nature reviews disease primers

https://doi.org/10.1038/s41572-026-00727-5

Primer

Check for updates

Influenza

Gabriele Neumann[1], Benjamin J. Cowling[2], Hualan Chen[3], Silke Stertz[4], Balaji Manicassamy[5], Ian G. Barr[6,7], Timothy M. Uyeki[8] & Yoshihiro Kawaoka[1,9,10,11]

Abstract

Influenza A and B viruses are considerable public health threats. Annual seasonal epidemics are driven by antigenic drift and cause an estimated 3–5 million severe cases and 290,000–650,000 deaths annually. The clinical presentation of seasonal influenza is typically an abrupt, uncomplicated acute respiratory illness with full recovery; however, it can lead to severe, life-threatening complications in individuals at high risk. Antigenic shift caused by reassortment of a seasonal influenza A virus with avian and/or swine influenza A viruses has led to unpredictable pandemics. The successful cross-species transmission of influenza A viruses requires key viral adaptations, including changes in receptor specificity and compatibility with host factors such as ANP32A. Host defence involves a layered innate response, which is antagonized by proteins, such as non-structural protein 1, and a robust adaptive immunity comprising cytotoxic $CD8^+$ T cells targeting conserved internal proteins and B cells producing neutralizing antibodies. Diagnosis primarily depends on highly sensitive PCR-based methods and multiplexed rapid antigen tests. Prevention involves annually updated seasonal vaccines (including inactivated, live attenuated and protein-based vaccines), while treatment relies on early use of neuraminidase and polymerase acidic protein inhibitors. Research priorities include the development of improved vaccines and a better understanding of influenza virus transmission from animals to humans.

Sections

[1]Influenza Research Institute, Department of Pathobiological Sciences, School of Veterinary Medicine, University of Wisconsin–Madison, Madison, WI, USA. [2]School of Public Health, The University of Hong Kong, Hong Kong, China. [3]State Key Laboratory of Animal Disease Control and Prevention, Harbin Veterinary Research Institute, CAAS, Harbin, China. [4]Institute of Medical Virology, University of Zurich, Zurich, Switzerland. [5]Department of Microbiology and Immunology, University of Iowa, Iowa City, IA, USA. [6]WHO Collaborating Centre for Reference and Research on Influenza, The Peter Doherty Institute, Melbourne, Victoria, Australia. [7]Department of Microbiology and Immunology, University of Melbourne, Melbourne, Victoria, Australia. [8]Influenza Division, Centers for Disease Control and Prevention, Atlanta, GA, USA. [9]Division of Virology, Department of Microbiology and Immunology, The Institute of Medical Science, University of Tokyo, Tokyo, Japan. [10]International Virus Infectious Disease Research Center, National Institute of Global Health and Medicine, Japan Institute for Health Security (JIHS), Tokyo, Japan. [11]The University of Tokyo Pandemic Preparedness, Infection and Advanced Research (UTOPIA) Center, Tokyo, Japan. e-mail: yoshihiro.kawaoka@wisc.edu

Introduction

In humans, influenza A (genus *Influenzavirus A*) and influenza B (genus *Influenzavirus B*) viruses are considerable public health concerns, causing seasonal epidemics and periodic pandemics (influenza A viruses only). The disease manifests with signs and symptoms such as fever, cough, sore throat, nasal discharge, muscle aches and fatigue. While most infections are mild, severe complications, such as pneumonia, can occur, particularly in individuals considered to be at increased risk such as young children, older individuals or those with certain underlying medical conditions.

Seasonal epidemics occur annually because of antigenic drift, which is caused by the gradual accumulation of mutations in the haemagglutinin (HA) and neuraminidase (NA) proteins, the two major viral antigens on the virus surface. These changes enable the virus to evade the immunity gained from previous infections or vaccinations. By contrast, pandemics are large-scale, global outbreaks that occur unpredictably when a new influenza A virus emerges that is antigenically substantially different from viruses previously circulating in humans and has the ability for sustained human-to-human transmission. The lack of pre-existing immunity in the global population enables the virus to spread rapidly worldwide. Previous pandemics have been caused by wholly avian influenza A viruses that acquired the ability to infect humans (1918 pandemic)[1,2] or by reassortments between human and avian (1957 and 1968 pandemics)[3,4] or human, avian and swine (2009 pandemic)[5–7] influenza A viruses. Avian influenza A viruses, including those of the A(H5Nx), A(H7Nx) and A(H9N2) subtypes (x indicates different NA subtypes), are considered to have increased pandemic potential. High-pathogenicity avian influenza (HPAI) A(H5Nx) viruses are a concern owing to infections of mammals and large outbreaks in dairy cattle in the USA[8,9] (Box 1).

The genome of influenza A and B viruses is comprised of eight segments of negative-sense, single-stranded RNA that encode the components of the viral replication machinery (that is, the polymerase subunits polymerase basic protein 2 (PB2), PB1, polymerase acidic protein (PA) and the nucleoprotein (NP)), the aforementioned HA and NA proteins, structural proteins, including matrix protein M1, the ion channel protein M2, and non-structural protein 2 (NS2; now also called nuclear export protein (NEP)), and proteins directly or indirectly counteracting host innate immune defences (NS1, PB1-F2 and PA-X) (Fig. 1). Several of these proteins, primarily HA and PB2, are crucial in the host range restriction and pathogenicity of influenza viruses.

Seasonal influenza vaccines are the primary prophylactic defence against influenza, yet these have moderate effectiveness in preventing symptomatic infection and severe disease. Antiviral drugs that target the NA protein (such as oseltamivir phosphate or oseltamivir) or the PA protein (such as baloxavir marboxil or baloxavir) can shorten the duration of illness and prevent serious complications when taken within 48 h of symptom onset.

In this Primer, we discuss the epidemiology and pathophysiology of influenza virus infections. We also discuss current strategies to control these infections and summarize research priorities for the next several years.

Epidemiology

Human influenza

Transmission. Seasonal influenza A and B viruses circulate among people worldwide, causing up to 1 billion infections globally (~10–15% of the world population each year)[10,11] and causing substantial morbidity, mortality, and economic burden[12–14]. Infection spreads from one person to another through infectious respiratory particles produced when infected individuals cough, sneeze, talk or breathe, with transmission also thought to be possible via contact with contaminated surfaces (fomites)[15]. At the start of a seasonal influenza epidemic, the virus reproduction number, which indicates the average number of secondary cases generated by one infected person, is thought to fall in the range 1.2–1.3, reflecting moderate transmissibility[16]. The incubation period reflects the delay between infection and the appearance of symptoms, which is short for influenza, usually 1–4 days, with contagiousness highest around the time symptoms appear, resulting in rapid spread through the community[17]. Asymptomatic or presymptomatic individuals can also spread the virus, complicating control efforts[18]. Children have a particularly important role in influenza transmission, amplifying outbreaks within communities owing to their higher contact rates and propensity to shed the virus in greater quantities and for longer durations[19], perhaps as a consequence of their less mature immune systems[20]. Transmission occurs in closed (indoor) settings such as households, schools, workplaces and other crowded settings.

Box 1 | Influenza virus types and subtypes, nomenclature, reassortment and pathogenicity

Types and subtypes

Influenza viruses of two types (type A and type B) are medically relevant in humans and will be discussed here. Based on their antigenic properties, influenza A viruses are further divided into 19 haemagglutinin and 11 neuraminidase subtypes. Type B viruses are further divided into two lineages, Victoria and Yamagata. Viruses of the Yamagata lineage have not been detected since the beginning of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic in early 2020 (ref. 25).

Nomenclature

Each isolate receives a unique name comprising the type, origin of isolation, isolate number and year of isolation. For non-human isolates, the species of origin is added after the type. The influenza A virus subtype may also be added. Examples are A/New York/1/2025 (H3N2) and A/chicken/New York/123/2024 (H5N1).

Reassortment

Reassortment is a hallmark of influenza viruses in which the segmented genome of influenza viruses can be rearranged in different combinations in cells infected with two different influenza A or B viruses. Theoretically, 254 novel gene constellations (2^8=256, minus the 2 parent viruses) can be created in each reassortment event.

Pathogenicity

According to the World Organisation for Animal Health, high or low pathogenicity in poultry is determined by the "intravenous inoculation of a minimum of eight susceptible 4- to 8-week-old chickens with infectious virus; strains are considered to be of high pathogenicity if they cause more than 75% mortality within 10 days, or inoculation of 10 susceptible 4- to 8-week-old chickens resulting in an intravenous pathogenicity index (IVPI) of greater than 1.2"[36].

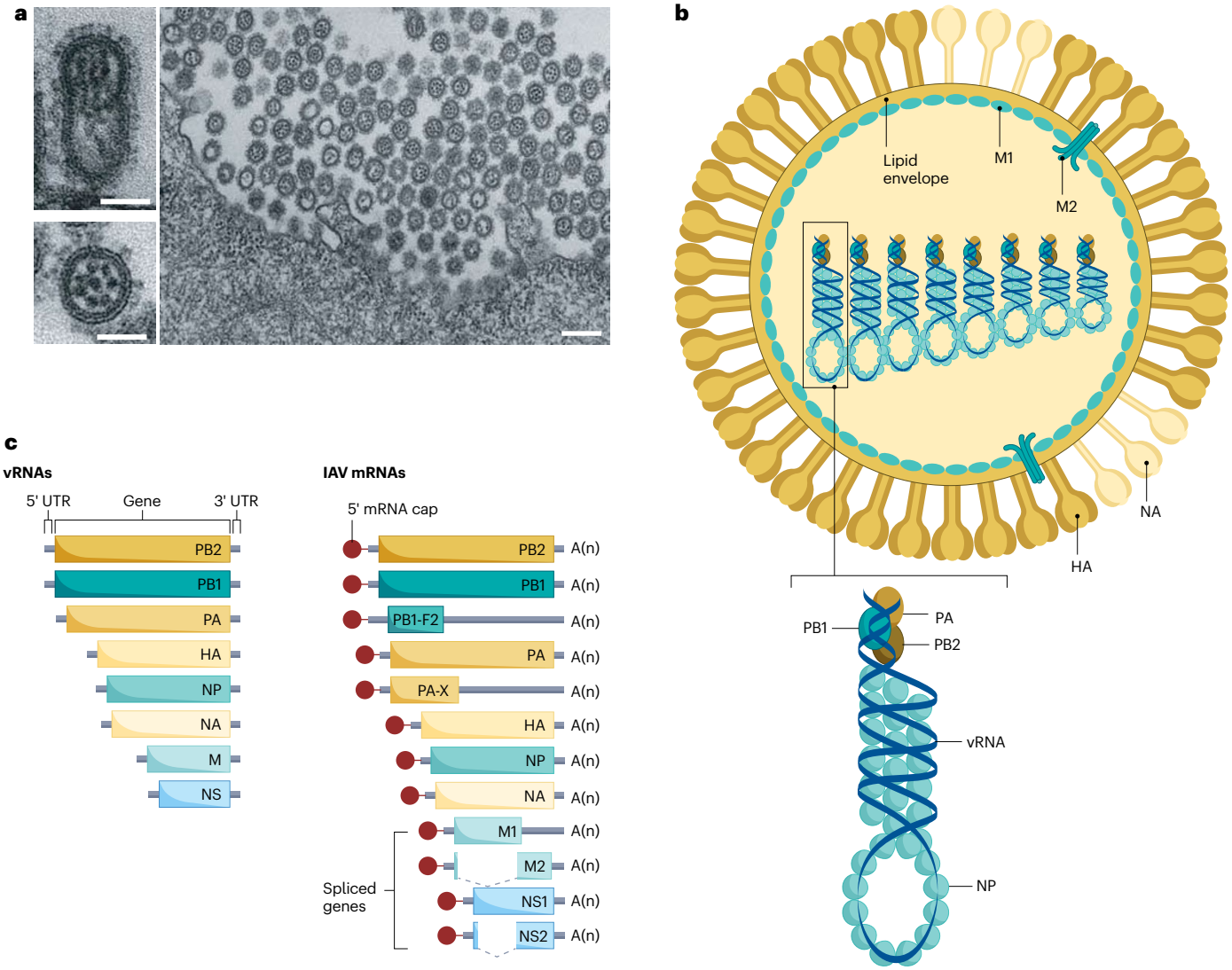

Fig. 1 | Structure and genome organization of influenza A viruses. a, Influenza virions show a characteristic arrangement of the eight viral RNA (vRNA) segments, typically with one vRNA segment in the centre surrounded by seven other vRNA segments. However, some virions contain fewer than eight vRNA segments. Scale bars, 50 nm (upper left and lower left) and 200 nm (right). **b**, Schematic diagram of an influenza A virus. The haemagglutinin (HA) and neuraminidase (NA) glycoproteins are embedded in the lipid membrane, together with the ion channel M2 protein. Viral ribonucleoprotein complexes consist of vRNA, the three polymerase proteins polymerase basic protein 2 (PB2), PB1 and polymerase acidic protein (PA), and nucleoprotein (NP). **c**, Genome organization of influenza A viruses (IAVs). The eight influenza A vRNAs (left panel) encode one or two proteins each (right panel). NS1, non-structural protein 1; UTR, untranslated region. Part **a** is reprinted from ref. 240, Springer Nature Limited. Part **b** is reprinted from ref. 241, Springer Nature Limited. Part **c** is adapted from ref. 242, CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/).

Transmission reduction. Seasonal influenza vaccination remains the cornerstone of influenza prevention. Annual influenza vaccines are formulated based on predictions of dominant strains. Groups at increased risk of complications from influenza are prioritized for vaccination, yet global uptake remains suboptimal, particularly in resource-limited settings. Antivirals provide options for treatment and post-exposure prophylaxis, are most effective when administered early after symptom onset or exposure, respectively, and can reduce influenza virus transmission[21–23]. Non-pharmaceutical interventions, including hand hygiene, mask-wearing and social distancing, also reduce transmission, as demonstrated during the COVID-19 pandemic when influenza activity dropped substantially owing to widespread public health measures[24], with influenza B viruses of the B/Yamagata lineage becoming extinct[25].

Seasonality. Seasonality is a hallmark of influenza epidemiology, with distinct patterns varying by geographic region. In temperate climates, such as North America and Europe, influenza activity peaks during winter months. This seasonality is driven by environmental factors such as low humidity and cooler temperatures, which enhance virus

stability and survival, as well as social factors such as indoor crowding during colder months[26]. In tropical and subtropical regions, influenza often circulates year-round, with less pronounced peaks, sometimes aligning with rainy seasons.

Disease burden. The burden of influenza is substantial, with estimates of 3–5 million severe cases and 290,000–650,000 deaths annually[14], primarily among older adults and individuals with chronic conditions such as diabetes mellitus, cardiovascular disease or lung disease. Influenza-associated hospitalization rates are highest among those 65 years of age and older, in whom complications such as pneumonia are common. Pregnant women are at increased risk for influenza-related hospitalization[27]. Children under 5 years, and especially those younger than 2 years, also face elevated risks of severe outcomes, particularly in low-resource settings[28]. An estimated 99% of global influenza-associated deaths in children under 5 years occur in low-income and middle-income countries[29], and ~82% of in-hospital deaths in this age group are concentrated in low-income and lower-middle-income settings[28]. This excess death stems from very low influenza vaccination coverage, higher prevalence of comorbidities and health challenges (including malnutrition, HIV and indoor air pollution), more frequent bacterial co-infections, and limited access to timely diagnosis, antivirals, oxygen and intensive care, all of which drive substantially higher case–fatality ratios than in high-income settings[28,30,31].

Animal influenza and transmission

Animal influenza is caused by various subtypes of influenza A viruses. Viruses of subtypes H1–H16 and H19, and N1–N9, have been detected in wild waterfowl[32], and only viruses of certain subtypes are widely prevalent among poultry and animals (Fig. 2). Viruses of three HA subtypes, A(H5Nx), A(H7Nx) and A(H9N2), have been detected in domestic poultry, whereas viruses of two HA subtypes, A(H1) and A(H3), have spread in pigs across wide geographic areas, including North America, Europe and Asia[33]. Viruses of subtype A(H3N8) are frequently detected in horses, while canines and felines are often infected by A(H3N2) and A(H3N8) viruses. Additionally, A(H5Nx) viruses have spread to dairy cows and various terrestrial mammals, and viruses of types A(H1, H3, H4, H5, H7, H10 and H13) have also been identified in marine mammals. The genetic materials of H17 and H18 HA and N10 and N11 NA have been identified exclusively in Central and South American bats[34,35].

