Risk evaluation of circulating Middle East respiratory syndrome coronavirus (MERS-CoV) clades and lineages

This document reviews current evidence from the global genomic surveillance of Middle East respiratory syndrome coronavirus (MERS-CoV) to highlight gaps in existing knowledge, proposes recommendations for further studies, and focus on better understanding the genetic diversity associated with this zoonotic virus.[a]

Emergence, epidemiology and transmission

MERS-CoV, a member of the *Merbecovirus* subgenus of the *Betacoronavirus* genus [1], was first identified in Saudi Arabia in 2012 [2]. This genus also includes SARS-CoV, first identified in 2003 in the People's Democratic Republic of China, and SARS-CoV-2, which caused the COVID-19 pandemic, which are both part of the *Sarbecovirus* subgenus. Since 2012, over 2,600 laboratory-confirmed human MERS cases have been reported from 27 countries [3–5], predominantly in the Middle East (Figure 1), with spillover events linked to contact with infected dromedary camels, which are the animal reservoir of this zoonotic virus. MERS-CoV has been found to circulate in dromedary camel populations in the Middle East, northern Africa and southern Asia [6]. Retrospective studies on archived samples have revealed MERS-CoV antibodies in camel populations from Saudi Arabia and Kenya as early as 1992 [7,8]. The virus is asymptomatic or mildly symptomatic in camels. In humans, MERS-CoV has an overall high case-fatality ratio in humans (~36%), and causes severe disease especially among individuals with comorbidities [9,10]. Human-to-human transmission appears inefficient, but occurs, notably in healthcare settings, with large healthcare-related outbreaks reported in the past (2014-2016), and has occurred also in close-contact community settings [10,11]. There is currently no evidence of vertical or sexual transmission of MERS-CoV in humans [12]. Sustained human transmission has not been observed, but the virus remains a persistent threat due to its widespread occurrence in the animal reservoir.

[a] Please visit https://www.who.int/health-topics/middle-east-respiratory-syndrome-coronavirus-mers for WHO key documents on MERS, including Middle East respiratory syndrome: global summary and assessment of risk

