Respiratory infections due to human common cold coronaviruses, SARS-CoV, MERS-CoV, and SARS-CoV-2: epidemiology, pathogenesis, clinical features, diagnostics, therapeutics, and vaccine landscapes

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Over the past half-century, perceptions of human coronaviruses have evolved from their initial characterisation as causes of the common cold to recognition of their capacity to trigger severe disease and global epidemics. The emergence of three zoonotic coronaviruses—severe acute respiratory syndrome coronavirus (SARS-CoV) in 2002, Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012, and SARS-CoV-2 in 2019, has had profound health, economic, and societal consequences and continues to influence global epidemic-preparedness strategies. All three viruses remain on the WHO Blueprint of priority pathogens for research and development. This Review summarises current knowledge on human coronaviruses, drawing lessons from the past 25 years of epidemic outbreaks. The shared and divergent features of SARS-CoV, MERS-CoV, and SARS-CoV-2, including their origins, evolution, transmission determinants, zoonotic transmission, viral entry pathways, pathogenesis, spectrum of clinical manifestations, long-term sequelae, and case-fatality profiles are highlighted. The full range of clinical manifestations, from asymptomatic or atypical presentations to severe acute respiratory and multisystem disease, are outlined together with risk factors for progression and populations with the greatest susceptibility. Diagnostic approaches, including molecular assays, antigen-based tests, and imaging modalities are described alongside current therapeutics, antiviral strategies, immunomodulators, supportive care principles, and evidence from clinical trials. Advances in diagnostics, vaccines, therapeutics, and infection-control practices are examined together with persistent challenges in early recognition, particularly in resource-limited settings. Strengthening multinational clinical trial capacity, leveraging digital innovations, and embedding One Health approaches are essential to mitigating spillover risks and improving global readiness. We review the latest data, identify gaps and opportunities, and outline forward-looking strategies to anticipate and prepare for the threat of future coronaviruses, and other existing or new respiratory pathogens with epidemic potential. Clinicians and other health-care workers play a central role in detecting and reporting possible lethal coronavirus infection including atypical presentations, enabling rapid, coordinated infection control and management responses.

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Introduction

Coronaviruses are a diverse family of RNA viruses that infect humans and numerous animal species.[1] For much of the 20th century, human coronaviruses were understood primarily as causes of mild upper respiratory illness, responsible for a modest but steady share of seasonal common colds.[2,3] HCoV-229E and HCoV-OC43 were first identified in the 1960s, and two additional endemic strains, HCoV-NL63 and HCoV-HKU1, were discovered in 2004 and 2005.[4,5] This view changed markedly in the 21st century with the emergence of three highly pathogenic zoonotic coronaviruses: severe acute respiratory syndrome coronavirus (SARS-CoV) in 2002–03, Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012, and SARS-CoV-2 in 2019.[6–8] Each showed the potential of coronaviruses to cause severe disease, efficient cross-border transmission, and large-scale societal disruption. Collectively, these events transformed global understanding of coronavirus biology and epidemiology and exposed persistent vulnerabilities and inequities in public health systems worldwide.[9] All three viruses remain on the WHO Blueprint, a list of priority pathogens for research and development.[10]

The repeated emergence of epidemic coronaviruses reflects their intrinsic biological characteristics, the absence of pre-existing immunity in humans, and ecological conditions favouring zoonotic spillover.[11,12] Coronaviruses possess large RNA genomes, high recombination rates, and broad host ranges, enabling rapid adaptation and cross-species transmission.[1,11–15] Extensive circulation in bats and other wild animals, rodents, camels, domestic pets, and livestock provides a reservoir of genomic diversity from which new variants can arise.[1,13–16] Concurrently, expanding interfaces between humans and animals, through urbanisation, agricultural intensification, wildlife trade, and environmental change have increased opportunities for spillover and amplification.[11,16] For these reasons, coronaviruses remain prioritised by WHO as leading candidate pathogens with pandemic potential for a future so-called disease X event.[9,10]

Since the early 2000s, there have been important advances in understanding of coronavirus biology, detection, transmission dynamics, clinical expression, immune responses, pathogenesis, and sequelae. International collaboration during the COVID-19 pandemic accelerated vaccine development, diagnostic

Key messages

Over the past 25 years, three coronaviruses—SARS (severe acute respiratory syndrome)-CoV, MERS (Middle East respiratory syndrome)-CoV, and SARS-CoV-2—have emerged as lethal zoonotic spillover pathogens. These coronaviruses were responsible for three major epidemics: SARS, MERS, and COVID-19. These high-consequence coronaviruses with epidemic potential remain on the WHO Blueprint priority pathogens list for priority research and development.

- SARS, MERS, and COVID-19 exhibit a wide clinical spectrum, from asymptomatic or mild upper respiratory disease to severe viral pneumonia, multiorgan involvement, fulminant respiratory failure, and long-term functional disability. Although the three viruses share overlapping features, they differ substantially in transmissibility, pathogenesis, extrapulmonary manifestations, and clinical outcomes.
- Clinicians and health-care workers play a central role in recognising zoonotic coronavirus infections. Timely diagnosis, awareness of atypical or multisystem presentations, and early detection of unusual clusters are essential for rapid reporting and implementation of infection-prevention measures.
- The COVID-19 pandemic catalysed an unprecedented global response, accelerating vaccine, diagnostic, and therapeutic development, and laying foundations for more rapid future pandemic preparedness.
- Persistent inequities in access to diagnostics, vaccines, and therapeutics, together with gaps in One Health surveillance across human, animal, and environmental interfaces, continue to challenge outbreak detection and response, particularly in low-income and middle-income countries.
- Integrating new diagnostics and digital innovations into patient care pathways, strengthening surveillance, and operationalising One Health approaches are important for reducing spillover risk and enhancing global preparedness for future coronavirus threats.

See Online for appendix

innovation, and antiviral discovery at unprecedented speed, illustrating what can be achieved under urgent mobilisation. However, the pandemic also highlighted profound inequities in access to diagnostics, oxygen, therapeutics, and vaccines, particularly in low-income settings, reinforcing the need for equitable preparedness and sustained research capacity.[9,17]

This Review provides comprehensive, holistic, and multifaceted analyses of the literature on common cold coronaviruses (HCoV-229E, HCoV-OC43, HCoV-NL63, and HCoV-HKU1) and epidemic zoonotic coronaviruses (SARS-CoV, MERS-CoV, and SARS-CoV-2). First, it examines shared and divergent features of biology, epidemiology, pathogenesis, clinical manifestations, and management. Second, it critically appraises the strengths and limitations of existing evidence across epidemiology, diagnostics, therapeutics, and vaccines. Third, it draws cross-cutting lessons from the COVID-19 pandemic, particularly in surveillance, clinical care, genomic monitoring, and global equity, that directly inform preparedness for future coronavirus threats. Finally, it offers forward-looking guidance based on emerging science, including pan-coronavirus vaccines, broad-spectrum antivirals, digital epidemic intelligence, and the pressing need for One Health approaches to prevent zoonotic spillover and epidemics.

Origins, classification, and evolution of coronaviruses

Coronaviruses are enveloped, positive-sense, single-stranded RNA viruses that were first recognised as pathogens in livestock and other animals before being identified as causes of human infection.[1–5,11–16] They have the largest genomes among RNA viruses (26–32 kilobases) and are characterised by crown-like surface projections formed by the spike glycoprotein, which mediates host cell entry. Their taxonomy, natural reservoirs, host receptors, and clinical presentations are summarised in table 1. Additional details on taxonomy are provided in the appendix (pp 2, 3).

The family Coronaviridae (order Nidovirales, subfamily Orthocoronavirinae) includes four genera: *Alphacoronavirus*, *Betacoronavirus*, *Gammacoronavirus*, and *Deltacoronavirus*.[1] Nine coronaviruses are recognised in humans, including alphacoronaviruses HCoV-229E and HCoV-NL63; betacoronaviruses HCoV-OC43 and HCoV-HKU1 (lineage A), SARS-CoV and SARS-CoV-2 (lineage B), and MERS-CoV (lineage C). Two additional zoonotic detections, CCoV-HuPn-2018 from a child with pneumonia,[14] and a porcine deltacoronavirus identified in Haitian children,[15] illustrate ongoing cross-species transmission. No human infections with gamma-coronaviruses have been identified yet.

Evolutionary origins

All human coronaviruses are zoonotic in origin. Metagenomic and phylogenetic studies comparing coronaviruses sampled from animals in contact with humans with those sampled from farmed and wild animals in different geographic settings have helped identify likely reservoirs and intermediate hosts for SARS-CoV, SARS-CoV-2, and MERS-CoV. Molecular analyses indicate that several endemic human coronaviruses emerged through spillovers during the past few centuries, with some introductions likely occuring as recently as the 18th to 19th centuries (appendix (pp 4–13). HCoV-OC43 likely diverged from bovine coronavirus in the late 19th century.[4] HCoV-229E appears to involve bat-derived viruses with camelid intermediates and divergence estimates vary (~18–19th century).[4,5] HCoV-NL63 is closely related to bat coronaviruses, whereas HCoV-HKU1 likely arose from rodent lineages, although the timing of its emergence in humans remains uncertain.[2,3] Taken together, evidence supports multiple independent

	Genus (lineage)	Natural reservoir	Intermediate host	Host receptor	Clinical presentation summary
HCoV-229E (1960s)*	*Alpha*	Bats	Unknown (camelids suspected)	hAPN (CD13)†	Mild URTI; common cold
HCoV-NL63 (2004)*	*Alpha*	Bats	Unknown	ACE2‡	Mild URTI; croup in children; bronchiolitis
Canine coronavirus (2018)§	*Alpha* (recombinant)	Dogs, cats, pigs, wolves, and foxes	Unknown (zoonotic spillover from dogs suspected)	Aminopeptidase N (AP-N; canine, feline, or porcine; hAPN is not an efficient functional receptor)	Mild fever, pneumonia in rare human cases; detected in hospitalised pneumonia cases (Sarawak, Malaysia, 2017–18); causality and spectrum still being defined
HCoV-OC43 (1960s)*	*Beta* (A)	Cattle	Unknown (cattle widely considered the intermediate host from a rodent-origin BCoV)	9-O-acetylated sialic acid¶	Common cold; bronchitis
HCoV-HKU1 (2005)*	*Beta* (A)	Reservoir not definitively identified; likely rodent origin	Unknown	9-O-acetylated sialic acids (attachment) and TMPRSS2|| (protein receptor implicated in structural studies)	Mild respiratory illness; bronchitis; pneumonia in immunocompromised individuals
SARS-CoV (2002–2003)**	*Beta* (B)	Bats	Masked palm civet cats, racoon dogs, and other small mammals (postulated)	ACE2	Spectrum: mild to fatal (severe pneumonia, 10% CFR)
MERS-CoV (2012)**	*Beta* (C)	Bats	Dromedary camels	DPP4 (CD26)††	Spectrum: mild to fatal (severe pneumonia with renal and GI involvement, 35% CFR)
SARS-CoV-2 (2019)**	*Beta* (B)	Bats	Pangolins and other wildlife proposed; minks are susceptible animal-to-human transmission in farm settings, but no single intermediate host confirmed	ACE2 (TMPRSS2 activates spike)	Spectrum: asymptomatic, mild to fatal; severe pneumonia, multisystem disease
PDCoV (2004)	*Delta*	Avian origin proposed for deltacoronaviruses; PDCoV is established in pigs	Pigs	hAPN	Acute undifferentiated febrile illness reported in Haitian children (zoonotic spillover); typically, diarrhoea or vomiting in pigs

All human coronaviruses are zoonotic in origin, with multiple suspected spillover events. The human infections identified so far with canine coronavirus and PDCoV appear to be rare spillover events, with no evidence of human-to-human transmission. BCoV=betacoronavirus. CFR=case-fatality rate. GI=gastrointestinal. PDCoV=porcine deltacoronavirus. URTI=upper respiratory tract infection. *Now cause approximately 15–30% of common colds worldwide. †Expressed in respiratory and GI epithelium. ‡Highly expressed in alveolar epithelial cells, GI tract, heart, and kidneys. §First identified as a potential human pathogen in a patient sample collected in 2018, leading to research published in 2021. The human-infecting strain discovered was a recombinant virus with genetic material from canine and feline coronaviruses, and potentially from pigs. ¶Uses 9-O-acetylated sialic acids for attachment; HLA class I use is theorised but not definitive. ||A serine protease that facilitates coronavirus entry via S protein priming. Co-expression with coronavirus receptor is key for infectivity. **Have caused global or regional outbreaks with high mortality and systemic complications. ††Widely expressed, including on renal, hepatic, and immune cells.