The severity of diseases resulting from influenza A virus infections in animals varies according to the host species and the specific viral strains involved. In poultry, avian influenza viruses are classified as either low-pathogenicity avian influenza (LPAI) or HPAI viruses according to standardized pathogenicity criteria[36]. Most influenza A viruses are classified as LPAI strains in poultry, capable of spreading undetected among bird populations without inducing clinical symptoms[36]. Only specific strains possessing HA genes of the A(H5Nx) or A(H7Nx) subtypes exhibit high pathogenicity in poultry. These HPAI viruses have caused numerous outbreaks worldwide and, since 2005, over 680 million poultry have died or been culled[37]. A(H5Nx) and A(H7Nx) influenza viruses are, therefore, posing severe challenges to the global poultry industry.

Migratory wild birds contribute to the cross-border and long-distance transmission of avian influenza viruses, whereas disease management strategies and animal behaviour influence local transmission dynamics and the expansion of the pathogen's host range. The most compelling evidence regarding this aspect is the spread and prevalence of the HPAI A(H5N1) viruses bearing the clade 2.3.4.4b HA gene, which were initially identified in the Netherlands and subsequently spread by wild birds to other European countries and other continents, including

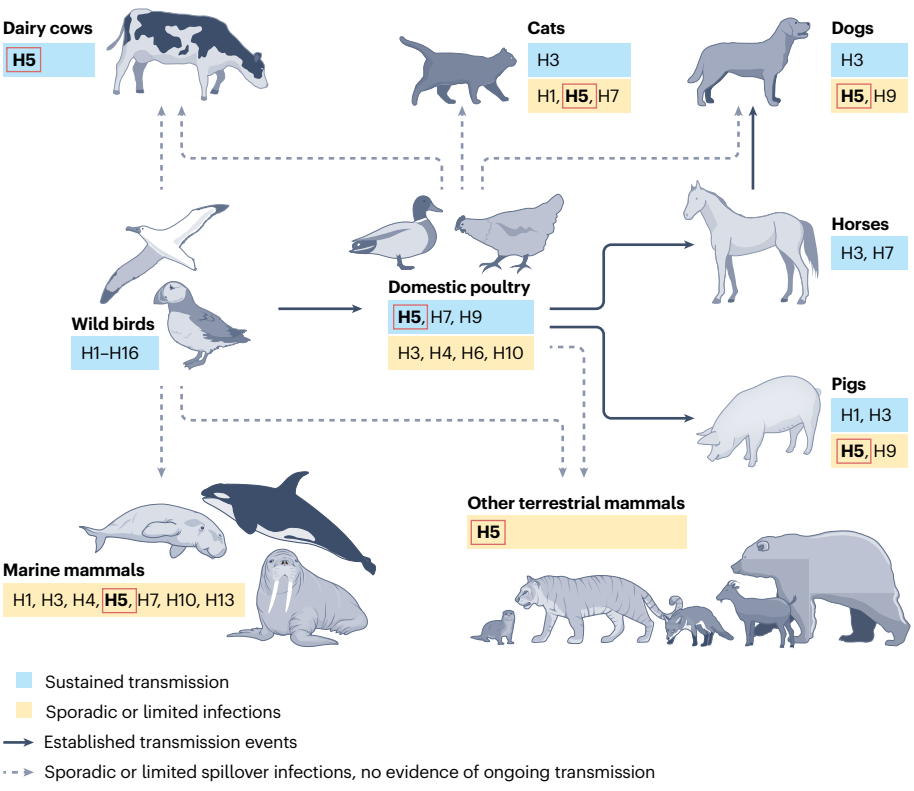

Fig. 2 | Ecology of influenza A viruses. Wild birds function as the natural reservoir of viruses of the H1–H16 subtypes. From this reservoir, sporadic spillover infections (dashed lines) are observed across numerous species, including cats, dogs, dairy cows, pigs and marine mammals. Domestic poultry serves as another critical host, facilitating sustained transmission of specific subtypes (H5, H7 and H9) and acting as a conduit for transmission to other animals. H5 viruses (outlined in red) are widespread with sustained transmission in domestic poultry and dairy cows and sporadic infections of multiple other animal groups, emphasizing their broad host range and significant potential for continued cross-species spillover.

Africa, Asia, North America and South America[38–40], where they reassorted with LPAI viruses and formed numerous genotypes[41–43]. Certain HPAI A(H5N1) viruses have spread to many other wild and domesticated mammals, including pigs, goats and, most prominently, dairy cattle[9,44]. The HPAI A(H5N1) viruses infected the mammary glands of dairy cattle[45], and the widespread transmission among dairy cattle may increase the pandemic potential of HPAI A(H5N1) viruses.

The clade 2.3.4.4b A(H5N1) viruses have caused substantial economic losses to the global poultry industry since 2020; these losses have been less substantial in countries where poultry vaccination strategies have been adopted[37,46]. Vaccination of poultry is now being recommended by the World Organisation for Animal Health and considered by a growing number of countries, including the USA, France, the UK and the Netherlands[47–50].

Mechanisms/pathophysiology

While influenza A and B viruses can cause seasonal epidemics in humans, only influenza A viruses have pandemic potential owing to their extensive reservoir in different animals and their larger antigenic diversity. In this section, we therefore focus on influenza A viruses.

Tropism, pathogenesis and transmission

Tropism, pathogenesis and transmission dynamics of influenza A viruses vary considerably, not only between host species but also among influenza A viruses. In aquatic birds, influenza A viruses predominantly exhibit gastrointestinal tropism and are transmitted via faecal contamination of water[51,52]. As reservoir hosts, aquatic birds typically show no overt signs of disease.

In mammals, including humans, influenza A virus infections are typically confined to the respiratory tract. While primarily a respiratory pathogen, some influenza A virus strains can occasionally cause gastrointestinal symptoms or conjunctivitis in humans, highlighting the diversity of host responses and viral characteristics[53,54].

Replication cycle

Influenza viruses replicate primarily in epithelial cells of the respiratory tract in humans and other mammals. Infection begins with the binding of influenza A viruses to host cells via their HA protein (Fig. 3). The receptor-binding specificity of HA varies by host species: mammalian influenza A viruses preferentially bind sialic acid linked to the penultimate sugar galactose in an α2,6 linkage, whereas avian influenza A viruses preferentially bind sialic acid in an α2,3 linkage[55,56]. This dichotomy remains a useful generalization but it is now clear that additional glycan features, such as sugar topology, chain length and modifications such as fucosylation, also modulate HA binding specificity and affinity[57]. Influenza A viruses of subtypes H17, H18 and H19 utilize major histocompatibility complex class II (MHC-II) molecules, but not sialic acid, for cell entry[58,59]. Some influenza A viruses of the H2 and H3 subtypes exhibit dual receptor specificity, using either sialic acid or MHC-II for infection[60,61]. Following attachment, influenza A viruses are internalized primarily via receptor-mediated endocytosis and trafficked through the endocytic pathway. During transition through the endocytic pathway, exposure to a low pH triggers key conformational changes in HA that mediate fusion of the viral and endosomal membranes. For this fusion activity, HA must first be proteolytically cleaved into HA1 and HA2 subunits. This cleavage is catalysed either by host proteases in the secretory pathway of virus-producing cells or by alternative proteases at the plasma membrane of newly infected cells[62]. Low endosomal pH also activates the viral M2 ion channel, enabling acidification of the virion interior, which in turn facilitates the dissociation of viral ribonucleoprotein complexes (vRNPs) from M1, enabling their transport into the nucleus via the cellular import machinery[63,64].

Once in the nucleus, the viral RNA-dependent RNA polymerase initiates transcription of viral mRNAs. A hallmark of influenza A virus transcription is 'cap-snatching', whereby the polymerase cleaves 5′-capped fragments from host pre-mRNAs to prime viral mRNA synthesis[65]. Unlike most RNA viruses, influenza viruses utilize the host nuclear splicing machinery for processing a subset of their transcripts — an adaptation that expands coding capacity but necessitates nuclear replication[66]. Translation of all viral mRNAs occurs on host ribosomes in the cytoplasm. Besides transcription, the viral polymerase also synthesizes negative-sense viral genomic RNA (vRNA) through a complementary positive-sense intermediate, known as cRNA. Efficient replication of vRNA depends critically on the host protein acidic nuclear phosphoprotein 32 family member A (ANP32A), which facilitates the supply of NP for the assembly of progeny vRNPs, stabilizes the polymerase complex, and supports both vRNA and cRNA synthesis[67–69].

As vRNPs accumulate, they are exported from the nucleus into the cytoplasm through a process requiring the viral proteins NS2 (also known as NEP) and M1, which mediate interaction with the cellular nuclear export machinery[70,71]. This process is promoted by virus-induced cell signalling to ensure that ribonucleoprotein export only occurs in late stages of the replication cycle. The vRNPs are subsequently organized into bundles of typically eight segments and transported to viral assembly sites at the plasma membrane, a process that relies on the host factor Rab11 (ref. 72). At the plasma membrane, the vRNP bundles are packaged into budding virions, which then bud from the cell surface. NA cleaves sialic acid residues from host cell surface glycoproteins and from the virion envelope, thereby preventing HA-mediated aggregation and facilitating release of progeny virions[73].

In addition to structural proteins, influenza A viruses encode several non-structural proteins, such as NS1, PA-X or PB1-F2, that antagonize host immune responses and modulate cellular pathways to enhance viral replication[74–76].

Adaptation to new hosts

Influenza A viruses have repeatedly crossed species barriers to establish infections in a wide range of new hosts, including chickens, pigs, dogs, horses, cats, cattle and humans. The virus encodes an RNA-dependent RNA polymerase that lacks proofreading capability, resulting in a high mutation rate and the generation of a heterogeneous population of viral variants — often referred to as quasispecies — within each infected host[77]. In addition, the segmented nature of the influenza A virus genome permits reassortment, whereby gene segments are exchanged when a cell is co-infected with two distinct influenza A viruses. This process can give rise to novel viral genotypes with potentially advantageous traits[78].

At the cellular and molecular level, numerous studies have characterized the viral genetic determinants that facilitate cross-species transmission (Fig. 3). One of the key molecular adaptations enabling avian influenza A viruses to infect mammals involves a switch in receptor-binding preference, as described above[79,80]. Another major determinant of host range involves polymerase function: avian influenza A virus polymerases must acquire the ability to efficiently utilize mammalian ANP32A proteins to support genome replication in mammalian cells[67]. Additional adaptations include changes in NA activity and stalk length[81], pH stability of HA[82], and sensitivity to the antiviral restriction factors myxovirus resistance protein A (MxA)[83] and butyrophilin subfamily 3 member 3a (BTN3A3)[84], among others.

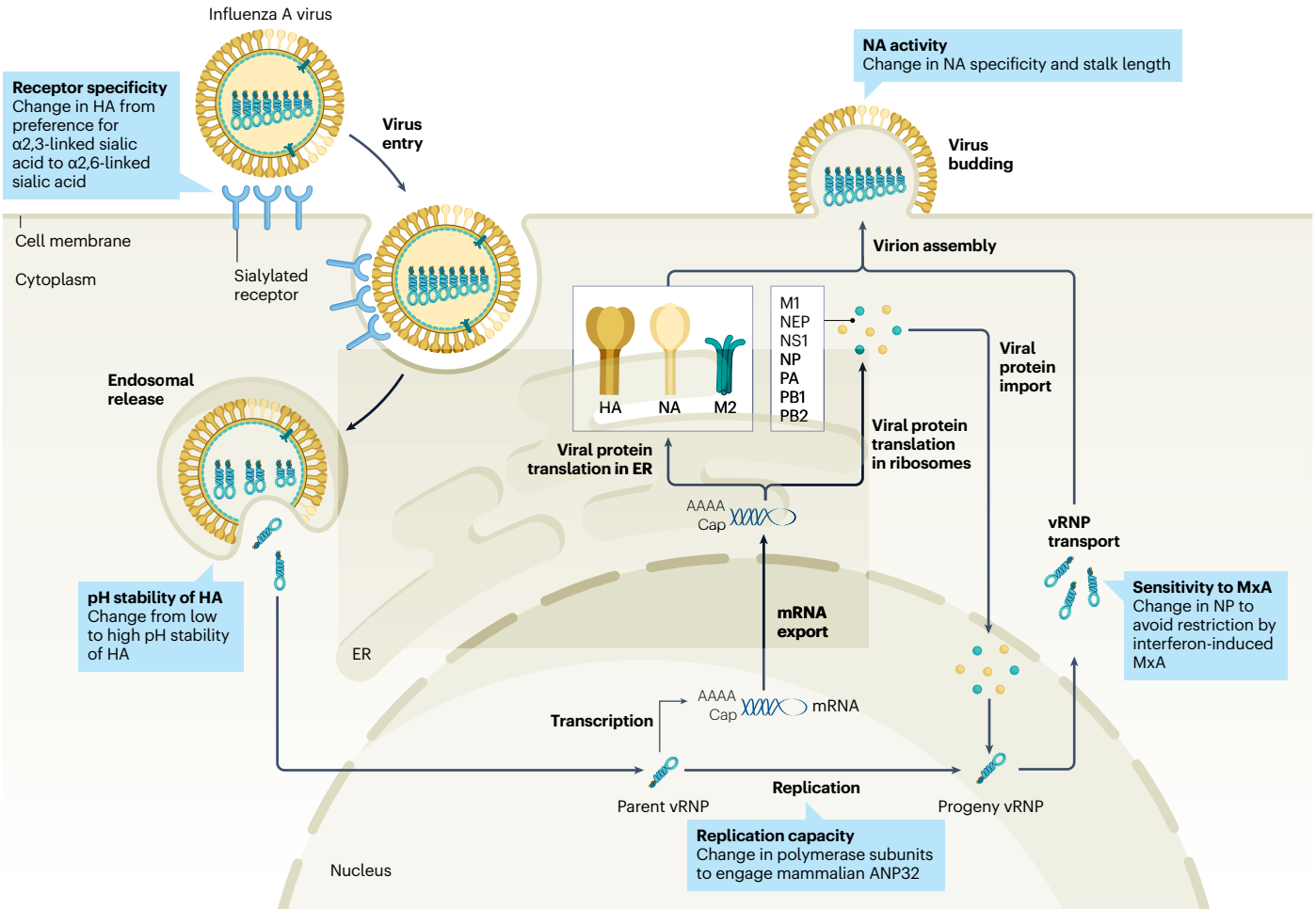

Fig. 3 | Replication cycle of influenza A viruses and adaptations during zoonosis. Influenza A viruses attach to host cells by haemagglutinin (HA) binding to receptor-linked sialic acid, which leads to receptor-mediated endocytosis. A drop in pH in the late endosome triggers conformational rearrangements in HA that enable fusion of the viral and endosomal membranes. In parallel, low pH-induced changes in M1 conformation enable the detachment of the viral ribonucleoprotein complexes (vRNPs) from the viral envelope and, therefore, release into the cytosol, followed by nuclear import. In the nucleus, viral transcription and replication take place. Viral mRNAs are exported from the nucleus for translation. In processes that are not well understood, all components are transported to viral assembly sites where formation and scission of new viral particles take place. The receptor-destroying activity of and neuraminidase (NA) prevents virions from reattaching to the producer cells or to neighbouring virions, enabling release. Well-studied examples of adaptations in different steps of the replication cycle, which are required for zoonotic influenza A viruses to adapt to mammals, are highlighted in blue. ANP32A, acidic nuclear phosphoprotein 32 family member A; ER, endoplasmic reticulum; MxA, myxovirus resistance protein A; NEP, nuclear export protein; NP, nucleoprotein; NS1, non-structural protein 1; PA, polymerase acidic protein; PB, polymerase basic protein.

Pigs may serve as important mixing vessels for influenza A viruses. Waterfowl-derived influenza A viruses can infect swine, as can human-origin influenza A viruses, leading to the establishment of novel swine-adapted lineages. The 2009 A(H1N1) influenza pandemic virus exemplifies the complexity of such evolutionary events: it emerged from reassortment between North American and Eurasian swine influenza lineages and contained gene segments of avian (PB2 and PA), swine (HA, NP, NA, M and NS) and human (PB1) origin[7].

