Commentary

Preparing for the Next Influenza Pandemic: Vaccine Progress, Challenges, and Prospects

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ABSTRACT

Influenza pandemics arise when novel influenza virus subtypes emerge in populations with little or no pre-existing immunity. The recent expansion of H5N1 virus circulation in mammals — including documented spread in cattle and sporadic human infections — coupled with the emergence of mutations associated with enhanced pandemic potential, underscores the persistent threat of novel influenza strains. Pandemic preparedness critically depends on developing effective vaccines capable of providing broad protection across diverse viral strains. While vaccination remains the most effective strategy for preventing influenza and its complications, pandemic vaccine development faces substantial challenges. These include the rapid mutation rates characteristic of influenza viruses, driven by error-prone RNA replication, broad host range, environmental selection pressures, and frequent genetic recombination. Such factors complicate predictions of which strain will trigger the next pandemic and hinder efforts to create universal vaccines. Recent advances in vaccine production platforms, bioinformatics, and artificial intelligence have accelerated pandemic vaccine development capabilities. Continued research is essential to enhance vaccine technology, expedite production timelines, and broaden vaccine efficacy against the full spectrum of influenza virus strains.

Influenza is an acute respiratory disease caused by influenza viruses, characterized by rapid viral mutations that occur through antigenic drift and antigenic shift. This disease has posed a persistent threat to global public health, with seasonal epidemics occurring annually and occasional pandemics that can have far-reaching consequences (*1*–*2*). An influenza pandemic is defined by the global spread of a novel influenza A virus subtype, against which most of the world's population possesses little or no pre-existing immunity, resulting in rapid international transmission. The 1918 Influenza Pandemic, caused by the H1N1 influenza virus, resulted in an estimated 50 million deaths worldwide (with some estimates reaching 100 million) and significantly reduced global life expectancy by 10–12 years, marking it as one of the most catastrophic public health events in human history. Subsequent pandemics — including the 1957 H2N2 influenza, the 1968 H3N2 influenza, and the 2009 H1N1 influenza — were generally less severe than the 1918 event but nonetheless remained serious threats to human life and economic stability (*3*). The substantial impacts of influenza pandemics on global public health, economies, and societies underscore the critical importance of effective preparedness and response strategies to reduce pandemic severity, save lives, and minimize socio-economic disruptions. Vaccines represent the most effective intervention for preventing influenza and its complications. However, developing vaccines for pandemic influenza viruses presents significant challenges. The virus mutates rapidly, and predicting which strain will trigger the next pandemic remains difficult. Here we address the progress, challenges, and prospects for vaccine development in preparation for the next influenza pandemic.

Etiological Basis of Influenza Pandemics

Pandemic influenza strains primarily arise from genetic reassortment between human seasonal influenza viruses and zoonotic influenza viruses. For example, the hemagglutinin (HA), neuraminidase (NA), and polymerase basic protein 1 (PB1) genes of the 1957 H2N2 influenza pandemic strain originated from avian influenza viruses; the NA and PB1 genes of the 1968 H3N2 influenza strain were similarly avian-derived; and the 2009 H1N1 influenza strain emerged from a triple reassortment involving human, avian, and swine influenza viruses (*4*). Consequently, strengthening surveillance and research on animal influenza viruses, particularly avian influenza viruses, is essential for pandemic preparedness. The potential threats posed by H7N9 and H5Nx subtypes warrant particular attention (*5*). Historically, H7N9 viruses acquired dual receptor-binding capability (recognizing both avian α 2,3-linked and human α 2,6-linked sialic acid receptors) through G186V and Q226L mutations in their HA protein, thereby identifying these viruses as high-pandemic-risk candidates (*6*). Similarly, H5Nx viruses have demonstrated extensive global spread and host adaptability since their first emergence in humans in 1997. Among these subtypes, H5N1 and H5N6 pose the greatest threat to humans, with case fatality rates exceeding 50% (*7*–*8*). Since 2021, H5Nx clade 2.3.4.4b viruses have caused large-scale outbreaks in avian populations, subsequently expanding to infect over 48 genera of terrestrial and marine mammals, including cattle, thereby elevating the risk of novel virus emergence (*9*–*10*). Notably, dual receptor (α 2,3 and α 2,6) binding capacity has been documented for bovine clade 2.3.4.4b H5N1 highly pathogenic avian influenza viruses (HPAIVs), which, combined with mammalian-adaptive mutations such as E627K in the polymerase basic protein 2 (PB2) protein, significantly increases their pandemic risk (*11*). Animal experiments have further confirmed that these viruses can undergo airborne transmission in ferrets (*12*–*13*). Concurrently, other subtypes, including H10N3 and H3N8 viruses, continue to enhance their mammalian adaptability and transmission capacity through key mutations, indicating that the risk posed by strains with pandemic potential cannot be ignored (*14*–*15*). These findings collectively underscore the critical importance of early detection and identification of emerging influenza virus strains.