Table 1: **Year discovered, taxonomy, origins, host receptors, and clinical presentations of coronaviruses**

zoonotic introductions, although sparse sampling and frequent recombination limit temporal precision.

SARS-CoV

The emergence of SARS-CoV in 2002–03[6,18–21] marked a turning point in recognising the pandemic potential of coronaviruses. It was named SARS-CoV and in 2020 was colloquially renamed by WHO as SARS-CoV-1 to distinguish it from SARS-CoV-2, which caused the COVID-19 pandemic.[6,8] Although the name SARS-CoV-1 in now used in contemporary literature, its usage is conventional rather than a formal International Committee on Taxonomy of Viruses renaming. The virus is most likely a horseshoe bat-origin sarbecovirus, with masked palm civets, raccoon dogs, and other wildlife in live-animal markets implicated as intermediary hosts.[6,18–21] SARS-CoV first emerged in Guangdong Province, China, in November, 2002, and spread rapidly across regions in Asia, North America, and Europe, showing how modest genetic changes can alter host range and pathogenicity. The outbreak was largely contained, with no sustained community transmission reported after July, 2003, and the epidemic subsided. Only laboratory-aquired infections were subsequently reported in 2004. SARS-CoV is therefore no longer considered to be in circulation in humans.[6]

MERS-CoV

MERS-CoV was first identified in 2012.[7,22] It is a merbecovirus within the genus *Betacoronavirus*, thought

to have originated in bats, with dromedary camels serving as the principal animal reservoir responsible for most zoonotic infections in humans.[23–26] Persistent camel circulation, extensive viral diversity across Africa and the Middle East, and repeated spillover events sustain epidemic concerns.[6,26,27] MERS-CoV continues to cause sporadic cases, mainly in Saudi Arabia, and occasional travel-related cases. It remains on the WHO Blueprint list of priority pathogens for research and development because of its high case-fatality rate (CFR) and the potential emergence of more transmissible variants.[10]

SARS-CoV-2

Emerging in late 2019, SARS-CoV-2 belongs to sarbecovirus lineage B and is most closely related to bat-associated viruses.[8,28–30] Its appearance reflects complex wildlife–human interfaces involving ecological disruption, live-animal trade, and dense contact settings. SARS-CoV-2 achieved sustained human-to-human transmission, followed by extensive diversification into multiple lineages and variants shaped by immune evasion, receptor affinity, and transmission fitness.[8,29–31]

Recombination and diversification

Coronaviruses exhibit exceptionally high recombination rates, attributable to discontinuous RNA transcription and frequent template switching.[3–5,12,30,31] Recombination drives lineage diversification, host-range shifts, and antigenic evolution. Illustrative examples include the canine–feline recombinant CCoV-HuPn-2018 detected in Malaysia[14,32] and recurrent recombination among camel coronaviruses such as HKU23 across Africa and the Middle East.[33] These findings highlight ongoing human exposure to diverse animal coronaviruses, even in the absence of sustained transmission.

Epidemiology

Human coronaviruses display heterogeneous epidemiological patterns shaped by host range, receptor usage, viral replication kinetics, population immunity, and environmental factors. The sequential emergence of SARS-CoV, MERS-CoV, and SARS-CoV-2 has reshaped understanding of coronavirus evolution, spillover risk, and pandemic threat.[6–8] Their histories show high propensity for cross-species transmission and rapid adaptation to human receptors including ACE2 (SARS-CoV lineages) and DPP4 (MERS-CoV).[30–34] Their pronounced genetic plasticity, and wide clinical variability, from mild illness to severe pneumonia and multisystem disease, suggest that coronavirus spillovers are recurrent rather than rare, and that contemporary ecological, agricultural, and societal dynamics continue to amplify emergence risk.

Human common cold coronaviruses

HCoV-229E, HCoV-OC43, HCoV-NL63, and HCoV-HKU1 are well established, globally circulating endemic human coronaviruses that are major causes of the common cold and other mild acute respiratory illnesses. Collectively, these viruses are estimated to account for approximately 5–30% of acute upper respiratory tract infections worldwide, with substantial variation by age group, season, geographical region, and intensity of surveillance.[1–5,35–37] Common cold coronaviruses co-circulate as multiple genetic lineages with evidence of recombination, highlighting their evolutionary flexibility and potential for phenotypic change. Their transmission peaks during winter in temperate regions, although considerable geographical variability has been documented, including prolonged or year-round transmission in tropical settings. Reinfections occur frequently owing to short-lived mucosal immunity and ongoing antigenic drift. Large surveillance studies consistently show that infection occurs across all age groups, with the highest incidence in young children. Although common cold coronavirus activity, together with that of most other respiratory viruses except for rhinoviruses, was suppressed during the early stages of the COVID-19 pandemic as a result of the widespread use of mitigation measures to contain the pandemic,[36] it appears that seasonal human coronavirus activity has now returned to pre-pandemic patterns.[37]

SARS-CoV

The 2002–03 SARS-CoV epidemic marked the first recognition that coronaviruses could spillover from animal to humans and drive a major international outbreak.[6,18–21,38] C_lusters of severe respiratory disease emerged in Guangdong, China, in late 2002,[39–41] and the causative coronavirus was identified in February, 2003.[18,20,40] The virus spread globally after a single superspreading event in a Hong Kong hotel, initiating outbreaks in Canada, Singapore, Vietnam, and elsewhere. Older age and comorbidities increased risk of severe outcomes.[39–42] Viral load and transmissibility peaked late in illness, particularly in hospitalised patients undergoing aerosol-generating procedures, which allowed early case-based detection, isolation, and outbreak containment. By July, 2003, 8096 cases and 774 deaths (9·6% CFR) were reported.[6,39–42] Superspreading was a major feature, and estimated hospital R_0 values were 2–3, similar to ancestral SARS-CoV-2. *Rhinolophid spp* bats were shown as the natural reservoir and civets, raccoon dogs, and other market-traded mammals as likely intermediates.[11,18,43,44]

MERS-CoV

MERS-CoV was first identified in September, 2012, in respiratory samples obtained from a patient who died of severe pneumonia in Jeddah, Saudi Arabia.[22] Subsequent retrospective investigations traced earlier cases to a hospital-associated outbreak in Jordan in April, 2012, in which at least ten health-care workers were infected, as confirmed by RT-PCR and serological analyses.[45] Serological and genomic evidence indicates that MERS-CoV has been enzootic in dromedary camels since

at least 1992 and is widely distributed throughout the Middle East and Africa.[26,46,47] Viral genomes isolated from nasal swabs of dromedary camels are genetically indistinguishable from those obtained from infected humans, strongly implicating camels as the primary reservoir and the principal source of zoonotic transmission to humans.[24–26] A summary of the phylogenetic structure and proposed clade designations of MERS-CoV since its identification in 2012 is shown in the appendix (pp 5–8). MERS-CoV has shown epidemic potential through international spread. The timelines of MERS-CoV clade evolution and major outbreaks within and outside the Middle East are depicted in the appendix (p 6). MERS-CoV continues circulating and genetically evolving in dromedary camels across large parts of the Middle East, northern and sub-Saharan Africa, and central and south Asia.[6,26,46–48]

Figure 1A summarises MERS-CoV transmission at the animal–human and human–human interface. Dromedary camels are the primary reservoir, with sustained camel-to-camel transmission and recurrent zoonotic spillover to humans through direct or indirect contact with infected animals or camel products. The cumulative number of human MERS cases and their geographical distribution from 2012 to date is given in figure 1B. The appendix (p 6) depicts the numbers of MERS-CoV cases reported to WHO (by week) since 2012.[48] As of Jan 5, 2026, 2635 laboratory-confirmed cases of MERS, including 964 associated deaths (CFR 37%) have been reported from 27 countries across the Middle East, north Africa, Europe, the USA, and Asia.[48–55] Saudi Arabia accounts for approximately 84% of reported human MERS cases globally. Reports from outside the Middle East largely reflect travel-associated infections or secondary transmission. The true mortality risk is likely to be lower than suggested by crude CFR estimates, because mild, asymptomatic, and subclinical infections are often undetected, and therefore underrepresented in surveillance data.

Since 2019, the incidence of MERS in Saudi Arabia and the Arabian Peninsula declined markedly (appendix p 6).[7,48–50] Possible reasons for this decline include underreporting, behavioural changes during COVID-19, shifting viral ecology, or host immunity. However, current evidence suggests that SARS-CoV-2 infection or vaccination were unlikely to confer meaningful cross-protective immunity against MERS-CoV. Although these exposures elicit cross-reactive T-cell responses and induce antibodies against the conserved S2 subunit of the MERS-CoV spike protein, they do not generate the cross-neutralising antibody responses against the S1 subunit required for viral inhibition.[53] In 2015, South Korea experienced the largest MERS outbreak outside the Middle East, emanating from a single returning traveller, which resulted in 186 confirmed cases (185 cases in Korea and one in China) and 38 deaths. It also led to the closure of more than 2700 schools, and quarantine of nearly 17 000 individuals.[51,52] Within Saudi Arabia, large nosocomial outbreaks have also occurred in the early years after MERS-CoV was identified, before proper infection control measures were introduced.[7,23,24,27,47,51–55] These outbreaks were driven by delayed recognition, overcrowded emergency departments, and aerosol-generating procedures, together with a high degree of transmission heterogeneity.