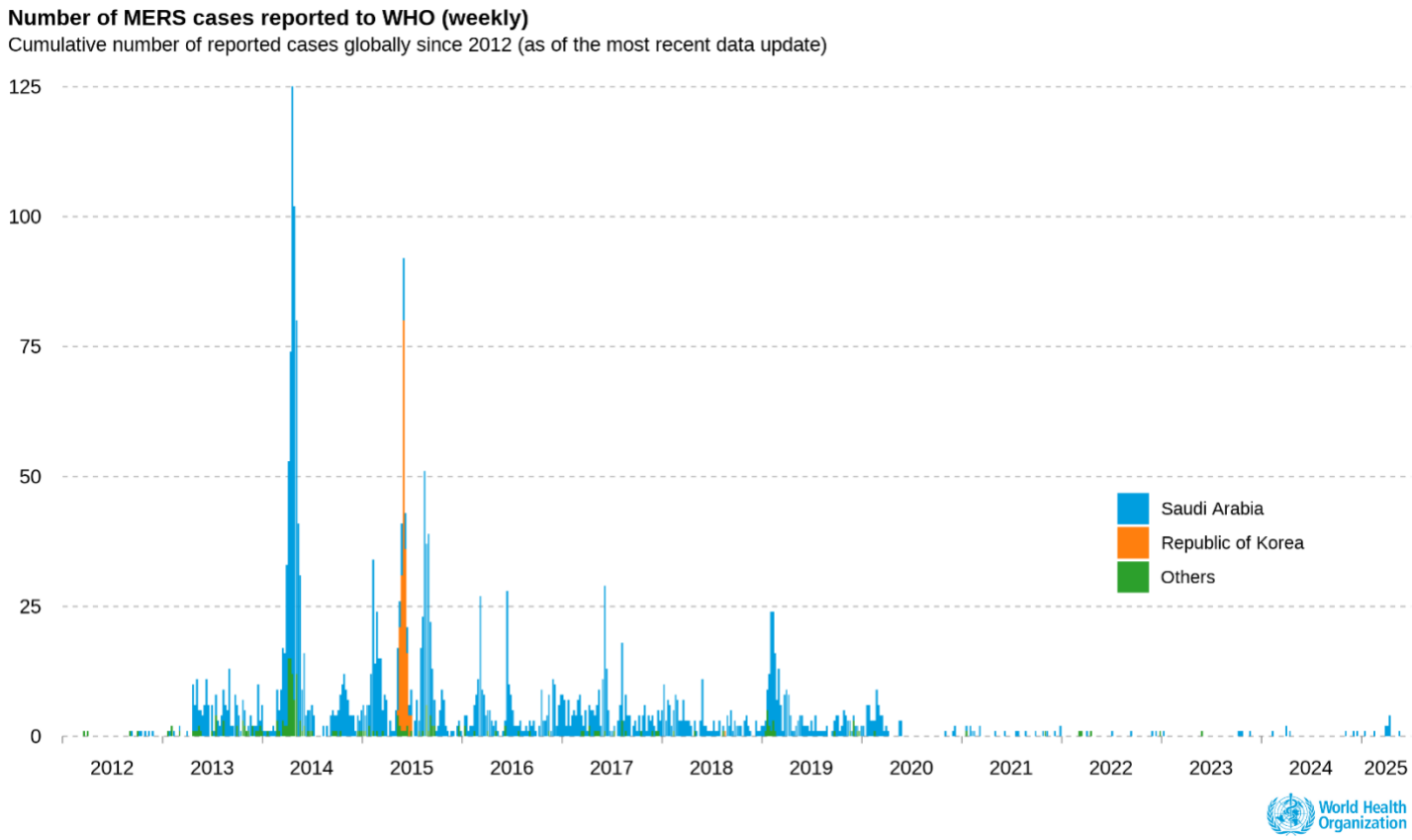

Figure 1. Epidemiological curve of MERS-CoV infections, 2012-2024 (Y-axis = monthly confirmed cases; X-axis = Jan 2012 - May 2025; Source: WHO MERS Dashboard, 2025 [13])

Genetic Diversity and Evolution

MERS-CoV evolves through point mutations and recombination between closely related strains within its species and subgenus (*Merbecovirus*) [14]. While recombination is a recognized mechanism shaping *Betacoronavirus* evolution, recombination is strongly constrained by genetic relatedness. Events are largely restricted to viruses of the same species or very closely related lineages, with a sharp decline in recombination frequency at pairwise genetic distances exceeding ~0.20 [15]. Furthermore, recombination hotspots in coronaviruses have been mapped to specific genomic regions, particularly the spike (S) gene, the nucleocapsid (N) gene, and accessory ORFs 6-8. These regions are often involved in host adaptation and immune modulation and may be preferentially retained in viable recombinants due to their role in virus-host interactions. In contrast, other genomic regions appear more recombination-constrained due to functional or structural limitations [15].

Global genomic surveillance has identified three major clades: A, B, and C, further subdivided into lineages (Figure 2, Table 1). Clade A was only circulating during the early outbreak period (2012-2015) and has not been detected after 2015 in humans or camels. Clade B dominates both camel and human infections in the Middle East, whereas Clade C, which circulates in camels across Africa, has no virologically confirmed human infections to date, though serological and T-cell studies suggest possible undetected or subclinical zoonotic exposures among some people [16–19]. The clade circulating in dromedaries in southern Asia remains unknown as no sequences have been generated to date. In recent years lineage B5 has been detected in humans in Saudi Arabia [20]. Genomic analyses suggest that this lineage likely emerged through recombination events between co-

circulating lineages, as evidenced by mosaic genome architectures in both dromedary camel and human isolates [20]. All the recent MERS-CoV-positive samples in camels from Saudi Arabia were belonging to clade B.5 (B.5 2023.1 to B.5 2023.5), and these sub-clades several mutations and have not been previously detected in humans. The phenotype of these lineages should be studied further to assess the risk of those lineages for human public health, as compared to clade B lineages circulating in humans.

