

Co-existence and co-infection of influenza A viruses and coronaviruses: Public health challenges

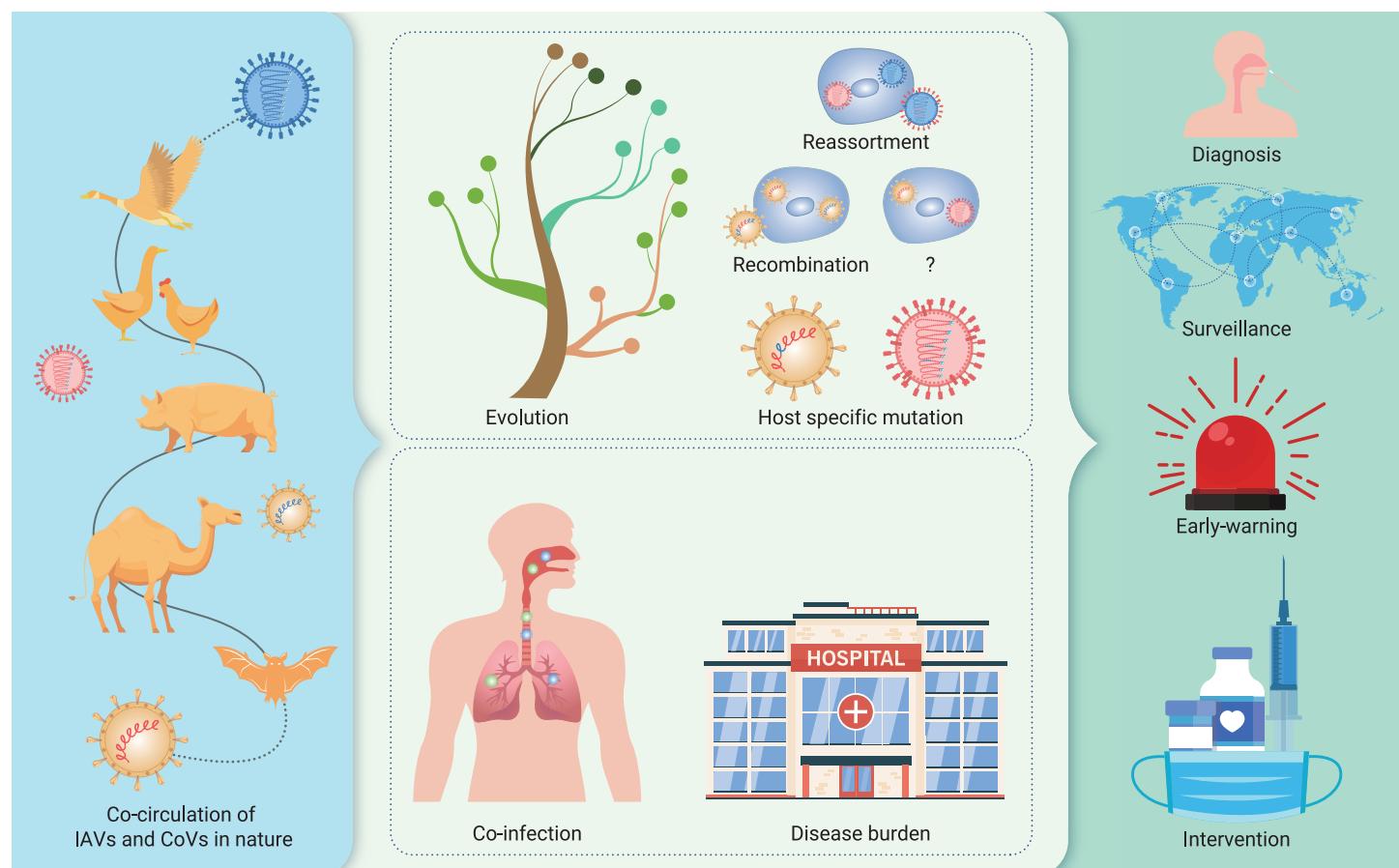
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GRAPHICAL ABSTRACT