To date, sustained community transmission outside health-care settings has been rare.[7,47,48,50] The persistence of occasional zoonotic spillover events, combined with incomplete genomic surveillance in Africa and the Middle East, underscores concern regarding the potential emergence of more transmissible variants. The index case in such spillover events often goes unrecognised, as initial infection can occur in otherwise healthy adults with asymptomatic or mild disease. Secondary transmission is typically detected once older individuals or those with comorbidities acquire infection and disease severity is greatest.[47] Related merbecoviruses such as NeoCoV have been identified in bats, but these remain genetically distant from MERS-CoV, and in some cases use ACE2 rather than DPP4 as the cellular entry receptor.[56]

Notably, MERS-CoV is widespread in dromedary populations across the Middle East, north and east Africa, and south Asia, with more than 75% of infected animals residing in Africa.[26,57,58] Viral strains circulating in Africa are genetically diverse, often carrying deletions in accessory genes.[57] More recently clade B viruses have been identified in camels of African origin highlighting the risk of introduction from the Arabian Peninsula into African camel populations.[49] Despite high seroprevalence in camels, no case of confirmed human disease has been reported from Africa (appendix pp 8–10). Possible explanations include limited awareness of MERS-CoV as a cause of severe respiratory illness, insufficient diagnostic capacity, and potential biological differences between Arabian Peninsula clade B viruses and African clade C viruses. Serological and cellular immunological studies conducted in Africa among individuals with close and frequent exposure to dromedary camels have shown evidence of previous MERS-CoV infection.[5] However, these findings are based on antibody and T-cell responses, and to date, there have been no reports of PCR-confirmed disease cases.[58–60] Genomic surveillance remains sparse and only very few MERS-CoV sequences obtained from human samples have been reported in recent years, particularly from the Arabian Peninsula, restricting analyses of viral evolution.[26,61] Other coronaviruses, including HKU23, a betacoronavirus, and 229E-related alphacoronaviruses also co-circulate in dromedaries, raising concern for recombination.[33]

SARS-CoV-2

The epidemiology and biology of SARS-CoV-2 has been extensively reviewed[8,62–72] Emerging in Wuhan, China, as

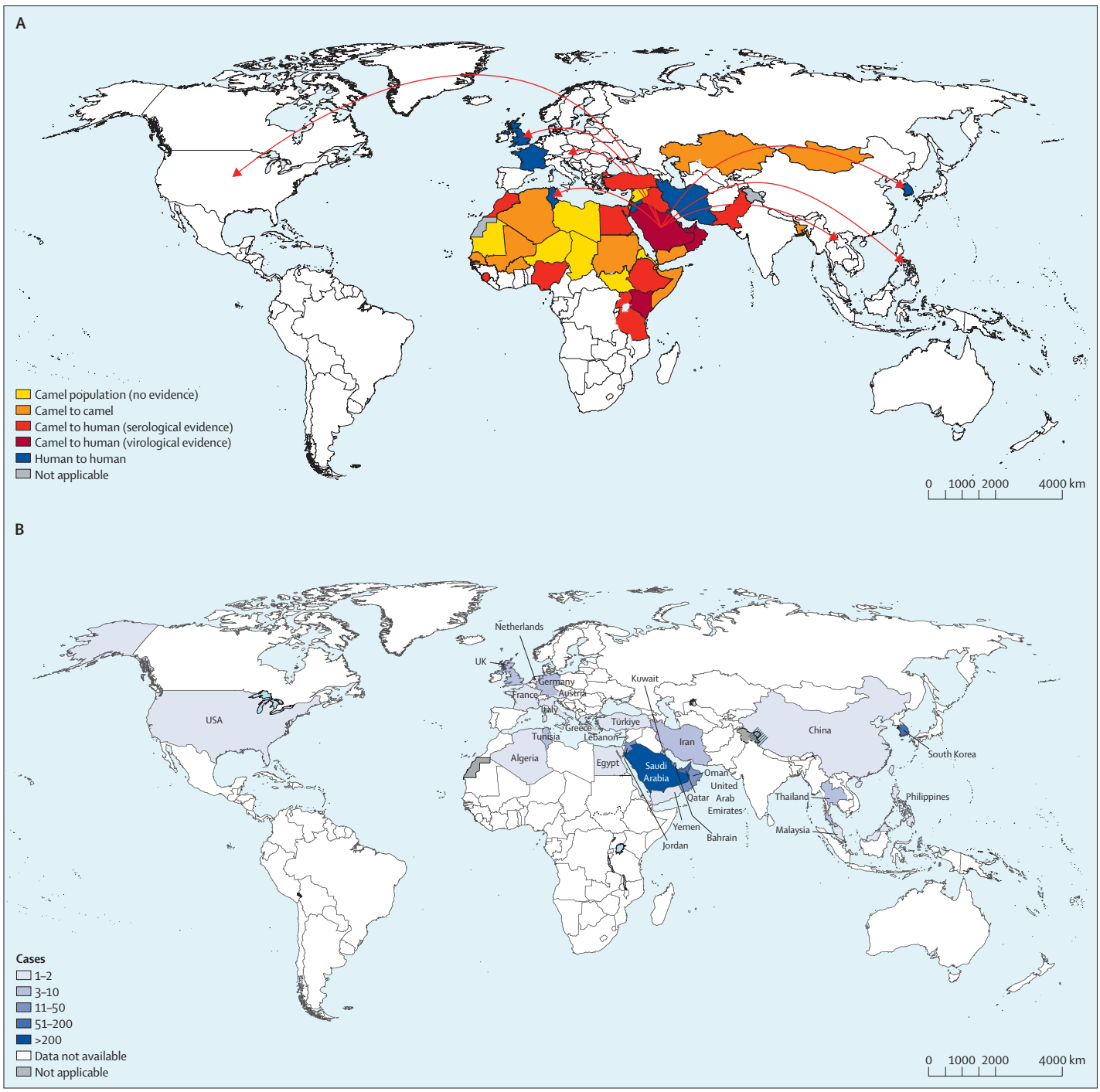


Figure 1: **MERS-CoV transmission pathways and global distribution of reported human cases, 2012–25**
(A) Zoonotic and human-to-human transmission of MERS-CoV. The red arrows highlight exportation of human cases with exposure in the Middle East, but detection in other countries. The red arrows illustrate the global nature of MERS-CoV risk, beyond areas where there are dromedary camels with history of MERS-CoV infection. Not applicable indicates no reported cases. Data sourced from WHO and the Food and Agriculture Organization of the UN under the CC BY-NC-SA 3.0 IGO licence. (B) Confirmed human cases of MERS reported to WHO from 2012–25. CoV=coronavirus. MERS=Middle East respiratory syndrome.

For more on the **WHO COVID-19 Dashboard** see https://data.who.int/dashboards/covid19/cases

zoonotic spillover to humans in late 2019, it exhibits the highest transmissibility among known human coronaviruses HCoVs.[62–68] According to the WHO COVID-19 Dashboard (which aggregates confirmed cases and deaths reported to WHO by member states), from Dec 31, 2019, to March 27, 2026, there were more than 779 million cumulative confirmed COVID-19 cases and more than 7 million deaths had been reported globally

(CFR=0·9%), although these figures likely underestimate the true burden. Unlike SARS-CoV, peak viral shedding occurs at or before symptom onset, enabling presymptomatic and asymptomatic transmission.[67–72] Infection spreads via droplets, aerosols in poorly ventilated settings, and via contaminated surfaces under specific conditions.[70–72] Overdispersion is marked, with a minority of cases responsible for most secondary infections.[67–71]

Rapid global spread has been accompanied by substantial viral evolution, reflected in WHO variant nomenclature (alpha, beta, gamma, delta, omicron) and Pango designations (B.1.1.7, B.1.351, P1, B.1.617.2, BA.1–2, and XBB.1.5).[73–75] Successive waves have shown increased transmissibility, immune escape, or altered severity, for example, D614G enhancement of infectivity, high viral loads with delta, and extensive antigenic drift within omicron lineages.[74,75] The SARS-CoV-2 variant evolutionary timelines are summarised in the appendix (pp 12, 13).

Risk factors for severe COVID-19 have remained broadly consistent across successive variant waves, with older age and underlying medical conditions the strongest predictors of hospitalisation and death.[74–77] Pregnancy is associated with increased risk of severe maternal and perinatal outcomes, particularly among individuals who are unvaccinated.[78–85] Protection against severe disease is substantially reduced by immunity from vaccination and previous infection, despite waning protection against infection.[80] Observed disease severity is also influenced by circulating SARS-CoV-2 variants, with omicron lineages associated with lower severity than delta, especially in immune-experienced populations.[74] Co-infections with other respiratory pathogens are common and can increase severity, particularly influenza virus–SARS-CoV-2 co-infection.

Pregnancy and SARS, MERS, and COVID-19

Pregnancy confers heightened vulnerability across all three epidemic coronaviruses.[78–85] The effects on maternal and neonatal health need further definition. SARS-CoV and MERS-CoV were associated with poor maternal outcomes, whereas SARS-CoV-2 is associated with increased risks of preterm birth (<37 weeks), pre-eclampsia, maternal intensive care unit (ICU) admission, and stillbirth, particularly in women who are unvaccinated.[81] These outcomes might reflect shared mechanisms of altered immunity, increased cardiorespiratory demand, and placental susceptibility. Placental infection with SARS-CoV-2, although uncommon, has been associated with inflammatory villous lesions, vascular malperfusion, and fetal compromise. There appears to be no effect on birthweight or congenital malformations in women affected by SARS-CoV-2, and infection in pregnancy and neonatal infection are uncommon.[80] Reports of SARS-CoV infection during pregnancy describe substantial morbidity. In one series, six (60%) of ten women required ICU admission compared with 36 (17·5%) of 206 non-pregnant adults, and four (40%) of ten women required mechanical ventilation compared with 26 (12·5%) non-pregnant adults; maternal mortality ranged from three (25%) of 12 to three (30%) of ten patients.[82] Adverse pregnancy outcomes were also frequent, including miscarriage in four (57%) of seven first-trimester infections and preterm birth in four (80%) of five infections occuring in the late second or third trimester (≥24 weeks' gestation).[81] Data for MERS-CoV in pregnancy are scarce. One series reported five pregnant women, all requiring ICU care, with maternal death in two (40%) of five and perinatal death in two (40%) of five.[83] Additional case reports describe stillbirth and severe maternal disease associated with MERS-CoV infection.[84,85] Although these patterns raise concern for substantial maternal and fetal risk, the very small sample sizes preclude precise estimates of incidence or generalisability of the associations. Nonetheless, these outcomes are biologically plausible, as both SARS-CoV and MERS-CoV cause severe hypoxaemic pneumonia and systemic inflammation, mechanisms known to impair placental function and compromise fetal wellbeing in critical maternal illness.[81]

Clinical features of human coronavirus infections

The key clinical features across all human coronavirus infections are given in table 2. These infections span a wide clinical spectrum, from asymptomatic illness or mild upper respiratory symptoms to severe pneumonia, acute respiratory distress syndrome (ARDS), septic shock, multiorgan failure, and disabling long-term sequelae.[40,47,55,66,86–93] Seasonal coronaviruses generally cause self-limiting disease, whereas SARS-CoV, MERS-CoV, and SARS-CoV-2 display substantially higher severity and systemic involvement. The appendix (pp 32, 33) provides a comparison of the epidemiological, virological, clinical, diagnostic, treatment, and prevention features of SARS-CoV, MERS-CoV, and SARS-CoV-2. Their shared and distinct features, including receptor usage, tissue tropism, and clinical patterns, are summarised in tables 1 and 2, with expanded discussion on viral tropism in the appendix (pp 14–17).