Antigenic shift and drift

When a novel HA segment is introduced into human influenza A viruses via reassortment, it results in a major antigenic change. Additional reassortment with an avian or swine strain that leads to replacement of the NA segment can further alter antigenicity. This process, known as antigenic shift, is associated with pandemic emergence. Importantly, the introduction of a new HA subtype often leads to the displacement or extinction of the previously circulating subtype; for instance, the emergence of A(H2N2) in 1957 led to the disappearance of A(H1N1) viruses from the human population for 20 years[85]. However, co-circulation of subtypes is possible, as evidenced by the re-emergence of A(H1N1) virus in 1977, which co-circulated with A(H3N2) virus[86] until it was replaced by the 2009 pandemic A(H1N1)pdm09 virus, which continues to circulate.

Reassortment between avian influenza A viruses and human or swine influenza A viruses could generate a mammalian-adapted virus with novel antigenicity. However, reassortment alone is insufficient for the emergence of pandemic viruses, as adaptations to mammals,

including human-type receptor-binding specificity, HA stability and high polymerase activity in mammalian cells, are also considered crucial. Once a new subtype is established in the human population, the virus undergoes continuous evolution to evade host immunity. This process, known as antigenic drift, involves the selection of viral variants with amino acid changes in HA or NA that confer a fitness advantage in the presence of neutralizing antibodies. While antigenic changes resulting from drift are more incremental than those resulting from shift, they can accumulate over time to produce substantial antigenic divergence[87,88]. To monitor and respond to antigenic drift, the WHO has coordinated global surveillance efforts. These include the collection and sequencing of circulating strains as well as antigenic characterization. The generated data guide[89] the annual update of seasonal influenza vaccines, which remain a key tool in reducing the number of cases and limiting the public health burden of seasonal influenza A and B viruses.

Innate immune responses

The innate immune system provides the first line of defence against influenza A virus infections. Multiple layers of innate defences act to prevent influenza virus entry, replication and spread in the respiratory tract. While timely activation of innate responses is critical for early viral control, excessive and uncontrolled activation can cause severe tissue damage and immunopathology (Fig. 4). Influenza A viruses utilizes several evasion strategies to counteract innate defences and establish infection.

Physical barriers. Mucins, collectins and other proteins in airway secretions serve as the primary physical and biochemical barrier against influenza A viruses[90,91]. Mucins secreted by goblet cells are rich in sialoglycans, which act as decoy receptors and physically trap virus particles. To evade this, NA cleaves sialic acid moieties to help virus particles penetrate the mucin layer and reach epithelial cells[92]. Collectins (collagen-containing C-type lectins), such as surfactant protein A (SP-A) and SP-D, produced by respiratory epithelial cells, bind to carbohydrates on viral glycoproteins HA and NA and agglutinate virus particles[93]. Together, they create a protective shield that serves to inhibit influenza A virus entry.

Cell-autonomous immune responses and viral antagonism. Upon successful viral entry, several host-specific factors can restrict or support influenza A virus replication[94,95]. Viral RNAs are detected by host-encoded pattern recognition receptors, initiating cell-autonomous (intrinsic) immune responses[96]. Retinoic acid-inducible gene I (RIG-I) is the primary cytoplasmic RNA sensor, broadly expressed in all cell types, that detects 5′-triphosphorylated viral genomic RNA[97]. In addition, Toll-like receptors (TLR7 and TLR8), expressed in the endosomes of B cells and plasmacytoid dendritic cells, recognize single-stranded viral RNA[98]. Triggering of these RNA sensors initiates signalling cascades that activate transcription factors, such as interferon regulatory factor 3 (IRF3) or IRF7, nuclear factor-κB (NF-κB) and activator protein 1 (AP1), resulting in the transcriptional upregulation of cytokines and chemokines, including type I and type III interferons[99,100]. Secreted interferon signals via interferon receptors in an autocrine and paracrine manner, inducing the transcription of hundreds of interferon-stimulated genes. Several of these interferon-stimulated genes directly inhibit distinct steps of the influenza A virus life cycle, including IFITM3 (blocks viral fusion in endosomes), MxA (traps vRNP complexes), PKR (shuts off protein translation), and OAS-RNase L (degrades viral and host RNA)[101]. Not surprisingly, human polymorphisms in these innate immune genes, such as those encoding IFITM3, MxA, RIG-I, IRF7, IRF9, OAS and IFNL, have been linked to increased susceptibility to influenza A viruses[102,103]. To counteract these defences, influenza A viruses encode NS1, a major interferon antagonist that suppresses RIG-I signalling through interactions with TRIM25 and RIPLET, blocks PKR and OAS-RNase L activation, and shuts off host gene expression by disrupting mRNA processing[104,105]. Other influenza A virus proteins contribute to host antagonism: PB2 and PB1-F2 associate with MAVS to disrupt RIG-I signalling, while PA-X (endonuclease) degrades host RNAs[106]. In addition to interferon responses, the NLRP3 inflammasome is activated during influenza A virus infection, leading to the production of cytokines IL-1β and IL-18 and the recruitment of innate immune cells into the lungs[107]. Intracellular ionic changes caused by M2 and mitochondrial stress induced by PB1-F2 primarily drive inflammasome activation. Together, cell-autonomous immune responses act to restrict influenza A virus replication and spread.

Controlled inflammation versus immunopathology. Once infection is established, resident macrophages and dendritic cells are activated, either by direct infection or sensing of the extracellular milieu. Together with infected respiratory epithelial cells, they secrete pro-inflammatory cytokines (IFNα, IFNβ, IL-6, IL-18, TNF and IL-1β) and chemokines (CXCL8 (IL-8), CCL2 (MCP1), CCL3 (MIP1α), CCL5 (RANTES), CXCL9 (MIG) and CXCL10 (IP10)), which recruit various innate immune cells, including monocytes, macrophages, neutrophils and natural killer cells, to contain viral infection[96]. These cytokines are also essential for efficient priming of adaptive immune responses by respiratory dendritic cells[108,109].

Innate inflammatory responses induced by infection with influenza viruses can vary greatly[110]. In healthy individuals, human-adapted influenza A viruses (seasonal influenza A viruses) primarily replicate in the upper respiratory tract, causing mild disease with controlled inflammation. However, the 1918 pandemic influenza A(H1N1), HPAI A(H5Nx) and A(H7Nx) viruses infected the lower respiratory tract. These viruses also activate various innate immune cells, generating excessive amounts of viral pathogen-associated molecular patterns and overstimulating host pattern recognition receptors[111,112]. This can trigger excessive and sustained production of pro-inflammatory cytokines and chemokines ('cytokine storm'), leading to massive recruitment of pathological inflammatory monocytes and neutrophils that worsen disease severity and cause immunopathology[113].

Adaptive immune responses

Adaptive immunity, mediated by T and B cells, is crucial in viral clearance and long-term protection (Fig. 4). Respiratory dendritic cells serve as a bridge between innate and adaptive responses and orchestrate the activation of T and B cells[96].

T cell immunity. Upon activation, $CD103^+CD11c^+$ and $CD11b^+$ respiratory dendritic cell subsets migrate to the draining lymph nodes and activate naive $CD8^+$ and $CD4^+$ T cells by presenting viral peptides on MHC-I and MHC-II, respectively[114]. Activated cytotoxic $CD8^+$ T cells migrate to the lungs and eliminate infected cells via cytolysis, thereby limiting viral replication[115]. $CD8^+$ T cells primarily recognize epitopes in conserved internal viral proteins such as NP, M1 and polymerase[116]. Activated $CD4^+$ T cells provide helper functions for the differentiation of activated B cells and signals critical for efficient priming of memory

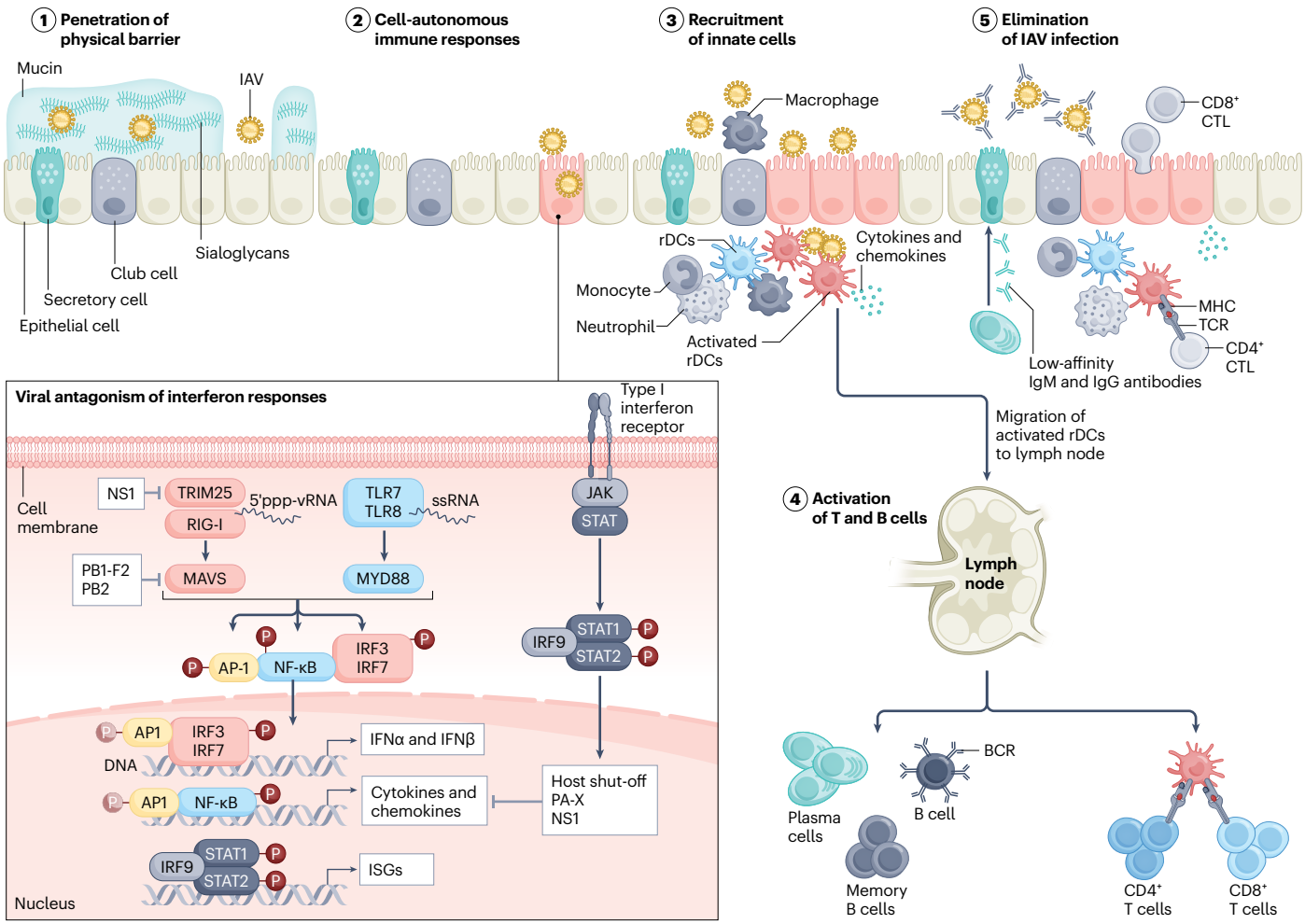

Fig. 4 | Innate and adaptive immune responses to influenza A virus infection. (1) Influenza A viruses (IAVs) penetrate the mucin barrier using viral neuraminidase and reach the surface of epithelial cells. (2) Host cells sense viral RNA through RIG-I, and TLR7 and TLR8, and initiate cell-autonomous immune responses, leading to activation of nuclear factor-κB (NF-κB), activator protein 1 (AP1), interferon regulatory factor 3 (IRF3) and IRF7, and subsequent production of type I interferon and pro-inflammatory cytokines and chemokines. Viral proteins non-structural protein 1 (NS1), polymerase basic protein 1 frame 2 protein (PB1-F2), polymerase basic protein 2 (PB2) and polymerase acidic X protein (PA-X) antagonize host interferon responses. (3) Pro-inflammatory cytokines and chemokines recruit various innate immune cells to the site of infection. In addition, respiratory dendritic cells (rDCs) become activated and migrate to the draining lymph nodes to initiate adaptive immune responses. (4) rDCs present viral antigens via major histocompatibility complex class I (MHC-I) and MHC-II to activate $CD4^+$ and $CD8^+$ T cells, respectively. B cells are activated by viral antigens and undergo differentiation into memory B cells and antibody-secreting plasma cells within germinal centres. (5) The viral infection is eliminated through antibody-mediated neutralization and the cytolytic activities of effector T cells. IAV-infected cells are shown in red. 5′ppp-vRNA, 5′-triphosphorylated viral genomic RNA; BCR, B cell receptor; CTL, cytotoxic T lymphocyte; ISGs, interferon-stimulated genes; RIG-I, retinoic acid-inducible gene I; ssRNA, single-stranded RNA; TCR, T cell receptor; TLR, Toll-like receptor.

$CD8^+$ T cells[117]. In addition, activated $CD4^+$ T cells produce cytokines and chemokines that augment innate responses by natural killer cells[118]. Studies from the 2009 H1N1 pandemic showed that memory $CD4^+$ T cell numbers correlated with reduced symptoms and mild disease, underscoring a protective role for $CD4^+$ T cells against heterologous influenza A viruses[119,120]. During primary influenza A virus infection, virus-specific T lymphocytes in the lungs peak around days 7–10 after infection and subsequently contract after viral clearance. A portion of these activated T cells differentiate into tissue-resident memory T cells in the respiratory tract and central memory cells in secondary lymphoid organs. Importantly, memory T cells that recognize conserved epitopes provide cross-protection against antigenically drifted and heterologous influenza A viruses[121]. Tissue-resident memory T cells are particularly important as they provide rapid protection during recall responses, which occur within 2–3 days post-infection.

B cell immunity. B cells are activated in the lymph nodes by viral particles or antigens released from dying dendritic cells. Initially, activated B cells differentiate into plasmablasts that mostly produce low-affinity IgM and IgG antibodies, limiting viral spread starting at ~day 7 (ref. 122). In the lymph nodes, some activated B cells enter germinal centres, where they undergo affinity maturation and antibody class switching

with help from follicular CD4$^+$ T cells, a process that occurs later in infection (~2–3 weeks)[123]. A subset of these high-affinity B cells differentiates into long-lived plasma cells and memory B cells, which home either to the respiratory tract as tissue-resident memory B cells or to lymphoid organs. Tissue-resident memory B cells, especially IgA-secreting cells, are crucial in neutralizing virus during re-infection. The majority of antibody responses target immunodominant or variable epitopes in the HA1 subunit (head and receptor-binding domain)[124]. These HA1-specific antibodies efficiently neutralize homologous virus particles but are less effective against antigenically drifted strains and ineffective against heterologous strains. By contrast, antibodies targeting conserved epitopes in the HA2 subunit (stem and fusion domain), albeit limited in number and less potent in neutralizing, confer broader protection across influenza A viruses within the same HA group (group 1 and group 2)[125,126]. In addition, these HA2-specific antibodies mediate antibody-dependent cellular cytotoxicity by natural killer cells or phagocytosis by neutrophils[127].

Diagnosis, screening and prevention

Diagnosis

As the clinical signs and symptoms of influenza are non-specific (see 'Clinical course' section) and can overlap with other co-circulating respiratory pathogens (for example, other respiratory viruses: severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), respiratory syncytial virus (RSV) and human coronaviruses), a clinical diagnosis may be inaccurate; therefore, influenza testing can inform clinical management. Influenza diagnostic tests available in clinical settings include antigen detection and molecular assays that can respectively detect influenza A and B viral antigens and influenza virus nucleic acids in respiratory specimens (Table 1). Molecular assays have higher sensitivity to detect influenza A and B viruses in respiratory specimens than rapid antigen tests (that is, false negative results are more common with antigen tests[128]). PCR-based methods with different detection methods, such as real-time reverse transcription PCR, digital PCR and loop-mediated isothermal amplification, are the 'gold standard' molecular assays for influenza diagnosis[129,130]. Both antigen detection and molecular assays have very high specificity, so false positive results are uncommon. Point-of-care influenza rapid antigen tests and rapid molecular assays that produce timely results to guide clinical management may be available in healthcare facilities, depending upon resource setting. Some molecular assays may require several hours or longer to yield results if the respiratory specimens are tested offsite at a clinical laboratory.

