceptible intermediate hosts such as cats or rats, which are in frequent contact with humans, warrants continued surveillance.

Taken together, merbecoviruses have independently evolved to use three distinct host receptors: DPP4, ACE2 and APN (Fig. 3). The capacity for receptor switching, combined with a low genetic threshold for acquiring human receptor recognition, suggests that merbecoviruses harbour the potential for pandemic risk. Notably, certain *Merbecovirus* groups, such as HKU5-CoV-2, already bind human ACE2, indicating the potential for direct zoonotic transmission. These insights define key molecular targets for risk monitoring and countermeasure design. Surveillance should prioritize viral lineages with known compatibility with human or intermediate-host receptors (for example, in felines and rodents), focusing on critical residues within the RBD. Mapping these evolutionary trajectories may ultimately

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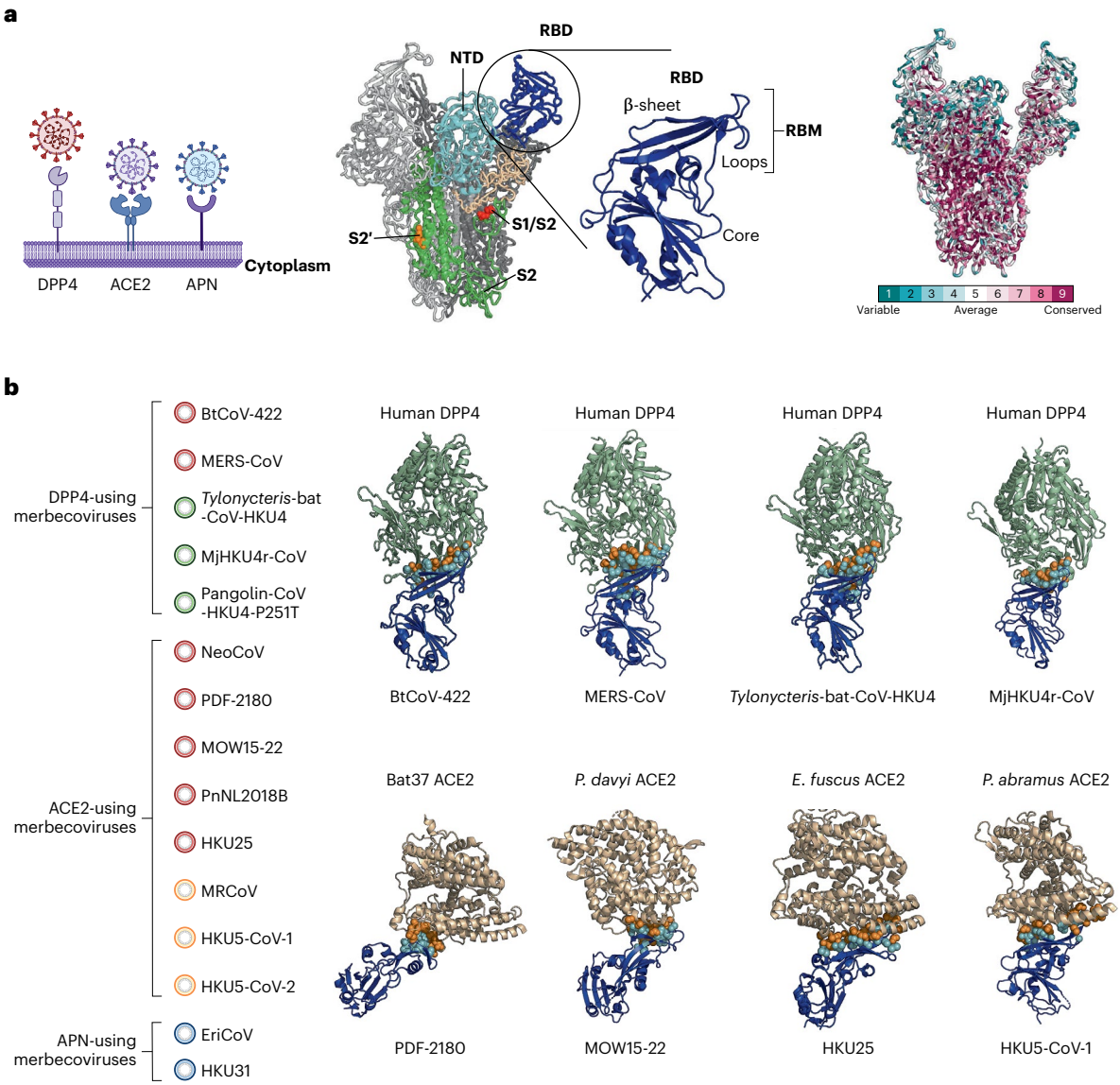