PUBLIC SUMMARY

- Influenza A viruses (IAVs) and coronaviruses (CoVs) have broad host ranges and share multiple hosts
- Co-existence and co-infection of IAVs and/or CoVs are inevitable based on virus-host ecology
- Co-circulation and co-infection could alter virus evolution and drive novel variant emergence
- Co-circulation and co-infection could affect disease transmission and burden in humans
- Active surveillance and countermeasures are necessary for the public health challenges

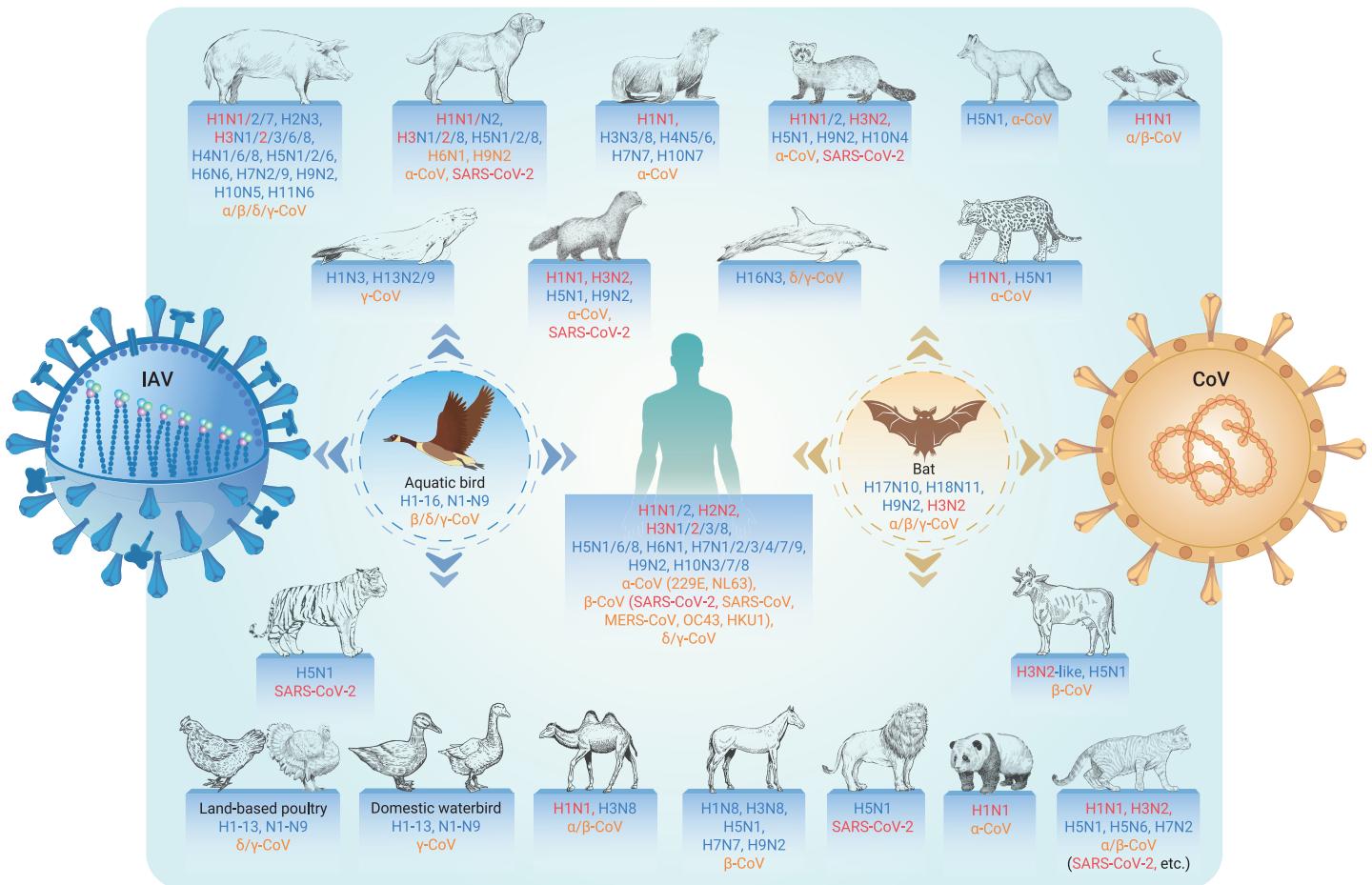


Figure 1. The shared host species of influenza A viruses and coronaviruses The reservoir hosts for influenza A viruses (IAVs; aquatic birds) and multiple coronaviruses (CoVs; bats) are highlighted by a dashed circle in blue and orange color, respectively. Dominant IAVs and CoVs isolated in each host species are listed in the text next to the stick figure. Names of IAVs and CoVs are colored in blue and orange, respectively. The same subtypes of IAVs and CoVs related to the pandemics are colored in red.