Human common cold coronaviruses

HCoV-OC43, HCoV-229E, HCoV-NL63, and HCoV-HKU1 are common causes of mild upper respiratory infection.[35–37] Typical symptoms include nasal congestion, sore throat, cough, and low-grade fever. HCoV-NL63 is often associated with croup in children, whereas HCoV-OC43 and HCoV-HKU1 can cause bronchiolitis or pneumonia in infants, older adults, and people who are immunocompromised. Severe disease is uncommon, but documented, in neonates and frail adults. Reinfection occurs frequently due to short-lived mucosal immunity and antigenic evolution. More severe disease

	Common cold coronaviruses (229E, NL63, OC43, and HKU1)	SARS-CoV	MERS-CoV	SARS-CoV-2 (all variants)
Incubation period	2–4 days	5–7 days	5–10 days	3–6 days
Reproductive number (R_0)	~1·1–1·5 (varies by setting and season; typically, lower than pandemic coronaviruses)	2–3	<1 overall; up to ~4 in outbreaks	2–3 (ancestral); 5–8 (delta); 8–10 (omicron)
Peak infectiousness relative to symptom onset	Day 2–3	Day 7–10	Day 7–10	Day –2 to +2
Superspreading events	Rare	Frequent (health-care settings)	Frequent (health-care settings)	Frequent (all settings)
Upper respiratory tract infection (eg, nasal congestion, sore throat)	Common	Uncommon (<10%)	Uncommon (15%)	Common (40–60%; especially omicron strains)
Lower respiratory tract involvement (viral pneumonia, acute bronchitis, bronchiolitis, interstitial pneumonitis, or acute respiratory distress syndrome)	Rare except in older people (>65 years) or immunocompromised individuals	20–50%	30–80%	Variable 15–50% (variable severity by VOC)
ARDS or respiratory failure	No	20–30%	25–50%	5–15% (higher in ancestral and delta strains)
Fever and systemic symptoms	<5%	~98%	~70%	~80%
Anosmia and ageusia	Rare	No	No	Common in early variants (~40–60%); lower with omicron (often ~10–30%)
Gastrointestinal symptoms (eg, diarrhoea, nausea)	Rare	~20–30%	~30–40%	~10–20%
Renal involvement (acute kidney injury)	No	~5–15%	Common in severe disease (~20–40%; cohort dependent)	~5–30% overall; higher in ICU (~20–50%; definition dependent)
Cardiac involvement (eg, myocarditis, arrhythmias, cardiac failure)	No	Rare (although viral RNA found in 35% of autopsied patients)	Common in severe disease and those with comorbidity (~20–40%)	~5–30% overall; higher in ICU (~20–50%; definition dependent); cardiac injury and arrhythmias in severe disease; myocarditis uncommon
Neurological presentations	Rare	Headache and confusion common (15–50%)	Variable (headache, confusion, encephalopathy, seizures, stroke, encephalitis, and cognitive dysfunction)	Common (5–35%); broad spectrum with wide-ranging estimates (headache, confusion or encephalopathy, stroke, and cognitive dysfunction)
Thromboembolic events (eg, pulmonary embolism, venous or arterial thrombosis, disseminated intravascular coagulation, stroke)	No	Venous thrombo-embolism (33%); stroke (2·5%)	Uncommon but reported; higher in severe disease in some cohorts (8% in one study)	Common in severe disease; VTE in ICU often ~20–30% (depends on screening and prophylaxis)
MIS	No	No	No	MIS-C (children) and MIS-A (adults) were uncommon but clinically important during the early pandemic and are now rare
Prolonged illness (including fatigue and other post-acute illness sequelae)	No	~40% (in patients with severe disease)	~40% (in patients with severe disease)	30–50% (in patients with severe disease)
Mortality (case-fatality rate)	<0·1%	9·6% (in hospitalised patients)	34·4% (in hospitalised patients)	~0·1–1·5% (higher in early pandemic); strongly age, VOC, and setting dependent
Individuals at high risk of severe disease or death	Older people (>65 years); severely immunocompromised	Older people (>65 years); immunocompromised; people with CVD or COPD	Older people (>65 years); people with diabetes, CKD, obesity, CVD, COPD, or cancer	Older people (>65 years); people with diabetes, CKD, obesity, CVD, COPD, liver disease, hypertension, cancer, HIV, or immunosuppression

Anosmia and ageusia were striking features of SARS [severe acute respiratory syndrome]-CoV-2 in early variants, but less prominent in omicron. SARS-CoV and MERS [Middle East respiratory syndrome]-CoV transmission peaks after symptom onset, but SARS-CoV-2 transmission may occur before symptom onset. A hyperinflammatory phase was described in SARS-CoV and SARS-CoV-2 in weeks 2–3, with elevated IL-6, ferritin, and CRP. MIS-C and MIS-A are post-acute SARS-CoV-2 syndromes, now rare. Most HCoVs cause mild illness in children; SARS-CoV and MERS-CoV have limited paediatric impact and SARS-CoV-2 is generally mild but associated with croup-like presentations (omicron) and MIS-C. ARDS=acute respiratory distress syndrome. CKD=chronic kidney disease. COPD=chronic obstructive pulmonary disease. CVD=cardiovascular disease. DVT=deep vein thrombosis. ICU=intensive care unit. MIS=multisystem inflammatory syndrome. R_0=basic reproductive number. VOC=variant of concern. VTE=venous thromboembolism.

Table 2: **Key clinical features of human coronaviruses**

is mainly observed in older people or comorbid populations.

SARS-CoV

SARS-CoV infection differs markedly from human common cold coronaviruses. After an incubation of 4–6 days, patients typically present with fever, malaise, myalgia, and dry cough, progressing to dyspnoea and hypoxaemia.[39–43] Radiographic pneumonia was common, and diarrhoea occurred frequently, consistent with gastrointestinal tropism. Laboratory abnormalities included lymphopenia, raised aminotransferases, and elevated lactate dehydrogenase. Illness often showed a biphasic pattern, with early viral replication followed by

immune-driven lung injury in week 2.[39–42] The CFR ranged from 10–15% and was highest among older adults and those with comorbidities.[21] Notably, no paediatric deaths were reported.

MERS-CoV

MERS-CoV infection has a spectrum of clinical presentations from asymptomatic mild cases in the community to a severe clinical course leading to hospitalisation requiring intensive care.[23–27,47–55] Fever, chills, cough, and rapidly progressive pneumonia are common early features. Gastrointestinal symptoms, including diarrhoea, nausea, and abdominal pain, are more prevalent than in SARS-CoV. Acute kidney injury is a notable complication, reflecting either direct viral tropism for renal tissue or secondary injury from systemic inflammation. Severe cases can progress to shock, coagulopathy, and multiorgan dysfunction. The overall CFR approaches 35%, with markedly increased mortality among older adults, individuals with diabetes, chronic kidney disease or cardiovascular disease, and patients who are immunocompromised.[53–55] Nosocomial acquisition is often associated with more severe outcomes, owing to delayed diagnosis and high comorbidity burdens among hospitalised populations.[55]

SARS-CoV-2

For ancestral strains of SARS-CoV-2, the median incubation is 4 days (IQR 2–6), although longer incubation periods have been described (up to 14 days).[66–72] With widespread immunity from infection and vaccination, viral shedding dynamics have evolved.[77–82] SARS-CoV-2 exhibits the broadest clinical spectrum of any human coronavirus. Symptoms range from asymptomatic infection to severe viral pneumonia, ARDS, thromboembolism, and multisystem disease. Common features include fever, fatigue, myalgia, cough, anosmia, ageusia, and sore throat, alongside gastrointestinal symptoms. Neurological, cardiac, and dermatological manifestations are increasingly recognised. Severe cases involve hypoxaemia, pulmonary inflammation, endothelial injury, and hypercoagulability, with frequent thromboembolic complications. In children, COVID-19 typically results in milder disease with better prognosis,[94] although the post-infectious multisystem inflammatory syndrome (MIS-C [in children] and MIS-N [in neonates]) manifested early in the pandemic with fever, mucocutaneous inflammation, gastrointestinal disease, cardiac dysfunction, and shock.[95]

Pathogenesis and immunology

Figure 2 highlights the comparative pathogenesis of SARS-CoV, SARS-CoV-2, and MERS-CoV, including animal reservoirs, sources of infection, transmission, host receptor interactions, cell entry, local replication, pathogenesis, and dissemination.[21,55,67,86–91,96–101] Human coronaviruses establish infection through spike-mediated binding to host receptors, followed by fusion of viral and cellular membranes. These molecular determinants of coronavirus entry, replication, and immune evasion are summarised in table 1 and detailed in the appendix (pp 14–20), including viral structural biology, the replication–transcription complex, and mechanisms of immune-evasion strategies.

Disease severity and immune dysregulation

Across all three epidemic coronaviruses, disease severity correlates with dysregulated immune responses, endothelial injury, and microvascular dysfunction with end-organ dysfunction.[90,91,100,101] Although the balance of viral cytopathology and immune-mediated injury varies by virus, these mechanisms underpin overlapping and distinct clinical patterns observed with SARS-CoV, MERS-CoV, and SARS-CoV-2. Differences in incubation period, receptor usage, tissue tropism, and systemic involvement are central to understanding disease manifestations (tables 1 and 2; appendix pp 18–21). These distinctions have important implications for clinical management and epidemic preparedness, highlighting the importance of early clinical suspicion, rapid diagnosis, and close monitoring of individuals at increased risk of severe disease.

Common cold coronaviruses

Common cold coronaviruses predominantly infect the upper respiratory tract, where cooler temperatures and locally expressed proteases favour viral replication.[35,36] Their restricted tissue tropism generally limits disease to the nasopharynx and conducting airways. Interferon-mediated innate immune responses usually prevent severe illness, although infants, older adults, and individuals with underlying immunological or cardiopulmonary disease might develop lower respiratory involvement.[2,3,35–37] Re-infection is common because mucosal immunity is short-lived and antibody responses lack durability and breadth, allowing repeated infection by antigenically evolving strains.

SARS-CoV

SARS-CoV exhibits a predilection for the lower respiratory tract and is associated with substantial pulmonary injury.[18–21,35,41,42] The virus utilises angiotensin-converting enzyme 2 (ACE2) for entry, in conjunction with TMPRSS2 and related proteases, enabling infection of ciliated airway epithelial cells, type II pneumocytes, and intestinal epithelium.[30] High replication in the lower respiratory tract leads to diffuse alveolar injury. Notably, viral loads peak in week 1, whereas clinical deterioration typically occurs in week 2, indicating that immune-mediated lung injury rather than direct cytopathy drives severe disease.[21,38,40,41] Marked cytokine release, including IL-6 and tumour necrosis factor-α, lymphopenia, and dysregulated interferon signalling characterise severe cases.[21] ACE2 distribution (table 1) supports pulmonary

A

	SARS-COV causing SARS	SARS-COV-2 causing COVID-19	MERS-COV causing MERS
Natural animal reservoir (suspected-evolutionary inference)	Horseshoe bats (*Rhinolophus* spp) 	Horseshoe bats (*Rhinolophus spp*) 	Bats (unconfirmed; suspected ancestral source) 
Intermediate host(s)	Presumed: masked palm civets (*Paguma larvata*) Secondary reservoirs: racoon dogs and other wildlife market-trade mammals 	Unconfirmed: raccoon dog (*Nyctereutes procyonoides*) Secondary reservoirs: farmed mink and white tailed deer; Other: wildlife market-trade small mammals (civet cats, foxes, among others) 	Confirmed: dromedary camels (*Camelus dromedarius*); Camels are the direct zoonotic source 
Sources of virus transmission to humans from infected animals)	• Direct contact with infected animals (eg, civets or other market wildlife), including handling, slaughtering, skinning, and exposure to respiratory secretions, blood, and excreta • Fomite or environmental exposure from contaminated cages, knives, surfaces, and drains • Aerosolised droplets and short-range airborne exposure in enclosed, poorly ventilated market environments, particularly during slaughter and cleaning activities		• Direct contact with MERS-CoV infected camels (via secretions, nasal discharge, saliva, stool, or urine) • Inhalation of camel respiratory droplets • Consumption of raw camel products (unpasteurised milk or undercooked camel meat)