Nasopharyngeal specimens (aspirates or swabs) have the highest yield for detection of seasonal influenza viruses from non-hospitalized patients, followed by nasal swabs (or combined nasal–throat swabs), followed by throat swabs[131,132]. Testing of sputum, endotracheal aspirate or bronchoalveolar lavage fluid specimens from patients with lower respiratory tract complications can detect influenza viruses in cases in which a specimen from the upper respiratory tract is negative; however, these specimens are not approved for all tests[133]. Multiplex antigen assays that can detect influenza A and B viruses and other respiratory viruses (for example, SARS-CoV-2 and RSV) and some multiplex molecular assays that can detect influenza and other respiratory viruses (for example, SARS-CoV-2 and RSV), influenza A(H1N1) and A(H3N2), influenza B virus, and some bacterial respiratory pathogens, are becoming increasingly used and are generally available at hospitals and larger or public health laboratories.

Rapid antigen tests or molecular assays that can detect influenza viruses in upper respiratory specimens may be available for use in non-clinical settings (for example, home use) in some countries[134]. Proper interpretation of influenza test results is important, particularly negative rapid antigen test results during periods of high influenza activity, because their lower sensitivity can result in false negative results. Serology does not inform clinical management of patients with influenza because results from a single serum specimen do not reliably diagnose acute influenza virus infection and require paired acute and convalescent sera collected ~3 weeks apart and tested at a public health or research laboratory.

Several other promising diagnostic methods are under development, including those based on CRISPR, nucleic acid sequence-based amplification, microarrays and various personal biosensors[135]. Next-generation sequencing (NGS) has rapidly advanced and has several advantages over conventional diagnostic methods if a metagenomics approach is adopted. A metagenomics NGS approach can provide an unbiased, broad-spectrum identification of known and novel pathogens, and can also identify resistance markers and virulence factors[136]. Alternatively, NGS hybrid capture methods can be used for a more focused detection of all respiratory pathogens[137]. While current limitations include longer turnaround times and higher costs, these are likely to decrease in the coming years.

Influenza virus surveillance

Public health laboratories conduct surveillance for influenza viruses utilizing molecular assays such as real-time reverse transcription PCR (rRT-PCR) to confirm influenza A and B viruses in respiratory specimens and for subtyping of influenza A(H1) and A(H3) viruses[138]. National influenza centres participating in the WHO Global Influenza Surveillance and Response System and WHO Influenza Reference Laboratories can isolate influenza viruses from respiratory specimens using embryonated eggs or tissue cell culture, and perform antigenic characterization of viruses using reference sera (for example, against influenza vaccine strains), sequencing and phylogenetic analyses. The data are then used to inform the biannual influenza vaccine strain selection process[139,140]. Use of specific primers and probes combined with sequencing can identify novel influenza A viruses of pandemic potential. Some national influenza centres and WHO Influenza Reference Laboratories perform in vitro and functional assays to assess virus susceptibility to antiviral drugs. As part of pandemic risk assessment, WHO and specialized research laboratories also perform pathogenicity and transmission studies of novel influenza A viruses using animal models (for example, mice, ferrets or non-human primates)[141,142].

Influenza vaccines

The goal of a universal influenza vaccine to protect humans against all seasonal and novel influenza A viruses of zoonotic origin has yet to be achieved; hence, the available seasonal influenza vaccines must be updated regularly because of ongoing antigenic drift in influenza viruses[143]. There are, however, a wider range of seasonal influenza vaccines now available (Fig. 5) that have been licensed for different age groups. These include inactivated split-virus vaccines, live attenuated vaccines and recombinant protein-based vaccines, with others in development such as mRNA vaccines[144]. Globally, wide regional variation exists in the kinds of influenza vaccines available, recommended priority groups for annual influenza vaccination and vaccine coverage by target group[145]. In four WHO regions, reported influenza vaccine coverage was highest in healthcare workers, older adults and pregnant women.

The most widely used influenza vaccines are still those that are produced by adapting and growing influenza viruses in embryonated

Table 1 | Influenza diagnostic tests in clinical settings

Methodology	Available tests	Accuracy and sensitivity	Time to results	Considerations
Influenza viral antigen detection in respiratory specimens	Rapid antigen test Rapid multiplex antigen test (may detect influenza A and B viruses, SARS-CoV, and RSV antigens in a single assay), usually based on lateral flow devices Immunofluorescence assay (rarely used today)	Most accurate <4 days from symptom onset Low to moderately high sensitivity (false negative results can occur) and very high specificity (false positive results are rare) compared with RT-PCR	~10–15 min Immunofluorescence assay may require up to 4 h	Optimal upper respiratory tract specimens for detection of seasonal influenza A or B viruses are nasopharyngeal swabs or aspirates, or nasal swabs Provides influenza A or B virus type identification only Does not provide information, identify or distinguish among seasonal influenza A virus subtypes and novel influenza A viruses of animal origin Some tests may be available for use in non-clinical settings such as lateral flow rapid antigen tests for home use
Influenza viral nucleic acid detection in respiratory specimens	Rapid molecular assay Other molecular assays, including RT-PCR Multiplex molecular assays (may detect nucleic acids from influenza A and B viruses, SARS-CoV and RSV, other respiratory viruses and some bacterial respiratory pathogens)	High to very high sensitivity (false negative results are uncommon) and very high specificity (false positive results are rare) compared with standard RT-PCR or viral culture	≤30 min to 6–8 h	Optimal upper respiratory tract specimens for detection of seasonal influenza A or B viruses are nasopharyngeal swabs or aspirates, or nasal swabs Can also use combined nasal swab and throat swab specimens Some assays can be used to detect influenza viral nucleic acids in lower respiratory tract specimens (for example, sputum, endotracheal aspirate and bronchoalveolar lavage fluid) Can detect influenza viruses for longer periods after symptom onset than antigen detection tests Many assays only provide information on influenza A or B virus type; a few multiplex assays can identify influenza A(H1) and A(H3) subtypes Detection of influenza A virus does not provide information or distinguish among seasonal influenza A virus subtypes and novel influenza A viruses of animal origin — specific primers and probes are needed to detect influenza A subtypes and novel influenza A viruses Has also been used to test non-respiratory clinical specimens (for example, conjunctival swabs, cerebrospinal fluid, whole blood, serum or plasma, faeces and urine) but most assays are not approved or validated for these clinical specimens
Virus isolation from clinical specimens (respiratory)	Viral culture using tissue cell culture or embryonated eggs at public health laboratories (not used as a diagnostic test)	High specificity but lower sensitivity than molecular assays	3–7 days Shell vial culture can produce cytopathic results in 1–2 days Does not produce timely results to inform individual patient clinical management	Can be used for upper and lower respiratory tract specimens Has also been used to test non-respiratory clinical specimens (for example, cerebrospinal fluid, whole blood, serum and plasma) Enables antigenic and other viral phenotypic characterizations at public health laboratories

RSV, respiratory syncytial virus; RT-PCR, reverse transcription PCR; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

hen's eggs, which are then purified, inactivated and detergent-split to obtain an inactivated, split influenza virus vaccine. These vaccines contain HA and NA from each of the three currently circulating human influenza viruses (A(H1N1), A(H3N2) and B/Victoria) along with other viral proteins and trace amounts of egg proteins, and are often referred to as 'standard-dose influenza vaccines'. Unfortunately, they are only moderately effective, with pooled vaccine effectiveness estimates of 30–83%, depending on the vaccine and age group[146,147]. Efforts to improve egg-based inactivated influenza vaccines include the addition of adjuvants to improve responses in adults ≥65 years of age (for example, MF-59)[148] or responses to pre-pandemic vaccines (for example, AS03)[149], or fourfold higher amounts of HA for use in adults ≥65 years of age (high-dose vaccine)[150]. The transition from egg-based vaccines to cell-based vaccines[151], or increased use of recombinant protein-based vaccines (which contain three times the antigen content of standard-dose inactivated vaccines), has been slow, with

only a few manufacturers making the shift, although these cell-based vaccines showed increased effectiveness over egg-based vaccines (owing to the lack of unwanted egg adaptations) in some years[152,153]. In a multi-year study, cell-based quadrivalent influenza vaccine demonstrated superior effectiveness to egg-based quadrivalent influenza vaccine in the prevention of test-confirmed influenza. Following the use of mRNA vaccines for COVID-19 (refs. 154–157), several companies are developing mRNA influenza vaccines, mostly incorporating influenza with other respiratory pathogens such as SARS-CoV-2, RSV, human metapneumovirus or other combinations[158]. The first of these, a dual mRNA vaccine targeting influenza and SARS-CoV-2 developed by Moderna, was given marketing approval for persons 50 years of age and older by the EMA on 22 April 2026 (ref. 159). The flexibility of mRNA vaccines has been demonstrated by the incorporation of HA antigens from all known influenza A virus subtypes and influenza B virus lineages into a nucleoside-modified mRNA–lipid nanoparticle vaccine. This vaccine elicited high levels of cross-reactive and subtype-specific antibodies in mice and ferrets that reacted to all 20 encoded antigens[160]. While no mRNA influenza (influenza-only) vaccines are currently licensed for human use as of July 2026, a phase III study showed favourable safety and immunogenicity results[161]. A trivalent version of this seasonal influenza mRNA vaccine (mRNA-1010) containing mRNA encoding HAs from two influenza A strains and one influenza B strain also demonstrated superior relative vaccine efficacy compared with a licensed standard-dose seasonal influenza vaccine in adults aged 50 years and older[162]. This enhancement was like that reported for high-dose inactivated influenza vaccine compared with a standard-dose vaccine in people aged 65 years and over[150]. Further advancements include self-amplifying mRNA, which offers potential advantages over conventional mRNA vaccines by enabling lower doses of mRNA, thus reducing reactogenicity, while enhancing immunogenicity, duration and cost-effectiveness[163]. Despite these advances, there is still substantial room for improvement with influenza vaccines in effectiveness, coverage and duration[164].

Management

Clinical course

The signs and symptoms of seasonal influenza can vary by age, immune status and underlying medical conditions. Fever is not always present among people of any age with influenza, particularly in adults aged ≥65 years[165]. Systemic symptoms such as chills, headache, myalgia and malaise can occur with respiratory symptoms such as non-productive cough, nasal discharge and sore throat. Gastrointestinal symptoms, such as nausea, vomiting, diarrhoea and abdominal pain, can occur in children but are less common in adults. Frail older adults can experience malaise, anorexia, dizziness, weakness and residual cough for prolonged periods. Ocular symptoms and rashes can occur but are uncommon. Most people with influenza experience abrupt onset of uncomplicated acute respiratory illness and return to baseline health after several days without seeking medical care or receiving specific treatment. However, persons at increased risk of influenza complications[166] and, infrequently, otherwise healthy people, can experience severe influenza.

Influenza virus infection of the upper respiratory tract can result in complications ranging from moderate (managed at home) to severe (requiring hospitalization) or fatal, and may involve one or more organ systems (Box 2). Like other respiratory virus infections, infants and young children with influenza can experience respiratory complications such as bronchiolitis, croup and otitis media. In children and adults who are otherwise healthy, the most common severe respiratory complication of influenza is pneumonia, which can be caused by influenza viral pneumonitis or community-acquired secondary bacterial (for example, *Staphylococcus aureus* or *Streptococcus pneumoniae*) co-infection[167,168]. Non-respiratory complications in otherwise healthy people include cardiac disease (myocarditis or pericarditis), musculoskeletal inflammation (myositis or rhabdomyolysis), gastrointestinal abnormalities (hepatitis or pancreatitis), kidney disease (acute kidney injury or renal failure) and neurological complications (transient to fulminant acute necrotizing encephalopathy, meningoencephalitis,

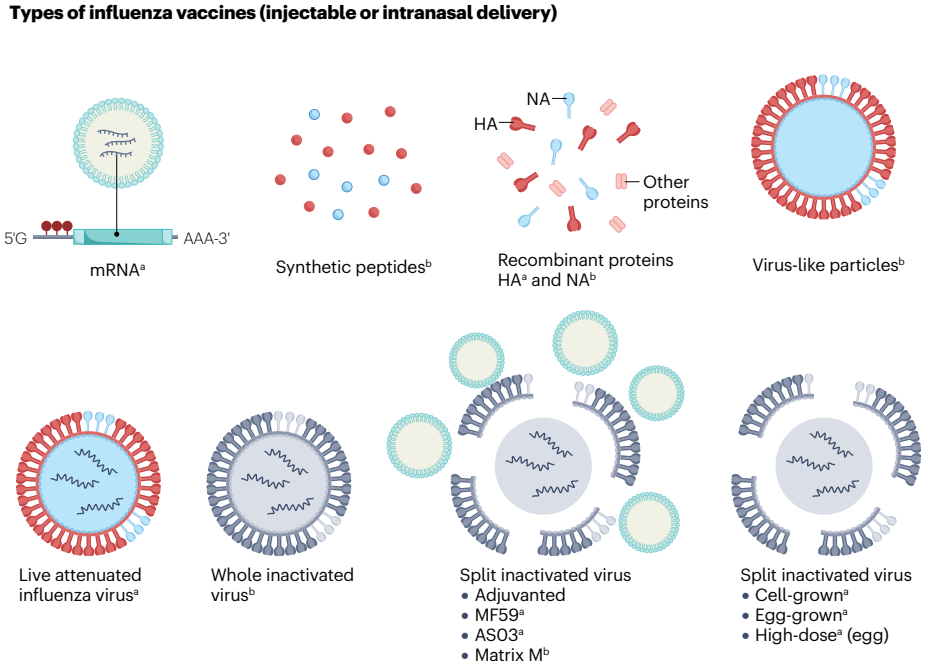

Fig. 5 | Types of influenza vaccines. A variety of seasonal and potential pandemic influenza vaccines exist. Several of these are licensed (marked with [a]) and are currently in use such as split inactivated viruses, recombinant HA proteins, live attenuated influenza vaccines and mRNA (currently only in combination with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) mRNA). Other vaccines are in development (marked with [b]), such as synthetic peptides of influenza proteins (including T cell vaccines), whole inactivated virions, and virus-like particles. All licensed vaccines are administered via injection except for live attenuated influenza vaccines, which are given by intranasal instillation. HA, haemagglutinin; NA, neuraminidase.

transverse myelitis, acute demyelinating encephalomyelitis and, rarely, Guillain–Barré syndrome)[169]. In persons with chronic disease, particularly uncontrolled comorbidities, influenza can exacerbate underlying cardiopulmonary (for example, chronic obstructive pulmonary disease, asthma, coronary artery disease or heart failure), metabolic (for example, diabetes) and neurological (for example, cerebrovascular) disease. Community-acquired co-infections with other respiratory viruses (for example, SARS-CoV-2)[170,171], bacterial or fungal pathogens that colonize the respiratory tract can result in severe illness, especially in severely immunocompromised patients[172,173]. However, influenza virus infection can precipitate sepsis, septic shock, respiratory failure and multi-organ failure with or without bacterial co-infection[168,174]. Critically ill patients with influenza who are intubated are at risk of ventilator-associated pneumonia from multidrug-resistant bacterial or fungal infections[175].

Box 2 | Influenza complications

Complications are organized by organ system or underlying condition. Complications can vary by age, immune function and underlying medical conditions

Systemic
Sepsis, septic shock, systemic inflammatory response syndrome, toxic shock syndrome

Respiratory
Upper respiratory tract
Laryngotracheobronchitis (croup), otitis media, sinusitis

Lower respiratory tract
Pneumonia (viral pneumonitis, secondary community-acquired bacterial co-infection, ventilator-associated bacterial or fungal pneumonia), bronchiolitis, bronchitis, reactive airway disease, tracheitis, respiratory failure, acute respiratory distress syndrome, exacerbation of asthma or chronic obstructive pulmonary disease

Cardiac
Myocardial infarction (persons with underlying coronary artery disease), myocarditis, pericarditis, exacerbation of heart failure

Gastrointestinal tract
Hepatitis, hepatic failure, pancreatitis, severe abdominal pain

Musculoskeletal
Myositis, rhabdomyolysis, compartment syndrome

Kidney
Acute kidney injury, kidney failure

Central and peripheral nervous system
Seizures, transient to fulminant encephalopathy, meningoencephalitis, bacterial meningitis, cerebrovascular accident (persons with cerebrovascular disease), transverse myelitis, acute demyelinating encephalomyelitis, Reye syndrome (with salicylate exposure), Guillain–Barré syndrome

Pregnancy
Premature labour, fetal loss

Other
Exacerbation of chronic disease (for example, diabetes, sickle cell disease), parotitis

Infection prevention and control

Seasonal influenza A and B viruses are typically spread through the air via large and small infectious particles from a person with infection to a susceptible individual in close proximity[15,176]. In healthcare settings, patients with suspected or laboratory-confirmed influenza should be isolated in a single room or area. Recommended infection prevention and control (IPC) measures include standard (preventative measures for all patients, such as hand hygiene and use of personal preventive equipment based on exposure risk) and droplet precautions (use of facemasks) for 7 days after illness onset or until 24 h after fever and respiratory symptoms have resolved, although longer duration of IPC measures might be indicated for certain patients such as young infants and severely immunocompromised patients who might be infectious for prolonged periods, and airborne precautions are recommended for aerosol-generating procedures[177]. Influenza testing of serially collected respiratory specimens can inform duration of isolation and IPC measures.