pet ferrets, tigers, lions, snow leopards, pumas, gorillas, white-tailed deer, fishing cats, binturongs, and South American coatis (<https://www.oie.int/en/what-we-offer/emergency-and-resilience/covid-19/>). Of note, SARS-CoV-2 caused mink infections in farms, and the mink-derived mutant was found to be transmitted back to humans, highlighting the animal-to-human transmission risk for SARS-CoV-2.^{51,52} Experimentally, SARS-CoV-2 can infect hamsters, ferrets, dogs, rhesus macaques (*Macaca mulatta*), cynomolgus monkeys (*Macaca fascicularis*), and African green monkeys (*Chlorocebus sabaeus*).^{15,53–56} The potential host range of SARS-CoV-2 has also been estimated according to the binding ability between SARS-CoV-2 and angiotensin-converting enzyme 2 (ACE2) receptors of various species.⁵⁷

Given the overlapping ecology of IAVs and CoVs, multiple influenza subtypes and CoV variants co-circulate in wild and domestic animals and humans,^{9,13–16} which undoubtedly increases the probabilities of co-infections among different IAVs, different CoVs, or both IAVs and CoVs in one host. The co-infections may alter the genetic evolution trajectory of viruses and facilitate mutations related to cross-species transmission and adaption to humans. Moreover, the potentially long-term co-existence and co-infections of IAVs and SARS-CoV-2 in humans could aggravate the disease burden compared with independent infections.

GENETIC EVOLUTION AND MOLECULAR CHARACTERISTICS

Phylogenetic dynamics for IAVs and SARS-CoV-2

IAVs (eg, H1, H3, H5, and H7) have experienced rapid evolution and established divergent lineages and genotypes. Phylogenies of hemagglutinin (HA) genes of seasonal influenza H1N1 and H3N2 viruses exhibit ladder-like tree topologies and constant genetic diversity within lineages across time, and some lineages persist from one influenza season through to the next years.^{58–60} Given the ge-

netic divergence and phylogeny relationship of HA genes, global H1N1 and H3N2 viruses can be divided into different clades (Figure 2).^{61,62} Of multiple co-existent clades, H1N1 clade A5a and H3N2 clade A1b are the currently dominant clades circulating the world (Figure 2; <https://nextstrain.org/flu/seasonal/>).^{62,63} Regarding H5, H7, and H9 IAVs of public health concern, H5 influenza was designated into multiple clades by the WHO/OIE/FAO H5N1 Evolution Working Group according to the phylogenetic topology and genetic divergence of HA genes.⁶⁴ Two main lineages of novel H7N9 have been established based on the HA phylogeny relationship, the Yangtze River Delta lineage and the Pearl River Delta lineage, since its emergence in 2013.^{65,66} At least three HA clades of H9 IAVs are co-circulating among poultry.³⁹ Moreover, new subclades or lineages are gradually emerging as the evolution of H5, H7, and H9 IAVs.^{38,39}

A dynamic nomenclature system has been proposed for the expanding phylogenetically divergent SARS-CoV-2 viruses (https://cov-lineages.org/lineage_list.html).⁶⁷ The phylogeny of global SARS-CoV-2 can be grouped into two main lineages: lineage A and lineage B. Lineage A is a minor group and shares two nucleotides, at 8782 nt of ORF1ab and 28144 nt of ORF8, with the genetically close SARS-CoV-2-related bat CoVs RaTG13 and RmYN02.^{13,47} Lineage B includes the currently persistent and dominant SARS-CoV-2 variants. Based on the increased risk of SARS-CoV-2 variants to public health and corresponding biological and clinical features, WHO designated the variants of concern (VOC) and variants of interest (VOI) using the Greek alphabet (<https://www.who.int/en/activities/tracking-SARS-CoV-2-variants/>). On July 14, 2022, the VOC group includes Omicron (B.1.1.529) SARS-CoV-2 variants, and previously circulating VOCs, Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), and Delta (B.1.617.2), have been removed from this group. The VOCs and VOIs can be reclassified given the circulation, epidemiological situation, and biological properties of