Fig. 3 | Diverse receptor utilization and viral protein interactions. a, Left: schematic of *Merbecovirus* virions and the three host receptors used by members of the subgenus (that is, DPP4, ACE2 and APN). Middle: trimeric coronavirus spike protein structure (Protein Data Bank (PDB) ID 5X59), with one protomer coloured by domain (as indicated) and the remaining two shown in grey. The S2 subunit is labelled and residues at the host protease cleavage sites—located at the S1/S2 junction and within the S2 subunit (S2′)—are shown as spheres. The RBD and amino-terminal domain (NTD) are indicated within the S1 subunit. The RBD contains a core domain (core), multiple β-sheets, connecting loops (loops) and a key receptor-binding motif (RBM). Right: conserved and variable amino acid residues in the spike protein, generated using ConSurf based on the MERS-CoV spike structure (PDB ID 5X5C) and an alignment of 23 different betacoroaviruses sequences, including those of SARS-CoV and SARS-CoV-2. Residue conservation is colour coded from pink (highly conserved) to cyan (highly variable). **b**, Structural depictions of distinct merbecoviruses RBDs in complex with their corresponding receptors, illustrating three receptor types. Each viral group is coloured according to the scheme shown in Fig. 2. Cartoon depictions include: BtCoV-422 RBD, MERS-CoV RBD, *Tylonycteris*-bat-CoV-HKU4 RBD and MjHKU4r-CoV RBD bound to human DPP4 (PDB IDs 9JMJ, 4KR0, 4QZV and 9JMM, respectively); PDF-2180 RBD bound to Bat37 ACE2 (PDB ID 7WPZ); MOW15-22 RBD bound to *Pteronotus davyi* ACE2 (PDB ID 9C6O); HKU25 RBD bound to *Eptesicus fuscus* ACE2 (PDB ID 9N7E); and HKU5-CoV-1 RBD bound to *P. abramus* ACE2 (PDB ID 9D32). Residues at the receptor–RBD interface are shown as coloured spheres: receptor residues contacting the RBD are shown in orange and the corresponding RBD residues contacting the receptor are shown in cyan. Structural details of the EriCoV RBD interaction with hedgehog APN have been described in two non-peer-reviewed preprints[40,41], but the corresponding atomic structure has not yet been deposited in the PDB and is therefore not shown. Virions and receptors in **a** created in BioRender; Jiang, Z. https://biorender.com/qo5nh3x (2024).

enable the prediction of receptor switching events and guide the design of adaptive countermeasures that can adjust in parallel with viral emergence. Preventive strategies should prioritize the development of broad-spectrum countermeasures, including receptor-targeted therapeutics such as engineered receptor decoys or small-molecule inhibitors, together with vaccines that elicit cross-reactive protection.

Beyond receptor engagement, interactions with host cell-surface glycans can also facilitate coronavirus attachment and entry. The seasonal betacoronavirus HCoV-OC43 (subgenus *Embecovirus*) binds 9-*O*-acetylated sialic acid for attachment[44]. As sialic acids concentrate virions on the cell surface and enhance receptor access[45,46], similar mechanisms may apply to merbecoviruses. Indeed, MERS-CoV can bind to sialic acid, preferring α2,3-linked over α2,6-linked sialic acid. This preference correlates with the distribution of α2,3-linked sialic acid in the upper respiratory tract of dromedary camels and the lower respiratory tract of humans—the primary replication sites of MERS-CoV

in these species[45]. Targeting this interaction may provide a potential antiviral strategy.