Antiviral treatment and prophylaxis

Antivirals can be prescribed for treatment and/or prophylaxis of influenza but availability depends upon regulatory approvals, cost, and recommendations from clinical and public health organizations (Table 2). The most widely used antivirals for early treatment of uncomplicated influenza A and B are the NA inhibitors (NAIs) oseltamivir, zanamivir, laninamivir and peramivir, and the cap-dependent endonuclease inhibitor baloxavir. The M2-inhibitor adamantanes, amantadine and rimantadine, only have activity against influenza A viruses and are not recommended for treatment of seasonal influenza A owing to high prevalence of resistance among seasonal influenza A(H1N1)pdm09 and A(H3N2) viruses[169,178]. Clinical trials have shown that initiation of treatment within 1–2 days after symptom onset with NAIs or baloxavir can reduce the duration of illness and risk of some complications[179–182]. Baloxavir had greater clinical benefit against influenza B than oseltamivir in one clinical trial[180]. Whether early initiation of antiviral treatment can reduce the risk of progression to severe disease is unclear because sufficiently powered clinical trials are lacking. Since severely immunocompromised patients with influenza can have prolonged viral replication, antiviral monotherapy can lead to the emergence of antiviral-resistant viruses[173]. Early initiation of antiviral treatment with an NAI or baloxavir is recommended, particularly for patients at increased risk of complications and severe influenza[178]. Single doses of baloxavir have also been reported to reduce influenza virus transmission to close contacts[23].

Clinical trial data on antiviral treatment of hospitalized patients with severe influenza are limited[183] but two international adaptive platform clinical trials are assessing antivirals in patients hospitalized with influenza[184,185]. Observational studies have reported clinical benefit of oseltamivir in reducing duration of hospitalization and progression to severe disease outcomes when treatment was started at hospital admission compared with later or no treatment[186,187], and clinical guidelines recommend oseltamivir treatment as soon as possible in patients hospitalized with influenza[169,188]. Determining optimal antiviral treatment and treatment duration for severely ill patients with influenza remains a gap. An adaptive platform clinical trial reported that oseltamivir

Table 2 | Antivirals for treatment and prophylaxis of seasonal influenza

Mechanism of action	Drug and administration	Considerations
Neuraminidase inhibitor		
Inhibits viral neuraminidase to block release of viral particles from infected cells	Oseltamivir phosphate[a] (twice daily for 5 days for treatment of outpatients; oral capsule, oral suspension or can be administered enterically) Zanamivir (inhaled powder administered twice daily using inhaler device for treatment of outpatients) Laninamivir (single-dose inhaled powder administered using inhaler device for treatment of outpatients) Peramivir[a] (single-dose, administered intravenously for treatment of outpatients)	Oseltamivir may have decreased effectiveness against influenza B viruses Adjust neuraminidase inhibitor dose and frequency for reduced creatinine clearance Oseltamivir is recommended for prompt treatment of influenza in outpatients and hospitalized patients Oseltamivir is recommended promptly as post-exposure prophylaxis for controlling institutional influenza outbreaks; typical dose frequency is once daily Zanamivir may be effective against some oseltamivir-resistant influenza viruses Laninamivir is only approved in Japan for treatment of influenza
Polymerase inhibitor		
Cap-dependent endonuclease inhibitor within the polymerase acidic protein subunit of influenza viral polymerase; blocks viral replication	Baloxavir marboxil[a] (single-dose oral tablet)	Single dose is equivalent to 5 days of twice-daily oseltamivir treatment Greater clinical benefit against influenza B compared with oseltamivir Significantly greater reduction in upper respiratory viral RNA levels compared with oseltamivir Treatment has modest effect in reducing transmission to household members Single dose can be given promptly for post-exposure prophylaxis Risk of emergence of viruses with reduced susceptibility; higher risk in young children Not recommended as monotherapy for severely immunocompromised patients
M2 ion channel inhibitor		
Blocks proton channel activity of the M2 protein of influenza A viruses	Amantadine[b] (oral capsule or tablet) Rimantadine[b] (oral tablet)	Not recommended for treatment or prophylaxis of seasonal influenza A viruses owing to high prevalence of resistance among circulating seasonal influenza A(H1N1)pdm09 and A(H3N2) viruses

[a]Dose varies by approved age and weight in children. [b]Only active against influenza A viruses.

treatment of critically ill patients with influenza was associated with increased 90-day mortality[189]. A post hoc analysis of clinical trial data in a subset of patients hospitalized with severe influenza caused by influenza A(H3N2) virus infection reported that combination antiviral treatment with a NAI (nearly all oseltamivir) and baloxavir significantly reduced 28-day mortality compared with oseltamivir monotherapy in patients with immunosuppression, diabetes or chronic lung disease (2.17% (2/92) versus 11.76% (6/51); $P = 0.02$)[190].

In addition to antiviral treatment of symptomatic persons and implementation of many other non-pharmaceutical interventions, post-exposure antiviral prophylaxis with oseltamivir is used to control institutional influenza outbreaks and can be considered for persons at very high risk of severe disease who may not respond to influenza vaccination (for example, severely immunocompromised individuals)[169]. A long-acting injectable antiviral (CD388) is under investigation in a phase III clinical trial for prevention of influenza over an entire season (NCT07159763)[191].

Management of complications

Influenza can exacerbate chronic disease, and targeted management of the underlying disease process is indicated (for example, exacerbation of asthma or chronic obstructive pulmonary disease, heart failure, myocardial infarction, status asthmaticus or diabetic ketoacidosis). In patients with influenza and pneumonia requiring respiratory supportive care (for example, oxygen delivered via high-flow nasal cannula, non-invasive ventilation or invasive mechanical ventilation), diagnostic testing may be indicated for community-acquired co-infections for which antimicrobial therapy is available (for example, SARS-CoV-2, *S. aureus* or *S. pneumoniae*). Critical care for sepsis, septic shock, acute respiratory distress syndrome and advanced organ support (for example, renal replacement therapy or extracorporeal membrane oxygenation) may be required for multi-organ failure and severe acute respiratory distress syndrome, and neurocritical care is essential for paediatric patients with acute necrotizing encephalopathy[192]. Corticosteroids have been administered to patients with influenza and severe pneumonia but observational studies have reported that high-dose corticosteroids may increase the risk of ventilator-associated pneumonia and mortality[193]. Corticosteroids and other immunomodulators are under investigation in adaptive clinical platform trials in hospitalized patients with severe influenza[184,185]. Other immunomodulators and drugs with anti-inflammatory effects have been studied for the treatment of severe influenza but further data from clinical trials are needed[194].

Management of novel influenza A virus infections

Novel influenza A viruses of avian or swine origin have infected humans sporadically, resulting in a wide clinical spectrum of disease severity from asymptomatic infection, mild uncomplicated upper respiratory tract illness or localized disease (for example, conjunctivitis) to severe disease (for example, pneumonia, encephalitis, respiratory failure, sepsis, septic shock or multi-organ failure)[195]. Some avian influenza A virus infections are associated with high mortality (for example, HPAI A(H5Nx), A(H7Nx) and LPAI A(H7N9)), although mild illness can occur with these virus infections[195]. Risk factors for avian influenza A virus infections are recent (for example, in the past week before symptom onset) direct or close exposure to sick or dead poultry or other infected animals (for example, dairy cattle in the USA) or visiting a live poultry market[196–198]. Limited, non-sustained human-to-human transmission has been reported in households and in healthcare settings[199–202]. For some cases, the source of infection was not identified. Most human infections with variant influenza A viruses of swine origin have resulted in clinically mild illness in children with recent exposure to swine, although severe disease and fatal outcomes have occurred[203–205].

Clinical treatment of patients with novel influenza A virus infections differs from that of patients with seasonal influenza in a few ways. In addition to standard, contact (for example, use of gown and gloves) and droplet precautions, patient placement in an airborne infection isolation room and airborne precautions (fitted N95 particulate filtering respirator or equivalent level of respiratory protection) and eye protection (goggles or face shield) are recommended for healthcare personnel caring for patients with novel influenza A virus infections associated with high mortality because of the potential for human-to-human transmission[199–202,206]. Although there are no clinical trials of antiviral treatment of patients with novel influenza A virus infection, observational studies have reported that initiation of oseltamivir treatment in patients with HPAI A(H5Nx) virus infection shortly after symptom onset has clinical and survival benefits[207]. Since the emergence of oseltamivir-resistant viruses can occur during or after oseltamivir monotherapy[208], combination treatment with antivirals with different mechanisms of action, including oseltamivir and baloxavir, has been used in some patients with HPAI A(H5Nx) virus infections[209–211]. Moderate and high-dose corticosteroids are not recommended because of the association with prolonged viral shedding and mortality in patients hospitalized with LPAI A(H7N9) virus infection[212,213]. Supportive care and advanced organ support, including renal replacement therapy, extracorporeal membrane oxygenation, vasopressors and interventions such as external ventricular drainage of cerebrospinal fluid and plasmapheresis, have been reported for critically ill patients with avian influenza A virus infections.

Quality of life

Most people recover from seasonal influenza and return to baseline health within a week; however, people with chronic medical conditions exacerbated by influenza and older adults may have prolonged illness or loss of function of activities of daily living. A German study reported that post-influenza symptoms were less frequent than post-COVID symptoms but persistence of symptoms at 3–6 months was similar[214]. A Canadian study reported that adults aged ≥65 years who were hospitalized for influenza complications had lower baseline function of activities of daily living and greater frailty than patients of the same age who were hospitalized for other causes of acute respiratory illness; in this study, those who survived hospitalization with influenza had significantly higher 30-day post-discharge mortality than those hospitalized without influenza (12.1% versus 6.2%; $P<0.01$)[215]. A study in Singapore reported that the risk of any post-acute diagnosis in patients >30 days after hospitalization for COVID-19 (Omicron variant) was significantly lower than in patients hospitalized for influenza (adjusted hazard ratio 0.82 (95% CI 0.74–0.92; $P<0.001$))[216]. In one study in the USA of older adults at high risk of influenza complications who were hospitalized with influenza, nearly 20% were discharged to a skilled nursing facility, and the 30-day readmission rate was 14%[217]. In this study, all-cause hospital mortality was 5.1% but increased to 9.3% within 30 days of influenza diagnosis. In a Canadian study of adults aged ≥65 years hospitalized with influenza, baseline frailty and increase in frailty were associated with poor recovery after discharge[218]. In another study in the USA of patients hospitalized with influenza over nine seasons, 5.5% died during hospitalization or within 30 days of discharge; 48% of deaths occurred in persons who survived hospitalization at a median of 9 days after discharge, and nearly 60% of the deaths were in persons aged 85 years and older[219]. A study in Austria among hospitalized children reported that there was no significant difference in the duration of hospitalization for COVID-19 versus influenza but the risk of hospital readmission was significantly higher for influenza[220].

Outlook

An important research priority for the coming years should be the development of more effective, long-lasting and broadly protective influenza vaccines, the development of which may require a better understanding of mucosal immunity. Other areas of priority are the development of antiviral treatments and other therapies, such as immunomodulators, that are effective during the late stages of infection, a better understanding of the antigenic evolution of human influenza viruses (which may aid the development of longer-lasting vaccines) and of influenza virus transmission among humans with the goal of implementing effective control measures and of influenza virus transmission from animals to humans (to inform interventions to reduce zoonotic transmission), and improving pandemic preparedness and response.

Vaccine development

The current seasonal influenza vaccines, which are reformulated annually, typically offer an effectiveness that is lower than desired[221]. This limited protection is in part owing to the virus's propensity for antigenic drift and the resulting difficulty in predicting which viral strains will dominate upcoming influenza seasons. Here, future research is expected to continue identifying and targeting highly conserved regions of the influenza virus such as the HA stalk domain[222]. The NA protein has also been investigated as a vaccine antigen[223,224] and future research is anticipated to test it as a second vaccine component in combination with HA. While the antibody titre measured by the haemagglutination inhibition assay is an established correlate of protection for inactivated influenza vaccines[225], this marker does not fully explain the protection conferred by vaccination, and other immune mechanisms are likely to be involved[226]. Several studies have associated protection with measures of antibodies against NA and antibodies against the conserved stalk region of the HA protein[227–229] and these markers are promising targets for vaccines. Novel vaccine platforms, such as mRNA vaccines, can present multiple antigens directed against a wider range of influenza subtypes and strains; these may include HAs presenting different subtypes or clades, or combinations of HA and NA, as mentioned above. Recognizing that secretory IgA and T cell and B cell immune responses are involved in protection against influenza virus infection[230–232], intranasal or inhaled vaccines which promote mucosal

immunity could also provide broader and more durable protection against infection[233]. Collectively, these approaches represent a substantial paradigm shift from the strain-specific, HA-targeted vaccines that are in use today.

It is now well established that prior exposure to influenza virus antigens shapes future immune responses. A key to the development of more efficacious, longer-lasting and broadly protective influenza vaccines will provide a better understanding of the effect of imprinting on B cell and T cell responses to infection and vaccination. Serological studies, the analysis of B cell and T cell populations, and the characterization of monoclonal antibodies from individuals with infection and/or who are vaccinated[234] are expected to shed light on the magnitude, kinetics and specificities of immune responses to influenza viruses.

In recognition of the need for improved influenza vaccines, the US National Institute of Allergy and Infectious Diseases funds several major programmes aimed at better understanding immunity to influenza exposure and developing next-generation influenza vaccines, including the Collaborative Influenza Vaccine Innovation Centers (www.niaidcivics.org), the Vaccine and Treatment Evaluation Units (https://www.niaid.nih.gov/research/vaccine-treatment-evaluation-units-services), and the Dissection of Influenza Vaccination and Infection for Childhood Immunity[235] programme, which investigates how initial encounters with influenza viruses shape lifelong immunity.

Mucosal immunity

Influenza vaccines that are administered intramuscularly primarily induce a systemic immune response characterized by the production of circulating antibodies. While these antibodies can neutralize the virus and prevent severe disease, they are less effective at preventing infection in the upper respiratory tract, which would require robust mucosal immunity with the production of secretory IgA antibodies that neutralize the virus. A better understanding of mucosal immunity is thus vital for developing improved vaccines that can block transmission. Live attenuated influenza virus vaccines were developed to induce both mucosal and humoral immunity and are licensed in some countries. Research in this area also involves developing new adjuvants and delivery systems that can effectively stimulate mucosal immune cells without causing inflammation or other adverse effects[236].

Virus transmission

Understanding the human-to-human transmission of seasonal influenza viruses is crucial for public health. These viruses spread primarily through respiratory droplets from coughing, sneezing, talking or breathing, while fomites also contribute to virus spread. However, a detailed understanding of the biophysical properties of influenza virus transmission among humans is still lacking. Such data will be important for public health to develop efficient intervention strategies.

An even less understood but equally important aspect is the avian-to-human transmission of potentially pandemic influenza viruses. Although an area of active research, the genetic and molecular determinants that enable these viruses to infect humans and adapt to them are still incompletely understood.

Global disease burden

Reducing the marked global disparities in influenza burden remains a crucial priority for the coming decade. Excess deaths and increased case–fatality ratios stem from very low seasonal vaccination coverage, an increased prevalence of comorbidities, health challenges, including malnutrition, HIV infection and indoor air pollution, more frequent bacterial co-infections, and limited access to timely diagnosis, antiviral treatments, oxygen and intensive care for those with severe disease. Although seasonal influenza vaccine manufacturing capacity has increased substantially since 2006, estimated global production capacity has been relatively unchanged since 2013, and nearly all vaccine production facilities are in high-income and upper-middle-income countries[237]. Governments in low-income and middle-income countries, in partnership with international organizations, including the WHO and Gavi, should prioritize integration of influenza vaccination into routine childhood and maternal immunization programmes, with targeted strategies to reach groups at high risk, such as young children, pregnant individuals, older adults and people with chronic medical conditions[238,239]. Concurrent investments are needed to strengthen laboratory and surveillance capacity, expand access to affordable point-of-care diagnostics and antivirals, improve critical care infrastructure and train frontline healthcare workers. Doctors, public health professionals and national programmes can drive progress through advocacy, context-specific operational research on local epidemiology and influenza vaccine effectiveness, community engagement to increase uptake, and integration of influenza prevention and control with broader respiratory disease and pandemic preparedness efforts. International collaboration to ensure fair technology transfer, sustainable financing, and development of thermostable or otherwise low-income and middle-income country-appropriate influenza vaccines and availability will be essential to narrow these preventable gaps and reduce the overall global burden of influenza.