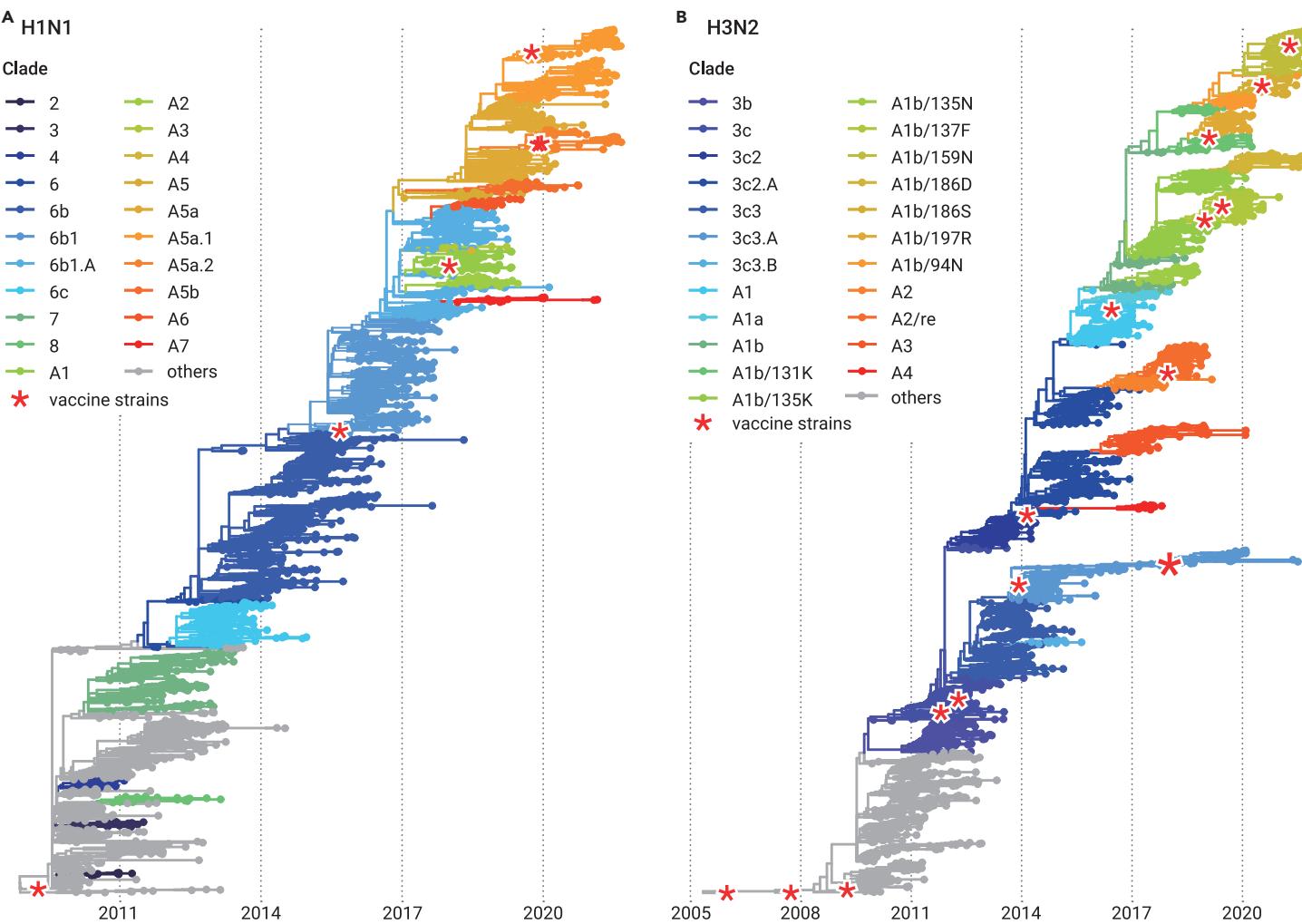


Figure 2. Time-scaled phylogenies of global H1N1 and H3N2 seasonal IAVs (A) Time-scaled phylogeny of H1N1 seasonal IAVs around the globe. Current seasonal influenza H1N1 viruses derive from the A(H1N1)2009 pandemic strains and completely replaced the seasonal H1N1 circulating before 2009 with different genetic and antigenic characteristics. (B) Time-scaled phylogeny of H3N2 seasonal IAVs around the globe. The tips in the tree are colored by the clade classification. The red asterisks represent the vaccine strains. The ladder-like evolution dynamics and seasonal epidemics of H1N1 and H3N2 are, to a large extent, attributed to their partial cross-immunity and the acute and short infectious period. Figures are reannotated from Nextstrain (<https://nextstrain.org/influenza/>), adapted from and courtesy of Creative Commons Attribution Licensing).

corresponding variants. In addition, the within host diversity of SARS-CoV-2 is relatively low, with narrow transmission bottlenecks at high viral loads (at least at the early infection), but the transmitted SARS-CoV-2 variant could spread rapidly.⁶⁸

The IAV and SARS-CoV-2 underwent genetic diversity and relatively rapid evolution dynamics. The partial cross-immunity and the acute and short infectious period, to a large extent, facilitate the evolutionary dynamics and seasonal epidemics of human H1N1 and H3N2 IAVs.⁶⁹ Of note, the vaccine breakthrough infection and reinfection with SARS-CoV-2^{70,71} mean that vaccine-induced and natural immunity are not enough to protect humans from virus infection, especially for the current variants, suggesting probably long-term co-circulation of SARS-CoV-2 with seasonal influenza viruses. In addition, the rapid evolution with antigenic changes and global persistence of seasonal influenza require the intensive surveillance of influenza activity and formulation of well-matched vaccines before each annual influenza season.⁷² These valuable lessons and experiences should be learned to control the current pandemic and possibly annual SARS-CoV-2 epidemics in the future.

Genetic reassortment and recombination in IAVs and HCoVs