Cell and tissue tropism

Receptor recognition is a crucial step in viral infection and a major determinant of cell and host tropism. Although the expression of DPP4, ACE2 and APN in tissues is different, all of them are expressed along the respiratory tract (Human Protein Atlas: ACE2, ENSG00000130234; DPP4, ENSG00000197635) and are also abundantly expressed in the small intestine[47]. Recent studies have shown that human primary intestinal epithelial cells, small intestinal explants and intestinal organoids are highly susceptible to MERS-CoV[48], suggesting the gastrointestinal tract as a possible infection route. This is consistent with the detection of MERS-CoV RNA in faecal samples from patients in clinic[48]. Similar intestinal tropism has been observed in other merbecoviruses infecting bat intestinal epithelium or human intestinal cell cultures[49,50].

MERS-CoV replicates in a wide range of cell types from humans, pigs, monkeys and bats[51–53]. Several bat-derived merbecoviruses can also infect various human cells. For example, BtCoV-422 can replicate in primary human airway epithelial cells, pulmonary endothelial cells and fibroblasts, albeit less efficiently than MERS-CoV[28]. HKU5-CoV-2 can infect human ACE2-expressing cell lines and human respiratory and enteric organoids[35].

Host receptor polymorphisms can also influence both viral infectivity and tissue tropism. Naturally occurring human DPP4 variants can be suboptimal for MERS-CoV entry, potentially modulating disease progression in infected individuals by attenuating viral replication[54]. Differential DPP4 expression in multi-ciliated cells of the human nasal epithelium has been linked to interindividual differences in MERS-CoV replication[55]. Viral genetic variation further contributes to phenotypic diversity. Comparative analysis of MERS-CoV isolates has suggested that viruses circulating in the Arabian Peninsula may have greater zoonotic potential for humans[56]. In contrast, isolates from Burkina Faso (BF785) and Nigeria (Nig1657) carry deletions in the accessory gene *ORF4b*, which contributes to the suppression of type I and III interferon responses, and show reduced replication competence in ex vivo human bronchial and pulmonary tissues[57]. Together, these findings suggest that the interplay between receptor specificity, host genetics and viral evolution determines the infection spectrum and spillover potential of merbecoviruses. However, it should be noted that in vitro susceptibility does not necessarily equate to productive in vivo infection, underscoring the need for integrated experimental and ecological studies to better assess zoonotic risk.

Addressing the potential threat of emerging merbecoviruses

The expanding diversity and molecular adaptability of *Merbecovirus* species suggest that the emergence of another zoonotic merbecovirus with the capacity for sustained human transmission remains a credible risk. Preventing such an event requires an integrated, cross-disciplinary approach. Yet, critical gaps persist, including the absence of species-wide diagnostic tools and the limited availability of well-characterized animal models for studying virus transmission (Box 2), which hinder our ability to define transmission dynamics, monitor viral evolution and conduct preclinical evaluation of candidate vaccines and antivirals. Addressing these deficiencies should be a priority for future research to strengthen preparedness against potential outbreaks of merbecoviruses.

Diagnostics and surveillance

Specific diagnostic tools currently exist only for MERS-CoV[58], whereas the detection of other merbecoviruses still relies largely on pan-coronavirus assays and metagenomic sequencing. Recent advances include sandwich enzyme-linked immunosorbent assays (ELISAs) employing monoclonal antibodies against the conserved nucleocapsid protein, but these remain limited in breadth[59]. Building on diagnostics developed during the coronavirus disease 2019 (COVID-19) pandemic, future efforts to detect merbecoviruses could integrate established molecular platforms (for example, quantitative PCR with reverse transcription) and serological assays (for example, ELISA and colloidal-gold immunochromatography[60]) with emerging technologies, including quantum-dot immunoassays, CRISPR–Cas-based methods (for example, CRISPR–Cas13

BOX 2

Animal models and in vivo assays

Clinically relevant animal models are essential for assessing viral infectivity, tissue tropism, pathogenicity and transmission. In dromedary camels, MERS-CoV spreads with remarkable efficiency: viral RNA becomes detectable in naive calves within 24–48 h of exposure[113] and seroconversion has been observed in controls housed 200 m away, indicating airborne transmission[114]. Dromedaries have also been successfully used in vaccine-challenge studies[115].