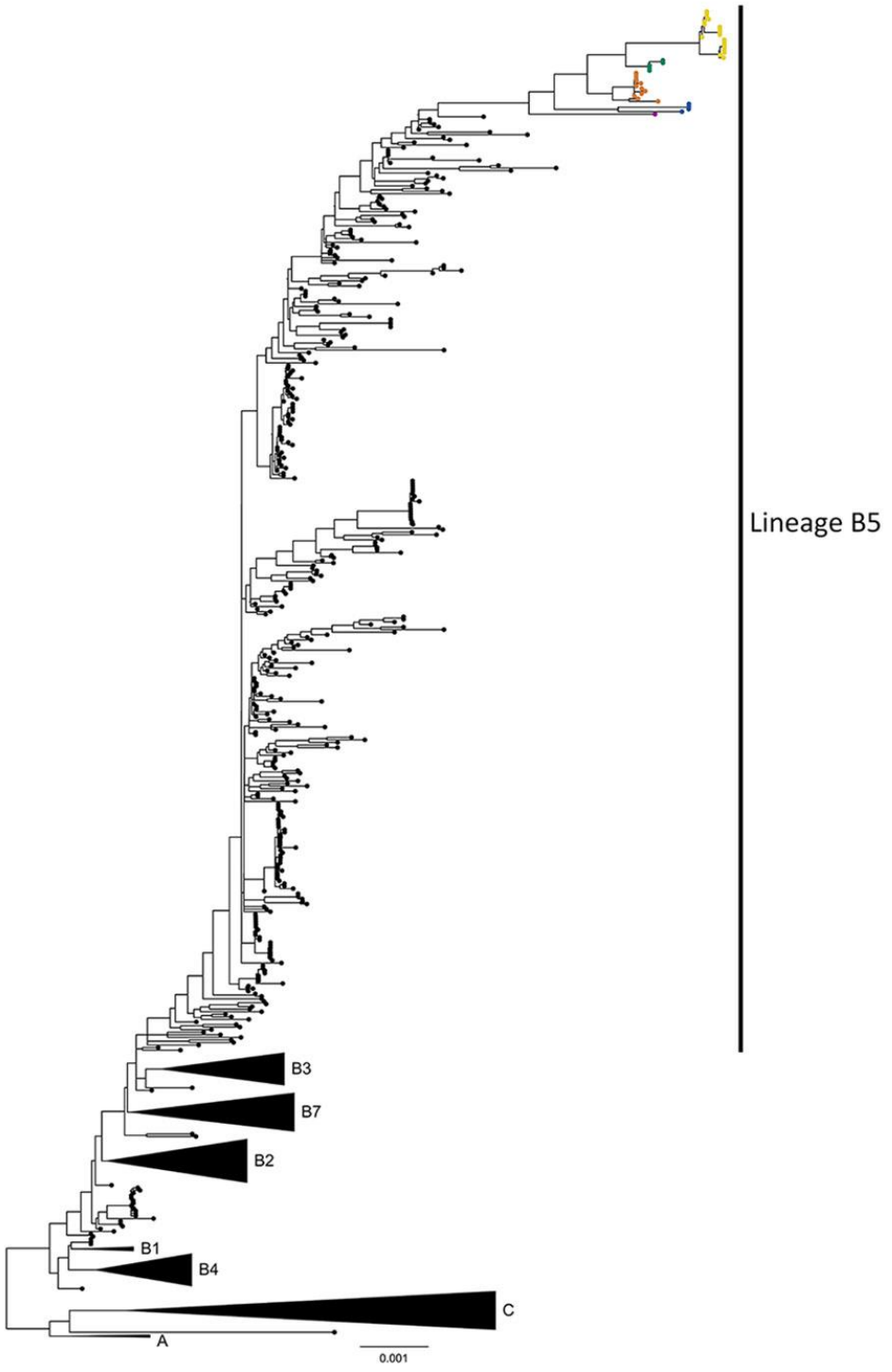

Figure 2*. Phylogenetic analysis of Middle East respiratory syndrome coronavirus (MERS-CoV) clades and sample distribution in study of ongoing evolution of virus, Saudi Arabia, 2023–2024. Tree was constructed by using the maximum-likelihood method. Black circles indicate 620 complete MERS-CoV genomes sampled until 2019; colored circles indicate 41 MERS-CoV genomes sequenced in this study. Blue circles indicate B5-2023.1, orange circles B5-2023.2, green circles B5-2023.3, yellow circles B5-2023.4, and magenta B5-2023.5 sublineages. Black triangles indicate collapsed clades A, C, B1–B4, and B7. Scale bar indicates nucleotide substitutions per site.

*Figure from Hassan *et al.*, 2025 [21]. This work is in the public domain.

Table 1: Clade and lineage distributions

Clade	Lineage	Origin	Most common in	First Detection	Reference
Clade A	A1	Arabian Peninsula	Human	2012	(Zaki *et al.,* 2012 [22])
Clade B	B	Arabian Peninsula	Humans and Camels	2013	(Cotten *et al.,* 2013 [23])
	B1		Humans		(Cotten *et al.,* 2014 [24])
	B2		Camels		(Sabir *et al.,* 2016 [20])
	B3				
	B4				
	B5		Humans and Camels	2014-2015	
	B5-2023		Camels	2023	(Hassan *et al.,* 2025 [25])
	B5-2023.1				
	B5-2023.2				
	B5-2023.3				
	B5-2023.4				
	B5-2023.5				
Clade C	C1	West/North Africa	Dromedary Camels	2013-2014	(Chu *et al.,* 2018 [26])
	C2	East Africa		2014	(Kiambi *et al.,* 2018 [27])
	C3	Egypt-specific lineage		2015	(Chu *et al.,* 2014 [28])

*Courtesy of Prof. Ezam I. Azhar

Host Ecology