Influenza Pandemic Prevention and Control: Current Progress of Vaccines

During the 2009 H1N1 influenza pandemic, clinical trials were conducted across multiple countries. China's advanced split influenza A virus vaccine demonstrated a protection rate exceeding 85%, with some formulations achieving over 90% efficacy. Although global deployment was delayed, the vaccine's excellent safety profile was subsequently confirmed through surveillance in 70 million recipients and comprehensive post-marketing monitoring, providing critical evidence for worldwide vaccination strategies (*16*). In response to ongoing pandemic threats and viral evolution, diverse platforms for influenza vaccine research and development have since been established globally, encompassing inactivated, split, live attenuated, subunit, adjuvanted, cell culture-based, nucleic acid, and universal influenza vaccines (*17*–*18*).

Inactivated influenza vaccines currently represent the most widely deployed vaccine type worldwide. The inactivation process employs chemicals such as formaldehyde or β-propiolactone to eliminate the virus's replicative capacity and pathogenicity while preserving its antigenic structure (*19*). Several countries, including China and the United States, have approved inactivated H5N1 subtype pandemic vaccines — China's SFDA granted approval in 2008, while the U.S. FDA approved formulations in 2007 and 2020. However, because these vaccines target previously circulating epidemic strains, regular updates to vaccine components are essential to maintain protective efficacy (*20*). Live attenuated influenza vaccines (LAIVs) utilize weakened influenza viruses that retain the ability to infect the respiratory mucosa without causing disease (*21*). Currently, no LAIVs have received approval for pandemic use. Recombinant protein vaccines represent an actively developing platform, produced by expressing specific influenza virus antigens — such as the HA protein — in heterologous expression systems including bacteria, yeast, or insect cells (*22*).

Notable progress has been achieved in novel vaccine platforms. Nucleic acid vaccines, encompassing both mRNA and DNA vaccines, offer the advantage of rapid development and production once the genetic sequence of the target virus is identified. These vaccines can be engineered to target multiple influenza strains simultaneously, potentially providing broader protection. They also eliminate the need for live virus in production, thereby simplifying the manufacturing process and reducing associated safety concerns (*23*). Several countries have initiated research and development of novel pandemic influenza vaccines for humans, with some vaccines approved to enter clinical trial stages and others receiving emergency use or conditional market approval. For example, the nanoparticle vaccine H5-MNP in Switzerland and the DNA vaccine pVAX-H5 in Russia are currently in the preclinical research stage (*24*–*25*); the self-amplifying mRNA H5N1 vaccine in Australia has entered Phase I clinical trials (*26*); and the mRNA-1018 (H7 and H5) in the United States, along with a codon-optimized mRNA influenza A(H5N1) prepandemic vaccine candidate, have advanced to Phase I/II clinical trials (*27*–*28*). In recent years, advances in bioinformatics and artificial intelligence have substantially accelerated the development of pandemic vaccine technology platforms.

China has demonstrated a transition from technology adoption to independent innovation in influenza vaccine research and development, providing valuable technical solutions and practical experience to global influenza prevention and control efforts. Madin-Darby canine kidney (MDCK) cell-based influenza vaccine technology offers an alternative that circumvents the egg supply limitations during pandemics and avoids potential egg-adaptation mutations associated with traditional egg-based production (*29*). Currently, nine domestic companies have advanced related cell-based vaccines into clinical trials in China: two have completed Phase I clinical trials, while four others are progressing through Phase I or Phase III clinical trials (Table 1). The advantages of low contamination risk and ease of scale-up production position this technology to facilitate industrial-scale manufacturing of cell culture-based influenza vaccines in China.