Among non-human primate (NHP) models, MERS-CoV infects mainly type II pneumocytes in cynomolgus monkeys, causing minimal alveolar oedema but no overt clinical signs[116], thus failing to recapitulate human pathology. In contrast, rhesus macaques support robust viral replication in alveolar cells, developing multifocal interstitial pneumonia similar to that seen in mild or moderate human disease[117]. These interspecies differences suggest that rhesus macaques provide a more suitable NHP model for MERS-CoV infection. Given that several newly identified merbecoviruses use primate (including human) ACE2 rather than DPP4 as their entry receptor (Supplementary Table 1), selected NHP models may offer physiologically relevant systems for investigating viral pathogenicity and evaluating candidate therapeutics and vaccines.

Small-animal models remain indispensable for laboratory research, although wild-type mice and hamsters exhibit low susceptibility to MERS-CoV. Gene-edited mice bearing two DPP4 amino acid substitutions to match the human sequence[118], or transgenic and knockin mice expressing human DPP4, overcome this limitation. In addition, mice transduced with adenoviral vectors expressing human DPP4 are highly susceptible, developing pneumonia with extensive inflammatory infiltration and clearing the virus within 6–8 days[119]. In the absence of type I interferon signalling in these mice, both disease severity and histopathological changes are markedly exacerbated[119]. MERS-CoV immunopathology in human DPP4-transgenic mice is age dependent[120]. Moreover, intragastric inoculation of these mice leads to both intestinal and respiratory infection, resulting in fatal disease[48]. Owing to their human-like pathology, these models are widely used to evaluate vaccine and therapeutic candidates[121] and are valuable for studying recently discovered DPP4-dependent bat merbecoviruses[28,122,123], such as BtCoV-422 and HKU4-related viruses. It should be emphasized, however, that although some merbecoviruses identified in animals can use human receptors, their pathogenicity in animal models is generally relatively weak. In parallel, human ACE2-transgenic or knockin mouse models provide complementary platforms for investigating ACE2-dependent merbecoviruses[17,35], enabling comparative assessment of viral pathogenesis and transmission dynamics across receptor-defined groups.

system[61]), biosensors and third-generation sequencing using portable devices such as MinION[62], to enable rapid point-of-care testing and the simultaneous detection and differentiation of multiple merbecovirus species.

We argue that surveillance across both human and animal interfaces is equally critical. Analyses of host susceptibility based on viral receptor usage[17,40] could guide targeted metagenomic sequencing and quantitative PCR with reverse transcription surveillance efforts of merbecovirus cross-species transmission in selected wild and farmed mammals, thereby improving the screening efficiency. When susceptible farmed or domestic animals at high-risk animal–human interfaces present a respiratory disease, targeted merbecovirus screening could be initiated, complemented by sero-epidemiological surveys, such as competitive ELISA or neutralization assays, to assess exposure risk. Together, cross-species diagnostic and surveillance systems could become an important component of pandemic preparedness efforts. However, how these approaches can be implemented in practice remains to be defined and will require further discussion among scientists, public health practitioners and policymakers.

Broad-spectrum vaccines

Although no *Merbecovirus* vaccine has yet been approved, multiple vaccine platforms expressing the full-length spike protein of MERS-CoV, including modified vaccinia Ankara and adenoviral vectors, protein nanoparticles, virus-like particles and DNA-based constructs[63], have advanced to phase I or II clinical trials[64–66]. Among these, the modified vaccinia Ankara platform candidate proved safe and immunogenic even in individuals exposed to SARS-CoV-2 (ref. 65), reinforcing its development rationale given persistent SARS-CoV-2 circulation. The approval of any effective MERS-CoV vaccine should also trigger systematic evaluation of its cross-protective potential across the subgenus *Merbecovirus*.

Even within the same subgenus, coronaviruses display extensive genetic divergence, particularly within the RBD, which poses a major challenge for universal vaccine design. This sequence variability underscores the need to proactively develop broad-spectrum vaccines, ideally including those suitable for veterinary use, since subgenus-specific formulations could confer protection against multiple related viruses. To achieve such breadth, several pan-coronavirus strategies have been explored. One approach targets the conserved regions of the spike protein, especially the S2 subunit. Another strategy employs mosaic designs that combine immunogens from diverse coronaviruses, including inactivated viruses, full-length spike proteins[67], RBDs[68] or S2 subunits[69], as well as proteins containing conserved B and T cell epitopes from the spike protein and non-structural proteins. A nanoparticle vaccine incorporating the S2 subunits of MERS-CoV, NeoCoV, HKU4 and HKU25 exemplifies this approach, eliciting cross-reactive merbecovirus-specific immunoglobulin G responses in mice, with titres comparable to those of antigen-matched controls[70]. Furthermore, computational approaches predicting future immune-escape mutations may also inform the design of next-generation vaccines with improved resilience to antigenic drift[71,72]. As artificial intelligence (AI) and generative modelling become increasingly integrated into pathogen research, their dual-use potential, particularly for the synthesis of novel viral variants, underscores the need for robust ethical oversight and transparent governance.