In summary, research over the next decade is expected to focus on the development of more effective influenza vaccines and improving prevention and control of seasonal influenza worldwide, which will also strengthen pandemic preparedness and response.

Published online: 06 August 2026

References

1. Reid, A. H., Fanning, T. G., Hultin, J. V. & Taubenberger, J. K. Origin and evolution of the 1918 "Spanish" influenza virus hemagglutinin gene. *Proc. Natl Acad. Sci. USA* **96**, 1651–1656 (1999).
2. Taubenberger, J. K., Reid, A. H., Krafft, A. E., Bijwaard, K. E. & Fanning, T. G. Initial genetic characterization of the 1918 "Spanish" influenza virus. *Science* **275**, 1793–1796 (1997).
3. Kawaoka, Y., Krauss, S. & Webster, R. G. Avian-to-human transmission of the PB1 gene of influenza A viruses in the 1957 and 1968 pandemics. *J. Virol.* **63**, 4603–4608 (1989).
4. Scholtissek, C., Rohde, W., Von Hoyningen, V. & Rott, R. On the origin of the human influenza virus subtypes H2N2 and H3N2. *Virology* **87**, 13–20 (1978).
5. Novel Swine-Origin Influenza A (H1N1) Virus Investigation Team et al. Emergence of a novel swine-origin influenza A (H1N1) virus in humans. *N. Engl. J. Med.* **360**, 2605–2615 (2009).
6. Garten, R. J. et al. Antigenic and genetic characteristics of swine-origin 2009 A(H1N1) influenza viruses circulating in humans. *Science* **325**, 197–201 (2009).
7. Smith, G. J. et al. Origins and evolutionary genomics of the 2009 swine-origin H1N1 influenza A epidemic. *Nature* **459**, 1122–1125 (2009).
8. Webby, R. J. & Uyeki, T. M. An update on highly pathogenic avian influenza A(H5N1) virus, clade 2.3.4.4b. *J. Infect. Dis.* **230**, 533–542 (2024).
9. Peacock, T. P. et al. The global H5N1 influenza panzootic in mammals. *Nature* **637**, 304–313 (2025).
10. Somes, M. P., Turner, R. M., Dwyer, L. J. & Newall, A. T. Estimating the annual attack rate of seasonal influenza among unvaccinated individuals: a systematic review and meta-analysis. *Vaccine* **36**, 3199–3207 (2018).
11. Hayward, A. C. et al. Comparative community burden and severity of seasonal and pandemic influenza: results of the Flu Watch cohort study. *Lancet Respir. Med.* **2**, 445–454 (2014).
12. de Courville, C., Cadarette, S. M., Wissinger, E. & Alvarez, F. P. The economic burden of influenza among adults aged 18 to 64: a systematic literature review. *Influenza Other Respir. Viruses* **16**, 376–385 (2022).
13. Putri, W., Muscatello, D. J., Stockwell, M. S. & Newall, A. T. Economic burden of seasonal influenza in the United States. *Vaccine* **36**, 3960–3966 (2018).
14. Iuliano, A. D. et al. Estimates of global seasonal influenza-associated respiratory mortality: a modelling study. *Lancet* **391**, 1285–1300 (2018).

15. Leung, N. H. L. Transmissibility and transmission of respiratory viruses. *Nat. Rev. Microbiol.* **19**, 528–545 (2021).
16. Biggerstaff, M., Cauchemez, S., Reed, C., Gambhir, M. & Finelli, L. Estimates of the reproduction number for seasonal, pandemic, and zoonotic influenza: a systematic review of the literature. *BMC Infect. Dis.* **14**, 480 (2014).
17. Lessler, J. et al. Incubation periods of acute respiratory viral infections: a systematic review. *Lancet Infect. Dis.* **9**, 291–300 (2009).
18. Cohen, C. et al. Asymptomatic transmission and high community burden of seasonal influenza in an urban and a rural community in South Africa, 2017–18 (PHIRST): a population cohort study. *Lancet Glob. Health* **9**, e863–e874 (2021).
19. Worby, C. J. et al. On the relative role of different age groups in influenza epidemics. *Epidemics* **13**, 10–16 (2015).
20. Sakleshpur, S. & Steed, A. L. Influenza: toward understanding the immune response in the young. *Front. Pediatr.* **10**, 953150 (2022).
21. Zhao, Y. et al. Antivirals for post-exposure prophylaxis of influenza: a systematic review and network meta-analysis. *Lancet* **404**, 764–772 (2024).
22. Hayden, F. G. et al. Reducing influenza virus transmission: the potential value of antiviral treatment. *Clin. Infect. Dis.* **74**, 532–540 (2022).
23. Monto, A. S. et al. Efficacy of baloxavir treatment in preventing transmission of influenza. *N. Engl. J. Med.* **392**, 1582–1593 (2025).
24. Tang, J. W. et al. Where have all the viruses gone? Disappearance of seasonal respiratory viruses during the COVID-19 pandemic. *J. Med. Virol.* **93**, 4099–4101 (2021).
25. Del Riccio, M. et al. Post-disappearance scenarios: policy implications following the potential disappearance of B/Yamagata lineage influenza viruses. *Eurosurveillance* **29**, 2400196 (2024).
26. Tamerius, J. et al. Global influenza seasonality: reconciling patterns across temperate and tropical regions. *Environ. Health Perspect.* **119**, 439–445 (2011).
27. Mertz, D. et al. Pregnancy as a risk factor for severe influenza infection: an individual participant data meta-analysis. *BMC Infect. Dis.* **19**, 683 (2019).
28. Wang, X. et al. Global burden of respiratory infections associated with seasonal influenza in children under 5 years in 2018: a systematic review and modelling study. *Lancet Glob. Health* **8**, e497–e510 (2020).
29. Nair, H. et al. Global burden of respiratory infections due to seasonal influenza in young children: a systematic review and meta-analysis. *Lancet* **378**, 1917–1930 (2011).
30. Nayak, J., Hoy, G. & Gordon, A. Influenza in children. *Cold Spring Harb. Perspect. Med.* **11**, a038430 (2021).
31. Spinardi, J. R., Thakkar, K. B., Welch, V. L., Jagun, O. & Kyaw, M. H. The need for novel influenza vaccines in low- and middle-income countries: a narrative review. *Braz. J. Infect. Dis.* **29**, 104465 (2025).
32. Olsen, B. R. et al. Global patterns of influenza A virus in wild birds. *Science* **312**, 384–388 (2006).
33. Nelson, M. I. et al. Global migration of influenza A viruses in swine. *Nat. Commun.* **6**, 6696 (2015).
34. Tong, S. et al. New world bats harbor diverse influenza A viruses. *PLoS Pathog.* **9**, e1003657 (2013).
35. Tong, S. et al. A distinct lineage of influenza A virus from bats. *Proc. Natl Acad. Sci. USA* **109**, 4269–4274 (2012).
36. World Organisation for Animal Health. *Manual of Diagnostic Tests and Vaccines for Terrestrial Animals* Ch. 3.3.4 https://www.woah.org/fileadmin/Home/eng/Health_standards/tahm/3.03.04_AI.pdf (WOAH, 2021).
37. Shi, J., Zeng, X., Cui, P., Yan, C. & Chen, H. Alarming situation of emerging H5 and H7 avian influenza and effective control strategies. *Emerg. Microbes Infect.* **12**, 2155072 (2023).
38. Tian, J. et al. Highly pathogenic avian influenza virus (H5N1) clade 2.3.4.4b introduced by wild birds, China, 2021. *Emerg. Infect. Dis.* **29**, 1367–1375 (2023).
39. Lewis, N. S. et al. Emergence and spread of novel H5N8, H5N5 and H5N1 clade 2.3.4.4 highly pathogenic avian influenza in 2020. *Emerg. Microbes Infect.* **10**, 148–151 (2021).
40. Food and Agricultural Organization of the United Nations. *Empres-i +* (FAO, 2024); http://empres-i.apps.fao.org/diseases.
41. Gu, W. et al. Novel H5N6 reassortants bearing the clade 2.3.4.4b HA gene of H5N8 virus have been detected in poultry and caused multiple human infections in China. *Emerg. Microbes Infect.* **11**, 1174–1185 (2022).
42. Cui, Y. et al. Evolution and extensive reassortment of H5 influenza viruses isolated from wild birds in China over the past decade. *Emerg. Microbes Infect.* **9**, 1793–1803 (2020).
43. Mostafa, A., Nogales, A. & Martinez-Sobrido, L. Highly pathogenic avian influenza H5N1 in the United States: recent incursions and spillover to cattle. *npj Viruses* **3**, 54 (2025).
44. Caserta, L. C. et al. Spillover of highly pathogenic avian influenza H5N1 virus to dairy cattle. *Nature* **634**, 669–676 (2024).
45. Shi, J. et al. H5N1 virus invades the mammary glands of dairy cattle through 'mouth-to-teat' transmission. *Natl Sci. Rev.* **12**, nwaf262 (2025).
46. Guinat, C. et al. Promising effects of duck vaccination against highly pathogenic avian influenza, France, 2023–2024. *Emerg. Infect. Dis.* **31**, 1468–1471 (2025).
47. Stokstad, E. Wrestling with bird flu, Europe considers once-taboo vaccines. *Science* **376**, 682–683 (2022).
48. Wille, M. & Barr, I. G. Resurgence of avian influenza virus. *Science* **376**, 459–460 (2022).
49. Cohen, J. Bird shots. *Science* **380**, 24–27 (2023).
50. Department for Environment, Food and Rural Affairs. New avian influenza vaccine trials begin in UK. *gov.uk* https://www.gov.uk/government/news/new-avian-influenza-vaccine-trials-begin-in-uk (2026).
51. Hinshaw, V. S., Webster, R. G. & Turner, B. Water-borne transmission of influenza A viruses? *Intervirology* **11**, 66–68 (1979).
52. Slemons, R. & Easterday, B. in *Wildlife Diseases* (ed. Page, L. A.) 215–224 (Springer, 1976).
53. Creager, H. M. et al. Infection and replication of influenza virus at the ocular surface. *J. Virol.* **92**, e02192-17 (2018).
54. Bullock, T. A. et al. The (digestive) path less traveled: influenza A virus and the gastrointestinal tract. *mBio* **16**, e01017-25 (2025).
55. Rogers, G. N. & Paulson, J. C. Receptor determinants of human and animal influenza virus isolates: differences in receptor specificity of the H3 hemagglutinin based on species of origin. *Virology* **127**, 361–373 (1983).
56. Baum, L. G. & Paulson, J. C. Sialyloligosaccharides of the respiratory epithelium in the selection of human influenza virus receptor specificity. *Acta Histochem. Suppl.* **40**, 35–38 (1990).
57. Thompson, A. J., de Vries, R. P. & Paulson, J. C. Virus recognition of glycan receptors. *Curr. Opin. Virol.* **34**, 117–129 (2019).
58. Karakus, U. et al. H19 influenza A virus exhibits species-specific MHC class II receptor usage. *Cell Host Microbe* **32**, 1089–1102.e10 (2024).
59. Karakus, U. et al. MHC class II proteins mediate cross-species entry of bat influenza viruses. *Nature* **567**, 109–112 (2019).
60. Karakus, U. et al. MHC class II proteins mediate sialic acid independent entry of human and avian H2N2 influenza A viruses. *Nat. Microbiol.* **9**, 2626–2641 (2024).
61. Cardenas, M. et al. MHC class II functions as a host-specific entry receptor for representative human and swine H3N2 influenza A viruses. *Nat. Commun.* **17**, 2560 (2026).
62. Bottcher-Friebertshauser, E., Klenk, H. D. & Garten, W. Activation of influenza viruses by proteases from host cells and bacteria in the human airway epithelium. *Pathog. Dis.* **69**, 87–100 (2013).
63. Pinto, L. H., Holsinger, L. J. & Lamb, R. A. Influenza-virus M2 protein has ion channel activity. *Cell* **69**, 517–528 (1992).
64. Schnell, J. R. & Chou, J. J. Structure and mechanism of the M2 proton channel of influenza A virus. *Nature* **451**, 591–595 (2008).
65. Plotch, S. J., Bouloy, M., Ulmanen, I. & Krug, R. M. A unique Cap(M7gpppxm)-dependent influenza virion endonuclease cleaves capped RNAs to generate the primers that initiate viral-RNA transcription. *Cell* **23**, 847–858 (1981).
66. Lamb, R. A. & Lai, C. J. Conservation of the influenza virus membrane protein (M1) amino acid sequence and an open reading frame of RNA segment 7 encoding a second protein (M2) in H1N1 and H3N2 strains. *Virology* **112**, 746–751 (1981).
67. Long, J. S. et al. Species difference in ANP32A underlies influenza A virus polymerase host restriction. *Nature* **529**, 101–104 (2016).
68. Carrique, L. et al. Host ANP32A mediates the assembly of the influenza virus replicase. *Nature* **587**, 638–643 (2020).
69. Bi, Z. Adaptation differences and mechanisms of influenza viruses to ANP32 proteins across species. *J. Virol.* **100**, e0190025 (2026).
70. Neumann, G., Hughes, M. T. & Kawaoka, Y. Influenza A virus NS2 protein mediates vRNP nuclear export through NES-independent interaction with hCRM1. *EMBO J.* **19**, 6751–6758 (2000).
71. Martin, K. & Helenius, A. Nuclear transport of influenza virus ribonucleoproteins: the viral matrix protein (M1) promotes export and inhibits import. *Cell* **67**, 117–130 (1991).
72. Amorim, M. J. et al. A Rab11- and microtubule-dependent mechanism for cytoplasmic transport of influenza A virus viral RNA. *J. Virol.* **85**, 4143–4156 (2011).
73. Palese, P., Tobita, K., Ueda, M. & Compans, R. W. Characterization of temperature sensitive influenza virus mutants defective in neuraminidase. *Virology* **61**, 397–410 (1974).
74. Garcia-Sastre, A. et al. Influenza A virus lacking the NS1 gene replicates in interferon-deficient systems. *Virology* **252**, 324–330 (1998).
75. Jagger, B. W. et al. An overlapping protein-coding region in influenza A virus segment 3 modulates the host response. *Science* **337**, 199–204 (2012).
76. Chen, W. et al. A novel influenza A virus mitochondrial protein that induces cell death. *Nat. Med.* **7**, 1306–1312 (2001).
77. Te Velthuis, A. J. W., Grimes, J. M. & Fodor, E. Structural insights into RNA polymerases of negative-sense RNA viruses. *Nat. Rev. Microbiol.* **19**, 303–318 (2021).
78. Bellido-Martin, B. et al. Evolution, spread and impact of highly pathogenic H5 avian influenza A viruses. *Nat. Rev. Microbiol.* **24**, 45–60 (2026).
79. Yamada, S. et al. Haemagglutinin mutations responsible for the binding of H5N1 influenza A viruses to human-type receptors. *Nature* **444**, 378–382 (2006).
80. Shinya, K. et al. Avian flu: influenza virus receptors in the human airway. *Nature* **440**, 435–436 (2006).
81. de Vries, E., Du, W., Guo, H. & de Haan, C. A. M. Influenza A virus hemagglutinin-neuraminidase-receptor balance: preserving virus motility. *Trends Microbiol.* **28**, 57–67 (2020).
82. Russell, C. J. Acid-induced membrane fusion by the hemagglutinin protein and its role in influenza virus biology. *Curr. Top. Microbiol. Immunol.* **385**, 93–116 (2014).
83. Zimmermann, P., Manz, B., Haller, O., Schwemmle, M. & Kochs, G. The viral nucleoprotein determines Mx sensitivity of influenza A viruses. *J. Virol.* **85**, 8133–8140 (2011).
84. Pinto, R. M. et al. BTN3A3 evasion promotes the zoonotic potential of influenza A viruses. *Nature* **619**, 338–347 (2023).
85. Palese, P. & Wang, T. T. Why do influenza virus subtypes die out? A hypothesis. *mBio* **2**, e00150-11 (2011).