In universal vaccine research, most candidates remain in the preclinical stage. The Fluaxe mRNA-LNP vaccine has demonstrated cross-protection in a BALB/c mouse model, inducing strong neutralizing antibodies against H1N1, H3N2, H5N1, H7N9 subtypes, and influenza B Victoria lineage virus strains, with neutralizing titers increasing 4- to 9.6-fold. Notably, the vaccine also elicited cross-neutralizing antibodies against strains not included in the original design, encompassing multiple influenza subtypes (e.g., H2, H6, H8, H11, H13, H15, H16). In challenge experiments, the vaccine conferred 100% protection against lethal doses of H1N1 and influenza B Victoria virus while significantly reducing lung viral loads by up to 180.9-fold (*30*). Similarly, an epitope-optimized nanoparticle vaccine targeting H9N2, developed in China, successfully elicited high levels of cross-reactive antibodies against 14 H9N2 strains from distinct clades in a BALB/c mouse model. In lethal challenge experiments, this vaccine conferred 100% survival and significantly reduced lung viral loads (*31*). Furthermore, a chimeric hemagglutinin-based mRNA-LNP vaccine platform has demonstrated the capacity to elicit robust and durable stalk-specific antibody responses in a rhesus macaque model. Following a two-dose immunization regimen, the induced serum antibody responses and bone marrow plasma cells persisted for at least 10 and 8 months, respectively. Critically, passive transfer of serum collected from vaccinated macaques conferred effective protection in mice against lethal challenge with heterologous influenza viruses, confirming the functional protective efficacy of the vaccine-induced antibodies (*32*). Collectively, these data provide compelling preclinical evidence supporting the continued development of universal influenza vaccines.

Core Challenges and Future Directions for Influenza Vaccines

Despite substantial progress in vaccine technology, the development and deployment of influenza vaccines for pandemic scenarios encounter several critical obstacles. First, the extended development and production timelines of traditional vaccines limit their capacity to deliver timely protection during the initial outbreak phase. During the 2009 H1N1 pandemic, for instance, vaccine availability in most countries lagged behind peak transmission, substantially diminishing the preventive impact (*42*). Second, achieving antigenic concordance between vaccine candidates and circulating viral strains represents a fundamental challenge for pandemic vaccine effectiveness. Current influenza vaccines — predominantly inactivated and live-attenuated formulations — rely on predictions of dominant strains for the upcoming season. When these predictions prove inaccurate, antigenic mismatch occurs, substantially reducing vaccine efficacy (*43*). Moreover, ongoing viral evolution can cause circulating strains to diverge from stockpiled vaccine strains, further compromising protective immunity. Even advanced platforms such as mRNA vaccines remain susceptible to this antigenic mismatch (*44*). Consequently, exploiting conserved viral antigens to engineer a universal influenza vaccine capable of conferring broad cross-subtype protection has emerged as a pivotal strategy for transcending the inherent limitations of strain-specific vaccine approaches. The successful development of such universal vaccines would facilitate advanced manufacturing and strategic stockpiling, thereby strengthening global pandemic preparedness infrastructure.

Although universal influenza vaccines demonstrate considerable potential for overcoming the limitations of traditional vaccines, no significant breakthrough has been achieved over the past two decades, and their development continues to face substantial challenges. First, universal vaccines target conserved viral antigens such as the HA stalk, M2 ectodomain (M2e), nucleoprotein (NP), and NA, which typically elicit relatively weak protective immune responses (*45*). Adjuvant development has emerged as a major research focus to overcome this bottleneck. However, adjuvant strategies introduce their own complexities. Adjuvant mechanisms are highly diverse and intricate, necessitating extensive experimental screening to identify optimal combinations with specific antigens. Furthermore, while adjuvants enhance immunogenicity, their potential safety risks must be rigorously controlled, imposing stringent demands on

TABLE 1. Cell-based influenza vaccines in clinical development in China.