Beyond antigen optimization, next-generation vaccine platforms, such as nanoparticle, DNA, messenger RNA or viral vector systems[73–76], can further expand immunogenic breadth and response durability, representing promising routes towards universal coronavirus protection. $CD8^+$ T cells help to eliminate infected cells, control viral replication and promote long-term immune memory, yet they are often not robustly induced by conventional subunit vaccines. Therefore, adjuvants designed to enhance $CD8^+$ T cell responses to a broad array of conserved viral epitopes may improve both the breadth and longevity of vaccine-induced immunity[77]. Refining delivery methods, such as with intranasal or lung-targeting formulations, could induce mucosal immunity and strengthen protection at the primary sites of infection, as demonstrated for SARS-CoV-2 and influenza vaccine candidates[78,79]. This strategy would reduce viral shedding and curb the transmission of respiratory pathogens[80].

Progress towards vaccine licensure faces substantial barriers, including limited commercial interest, low disease prevalence and the absence of confirmed human spillover for most viruses in the subgenus *Merbecovirus*. Consequently, traditional phase III efficacy trials based on disease incidence are not feasible. Alternative evaluation frameworks, similar to those used in phase III for chikungunya virus vaccines[81,82], could be adopted following phase I or II demonstration of safety and immunogenicity. These strategies rely on validated correlates of protection, such as neutralizing antibody titres shown to prevent disease in passive-transfer studies using animal models, rather than symptomatic infection rates in humans. Ultimately, developing a universal coronavirus vaccine platform tested pre-emptively across subgenera and integrated into global pandemic preparedness frameworks should become a cornerstone of prevention rather than a component of post-outbreak response.

Antiviral strategies for merbecoviruses

Currently, there is no fully approved drug for the treatment of MERS. Several monoclonal antibodies were developed with MERS-CoV as their primary target, mostly before the COVID-19 pandemic. Notable examples include REGN3048 and REGN3051 (ref. 83), as well as m336 (ref. 84), all of which target the viral spike protein. These candidates showed promising results in preclinical studies, but only REGN3048 and REGN3051 have advanced to phase I clinical trials. Because MERS outbreaks are sporadic and geographically limited, recruiting sufficient patient numbers for large-scale efficacy studies has proven difficult. In addition, some monoclonal antibodies are vulnerable to escape mutations in the spike protein, which can reduce or abolish their neutralizing activity. Advances in high-throughput single-B-cell screening in patients[85], deep mutational scanning and the computational de novo design of antibodies[86,87] now allow the selection of broadly neutralizing antibodies that retain activity against multiple coronaviruses, offering a potential path to overcome this limitation.

Another lesson from the COVID-19 pandemic is the need to develop small-molecule antivirals. This need was partly addressed by prioritizing the evaluation of antivirals originally developed for other viral infections and already in preclinical and clinical development. Using COVID-19 as a second indication allowed these compounds to enter phase III trials quickly. The approved antivirals target essential virus-encoded enzymes, such as RNA-dependent RNA polymerase (RdRp) and the main protease (M^{pro}), which processes non-structural proteins from a polyprotein precursor. For example, remdesivir and molnupiravir are both nucleoside analogues that interfere with RdRp-mediated transcription and replication, whereas nirmatrelvir is a peptidomimetic inhibitor of M^{pro}. Because these enzymatic targets are highly conserved across coronaviruses, such inhibitors also suppress the replication of MERS-CoV and other merbecoviruses with comparable efficiency (Table 1). Accordingly, the off-label use of these approved antivirals could be considered as an emergency measure in the event of *Merbecovirus* outbreak while dedicated trials establish their clinical efficacy against these viruses. Additionally, generative AI platforms that integrate multiple molecular design, synthesis and screening workflows may facilitate the optimization of lead compounds into drug candidates with clinical potential. Such platforms have already been applied to the development of broad-spectrum anti-coronavirus drug candidates targeting M^{pro} and hold promise for future applications across a wider range of therapeutic targets[88].