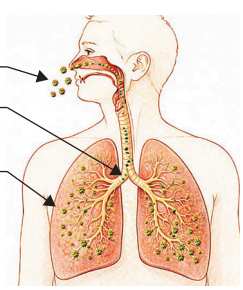
B

Transmission and entry into human respiratory tract
Humans inhale virus-infected droplets, aerosols, or particles. Humans self-infect from virus contaminated hands via touching nostril, mouth, or eyes

Upper respiratory tract
Mouth, nose and nasal cavity, pharynx, larynx, trachea

Bronchi
Ciliated epithelial cells, goblet cells

Lower respiratory tract
Upper lung lobes, lower lung lobes, bronchiolar club cells, alveoli, type I and II pneumocytes



	Cellular receptor	Lung cell types infected
SARS-CoV	ACE2	Ciliated airway epithelial cells; alveolar epithelial cells (type I and type II pneumocytes)
SARS-CoV-2	ACE2	Ciliated airway epithelial cells; alveolar epithelial cells (type I and type II pneumocytes); endothelial cells (reported in some studies)
MERS-CoV	DPP4 (CD26)	Non-ciliated airway epithelial cells; alveolar epithelial cells (predominantly type II pneumocytes); endothelial cells

Interaction with airway cells
Entry and replication of all three coronaviruses occur predominantly in airway cells, with cytoplasmic replication on double-membrane vesicles and virion assembly at the ER–Golgi intermediate compartment before release and respiratory shedding

(Figure 2 continues on next page)

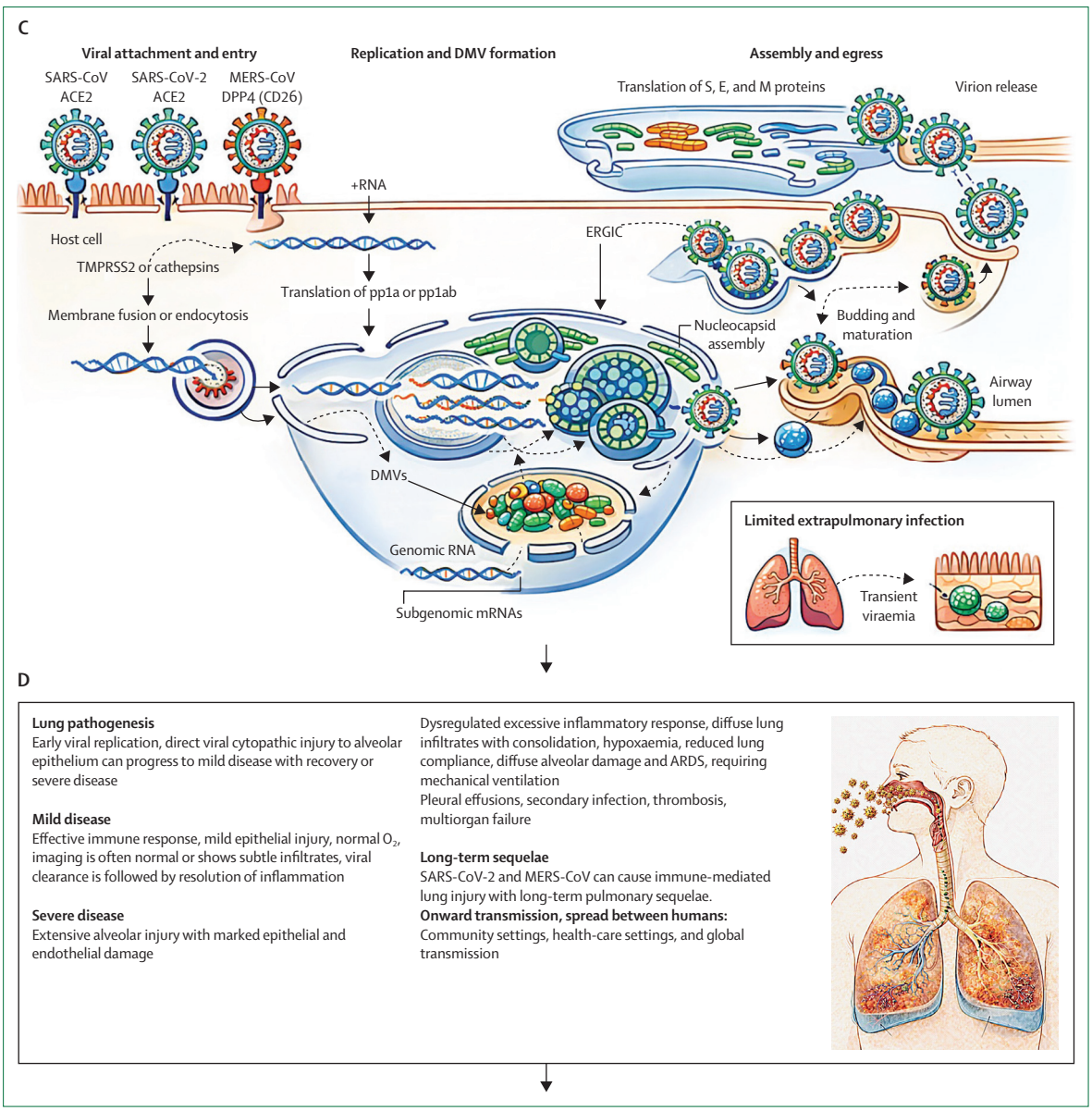
and gastrointestinal involvement, but direct involvement of additional organs remains unconfirmed.

MERS-CoV

MERS-CoV shows broader tissue tropism mediated by dipeptidyl peptidase 4 (DPP4), allowing infection of lower respiratory, renal, and gastrointestinal epithelium. High DPP4 expression in bronchiolar and alveolar cells is associated with rapidly progressive hypoxaemic pneumonia and acute respiratory distress syndrome. Acute kidney injury occurs more frequently in MERS than in SARS-CoV or SARS-CoV-2. Although ACE2 is expressed in renal tissue, the prominence of renal dysfunction in MERS is likely to reflect high renal DPP4 expression combined with systemic inflammatory and haemodynamic injury. Direct evidence of productive renal infection in humans, however, remains scarce. Histopathological findings include necrotising pneumonia, fibrin deposition, endothelial injury, and microvascular thrombosis, and impaired interferon responses and heightened inflammatory cytokine production contribute to disease severity. The high CFR reflects both intrinsic viral pathogenicity and the high prevalence of comorbid conditions in affected populations.[23,47,55] Molecular mechanisms of DPP4 binding, viral entry, and interferon antagonism are detailed in the appendix (pp 14–17).

SARS-CoV-2

SARS-CoV-2 also utilises ACE2 for entry but shows broader cellular tropism, influenced by increased



(Figure 2 continues on next page)

spike-protein affinity, efficient furin cleavage, and the activity of accessory proteins (appendix pp 14–17). High viral loads in the upper respiratory tract early in infection facilitate efficient transmission. Although pulmonary disease predominates, extrapulmonary manifestations are common. Dysfunction of endothelial cells, pericytes, adipose tissue, renal epithelium, intestinal epithelium, and neurovascular structures is thought to occur predominantly through indirect inflammatory and thrombotic mechanisms rather than widespread direct viral cytopathy.[88–100] There is clear evidence of infection of gastrointestinal epithelial cells, with viral RNA and protein detected in gastric, duodenal, and rectal glands, suggesting that the gastrointestinal tract could serve as a prolonged viral reservoir in some individuals.[99] There is evidence of elevated IL-6, IL-1β ferritin, D-dimer, and C-reactive proteins and of endothelial cell activation and microvascular thrombosis contributing to complications such as pulmonary embolism, myocardial injury, and stroke. Dysregulated interferon signalling and possible viral persistence in immune-privileged sites might contribute to prolonged or severe illness, particularly in people who are immunocompromised.[87–91,97–101]

Cross-cutting issues

Clear susceptibility differences are observed across human coronaviruses. Older age, male sex, the presence

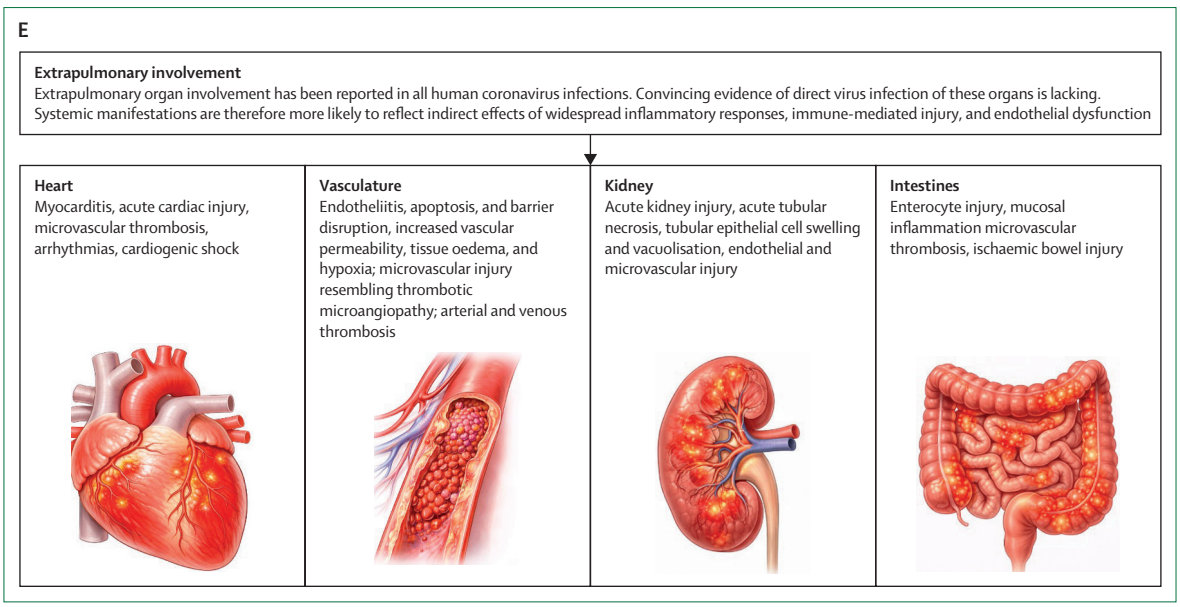


Figure 2: **Pathogenesis of SARS-CoV, MERS-CoV, and SARS-CoV-2**
ARDS=acute respiratory distress syndrome. DMV=double-membrane vesicles. ER=endoplasmic reticulum. ERGIC=endoplasmic reticulum–Golgi intermediate compartment. SARS=severe acute respiratory syndrome. MERS=Middle East respiratory syndrome. S=spike protein. M=membrane protein. E=envelope protein. N=nucleocapsid protein. RdRp=RNA-dependent RNA polymerase. ACE2=angiotensin-converting enzyme 2. DPP4=dipeptidyl peptidase 4.

of underlying cardiopulmonary disease, metabolic dysfunction (including diabetes and obesity), immunosuppression, and other major comorbidities consistently confer increased risk of severe disease and mortality with SARS-CoV, MERS-CoV, and SARS-CoV-2.[6–8,39–42,51–54,65–72,86–89,96,97] These shared vulnerability profiles suggest convergent host–pathogen interactions, with common pathways of impaired early antiviral responses, dysregulated inflammation, endothelial injury, and multiorgan dysfunction, despite differences in viral biology and epidemiology.