Human cases can occur in individuals with occupational or cultural exposure to dromedary camels [29], but are often diagnosed in patients with underlying disease such as diabetes or heart disease, with or without reported camel exposure. Serological studies confirm enzootic circulation in camel populations, with high infection rates (i.e RNA positive samples) observed particularly in < 2 years old [16–18,30–33]. Most camels acquire infection before reaching adulthood, and they can be reinfected [34]. MERS-CoV has been identified in camel populations across Africa, the Middle East, and South Asia, although genomic data remain limited. Despite evidence of human infections in Africa and Asia, many countries with large camel populations (e.g., Somalia, Pakistan, Sudan etc.) lack genomic data [35], limiting our understanding of MERS-CoV's full geographic spread and host adaptation dynamics.

Transmissibility in humans

Human-to-human spread remains limited, with transmission chains generally terminating in healthcare or household settings, but can still lead to significant outbreaks in closed settings such as hospitals, e.g. as highlighted by the 2014-2015 nosocomial outbreaks in KSA and the Republic of Korea [36,37]. Human adaptive mutations of MERS-CoV following zoonotic transmission has been reported [38]. Phylogenetic analyses and in vitro laboratory data revealed that clade B viruses, particularly lineage B5, demonstrate enhanced replication efficiency and immune evasion capacity in human cells, as compared to lineage B3 and B4 [39]. Spike protein L495P and V527L mutations found in recent B5 lineages from KSA may also improve spike protein cleavage and cell entry [21]. The evolution and phenotype of clade B should be closely monitored. In contrast, Clade C1.1 spike was associated with reduced virus replication competence in Calu-3 cells *in vitro*, in *ex vivo* human bronchus, and in lungs of hDPP4 knockin mice *in vivo* [40,41].