Both small-molecule inhibitors and monoclonal antibodies have been developed to target the conserved S2 subunit of the coronavirus

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Table 1 | Examples of promising inhibitors of *Merbecovirus* infection

Drug target	Inhibitor	Stage of development		Merbecoviruses tested
		Main indication	Merbecoviruses	
RdRp	Remdesivir	Approved (SARS-CoV-2)	In vivo (mouse and NHP models)	MERS-CoV[28,95,96], HKU5-CoV-1 (ref. 39), HKU5-CoV-2 (ref. 35) and BtCoV-422 (ref. 28)
	GS-5245	Clinical, phase III (SARS-CoV-2)	In vivo (mouse model)	MERS-CoV[97]
	Molnupiravir	Approved (SARS-CoV-2)	In vivo (mouse model)	MERS-CoV[28,98] and BtCoV-422 (ref. 28)
M^{pro}	Nirmatrelvir	Approved (SARS-CoV-2)	In vitro	MERS-CoV[28], HKU5-CoV-2 (ref. 35) and BtCoV-422 (ref. 28)
	AVI-4516 and ISM3312	Preclinical	In vivo (mouse model)	MERS-CoV[88,99]
M protein	JNJ-9676	Preclinical	In vitro	MERS-CoV[100]
	CIM-834	Preclinical	In vitro	MERS-CoV[101]
S protein	EK1 peptide and derivatives	Preclinical	In vivo (mouse model)	MERS-CoV[102], HKU5-CoV-1 (ref. 39), HKU5-CoV-2 (ref. 35), PnNL2018B[32], MOW15-2 (ref. 32) and HKU25 (ref. 33)
	mAbs to S2: S2P6, 76E1 and B6	Preclinical	In vitro	MERS-CoV[103,104], *Tylonycteris*-bat-CoV-HKU4 (ref. 103), HKU5-CoV-1 (ref. 39), HKU5-CoV-2 (ref. 35), PnNL2018B[32], MOW15-22 (ref. 32) and HKU25 (ref. 33)
	mAbs to RBD: REGN3048 and REGN3051	Clinical, phase I (MERS-CoV)	In vivo (mouse and NHP models)	MERS-CoV[83,105]
	mAbs to RBD: JC57-11	Preclinical	In vitro	MERS-CoV[28] and BtCoV-422 (ref. 28)
TMPRSS2	Camostat	Approved (pancreatitis)	In vitro	MERS-CoV[106], HKU5-CoV-1 (ref. 39), HKU5-CoV-2 (ref. 35), PnNL2018B[32], MOW15-22 (ref. 32) and HKU25 (ref. 33)

mAb, monoclonal antibody; M, membrane; NHP, non-human primate; S, spike; TMPRSS2, transmembrane protease serine 2.

spike protein, thereby blocking the conformational changes required for membrane fusion and viral entry[89]. S2-based vaccine candidates have likewise elicited cross-reactive responses and partial protection in animal models, further validating this region as a pan-coronavirus intervention target. In parallel, inhibitors of the viral membrane protein interfere with the structural rearrangements necessary for virion assembly. Although these compounds were originally designed against SARS-CoV-2, they also inhibit merbecovirus replication, underscoring their potential as pan-coronavirus therapeutics. The rational design and optimization of such agents depends on high-resolution structural characterization of these proteins in multiple functional states—an inherently challenging but essential step towards developing next-generation antivirals.

As observed with antiviral treatments for human immunodeficiency virus, hepatitis C virus and influenza virus, the emergence of resistance during monotherapy represents a major obstacle to sustained efficacy. This underscores the need for combination regimens that target multiple viral functions simultaneously. To extend protection beyond viral targets that can rapidly acquire resistance-conferring mutations, current efforts are also exploring host-directed approaches, such as the inhibition of cellular proteases (for example, transmembrane protease serine 2) required for efficient viral entry across coronaviruses. However, reliance on essential host pathways can narrow the therapeutic window and increase the likelihood of off-target effects, posing challenges for clinical applications.