86. Kendal, A. P., Noble, G. R., Skehel, J. J. & Dowdle, W. R. Antigenic similarity of influenza A (H1N1) viruses from epidemics in 1977–1978 to "Scandinavian" strains isolated in epidemics of 1950–1951. *Virology* **89**, 632–636 (1978).
87. Smith, D. J. et al. Mapping the antigenic and genetic evolution of influenza virus. *Science* **305**, 371–376 (2004).
88. Koel, B. F. et al. Substitutions near the receptor binding site determine major antigenic change during influenza virus evolution. *Science* **342**, 976–979 (2013).
89. Miller, J. et al. Report on influenza viruses received and tested by the Melbourne WHO Collaborating Centre for Reference and Research on Influenza during 2024. *Commun. Dis. Intell.* **50**, https://doi.org/10.33321/cdi.2026.50.014 (2026).
90. Sheng, Y. H. & Hasnain, S. Z. Mucus and mucins: the underappreciated host defence system. *Front. Cell Infect. Microbiol.* **12**, 856962 (2022).
91. Zanin, M., Baviskar, P., Webster, R. & Webby, R. The interaction between respiratory pathogens and mucus. *Cell Host Microbe* **19**, 159–168 (2016).
92. Vahey, M. D. & Fletcher, D. A. Influenza A virus surface proteins are organized to help penetrate host mucus. *eLife* **8**, e43764 (2019).
93. Reading, P. C., Tate, M. D., Pickett, D. L. & Brooks, A. G. Glycosylation as a target for recognition of influenza viruses by the innate immune system. *Adv. Exp. Med. Biol.* **598**, 279–292 (2007).
94. Long, J. S., Mistry, B., Haslam, S. M. & Barclay, W. S. Host and viral determinants of influenza A virus species specificity. *Nat. Rev. Microbiol.* **17**, 67–81 (2019).
95. Villalon-Letelier, F., Brooks, A. G., Saunders, P. M., Londrigan, S. L. & Reading, P. C. Host cell restriction factors that limit influenza A infection. *Viruses* **9**, 376 (2017).
96. Iwasaki, A. & Pillai, P. S. Innate immunity to influenza virus infection. *Nat. Rev. Immunol.* **14**, 315–328 (2014).
97. Pichlmair, A. et al. RIG-I-mediated antiviral responses to single-stranded RNA bearing 5′-phosphates. *Science* **314**, 997–1001 (2006).
98. Diebold, S. S., Kaisho, T., Hemmi, H., Akira, S. & Reis e Sousa, C. Innate antiviral responses by means of TLR7-mediated recognition of single-stranded RNA. *Science* **303**, 1529–1531 (2004).
99. Kawai, T., Ikegawa, M., Ori, D. & Akira, S. Decoding Toll-like receptors: recent insights and perspectives in innate immunity. *Immunity* **57**, 649–673 (2024).
100. Liu, G. & Gack, M. U. Distinct and orchestrated functions of RNA sensors in innate immunity. *Immunity* **53**, 26–42 (2020).
101. Schoggins, J. W. Interferon-stimulated genes: what do they all do? *Annu. Rev. Virol.* **6**, 567–584 (2019).
102. Mettelman, R. C. & Thomas, P. G. Human susceptibility to influenza infection and severe disease. *Cold Spring Harb. Perspect. Med.* **11**, a038711 (2021).
103. Langlois, R. A. & Casanova, J. L. The potential impacts of human genetics on virus emergence. *Proc. Natl Acad. Sci. USA* **122**, e2504318122 (2025).
104. Hale, B. G., Randall, R. E., Ortin, J. & Jackson, D. The multifunctional NS1 protein of influenza A viruses. *J. Gen. Virol.* **89**, 2359–2376 (2008).
105. Gack, M. U. et al. Influenza A virus NS1 targets the ubiquitin ligase TRIM25 to evade recognition by the host viral RNA sensor RIG-I. *Cell Host Microbe* **5**, 439–449 (2009).
106. Muñoz-Moreno, R., Martínez-Romero, C. & García-Sastre, A. Induction and evasion of type-I interferon responses during influenza A virus infection. *Cold Spring Harb. Perspect. Med.* **11**, a038414 (2021).
107. Kuriakose, T. & Kanneganti, T. D. Regulation and functions of NLRP3 inflammasome during influenza virus infection. *Mol. Immunol.* **86**, 56–64 (2017).
108. Kandasamy, M. et al. RIG-I signaling is critical for efficient polyfunctional T cell responses during influenza virus infection. *PLoS Pathog.* **12**, e1005754 (2016).
109. Koyama, S. et al. Differential role of TLR- and RLR-signaling in the immune responses to influenza A virus infection and vaccination. *J. Immunol.* **179**, 4711–4720 (2007).
110. Cheung, C. Y. et al. Induction of proinflammatory cytokines in human macrophages by influenza A (H5N1) viruses: a mechanism for the unusual severity of human disease? *Lancet* **360**, 1831–1837 (2002).
111. Tundup, S. et al. Endothelial cell tropism is a determinant of H5N1 pathogenesis in mammalian species. *PLoS Pathog.* **13**, e1006270 (2017).
112. Kandasamy, M., Furlong, K., Perez, J. T., Manicassamy, S. & Manicassamy, B. Suppression of cytotoxic T cell functions and decreased levels of tissue-resident memory T cells during H5N1 infection. *J. Virol.* **94**, e00057-20 (2020).
113. de Jong, M. D. et al. Fatal outcome of human influenza A (H5N1) is associated with high viral load and hypercytokinemia. *Nat. Med.* **12**, 1203–1207 (2006).
114. Helft, J. et al. Cross-presenting CD103$^+$ dendritic cells are protected from influenza virus infection. *J. Clin. Invest.* **122**, 4037–4047 (2012).
115. McGill, J., Van Rooijen, N. & Legge, K. L. Protective influenza-specific CD8 T cell responses require interactions with dendritic cells in the lungs. *J. Exp. Med.* **205**, 1635–1646 (2008).
116. Kim, S. H. et al. Influenza virus-derived CD8 T cell epitopes: implications for the development of universal influenza vaccines. *Immune Netw.* **24**, e19 (2024).
117. Sant, A. J., DiPiazza, A. T., Nayak, J. L., Rattan, A. & Richards, K. A. CD4 T cells in protection from influenza virus: viral antigen specificity and functional potential. *Immunol. Rev.* **284**, 91–105 (2018).
118. Swain, S. L., McKinstry, K. K. & Strutt, T. M. Expanding roles for CD4$^+$ T cells in immunity to viruses. *Nat. Rev. Immunol.* **12**, 136–148 (2012).
119. Ge, X. et al. Assessment of seasonal influenza A virus-specific CD4 T-cell responses to 2009 pandemic H1N1 swine-origin influenza A virus. *J. Virol.* **84**, 3312–3319 (2010).
120. Wilkinson, T. M. et al. Preexisting influenza-specific CD4$^+$ T cells correlate with disease protection against influenza challenge in humans. *Nat. Med.* **18**, 274–280 (2012).
121. Lee, S., Yeung, K. K. & Watts, T. H. Tissue-resident memory T cells in protective immunity to influenza virus. *Curr. Opin. Virol.* **65**, 101397 (2024).
122. Guthmiller, J. J., Utset, H. A. & Wilson, P. C. B cell responses against Influenza Viruses: short-lived humoral immunity against a life-long threat. *Viruses* **13**, 965 (2021).
123. Ueno, H. Tfh cell response in influenza vaccines in humans: what is visible and what is invisible. *Curr. Opin. Immunol.* **59**, 9–14 (2019).
124. Krammer, F. The human antibody response to influenza A virus infection and vaccination. *Nat. Rev. Immunol.* **19**, 383–397 (2019).
125. Graves, P. N., Schulman, J. L., Young, J. F. & Palese, P. Preparation of influenza virus subviral particles lacking the HA1 subunit of hemagglutinin: unmasking of cross-reactive HA2 determinants. *Virology* **126**, 106–116 (1983).
126. Krammer, F. & Palese, P. Universal influenza virus vaccines that target the conserved hemagglutinin stalk and conserved sites in the head domain. *J. Infect. Dis.* **219**, S62–S67 (2019).
127. He, W. et al. Epitope specificity plays a critical role in regulating antibody-dependent cell-mediated cytotoxicity against influenza A virus. *Proc. Natl Acad. Sci. USA* **113**, 11931–11936 (2016).
128. Merckx, J. et al. Diagnostic accuracy of novel and traditional rapid tests for influenza infection compared with reverse transcriptase polymerase chain reaction: a systematic review and meta-analysis. *Ann. Intern. Med.* **167**, 394–409 (2017).
129. Raza, M. A. et al. The peculiar characteristics and advancement in diagnostic methodologies of influenza A virus. *Front. Microbiol.* **15**, 1435384 (2024).
130. Luo, S., Yin, L., Liu, X. & Wang, X. Advances in virus biorecognition and detection techniques for the surveillance and prevention of infectious diseases. *Biosensors* **15**, 198 (2025).
131. Bernasconi, C., Katugampola, L. & Wildum, S. Comparison of influenza viral load in nasopharyngeal and midturbinate swabs. *Influenza Other Respir. Viruses* **18**, e13253 (2024).
132. Ngaosuwankul, N. et al. Influenza A viral loads in respiratory samples collected from patients infected with pandemic H1N1, seasonal H1N1 and H3N2 viruses. *Virol. J.* **7**, 75 (2010).
133. Rello, J. et al. Intensive care adult patients with severe respiratory failure caused by Influenza A (H1N1)v in Spain. *Crit. Care* **13**, R148 (2009).
134. US Food and Drug Administration. Influenza diagnostic tests. *FDA* https://www.fda.gov/medical-devices/in-vitro-diagnostics/influenza-diagnostic-tests (2024).
135. Qian, Q. et al. Advances in diagnostic techniques for influenza virus infection: a comprehensive review. *Trop. Med. Infect. Dis.* **10**, 152 (2025).
136. Chen, J., Qin, Z. & Jia, Z. The application status of sequencing technology in global respiratory infectious disease diagnosis. *Infection* **52**, 2169–2181 (2024).
137. Hsu, W. Y. et al. Performance of a hybrid capture-based target enrichment next-generation sequencing for the identification of respiratory pathogens and resistance-associated genes in patients with severe pneumonia. *Microbiol. Spectr.* **13**, e0213024 (2025).
138. World Health Organization. Global influenza programme. *WHO* https://go.nature.com/4vTFcMC (2025).
139. Hay, A. J. & McCauley, J. W. The WHO global influenza surveillance and response system (GISRS) — a future perspective. *Influenza Other Respir. Viruses* **12**, 551–557 (2018).
140. World Health Organization. Global Influenza Surveillance and Response System (GISRS). *WHO* https://www.who.int/initiatives/global-influenza-surveillance-and-response-system (2026).
141. Kim, Y. I. et al. PB2 and NP of North American H5N1 virus drive immune cell replication and systemic infections. *Sci. Adv.* **11**, eady1208 (2025).
142. Pulit-Penaloza, J. A. et al. Advancing A(H5N1) influenza risk assessment in ferrets through comparative evaluation of airborne virus shedding patterns. *Nat. Commun.* **17**, 2266 (2026).
143. Kim, H., Webster, R. G. & Webby, R. J. Influenza virus: dealing with a drifting and shifting pathogen. *Viral Immunol.* **31**, 174–183 (2018).
144. Taaffe, J. et al. Advancing influenza vaccines: a review of next-generation candidates and their potential for global health impact. *Vaccine* **42**, 126408 (2024).
145. Mesle, M. M. I. et al. Influenza vaccine recommendations and coverage (2018–2023): a foundation for pandemic preparedness and response. *Vaccine* **78**, 128391 (2026).
146. Osterholm, M. T., Kelley, N. S., Sommer, A. & Belongia, E. A. Efficacy and effectiveness of influenza vaccines: a systematic review and meta-analysis. *Lancet Infect. Dis.* **12**, 36–44 (2012).
147. Stuurman, A. L. et al. Real-world effectiveness of live attenuated influenza vaccines (LAIV) and inactivated influenza vaccines (IIV) in children from 2003 to 2023: a systematic literature review and network meta-analysis. *Expert Rev. Vaccines* **24**, 703–725 (2025).
148. Ko, E. J. & Kang, S. M. Immunology and efficacy of MF59-adjuvanted vaccines. *Hum. Vaccin. Immunother.* **14**, 3041–3045 (2018).
149. Rostad, C. A. et al. A phase 2 clinical trial to evaluate the safety, reactogenicity, and immunogenicity of different prime-boost vaccination schedules of 2013 and 2017 A(H7N9) inactivated influenza virus vaccines administered with and without AS03 adjuvant in healthy US adults. *Clin. Infect. Dis.* **78**, 1757–1768 (2024).
150. DiazGranados, C. A. et al. Efficacy of high-dose versus standard-dose influenza vaccine in older adults. *N. Engl. J. Med.* **371**, 635–645 (2014).
151. Zinnecker, T., Reichl, U. & Genzel, Y. Innovations in cell culture-based influenza vaccine manufacturing — from static cultures to high cell density cultivations. *Hum. Vaccines Immunother.* **20**, 2373521 (2024).