Virus ecology affects the genetic evolution of IAVs and CoVs. When co-infection of multiple IAVs or CoVs happens in the same host, genetic reassortment among IAVs and recombination among CoVs potentially occur and further facilitate virus evolution and novel variant emergence. To our knowledge, the genetic interactions between IAVs and HCoVs have not yet been documented, while the potential recombination between the two types of viruses might also occur during their co-infections in one host.

IAV is an enveloped virus with a negative-sense, RNA-segmented genome that can encode for more than 17 proteins.⁷³ The segmented genome drives the exchange of gene segments between IAVs (genetic reassortment) when they simultaneously infect the same host or cell.⁷⁴ Reassortment facilitates the formation of novel influenza variants with new genomic constellations. Moreover, the reassortant virus could obtain fitness advantage, cross-species transmission, evasion from host immune responses, and even cause pandemics/epidemics in humans.¹⁶ Since the 20th century, at least three of four influenza pandemics were caused by reassortants: the 1957/H2N2 virus (HA, NA, and PB1 from AIV, the other five genes from human IAV), the 1968/H3N2 virus (HA and PB1 from AIV, the other six genes from human IAV), and the 2009/H1N1 virus (PB2 and PA from AIV, PB1 from human IAV, and others from swine IAV). Notably, the novel H7N9 AIVs also emerged by reassortment in 2013 and have caused five infection waves in humans.^{65,75} The internal genes of H7N9 originate from H9N2 AIVs that adapted well in chickens and H7 and N9 genes from viruses found in aquatic birds (Figure 3). Later, the novel H7N9 strain evolved into more genotypes by further reassortments with diverse H9N2 variants and other AIV subtypes.^{66,76}

CoV is also an enveloped virus but carries a large, positive-sense, single-stranded RNA genome.⁷⁷ The common mutations and recombination in the positive-strand RNA viruses with the largest genome contribute to genetic divergence and novel CoV variant emergence.^{9,78,79} Following co-infection with more than one CoVs, recombination may occur during virus replication when multiple sub-genomic RNAs are generated, and genetically related genes are readily recombinant among different CoVs by template switching.⁸⁰ Genetic recombination has been reported in human and animal CoVs, but the recombination breakpoints are commonly random.^{9,12,81,82} In addition, the novel recombinant CoVs could lead to