For pandemic preparedness efforts and stockpiling, small-molecule antivirals are considerably more practical than monoclonal antibodies. Their chemical synthesis allows for rapid scale-up within weeks to months, their production is cheaper and most drugs remain stable at room temperature for extended periods of time, all of which would help with facilitating global storage and distribution. Oral drug formulations can enhance their use as patients can ingest them outside of hospital settings and therefore reduce the burden on the healthcare infrastructure during large outbreaks. Nevertheless, monoclonal antibodies remain valuable rapid-response biologics, as a single dose can provide protection for high-risk contacts over a period of weeks to months.

Outlook

The emergence of MERS-CoV in 2012 marked the first warning signal from a broad and still poorly understood viral lineage. The expanding diversity of *Merbecovirus* species and their demonstrated capacity either to use or rapidly adapt to human receptors position this subgenus as a credible source of future coronavirus spillover events, including those with pandemic potential. The World Health Organization has accordingly expanded its priority pathogen list from MERS-CoV to encompass the entire subgenus *Merbecovirus*, underscoring its broader public health relevance[90]. We argue that recognizing this risk should help to reorient global preparedness from reactive containment towards predictive prevention.

Although recent advances have clarified receptor usage, host range and viral evolution, the ecological and molecular processes driving adaptation to humans remain only partially understood. Addressing these gaps requires a coordinated, cross-disciplinary approach that includes expanded virus discovery, improved experimental models and the integration of ecological and virological surveillance. These efforts align with One Health frameworks, including the Food and Agriculture Organization of the United Nations–World Organisation for Animal Health–World Health Organization (FAO–WOAH–WHO) Tripartite initiatives for integrated zoonotic disease surveillance[91] and the Coalition for Epidemic Preparedness Innovations (https://cepi.net), which supports accelerated vaccine development and preparedness for emerging pathogens, including Disease X, through the integration of veterinary, wildlife and human data to strengthen global early-warning systems.

Strengthening data infrastructures will also be essential for characterizing virus–host interactions, performing high-resolution structural analyses and developing advanced diagnostic and assay platforms to evaluate antiviral efficacy. Integration with global preparedness frameworks, such as the Coalition for Epidemic Preparedness Innovations's 100 Days Mission[92], will be critical to enable prototype diagnostics, vaccines and therapeutics within 100 days of identifying a novel pathogen. Surveillance systems should be equipped with both virus-specific and broadly reactive diagnostic tools capable of differentiating among merbecoviruses, enabling early detection and

rapid containment of emerging threats. Public health outreach and education for high-risk occupational groups will further reinforce early-response capacity.

Preparedness also depends on the proactive development of medical countermeasures. Antivirals targeting conserved coronavirus enzymes, such as RdRp and M^{pro}, show promise against MERS-CoV, although data on their efficacy against other merbecoviruses remain limited. Likewise, vaccines targeting MERS-CoV and related viruses should advance through preclinical and early clinical development in advance of future outbreaks. There is growing international momentum towards developing pan-merbecovirus and pan-coronavirus vaccines[93], including approaches designed to protect not only against known viruses but also against yet-to-emerge variants. For example, modular RNA vaccine platforms[94] capable of rapidly exchanging antigen-encoding sequences in response to predicted viral evolution may enable near-real-time adaptation to emerging variants. Achieving these goals will require close collaboration among academia, industry and global health agencies to overcome scientific and logistical barriers. Ultimately, progress towards pre-empting coronavirus emergence, rather than merely responding to it, may shape future pandemic preparedness, with merbecoviruses providing an important testing ground for that transformation.

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Author contributions
S.S. conceived of the project. S.S., Xiaoling Li, M.K., X.-Y.J., A.M., M. Veit, H.D., W.-T.H., S.W., Z.P. and N.H. contributed to the conceptual framework, structure, writing and revision of the paper. Xiaoling Li, M.K., X.-Y.J., A.M. and M. Veit searched the literature and created the figures. H.D. summarized and analysed glycosylation. S.W. and X. Li summarized and analysed antiviral drugs. F.A.R., H.D., X.-Y.W., E.C.H., M. Varjak, S.M., D.W., Z.J., S.W. and X. Li reviewed and revised the paper. All authors reviewed and approved the final version of the paper and take full responsibility for the decision to submit for publication.

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