152. Cox, M. M., Izikson, R., Post, P. & Dunkle, L. Safety, efficacy, and immunogenicity of Flublok in the prevention of seasonal influenza in adults. *Ther. Adv. Vaccines* **3**, 97–108 (2015).
153. Coleman, B. L., Gutmanis, I., McGovern, I. & Haag, M. Effectiveness of cell-based quadrivalent seasonal influenza vaccine: a systematic review and meta-analysis. *Vaccines* **11**, 1607 (2023).
154. Tenforde, M. W. et al. Effectiveness of mRNA vaccination in preventing COVID-19-associated invasive mechanical ventilation and death — United States, March 2021–January 2022. *Morb. Mortal. Wkly Rep.* **71**, 459–465 (2022).
155. Rahmani, K. et al. The effectiveness of COVID-19 vaccines in reducing the incidence, hospitalization, and mortality from COVID-19: a systematic review and meta-analysis. *Front. Public Health* **10**, 873596 (2022).
156. Wong, B. K. & Mabbott, N. A. Systematic review and meta-analysis of COVID-19 mRNA vaccine effectiveness against hospitalizations in adults. *Immunother. Adv.* **4**, ltae011 (2024).
157. El Sahly, H. M. et al. Efficacy of the mRNA-1273 SARS-CoV-2 vaccine at completion of blinded phase. *N. Engl. J. Med.* **385**, 1774–1785 (2021).
158. Li, S., Zheng, L., Zhong, J. & Gao, X. Advancing mRNA vaccines for infectious diseases: key components, innovations, and clinical progress. *Essays Biochem.* **69**, EBC20253009 (2025).
159. European Commission Directorate-General for Health & Food Safety. Commission authorises first combined COVID-19 and influenza vaccine for people 50 years and older. *European Commission* https://ec.europa.eu/newsroom/sante/items/933339/en (22 April 2026).
160. Arevalo, C. P. et al. A multivalent nucleoside-modified mRNA vaccine against all known influenza virus subtypes. *Science* **378**, 899–904 (2022).
161. Soens, M. et al. A phase 3 randomized safety and immunogenicity trial of mRNA-1010 seasonal influenza vaccine in adults. *Vaccine* **50**, 126847 (2025).
162. Leroux-Roels, I. et al. Efficacy and safety of an mRNA seasonal influenza vaccine in adults. *N. Engl. J. Med.* **394**, 1803–1813 (2026).
163. Casmil, I. C. et al. The advent of clinical self-amplifying RNA vaccines. *Mol. Ther.* **33**, 2565–2582 (2025).
164. Ostrowsky, J. T. et al. Accomplishments and challenges in developing improved influenza vaccines: an evaluation of three years of progress toward the milestones of the influenza vaccines research and development roadmap. *Vaccine* **61**, 127431 (2025).
165. Falsey, A. R., Baran, A. & Walsh, E. E. Should clinical case definitions of influenza in hospitalized older adults include fever. *Influenza Other Respir. Viruses* **9**, 23–29 (2015).
166. Centers for Disease Control and Prevention. People at increased risk for flu complications. *CDC* https://www.cdc.gov/flu/highrisk/index.htm (2024).
167. Garg, S. et al. Pneumonia among adults hospitalized with laboratory-confirmed seasonal influenza virus infection — United States, 2005–2008. *BMC Infect. Dis.* **15**, 369 (2015).
168. Menis, A. A. et al. The effect on mortality of bacterial co-infections on critically ill patients with community-acquired COVID-19 and influenza pneumonia: a systematic review. *Viruses* **17**, 851 (2025).
169. Uyeki, T. M. et al. Clinical practice guidelines by the Infectious Diseases Society of America: 2018 update on diagnosis, treatment, chemoprophylaxis, and institutional outbreak management of seasonal influenzaa. *Clin. Infect. Dis.* **68**, e1–e47 (2019).
170. Swets, M. C. et al. SARS-CoV-2 co-infection with influenza viruses, respiratory syncytial virus, or adenoviruses. *Lancet* **399**, 1463–1464 (2022).
171. Adams, K. et al. Prevalence of SARS-CoV-2 and influenza coinfection and clinical characteristics among children and adolescents aged <18 years who were hospitalized or died with influenza — United States, 2021–22 influenza season. *Morb. Mortal. Wkly Rep.* **71**, 1589–1596 (2022).
172. Ison, M. G. Influenza prevention and treatment in transplant recipients and immunocompromised hosts. *Influenza Other Respir. Viruses* **7**, 60–66 (2013).
173. Memoli, M. J. et al. The natural history of influenza infection in the severely immunocompromised vs nonimmunocompromised hosts. *Clin. Infect. Dis.* **58**, 214–224 (2014).
174. Rice, T. W. et al. Critical illness from 2009 pandemic influenza A virus and bacterial coinfection in the United States. *Crit. Care Med.* **40**, 1487–1498 (2012).
175. Beck-Friis, J. et al. Intensive care unit-acquired infections more common in patients with COVID-19 than with influenza. *Sci. Rep.* **14**, 16655 (2024).
176. Wang, C. C. et al. Airborne transmission of respiratory viruses. *Science* **373**, eabd9149 (2021).
177. Centers for Disease Control and Prevention. Infection prevention and control strategies for seasonal influenza in healthcare settings. *CDC* https://www.cdc.gov/flu/hcp/infection-control/healthcare-settings.html (2025).
178. Centers for Disease Control and Prevention. Influenza antiviral medications: summary for clinicians. *CDC* https://www.cdc.gov/flu/hcp/antivirals/summary-clinicians.html (2023).
179. Hayden, F. G. et al. Baloxavir marboxil for uncomplicated influenza in adults and adolescents. *N. Engl. J. Med.* **379**, 913–923 (2018).
180. Ison, M. G. et al. Early treatment with baloxavir marboxil in high-risk adolescent and adult outpatients with uncomplicated influenza (CAPSTONE-2): a randomised, placebo-controlled, phase 3 trial. *Lancet Infect. Dis.* **20**, 1204–1214 (2020).
181. Malosh, R. E. et al. Efficacy and safety of oseltamivir in children: systematic review and individual patient data meta-analysis of randomized controlled trials. *Clin. Infect. Dis.* **66**, 1492–1500 (2018).
182. Dobson, J., Whitley, R. J., Pocock, S. & Monto, A. S. Oseltamivir treatment for influenza in adults: a meta-analysis of randomised controlled trials. *Lancet* **385**, 1729–1737 (2015).
183. Gao, Y. et al. Antivirals for treatment of severe influenza: a systematic review and network meta-analysis of randomised controlled trials. *Lancet* **404**, 753–763 (2024).
184. RECOVERY. *RECOVERY Trial Protocol* https://www.recoverytrial.net/files/recovery-protocol-v27-0-2023-09-13.pdf (RECOVERY, 2023).
185. REMAP-CAP. Current protocol documents. *REMAP-CAP* https://www.remapcap.org/protocol-documents (2025).
186. Tenforde, M. W. et al. Timing of influenza antiviral therapy and risk of death in adults hospitalized with influenza-associated pneumonia, Influenza Hospitalization Surveillance Network (FluSurv-NET), 2012–2019. *Clin. Infect. Dis.* **80**, 461–468 (2025).
187. Katzen, J., Kohn, R., Houk, J. L. & Ison, M. G. Early oseltamivir after hospital admission is associated with shortened hospitalization: a 5-year analysis of oseltamivir timing and clinical outcomes. *Clin. Infect. Dis.* **69**, 52–58 (2019).
188. World Health Organization. *Clinical Practice Guidelines for Influenza* https://www.who.int/publications/i/item/9789240097759 (WHO, 2024).
189. REMAP-CAP. REMAP-CAP results: oseltamivir for critically ill patients with influenza infection: information for healthcare professionals. *REMAP-CAP* https://remapcap.org/oseltamivir-clinician-faqs (2026).
190. Yan, M., Gu, X., Wang, Y. & Cao, B. Effects of baloxavir marboxil plus neuraminidase inhibitor vs neuraminidase inhibitor in high-risk patients hospitalized with severe influenza: a post hoc analysis of the flagstone trial. *Open Forum Infect. Dis.* **12**, ofaf439 (2025).
191. US National Library of Medicine. *ClinicalTrials.gov* https://clinicaltrials.gov/study/NCT07159763 (2026).
192. Silverman, A. et al. Influenza-associated acute necrotizing encephalopathy in US children. *JAMA* **334**, 692–701 (2025).
193. Lansbury, L., Rodrigo, C., Leonardi-Bee, J., Nguyen-Van-Tam, J. & Lim, W. S. Corticosteroids as adjunctive therapy in the treatment of influenza. *Cochrane Database Syst. Rev.* **2**, CD010406 (2019).
194. Lim, V. W., Tudor Car, L., Leo, Y. S., Chen, M. I. & Young, B. Passive immune therapy and other immunomodulatory agents for the treatment of severe influenza: systematic review and meta-analysis. *Influenza Other Respir. Viruses* **14**, 226–236 (2020).
195. Uyeki, T. M. & Peiris, M. Novel avian influenza a virus infections of humans. *Infect. Dis. Clin. N. Am.* **33**, 907–932 (2019).
196. Zhou, L. et al. Risk factors for human illness with avian influenza A (H5N1) virus infection in China. *J. Infect. Dis.* **199**, 1726–1734 (2009).
197. Zhou, L. et al. Risk factors for influenza A(H7N9) disease in China, a matched case control study, October 2014 to April 2015. *Open Forum Infect. Dis.* **3**, ofw182 (2016).
198. Rolfes, M. A. et al. Human infections with highly pathogenic avian influenza A(H5N1) viruses in the United States from March 2024 to May 2025. *Nat. Med.* **31**, 3889–3898 https://doi.org/10.1038/s41591-025-03905-2 (2025).
199. Wang, H. et al. Probable limited person-to-person transmission of highly pathogenic avian influenza A (H5N1) virus in China. *Lancet* **371**, 1427–1434 (2008).
200. Ungchusak, K. et al. Probable person-to-person transmission of avian influenza A (H5N1). *N. Engl. J. Med.* **352**, 333–340 (2005).
201. Chen, H. et al. Nosocomial co-transmission of avian influenza A(H7N9) and A(H1N1) pdm09 Viruses between 2 patients with hematologic disorders. *Emerg. Infect. Dis.* **22**, 598–607 (2016).
202. Fang, C. F. et al. Nosocomial transmission of avian influenza A (H7N9) virus in China: epidemiological investigation. *BMJ* **351**, h5765 (2015).
203. Jhung, M. A. et al. Outbreak of variant influenza A(H3N2) virus in the United States. *Clin. Infect. Dis.* **57**, 1703–1712 (2013).
204. Fraaij, P. L. et al. Severe acute respiratory infection caused by swine influenza virus in a child necessitating extracorporeal membrane oxygenation (ECMO), the Netherlands, October 2016. *Eurosurveillance* **21**, 30416 (2016).
205. Rovida, F. et al. Swine influenza A (H1N1) virus (SIV) infection requiring extracorporeal life support in an immunocompetent adult patient with indirect exposure to pigs, Italy, October 2016. *Eurosurveillance* **22**, 30456 (2017).
206. Centers for Disease Control and Prevention. Interim guidance for infection control within healthcare settings when caring for confirmed cases, probable cases, and cases under investigation for infection with novel influenza A viruses associated with severe disease. *CDC* https://www.cdc.gov/bird-flu/hcp/novel-flu-infection-control/index.html (2022).
207. Uyeki, T. M. & Belser, J. A. Antivirals for novel influenza a virus infections. *J. Infect. Dis.* **232**, S191–S209 (2025).
208. de Jong, M. D. et al. Oseltamivir resistance during treatment of influenza A (H5N1) infection. *N. Engl. J. Med.* **353**, 2667–2672 (2005).
209. Jassem, A. N. et al. Critical illness in an adolescent with influenza A(H5N1) virus infection. *N. Engl. J. Med.* **392**, 927–929 (2025).
210. Guan, W. et al. Baloxavir marboxil use for critical human infection of avian influenza A H5N6 virus. *Med* **5**, 32–41.e35 (2024).
211. MacBain, E. et al. Management of critical illness in an adolescent caused by highly pathogenic avian influenza A(H5N1) virus infection in British Columbia, Canada. *Lancet Infect. Dis.* **26**, e326–e334 https://doi.org/10.1016/S1473-3099(25)00773-X (2026).
212. Wang, Y. et al. Factors associated with prolonged viral shedding in patients with avian influenza A(H7N9) virus infection. *J. Infect. Dis.* **217**, 1708–1717 (2018).
213. Cao, B. et al. Adjuvant corticosteroid treatment in adults with influenza A (H7N9) viral pneumonia. *Crit. Care Med.* **44**, e318–e328 (2016).

214. Tesch, F. et al. Post-viral symptoms and conditions are more frequent in COVID-19 than influenza, but not more persistent. *BMC Infect. Dis.* **24**, 1126 (2024).
215. Andrew, M. K. et al. Persistent functional decline following hospitalization with influenza or acute respiratory illness. *J. Am. Geriatr. Soc.* **69**, 696–703 (2021).
216. Wee, L. E. et al. Long-term multisystemic sequelae post-hospitalisation for Omicron COVID-19 vs influenza: a retrospective cohort study. *Int. J. Infect. Dis.* **158**, 107946 (2025).
217. Bolge, S. C., Kariburyo, F., Yuce, H. & Fleischhackl, R. Predictors and outcomes of hospitalization for influenza: real-world evidence from the United States Medicare population. *Infect. Dis. Ther.* **10**, 213–228 (2021).
218. Lees, C. et al. Frailty hinders recovery from influenza and acute respiratory illness in older adults. *J. Infect. Dis.* **222**, 428–437 (2020).
219. O'Halloran, A. C. et al. The burden of all-cause mortality following influenza-associated hospitalizations: Influenza Hospitalization Surveillance Network, 2010–2019. *Clin. Infect. Dis.* **80**, e43–e45 (2025).
220. Wagenlechner, C. et al. Short and long-term outcomes of children and adolescents hospitalized with COVID-19 or influenza: results of the AUTCOV study. *Sci. Rep.* **15**, 22692 (2025).
221. Centers for Disease Control and Prevention. CDC seasonal flu vaccine effectiveness studies. *CDC* https://www.cdc.gov/flu-vaccines-work/php/effectiveness-studies/index.html (2026).
222. Nachbagauer, R. et al. A chimeric hemagglutinin-based universal influenza virus vaccine approach induces broad and long-lasting immunity in a randomized, placebo-controlled phase I trial. *Nat. Med.* **27**, 106–114 (2021).
223. Krammer, F. et al. NAction! How can neuraminidase-based immunity contribute to better influenza virus vaccines. *mBio* **9**, e02332-17 (2018).
224. Rajendran, M., Krammer, F. & McMahon, M. The human antibody response to the influenza virus neuraminidase following infection or vaccination. *Vaccines* **9**, 846 https://doi.org/10.3390/vaccines9080846 (2021).
225. Ohmit, S. E., Petrie, J. G., Cross, R. T., Johnson, E. & Monto, A. S. Influenza hemagglutination-inhibition antibody titer as a correlate of vaccine-induced protection. *J. Infect. Dis.* **204**, 1879–1885 (2011).
226. Cowling, B. J. et al. Influenza hemagglutination-inhibition antibody titer as a mediator of vaccine-induced protection for influenza B. *Clin. Infect. Dis.* **68**, 1713–1717 (2019).
227. Ng, S. et al. Novel correlates of protection against pandemic H1N1 influenza A virus infection. *Nat. Med.* **25**, 962–967 (2019).
228. Park, J. K. et al. Evaluation of preexisting anti-hemagglutinin stalk antibody as a correlate of protection in a healthy volunteer challenge with influenza A/H1N1pdm virus. *mBio* **9**, e02284-17 (2018).
229. Monto, A. S. et al. Antibody to influenza virus neuraminidase: an independent correlate of protection. *J. Infect. Dis.* **212**, 1191–1199 (2015).
230. Stacey, H. D. et al. Local B cell immunity and durable memory after live-attenuated influenza intranasal vaccination of humans. *Sci. Transl. Med.* **18**, eadz8439 (2026).
231. Okuya, K. et al. Potential role of nonneutralizing IgA antibodies in cross-protective immunity against influenza a viruses of multiple hemagglutinin subtypes. *J. Virol.* **94**, e00408-20 (2020).
232. van Riet, E., Ainai, A., Suzuki, T. & Hasegawa, H. Mucosal IgA responses in influenza virus infections; thoughts for vaccine design. *Vaccine* **30**, 5893–5900 (2012).
233. Reis, L. R. & Ross, T. M. Next-generation intranasal influenza vaccines: mechanisms, platforms, and translational progress. *Front. Immunol.* **17**, 1809302 (2026).
234. Sun, J. et al. B cell imprinting in children impairs antibodies to the haemagglutinin stalk. *Nature* **653**, 528–537 (2026).
235. National Institutes of Health. NIH announces two awards for multi-year studies of influenza immunity in children. *NIH* https://go.nature.com/3Tp9pWn (22 May 2019).
236. Morens, D. M., Taubenberger, J. K. & Fauci, A. S. Rethinking next-generation vaccines for coronaviruses, influenzaviruses, and other respiratory viruses. *Cell Host Microbe* **31**, 146–157 (2023).
237. Taaffe, J., Goldin, S., Lambach, P. & Sparrow, E. Global production capacity of seasonal and pandemic influenza vaccines in 2023. *Vaccine* **51**, 126839 (2025).
238. Bresee, J. S. & Lafond, K. E. The Partnership for International Vaccine Initiatives (PIVI): the importance and opportunity to develop influenza vaccination programs in low- and middle-income countries. *Vaccine* **42**, 126255 (2024).
239. Bresee, J. S. et al. The partnership for influenza vaccine introduction (PIVI): supporting influenza vaccine program development in low and middle-income countries through public-private partnerships. *Vaccine* **37**, 5089–5095 (2019).
240. Noda, T. et al. Architecture of ribonucleoprotein complexes in influenza A virus particles. *Nature* **439**, 490–492 (2006).
241. Krammer, F. et al. Influenza. *Nat. Rev. Dis. Primers* **4**, 3 (2018).
242. Dou, D., Revol, R., Ostbye, H., Wang, H. & Daniels, R. Influenza A virus cell entry, replication, virion assembly and movement. *Front. Immunol.* **9**, 1581 (2018).

Acknowledgements
Some of the authors are funded in part by Japan Agency for Medical Research and Development grants JP20wm0125002 and JP223fa627001 (to Y.K.) and by the NIAID Centers of Excellence for Influenza Research and Response (contract number: 75N93021C00014 to Y.K.). The Melbourne WHO Collaborating Centre for Reference and Research on Influenza is supported by the Australian Department of Health, Disability and Aged Care.

Author contributions
All authors contributed to the entire manuscript.

Competing interests
Y.K. has received grant support from Daiichi Sankyo Pharmaceutical, Toyama Chemical, Tauns Laboratories, Otsuka Pharmaceutical, Shionogi, Otsuka Pharmaceutical, KM Biologics, Kyoritsu Seiyaku, Shinya and Fuji Rebio. Y.K. and G.N. are co-founders of FluGen. B.J.C. has consulted for AstraZeneca, Fosun Pharma, GlaxoSmithKline, Haleon, Moderna, Novavax, Pfizer, Roche, Sanofi Pasteur and Seqirus. I.G.B. holds shares in CSL. All other authors report no competing interests.

Additional information
Peer review information *Nature Reviews Disease Primers* thanks E. Govorkova, R. Kennedy, S. Ludwig and the other, anonymous, reviewer(s) for their contribution to the peer review of this work.

Disclaimer The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.