Surveillance of MERS-CoV should be strengthened with region-specific priorities: in Africa, to better characterize the severity spectrum of clade C virus infections in humans, in addition to monitoring for potential introduction and spread of more pathogenic clade B strains via camel movement and tourism [41,42]; in Central Asia, to identify circulating virus lineages and assess any associated human disease; and in Southern Asia, to increase molecular testing (e.g. RT-PCR) and sequencing of camel samples to determine the viral clades and lineages present in animal reservoirs. Surveillance in Southern Asia can begin with testing SARI and ILI cases in regions with large camel populations and close human-camel contact. Countries in these regions should have the capacity to test suspected cases, particularly when there is an epidemiological link and/or severe respiratory disease [43,44].

Immune evasion in humans

Experimental infections and comparative studies demonstrate that some clade B lineages, particularly B5, replicate more efficiently in human airway cells and induce stronger innate immune antagonism than other clade B lineages [39]. Mutations in the spike protein and accessory genes may influence virus-host interactions. Seroprevalence data suggest minimal cross-neutralization with other coronaviruses [45], but cross-protection could still be mediated by other immune responses such as e.g. T cell responses. The recently published B5 sequences have the following mutations located in the Receptor Binding Domain (RBD) of the spike protein: S459N, H486Y, L495P R505L, and

V527L. The mutations L495P and V527L [21] are exposed to the spike surface and are major targets for human neutralizing antibodies. Studies are ongoing to identify whether those mutations are immune evasive in camels, too.

Cross-protection from COVID-19 vaccines or SARS-CoV-2 infection cannot be ruled out as a contributing factor to the recent observed decrease in MERS-CoV cases, despite the absence of cross-neutralizing antibodies [46,47]. COVID-19 vaccination generates spike-binding antibodies targeting the conserved S2 domain, as well as robust cross-reactive T-cell responses against conserved spike epitopes [48]. While indirect, these responses could potentially modulate MERS-CoV infection severity and reduce transmission potential, particularly among vaccinated individuals frequently exposed to camels. However, the extent of their contribution to protection against MERS-CoV in humans remains to be fully established [46].

Several vaccine and monoclonal antibodies candidates are in various phases of development, but none are licensed yet [49].

Severity in humans

MERS-CoV infections have a high severity, with a case-fatality ratio (CFR) of approximately 36%. This is likely an overestimation as individuals with mild primary MERS-CoV infections are often missed by current surveillance systems since they usually do not present to health-care facilities [50]. From the global case data WHO receives under the international health regulations, CFR in patients with comorbidities is 51% and in patients that were admitted to ICU is 64%. Severe outcomes are associated with underlying health conditions, delayed diagnosis, and nosocomial transmission [50]. There are no confirmed reports of congenital anomalies or pregnancy-related complications due to MERS-CoV [50], though data are limited.

A study showed that clade B caused more severe disease in mice, with delayed viral clearance, increased inflammatory cytokines, and decreased antiviral T cell responses, than the early clade A virus (EMC/2012) [51].

Diagnostic considerations

Diagnostic testing includes RT-PCR targeting E and ORF1a regions for active infections and serology (ELISA or IFA) confirmed by a neutralization assay for past infections, as per WHO recommendations [52]. Improved diagnostic coverage, particularly in countries with important camel populations and along camel trade routes, is necessary.

Therapeutic considerations

Remdesivir has demonstrated potent *in vitro* activity against MERS-CoV, with an EC_{50} of approximately 0.04 µM [53], while molnupiravir has shown efficacy in human DPP4 (hDPP4) transgenic mouse models [54]; Monoclonal antibodies such as SAB-301 and the REGN3048/3051 cocktail are currently undergoing Phase II clinical trials [55].

To date, no specific antiviral treatment or licensed vaccine is available for MERS-CoV [56], and supportive care remains the mainstay of clinical management [57]. However, based on bioinformatic

analyses, polymerase inhibitors approved for SARS-CoV-2, such as remdesivir and molnupiravir, may also be effective against MERS-CoV [58,59]. In contrast, the protease inhibitor Paxlovid may exhibit reduced efficacy due to structural differences in the nsp5 protease between SARS-CoV-2 and MERS-CoV [60].