Host genetic variation further modulates susceptibility and disease severity. Polymorphisms affecting innate immune signalling pathways and interindividual differences in ACE2 and DPP4 expression and regulation might influence viral entry, the efficiency of early antiviral defences, and downstream immunopathology.[90–101] In addition, pre-existing immunity derived from exposure to common cold coronaviruses might shape disease outcomes. Cross-reactive T-cell responses following common cold coronavirus infection have been detected in unexposed individuals and in patients with SARS-CoV-2 infection; however, the extent to which such responses confer clinically meaningful protection (including mitigation of severe disease) or instead contribute to immune dysregulation remains uncertain. Tables 1 and 2, together with the appendix (pp 14–20), provide a comparative overview of these host and viral determinants, linking key mechanisms of pathogenesis to clinical phenotypes, prognostic indicators, and potential therapeutic targets relevant to both current and future coronavirus threats.

Long COVID and post-viral infection sequelae

Long-term sequelae after acute coronavirus infections have been recognised for two decades, although their global impact only became fully evident with COVID-19.[102–106] Persistent complications were described after SARS-CoV and MERS-CoV, including fatigue, psychological distress, impaired pulmonary function, reduced exercise capacity, and radiographic abnormalities lasting months to years.[6,7,21,42,55] Many survivors reported chronic dyspnoea, sleep disturbance, anxiety, depression, and reduced quality of life, in some cases persisting for more than a decade. These observations foreshadowed the heterogeneous syndrome now termed post-acute sequelae of COVID-19 (PASC) or post-COVID-19 condition (also known as long COVID). Long COVID is defined by symptoms lasting at least 2 months, beginning within 3 months of infection, and not attributable to another diagnosis.[103–105] The syndrome encompasses fluctuating multisystem manifestations. Common symptoms include fatigue, exertional intolerance, dyspnoea, chest pain, palpitations, cognitive impairment known as brain fog, dysautonomia, altered taste or smell, musculoskeletal pain, psychological symptoms, and sleep disturbance. Prevalence estimates of long COVID vary widely according to case definitions, viral variant, vaccination status, illness severity, and timing of follow-up. WHO estimates suggest that approximately 6% of infected individuals develop persistent symptoms, with higher rates after hospitalisation and during the early pandemic waves. Reported risk factors include re-infection, female sex, older age, comorbidities, and

severe acute disease.[102–106] Vaccination reduces but does not eliminate risk of long COVID.

Mechanistic understanding remains incomplete, but proposed contributors include persistent viral reservoirs, chronic inflammation, immune dysregulation, endothelial injury, microvascular thrombosis, autonomic dysfunction, mitochondrial impairment, and metabolic or hormonal disturbance.[103–105] Persistent inflammatory markers and immune activation have been detected months after infection. Viral antigen persistence in tissues such as the gastrointestinal tract might sustain symptoms in some individuals. Endothelial dysfunction and impaired microcirculatory flow might contribute to exertional intolerance, chest discomfort, and cognitive deficits, while dysautonomia, including postural orthostatic tachycardia syndrome, are increasingly recognised.

Pulmonary sequelae are common after moderate or severe COVID-19, with persistent dyspnoea, impaired gas transfer, radiological abnormalities, and fibrotic changes documented months to years after infection. Interstitial lung abnormalities after COVID-19 range from mild reticulation to established fibrosis and are influenced by age, severity of pneumonia, and pre-existing lung disease. Cardiovascular sequelae include chest pain, palpitations, myocarditis, pericarditis, arrhythmias, and endothelial dysfunction, consistent with inflammatory and microvascular injury observed across SARS, MERS, and COVID-19.

Neurological sequelae extend beyond cognitive impairment to include neuropathic pain, headache, sleep disturbance, anosmia, and autonomic instability. Emerging data link SARS-CoV-2 infection to increased risks of stroke, seizures, and neurodegenerative syndromes, although causality remains uncertain.[95] Renal sequelae are also increasingly recognised: acute kidney injury during infection is associated with a higher risk of chronic kidney disease and persistent renal dysfunction, with proteinuria and reduced estimated glomerular filtration rate reported months after infection.

Long COVID is less common in children than adults but remains clinically significant.[103,105] Symptoms include fatigue, headache, sleep disturbance, cognitive difficulties, and abdominal pain. Although most children recover within weeks, a subset develop prolonged impairment affecting education and wellbeing.

The breadth of manifestations and uncertain clinical course of long COVID have placed substantial demands on health-care systems. Multidisciplinary care incorporating rehabilitation, mental health support, and structured long-term follow-up is essential.[102,106] Current management focuses on symptom control and optimisation of comorbidities, while research efforts target disease-modifying therapies, biomarkers, and risk stratification. Long COVID remains a major global public health challenge, underscoring the need for sustained surveillance and coordinated research into post-viral syndromes.[106]

Advances in infection diagnostics

Accurate and timely diagnosis is central to clinical management, infection control, and outbreak response. Laboratory testing has underpinned the detection and containment of all human coronavirus infections.[92,102–113] The SARS-CoV epidemic accelerated adoption of PCR-based diagnostics, whereas MERS-CoV established real-time RT-PCR as the gold standard, complemented by serology for retrospective case finding and contact tracing.[92] The COVID-19 pandemic drove unprecedented diagnostic innovation, expanding platforms from conventional RT-PCR to high-throughput automation, decentralised antigen testing, CRISPR-based assays, and widespread use of next-generation sequencing.[104,112] Diagnostic performance is shaped by viral load dynamics, sample type, and timing, all of which clinicians must consider. Point-of-care assays and multiplex respiratory panels facilitate early differentiation from other pathogens, guiding treatment and infection-prevention decisions.[110–112] Table 3 summarises the diagnostic modalities and their operational characteristics.

Molecular diagnostics

RT-PCR remains the reference standard for coronavirus detection.[92,107–109] Most assays target conserved genomic regions, including *E*, *N*, *S2*, and *RdRp* genes. Sensitivity varies by sample type; bronchoalveolar lavage and sputum outperform nasopharyngeal swabs, particularly later in illness, and false negatives might occur early or late in infection. Blood, stool, and urine testing can support diagnosis in specific contexts. Multiplex molecular platforms that detect SARS-CoV-2, influenza, respiratory syncytial virus, and other respiratory viruses increasingly inform clinical management and infection prevention and control (IPC) planning.

Antigen-based diagnostics

Rapid antigen detection tests, usually targeting N protein, were central to COVID-19 control by enabling decentralised rapid testing.[92,107–110] Although less sensitive than RT-PCR, especially in asymptomatic or low-load infections, their speed and accessibility made them valuable. Negative antigen results in symptomatic individuals often require confirmatory RT-PCR.

Serology

Serological assays detect IgM, IgG, and IgA directed mainly against S and N proteins. Although unsuitable for early diagnosis due to delayed antibody responses, they are important for surveillance, vaccine monitoring, and population-level immunity estimation. During COVID-19, serological surveillance informed exposure estimates, immunity gaps, and public health policy.

Genomics and sequencing

SARS-CoV-2 catalysed global adoption of next-generation sequencing, including whole-genome sequencing and

	Target (gene, protein, or antibody)	Sensitivity	Specificity	Status (regulatory or WHO)	Clinical uses	LMIC use*
NAATs						
RT-PCR	Viral RNA for SARS-CoV-2: commonly *N*, *E*, *RdRp* or *ORF1ab*; for MERS-CoV: screening upstream of the *E* gene, with confirmatory targets in *ORF1a*, *ORF1b*, or *N*	~90–98%; high, but variable; false negatives persist in practice depending on timing and specimen	≥99%; high analytical specificity when primers and probes are appropriately designed	Widely authorised; many assays on WHO EUL and PQ	Clinical reference standard; best early in infection; requires lab, cold chain, and trained staff	Conditional: feasible in hubs or tiers; limited utility in rural sites
dPCR or ddPCR	Viral RNA	~95–99%; often equal or better than RT-PCR; improved detection at low viral loads	~99–100%; very high (platform or assay dependent)	In use (mostly specialist, reference, and surveillance settings)	High precision quantification; useful for detecting low viral loads in wastewater surveillance; slower and more costly than conventional real-time RT-PCR	Limited by infrastructure and high cost
RT-LAMP (isothermal)	Viral RNA	~80–95%; varies by workflow; highest in samples with higher viral loads or early symptomatic cases	~95–99% (assay dependent)	Some kits authorised in various jurisdictions	Rapid (~30–45 min), no thermocycler required; colorimetric and fluorescent detection options; strong decentralisation potential	Feasible: well suited for decentralised settings
CRISPR-based (eg, DETECTR and SHERLOCK)	Viral RNA (detected using CRISPR-Cas12 or Cas13 proteins; often with pre-amplification)	~85–95% (platform dependent)	~98–100% (assay dependent)	Some assays had FDA Emergency Use Authorisation; others are in development	Fast, specific; lateral flow or fluorescence readouts; active development	Conditional: promising, but limited by supply and standardisation
Portable cartridge-based (eg, Xpert Xpress [Cepheid], ID NOW [Abbott])	Viral RNA	Xpert: ~95–100%; ID NOW: ~80–90%	>95–100%	Widely authorised; Xpert and other NAATs have had WHO emergency procurement eligibility	Sample-to-answer (result) in 15–45 min; minimal handling; used in emergency and POC settings	Feasible: widely deployed via existing molecular platforms (eg, tuberculosis programmes) and laboratory networks, often with donor support
Saliva-based nucleic acid amplification tests (PCR or LAMP	Viral RNA (saliva)	~80–95% (platform dependent)	Variable by workflow (PCR: ≥99%; LAMP: ≥98%)	Authorised or in use in multiple settings	Non-invasive; useful for mass and community screening; reduces PPE and swab cost	Feasible: suitable for schools and community programmes if logistics and quality assurance are in place
Multiplex respiratory panels	Multiple pathogens ie, flu, RSV, and CoVs including SARS-CoV-2	Platform dependent	Platform dependent	Authorised (product-specific)	Detects co-infection; stewardship and bed management; supports clinical decisions	Limited: mainly referral hospitals

(Table 3 continues on next page)

metagenomic approaches. These enabled real-time monitoring of viral evolution, identification of variants of concern, tracking of transmission, primer redesign, and assessment of immune escape. The appendix (pp 7–13, 34) details sequencing platforms, lineage nomenclature, and applications across human and animal coronaviruses.