Recommended studies

WHO and its Technical Advisory Group on Virus Evolution (TAG-VE) continue to recommend that Member States prioritize specific actions to better address uncertainties relating to transmissibility, immune escape and severity of MERS-CoV. Timelines for this work will vary from one country to another based on national capacities. A MERS-CoV clade C isolate is available upon request to the WHO BioHub System for laboratories that meet the required Biosafety & Biosecurity standards and will use the materials under the WHO BioHub System permissions. The recommended analyses include:

- Proportionate testing in countries without intrinsic zoonotic risk
- Longitudinal cohort studies in camels, occupationally exposed humans and their communities (with serological, T-cell and virological testing as well as behavioral and anthropological surveys) in camel-dense regions to assess zoonotic spillover risks [see WHO MERS-CoV Investigations and Studies for guidance and One Health questionnaires [43]
- Genomic surveillance in camels and humans in currently unsampled regions with large camel populations, especially where sequence information has never been generated (e.g. Central Asia), including in areas where B.5 2023 subclades have been identified.
- Enhanced surveillance and sequencing of human cases, especially in areas where the lineage B.5 2023 sub-clades are circulating in camels.
- Phenotypic characterization of the lineage B.5 2023 sub-clades.
- Phenotypic studies comparing clade B and C virus infectivity and replication in human (and if possible, camel) cell lines, and characterizing the B.5 2023 sub-clades identified in camels from Saudi Arabia.
- Analysis of recombination hotspots and adaptive mutations in clade B lineages
- Improved testing of ILI, ARI and SARI cases in camel-dense regions where populations are exposed to camels but with little evidence for spillover to humans (Africa, South Asia)
- Investigate cross-protection from SARS-CoV-2 infection or COVID-19 vaccination against MERS-CoV infection and any implications for infection severity, and transmission risk
- Testing of antivirals (polymerase and protease inhibitors) approved for SARS-CoV-2 against MERS-CoV *in vitro, in vivo* and then in clinical studies

Acknowledgements

Thanks to:

• Advisors: Francis Amirtharaj Selvaraj, Abu Dhabi Public Health Centre, UAE & CoViNet reference laboratory, Asma Mohammad, Abu Dhabi Agriculture and Food Safety Authority, UAE & CoViNet reference laboratory; Ahmed Mohammed Albarraq, Public Health Authority, Kingdom of Saudi Arabia; Isaac Ngere, Washington State University, Kenya.

• TAG-VE members: Anurag Agrawal, Laith Jamal Abu-Raddad, Esam I. Azhar, Leon Caly, Christian Drosten, Nuno R. Faria, Adeola Fowotade, Baoying Huang, Bette Korber, Nada M. Melhem, Vincent J. Munster, Malik Peiris, Gustavo Palacios, Andrew Rambaut, Paola Resende, Senjuti Saha, Yee-Sin Leo, Tadaki Suzuki, Pragya Yadav, Tulio de Oliveira, Placide Mbala-Kingebeni, Jason Kindrachuk, Marion P.G. Koopmans, Meera Chand, Anne von Gottberg

• WHO Secretariat: Abdullah Al Sayafi, Amal Barakat, James Richard Otieno, Christopher Ruis,

Lorenzo Subissi, Maria D. Van Kerkhove, Sophie von Dobschuetz.

•Leo Poon (Hong Kong University), Dr Ghazi Kayali (Human Link, Lebanon), Prof. Mohamed A. Ali (National Research Centre, Egypt) for sharing MERS-CoV clade C isolate with the WHO BioHub System, and the WHO BioHub Facility: Spiez Laboratory Switzerland.

Overall risk evaluation: **High** for people exposed to camels, working in healthcare settings or having underlying health conditions in endemic areas **Low to Moderate** for the remaining population of and travelers to endemic areas **Low** for the remaining global population	Global genomic surveillance has identified three major clades: A, B, and C, further subdivided into lineages. MERS-CoV Clade A has only been detected in humans in 2012 and in a camel sample in 2015 and has not been observed ever since. Clade C circulates in camels from Africa, and is also believed to cause infections in humans, as evidenced by serological and T-cell studies, however MERS-CoV surveillance in African countries with important camel populations should be enhanced to better understand the extent and severity of this public health risk. Enzootically circulating in camel populations in the Middle East, Clade B viruses continue to cause sporadic human infections, even though the number of cases has dropped substantially since 2020. This observed decline in human cases could partly reflect cross-protection conferred by SARS-CoV-2 infection and COVID-19 vaccination, through spike-binding antibodies and cross-reactive T-cell responses, even in the absence of cross-neutralizing antibodies. Reduced virulence in current strains is still under investigation, but preliminary data do not support significant attenuation. Definitive conclusions await further genomic and phenotypic studies. The risk of camel-to-human transmission of MERS-CoV in endemic regions is assessed as high for occupationally exposed humans, healthcare personnel and people with underlying health conditions, considering the high and continuing levels of MERS-CoV circulation amongst camels. More genomic surveillance is needed to assess whether this risk is lower in countries with camel populations outside of the Middle East, where different MERS-CoV clades are circulating. The risk of onwards human-to-human transmission of MERS-CoV is overall assessed to be low for the general population but remains possible in close contact settings such as healthcare or households in endemic areas, especially where infection prevention and control measures are not adequate in healthcare settings.		
Indicator	Evidence	Level of risk	Level of confidence
Transmissibility	Camel-to-Human: Latest evidence confirms very high infection rates in dromedary camels (up to 40% of positive camels by RT-PCR during the calving season), placing persons in close contact with camels at risk of exposure and thus infection. However, there has been a recent observed decrease in MERS-CoV cases	High	Moderate

	in humans since 2020, likely due to changes in movement and contact because of the COVID-19 pandemic. As infection rates in dromedary camels remain high, it is unknown whether the decrease in human cases could arise from a decrease in transmissibility of strains currently circulating in camels. Further phenotypic studies need to be conducted.		
	Human-to-human: While this transmission route may seem inefficient, it can cause large outbreaks in health care settings, especially if isolation, appropriate infection prevention and control measures as well as contact tracing are not promptly established, as highlighted by large outbreaks in KSA and the Republic of Korea in 2014-2015.	Low to Moderate	High
Immune escape	Experimental infections and comparative studies demonstrate that new MERS-CoV strains can emerge with mutations on the spike protein receptor binding domain (RBD), major target for human neutralizing antibodies, and potentially induce stronger innate immune antagonism [39]. However, immune escape is unlikely to be a major driver of MERS-CoV evolution. COVID-19 vaccination generates spike-binding antibodies targeting the conserved S2 domain, as well as robust cross-reactive T-cell responses against conserved spike epitopes [46,47], and even more so does SARS-CoV-2 infection. However, the extent of their contribution to protection against MERS-CoV in humans remains to be established.	Low	Moderate
Severity and clinical/diagnostic considerations	Although the case fatality ratio of MERS-CoV may be overestimated due to the lack of comprehensive reporting of subclinical or mild infections, MERS-CoV remains a very severe infection and if spread efficiently, could have a very severe public health impact. Reduced virulence of currently circulating MERS-CoV strains remains under	High	Low

	investigation, although preliminary data from in vitro growth kinetics and partial sequencing indicate no major attenuation in circulating strains. No specific antiviral treatment or licensed vaccine is available for MERS-CoV, and the effectiveness SARS-CoV-2 inhibitors such as molnupiravir, remdesivir and paxlovid against MERS-CoV needs further studies.		

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Suggested citation. Risk Evaluation of Circulating Middle East Respiratory Syndrome Coronavirus (MERS-CoV) Clades and Lineages. Geneva: World Health Organization; 2025. https://doi.org/10.2471/B09600