Diagnostics, early detection of coronavirus spillover, and One Health surveillance

SARS-CoV-2 emerged within a predictable pattern of repeated coronavirus spillover. Ecological and societal drivers, including deforestation, agricultural expansion, wildlife trade, and climate change, have intensified human–animal interfaces. Once spillover occurs, global travel infrastructure accelerates spread, transforming local outbreaks into epidemics or pandemics. These converging pressures highlight the necessity of a One Health approach linking human, animal, and environmental health. Integrated surveillance at high-risk interfaces such as wildlife markets, livestock systems, camel trade hubs, and peri-urban bat–human environments is crucial. Sentinel surveillance, portable diagnostics, genomic sequencing, and coordinated veterinary–public health networks enable real-time monitoring and risk mapping.[114–116] Wastewater surveillance proved highly valuable for population-level monitoring and variant detection during COVID-19[115,116] and adds sensitivity independent of health care-seeking behaviour. Wastewater sequencing supported early variant detection and provided population-level insight into viral evolution.[115,116] This approach is adaptable to other pathogens, offering a foundation for integrated surveillance beyond coronaviruses.[96] Although COVID-19 showed the benefits of rapid data sharing, it also exposed weaknesses in national and international epidemic

	Target (gene, protein, or antibody)	Sensitivity	Specificity	Status (regulatory or WHO)	Clinical uses	LMIC use*
(Continued from previous page)						
Antigen-based tests						
Rapid antigen (lateral flow)	Viral N protein	~55–75% overall; ≥80% in early symptomatic and high viral load	~98–100%; very high on average	Widely authorised; WHO minimum performance commonly cited as ≥80% sensitivity and ≥97% specificity	15–30 min; best within 5–7 days of symptoms; limited utility and reduced sensitivity in asymptomatic screening	Feasible: cornerstone of community testing; WHO (STANDARD Q and Flowflex self-test)
Microfluidic immunoassays	Viral antigens or host antibodies	~80–95%; variable (platform dependent)	~95–98%; variable (platform dependent)	Some platforms authorised; many in development	Lab-on-chip; multiplexable; small sample volume; automated	Conditional: promising if costs fall and supply chains strengthen
Biosensor-based (electrochemical and optical)	Viral antigens or RNA	~80–95% (prototype dependent)	~90–98% (prototype dependent)	In development	Ultra-rapid; potential integration with smartphones and wearable devices	Limited: pre-commercial stage
Antibody-based tests						
Serology (ELISA and CLIA)	IgM, IgG, and IgA to S or N proteins	~70–90% (from day 7–14); sensitivity rises after ~day 7 post-onset	>95% (assay dependent)	Widely authorised	Not for acute diagnosis; useful for past infection, vaccination response, and serosurveys	Feasible: basic laboratory setup is sufficient
Neutralisation assays (PRNT and sVNT)	Functional neutralising antibodies	~90–99% (timing dependent)	~100%	Reference standard	Gold standard for protective immunity; sVNT avoids live BSL-3 virus	Limited: primarily used in research and reference laboratories
Other methods						
Next-generation sequencing	Whole genome	NA	NA	Approved for surveillance	Variant detection, lineage assignment, and outbreak tracking	Limited: accessible in centralised laboratories only
AI-assisted imaging (CXR) and CT using machine learning algorithms for detection, triage, and severity assessment	Pneumonia patterns	NA	NA	Investigational; not stand-alone diagnostic	WHO guidance: imaging not stand-alone for diagnosis; could help when virological testing unavailable or delayed	Limited: requires radiology and information technology infrastructure

Performance varies by specimen type, timing after symptom onset, viral load, assay or platform, and reference comparator. Sensitivity varies by specimen type, timing since symptom onset, and comparator assay. AI=artificial intelligence. BSL-3=biosafety level 3. CLIA=chemiluminescent immunoassay. CXR=chest X-ray. dPCR=digital PCR. ddPCR=droplet digital PCR. EUL=emergency use listing. RT-LAMP=reverse transcription loop-mediated isothermal amplification. LMIC=low-income and middle-income countries. NA=not applicable. NAAT=nucleic acid amplification test. N=nucelocapsid. ORF=open reading frame. POC=point-of-care. PPE=personal protective equipment. PRNT=plaque reduction neutralisation test. RSV=respiratory syncytial virus. S=spike. sVNT=surrogate virus neutralisation test. PQ=prequalification. *LMIC feasibility reflects infrastructure, procurement, training, and quality-assurance requirements.

Table 3: **Sensitivity, specificity, and clinical uses of diagnostic tests**[109–116]

preparedness. Future readiness against coronavirus threats—including MERS-CoV, emerging SARS-CoV-2 variants, and potential disease X agents—requires stronger diagnostics, broad-spectrum vaccines and therapeutics, equitable access, and improved global coordination.[117–120]

Diagnostic challenges in resource-limited settings

Portable RT-PCR devices and rapid antigen kits have expanded access to testing in resource-limited settings. Emerging innovations including loop-mediated isothermal amplification (LAMP), CRISPR-based assays, paper-based platforms, smartphone-linked tools, and artificial intelligence-enabled readers, could further democratise diagnostics; however, regulatory, logistical, and scalability barriers remain. Persistent inequities in testing, supply chains, and skilled personnel limit access in many LMICs.[117–119] Strengthening local manufacturing, workforce capacity, and infrastructure is essential, along with cost-saving strategies such as pooled testing. Integrating diagnostics into a One Health framework, including leveraging veterinary laboratory networks, could enhance early detection and genomic surveillance in regions where human–animal interfaces are prominent.[120] Such cross-sectoral approaches align with global post-pandemic priorities and support preparedness against future zoonotic coronavirus threats.

Treatment and management

Therapeutic management of human coronavirus infections has evolved markedly over two decades, informed by experience with SARS-CoV (2002–03), MERS-CoV (2012), and COVID-19. Although disease biology and CFRs differ across viruses, treatment principles converge on targeting viral replication, modulating dysregulated inflammation, and supporting failing organ systems. WHO-recommended and investigational therapies are summarised in the appendix (pp 21–25).

SARS-CoV and MERS-CoV therapeutics

During the SARS-CoV outbreak, care relied on supportive treatment and empirical use of ribavirin, corticosteroids, and interferons, but efficacy was uncertain and toxicity common.[31–34,40] For MERS-CoV, studies of lopinavir–ritonavir, interferon beta, monoclonal antibodies, and convalescent plasma did not show clear benefit, and no licensed antiviral has proven efficacy.[37–41,44,45] Treatment therefore remains largely supportive, with investigational agents used in research settings. Repurposed antivirals, including ribavirin combinations and lopinavir–ritonavir showed inconsistent outcomes and notable adverse effects, particularly with ribavirin.[37,39] Corticosteroid therapy in patients with MERS was not associated with a difference in mortality after adjustment for time-varying confounders but was associated with delayed MERS-CoV RNA clearance.[41]

COVID-19 therapeutics

COVID-19 catalysed unprecedented therapeutic development (appendix pp 24, 25). Large, randomised trials such as RECOVERY,[51,54,56] and Solidarity[50] established the value of corticosteroids, IL-6 inhibitors, JAK inhibitors, and targeted antivirals. Development pipelines continue to expand, including agents targeting viral proteases, polymerases, conserved spike regions, or host pathways such as dihydroorotate dehydrogenase. However, emerging SARS-CoV-2 variants with resistance to first-generation monoclonal antibodies underscore the need for adaptable treatment platforms and surveillance-guided use.

Global guidelines for COVID-19 management

The WHO Clinical Management Guideline and the Infectious Diseases Society of America Clinical Practice Guidelines remain global reference guides for coronavirus treatment.[93,121] WHO recommends systemic corticosteroids (eg, dexamethasone 6 mg daily for up to 10 days) for severe or critical COVID-19, based on demonstrated mortality reductions. IL-6 receptor blockers (tocilizumab and sarilumab) are advised for selected patients with systemic inflammation, usually alongside corticosteroids. JAK inhibitors, particularly baricitinib, are recommended when IL-6 blockade is unavailable or contraindicated. For early-stage infection in non-hospitalised, high-risk patients—including older adults, individuals with underlying comorbidities (eg, cardiovascular disease, chronic respiratory disease, diabetes, chronic kidney disease, or obesity), immunocompromised individuals, and those with advanced age-related frailty—targeted antivirals, including nirmatrelvir–ritonavir, remdesivir, or molnupiravir are recommended, depending on availability and susceptibility, with greatest benefit when started soon after symptom onset. WHO advises against convalescent plasma except in selected immunocompromised patients and strongly recommends against ivermectin, hydroxychloroquine, and azithromycin due to a consistent lack of efficacy.

Supportive care

Supportive care remains the cornerstone across all human coronaviruses.[6–8] For mild to moderate disease, key components include oxygen supplementation where indicated, fluid and electrolyte management, analgesia, thromboprophylaxis, and monitoring for deterioration, especially in older or comorbid patients. Severe disease might require high-flow nasal oxygen, non-invasive ventilation, invasive mechanical ventilation, vasopressors, and renal replacement therapy. Acute kidney injury is particularly notable in MERS-CoV infection. Management of complications such as bacterial co-infection, thromboembolism, and cardiac dysfunction is essential in all severe coronavirus cases.

Research priorities and challenges for treatment

Despite major progress, notable gaps, research priorities, and challenges persist (appendix pp 34–37).[93,121–126] Antiviral resistance is an emerging concern, especially with monotherapy, requiring combination strategies and genomic surveillance to detect escape variants. Effective, widely available antivirals for MERS-CoV and other zoonotic coronaviruses remain lacking, an important gap given recurrent spillover risk. Developing broad-spectrum antivirals and host-directed therapies less vulnerable to viral escape is a key priority but demands investment in translational research and trial infrastructure. Monoclonal antibodies can be highly effective when antigenically matched but require continual updates, face high manufacturing and cold-chain constraints, and often lose activity against evolving variants. Persistent inequities in treatment access—highlighted during COVID-19 across LMICs—remain a major global health concern.[117–120] Strengthening trial networks, expanding research representation, and applying One Health principles will be essential for preparedness against future coronavirus threats.

Prevention and control of coronavirus infections

Repeated outbreaks of human coronavirus infections show both the fragility and crucial importance of prevention through IPC systems, scaling up of available vaccines, and investing in development of new vaccines. Nosocomial transmission—spread within health-care facilities—was central to amplification of the SARS-CoV and MERS-CoV outbreaks, with hospitals functioning as early epicentres. By contrast, SARS-CoV-2 displayed extensive community transmission and high infectivity during presymptomatic and asymptomatic phases, necessitating unprecedented revision of IPC strategies across health-care and community environments. Cross-cutting IPC lessons and failure points from SARS-CoV (2002–03) and MERS-CoV (2012 to present) are detailed in the appendix (pp 26, 27), including environmental and aerosol-related risks and

	SARS-CoV-2	MERS-CoV
First reported human cases	December, 2019 (Wuhan, China)	First identified in 2012 (Jeddah, Saudi Arabia); retrospective cluster also reported in 2012 (Jordan)
Global burden (best-supported WHO framing)	WHO has emphasised that reported confirmed cases and deaths are now substantial underestimates due to reduced testing and reporting; a WHO epidemiological update reported >777 million confirmed cases and >7 million deaths as of Jan 5, 2025	2635 laboratory-confirmed cases and 964 deaths globally as of Jan 1, 2025
Primary reservoir	Zoonotic origin; closest known relatives are bat sarbecoviruses; intermediate host remains unresolved (widely accepted)	Dromedary camels are the established reservoir and major source of primary human infection
Transmission	Predominantly via inhalation of infectious aerosols; droplets can contribute at close range; fomite transmission is possible but not thought to be the main route	Predominantly zoonotic spillover from camels; limited human-to-human transmission, mainly health-care or close-contact clusters; no sustained community transmission documented
Vaccine approvals	Many products authorised nationally; WHO EUL has included multiple COVID-19 vaccines (platforms include mRNA, protein subunit, viral vector, and inactivated)	No vaccine licensed for human use
Total vaccine candidates in development	>300 tracked during peak pandemic R&D; 2024–26 landscape is dominated by variant-updated boosters and next-gen concepts (pan-sarbecovirus, mucosal, etc)	Human pipeline remains small and episodic; mostly in early clinical development
Notable vaccine candidates	BNT162b2, mRNA-1273, ChAdOx1 nCoV-19, NVX-CoV2373, and Ad26.COV2.S, among others	ChAdOx1 MERS (phase 1 safety and immunogenicity studies conducted in the UK and Saudi Arabia); MVA-MERS-S (phase 1/2 dose and schedule evaluation studies); and INO-4700 (DNA vaccine; phase 1 completed, with phase 2 evaluation ongoing)
Advanced pipeline features	Variant-updated boosters; pan-sarbecovirus and pan-CoV R&D; mucosal (intranasal or oral) candidates; thermostable or lyophilised approaches; computational antigen design	Some One Health emphasis in reducing spillover via camel vaccination strategies; most human candidates still early-phase
Regional manufacturing capacity	Broad global manufacturing footprint; multiple technology-transfer initiatives; WHO-linked capacity building (eg, mRNA technology transfer hub-and-spoke model, including central hubs and regional spokes)	More limited; largely clinical-trial supply and targeted preparedness programmes (eg, CEPI-linked efforts)
Clinical trial limitations	Large efficacy trials were feasible during widespread transmission; now many studies rely on immunobridging approaches and are focused on variant (strain) updates	Sporadic cases constrain classic efficacy trials; studies concentrated in endemic regions and rely on immunogenicity or animal correlates, or both
Veterinary vaccines explored	Zoo and other captive animal vaccination occurred (eg, Zoetis donated experimental doses to zoos and Russia registered Carnivac-Cov for animals in 2021)	Camel vaccination explored experimentally (including platforms related to human candidates) to reduce shedding and spillover; not widely implemented at scale
Cross-platform readiness	Rapid retargeting via mRNA, protein, and vector platforms; establishment of a broader vaccine strategy	Viral-vector and DNA platforms are adaptable; preparedness value high but development slowed by epidemiology
International coordination	WHO, CEPI, Gavi and pandemic-era mechanisms accelerated development and access (historically)	More limited global market; CEPI-led preparedness and regional partnerships prominent
Potential role in future outbreaks	Platform-based rapid design and regulatory pathways provide reusable model	Ongoing zoonotic spillover and epidemic potential; vaccines could protect at-risk humans and inform broader coronavirus preparedness; camel vaccination could reduce zoonotic risk

CEPI=Coalition for Epidemic Preparedness Innovations. EUL=emergency use listing. Gavi=Gavi, the Vaccine Alliance. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2. MERS-CoV=Middle East respiratory syndrome coronavirus. R&D=research and development.

Table 4: **Comparative overview of SARS-CoV-2 and MERS-CoV vaccine pipelines**

well recognised settings for nosocomial spread. Across outbreaks, delays in recognising transmission potential enabled early seeding events, particularly within health-care facilities. Early implementation of IPC measures, including case isolation, contact tracing, appropriate personal protective equipment (PPE), environmental cleaning, and ventilation optimisation remains essential. Sustained IPC success requires investment in workforce training, reliable supply chains for PPE and diagnostics, and preparedness plans suited to high-risk clinical environments. Experience with SARS and MERS informed early COVID-19 responses in parts of Asia and the Middle East, underscoring the value of institutional memory and routine IPC readiness. Looking ahead, maintaining robust surveillance, rapid risk assessment, and the ability to escalate IPC protocols within days will be indispensable for mitigating future coronavirus threats.

Coronavirus vaccines and developmental pipelines

Vaccination remains the most effective public health tool for preventing infection, reducing severe disease,

Search strategy and selection criteria

We searched the English-language literature in PubMed and Google Scholar for publications between Jan 1, 1995, and Jan 1, 2026, and additionally screened Embase where available. Search terms included combinations of virus identifiers ("coronavirus" OR "CoV" OR "severe acute respiratory syndrome" OR "SARS" OR "SARS-CoV" OR "SARS-CoV-1" OR "Middle East respiratory syndrome" OR "MERS" OR "MERS-CoV" OR "SARS-CoV-2" OR "COVID-19") with scientific domains ("phylogeny" OR "phylodynamics" OR "evolution" OR "genomics" OR "whole genome sequencing" OR "variant*" OR "lineage*" OR "recombination" OR "molecular epidemiology" OR "epidemiology" OR "aetiology" OR "transmission" OR "virology" OR "pathogenesis"), zoonotic and One Health concepts ("zoonosis" OR "spillover" OR "cross-species transmission" OR "reservoir" OR "intermediate host" OR "wildlife trade" OR "live animal market" OR "wet market" OR "One Health" OR "serology" OR "seroprevalence"), viral entry pathways ("ACE2" OR "DPP4" OR "CD26" OR "TMPRSS2" OR "furin" OR "spike protein" OR "receptor binding domain"), clinical and public health aspects ("clinical features" OR "severity" OR "mortality" OR "case fatality" OR "risk factor" OR "long COVID" OR "post-acute sequelae" OR "PASC" OR "diagnosis" OR "diagnostic tests" OR "PCR" OR "NAAT" OR "antigen test*" OR "imaging"), and management and prevention ("treatment" OR "therapy" OR "antiviral" OR "immunomodulator" OR "supportive care" OR "clinical trial" OR "randomized controlled trial" OR "vaccine" OR "infection prevention and control" OR "IPC" OR "nosocomial" OR "hospital" OR "healthcare worker" OR "aerosol" OR "airborne" OR "PPE"). We also reviewed grey literature, technical reports, risk assessments, and surveillance dashboards from major public health agencies and initiatives: WHO, WHO Regional Office for the Eastern Mediterranean, UN Food and Agriculture Organization, US Centers for Disease Control and Prevention, UK Health Security Agency, European Centre for Disease Prevention and Control, Saudi Health Ministry, World Organisation for Animal Health, the Center for Infectious Disease Research and Policy, the Coalition for Epidemic Preparedness Innovations, COVAX, and ProMED. Given the rapid expansion of coronavirus research since 2020, the Review prioritised literature from 48 months preceding Jan 1, 2026, while incorporating earlier foundational studies to provide historical and mechanistic context.

and limiting transmission. Before SARS-CoV-2, no licensed vaccines existed for human coronaviruses despite earlier SARS-CoV and MERS-CoV outbreaks. SARS-CoV vaccine programmes were discontinued after containment in 2003, and MERS-CoV vaccine development progressed slowly due to sporadic outbreaks, low case numbers, and weak commercial incentives. Table 4 summarises current SARS-CoV-2 and MERS-CoV vaccine developmental pipelines (as of January, 2026). Expanded discussion on the vaccine landscape for MERS-CoV and SARS-CoV-2 including platforms, development stage, and key considerations are given in the appendix (pp 27–31).

MERS-CoV

Several MERS-CoV vaccine candidates remain in phase 1/2 trials among high-risk groups such as camel handlers and health-care workers, including ChAdOx1 MERS, INO-4700, and GLS-5300. mRNA and protein-subunit platforms are also under preclinical evaluation (appendix pp 27–30). Experience developing the adenovirus-vectored ChAdOx1 MERS vaccine enabled rapid repurposing of this platform during the SARS-CoV-2 emergency, culminating in the ChAdOx COVID-19 vaccine.

COVID-19

Recognition of COVID-19 as a pandemic in early 2020 triggered unprecedented vaccine innovation. Building on knowledge from SARS, Ebola virus vaccine development, and MERS-CoV research, manufacturers advanced diverse platforms—mRNA, DNA, viral vectors, recombinant proteins, inactivated and live-attenuated constructs. Most targeted the SARS-CoV-2 spike glycoprotein, based on evidence that neutralising antibodies blocking receptor-binding domain–ACE2 interaction confer protection. The scope and speed of COVID-19 vaccine development are detailed further in the appendix (pp 27–31).

Future directions

Next-generation vaccines aim to induce broader and longer-lasting immunity, including protection against zoonotic coronaviruses. Approaches under investigation include pan-sarbecovirus, pan-merbecovirus, and pan-betacoronavirus vaccines; intranasal or inhaled platforms to enhance mucosal immunity; and multivalent constructs incorporating conserved spike, nucleocapsid, or non-structural protein epitopes. Advances in structural biology, adjuvant engineering, and mRNA platforms support improved durability and escape resistance. Continued spillover risk from bat, camelid, rodent, and livestock coronaviruses reinforces the need for sustained investment in vaccine pipelines and integrated global surveillance.

Equity and implementation challenges

Despite remarkable scientific advances, access to diagnostics, vaccines, and therapeutics has remained deeply unequal. [93,117–123] Achieving equity and coordinated global responses will require binding agreements and sustainable financing. During the first year of

COVID-19, early vaccine supply was concentrated in high-income settings, whereas low-income nations depended heavily on COVAX, which delivered approximately 2 billion doses before closing in 2023. Challenges persist, including vaccine hesitancy, cold-chain requirements, and manufacturing disparities. Proposed solutions include regional manufacturing hubs, such as the WHO mRNA hub in South Africa, technology transfer, and development of thermostable vaccines to expand reach.

Research priorities for coronaviruses and other pathogens with epidemic potential have been defined (appendix pp 34–37),[93,121–123] with a specific technical brief by WHO.[124] The latest WHO Strategic Plan for Coronavirus Disease Threat Management 2025–2030[125] establishes a unified, forward-looking framework for integrating COVID-19, MERS, and emerging coronavirus threats into sustainable national health systems and broader respiratory disease strategies, consolidating lessons from recent epidemics to guide long-term preparedness.[125] Continued investment, innovation, and global data sharing are essential to maintain preparedness against known and emerging coronavirus threats. The SARS-CoV-2 pandemic experience—encompassing both the scale of global morbidity and mortality and the unprecedented impact of rapidly developed countermeasures, particularly vaccines—underscores the importance of sustained development pipelines for vaccines, diagnostics, and therapeutics,[104,105] coupled with integrated surveillance to detect divergent strains early and inform rapid countermeasure deployment.

Conclusions

Zoonotic coronaviruses continue to pose a major and evolving threat to global public health security. The emergence of SARS-CoV, MERS-CoV, and SARS-CoV-2 has shown that novel coronaviruses can rapidly cross borders, overwhelm health systems, and leave lasting health, economic, and societal consequences. The recent Middle East-travel-associated cases of MERS detected in France on Dec 3, 2025,[59] highlight the need to maintain proactive surveillance. Preparedness for the next epidemic must be anticipatory rather than reactive. Priority research areas include systematic characterisation of understudied coronavirus lineages, development of broadly protective vaccines, and host-targeted antiviral strategies resilient to viral evolution. Strengthening early warning systems, integrating clinical surveillance, genomic monitoring, wastewater detection, and wildlife viral discovery, will be essential to identify spillover events before sustained transmission occurs. Ensuring equity, through decentralised manufacturing, regional trial networks, and thermostable vaccine technologies, is essential to avoid the disparities witnessed during COVID-19.

For clinicians and health-care workers, key challenges include early recognition of atypical respiratory disease, appropriate diagnostic use to distinguish emerging coronaviruses from endemic infections, and prompt initiation of infection-prevention measures and reporting. Vigilance at the bedside, supported by robust surveillance systems, remains indispensable for rapid outbreak detection and containment. Strengthened clinical trial networks, improved access to therapeutics, and integration of digital tools into care pathways will further enhance outcomes.

Preventing the next pandemic will require a comprehensive One Health strategy that links human, animal, and environmental health; reduces zoonotic spillover risk; and ensures clinicians play a central role in translating bedside signals into public health action. Only through coordinated global action, sustained clinical vigilance, and a One Health approach can future coronavirus pandemics be effectively mitigated.

Contributors

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Declaration of interests

All authors have a specialist interest in coronaviruses, with AZ, MP, and SP involved in funded research on coronaviruses.
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