Institution	Vaccine	Clinical phase	Target population	Study design	Registration or acceptance ID
Shanghai Institute of Biological Products	Quadrivalent influenza split vaccine (MDCK cells)	Phase I (completed)	≥6 months	Randomized, double-blind, controlled	CTR20241054 (33)
Changchun Institute of Biological Products	Quadrivalent influenza subunit vaccine (MDCK cells)	Phase I (Completed)	≥3 years	Randomized, double-blind, controlled	CTR20241413 ((34)
Wuhan Institute of Biological Products	Quadrivalent influenza split vaccine (MDCK cells)	Phase III	≥3 years	Randomized, double-blind, controlled	CTR20233159 (35)
Tianyuan Bio-Pharma	Quadrivalent influenza split vaccine (MDCK cells)	Phase I	≥6 months	Randomized, double-blind, controlled	CTR20240729 (36)
Chengdu Olymvax, Chengdu Xinnuoming, and Lanzhou Bailing Biotechnology Co., Ltd.	Quadrivalent influenza split vaccine (MDCK cells)	Phase I	≥6 months	Randomized, double-blind, controlled	Phase Ⅰ CTR20250319 (37) Phase Ⅲ: CTR20254267 (38)
	Trivalent influenza split vaccine (MDCK cells)	Phase I	≥6 months	Randomized, double-blind, controlled	CTR20250309 (39)
Shenzhen Kangtai Biological Products Co., Ltd. & Lanzhou Bailing Biotechnology Co., Ltd.	Quadrivalent influenza split vaccine (MDCK cells)	Clinical trial approval	≥6 months	Randomized, double-blind, controlled	CXSL2400449 (40)
	Trivalent influenza split vaccine (MDCK cells)	Clinical trial implied permission	≥3 years	Randomized, double-blind, controlled	CXSL2500428 (40)
National vaccine and serum institute	Quadrivalent influenza split vaccine (MDCK cells)	Clinical trial implied permission	–	–	CXSL2300148 (40)
AIM Vaccine Co., Ltd.	Quadrivalent influenza split vaccine (MDCK cells)	Clinical trial implied permission	–	–	CXSL2400629 (40)
Shenzhen Kangtai Biological Products Co.	Quadrivalent influenza split vaccine (MDCK cells)	Phase I	≥6 months	Randomized, double-blind, controlled	CTR20254299 (41)

Note: "–" represents missing data.
Abbreviation: MDCK=madin-darby canine kidney.

rational adjuvant design (46). Consequently, adjuvant technology represents not merely a solution but also a critical bottleneck in universal influenza vaccine development. Second, vaccine efficacy assessment systems require urgent updating. Traditional influenza vaccines rely on neutralizing antibody titers as correlates of protection, whereas universal vaccines may depend more heavily on T-cell immunity or on non-neutralizing antibodies (36). This shift toward new immunological testing paradigms necessitates the development of novel immune correlates and efficacy benchmarks, which pose significant regulatory and clinical challenges. Third, the breadth of protection remains limited. Multi-target strategies that combine conserved internal antigens (e.g., NP) with optimized surface proteins (e.g., the HA stalk) are therefore imperative to broaden the protective spectrum (21). Finally, large-scale production processes for novel vaccine platforms, including messenger RNA (mRNA) and virus-like particles (VLPs), remain underdeveloped. Given these multifaceted challenges, universal influenza vaccines will only fulfill their potential following systematic advances in antigen design, adjuvant technology, evaluation criteria, and manufacturing capabilities (47). Until such progress is achieved, the timely updating of vaccine strains in response to viral evolution remains the cornerstone of effective influenza immunization.

Summary

Vaccine technology has undergone a transformative evolution — from the complete absence of viral vaccines during the 1918 pandemic to the rapid deployment achieved during the 2009 H1N1 outbreak and subsequent innovations. These technological advances, combined with the global influenza surveillance network, have positioned the international community more strategically than ever to combat future influenza pandemics. Nevertheless, we face substantial challenges in translating this technological potential into effective prevention and control capabilities. Critical issues regarding the immunogenicity, evaluation systems, and production processes of universal vaccines remain unresolved.

Moreover, vaccines alone cannot terminate outbreaks. Their effectiveness depends on sustained viral surveillance and integration within a comprehensive strategy that encompasses antivirals and non-pharmaceutical interventions (NPIs). Evidence demonstrates that NPIs — including mask-wearing, social distancing, and public space disinfection — that were implemented during the COVID-19 pandemic resulted in a 46.3% reduction in global influenza cases during the 2020–2021 winter season (*48*). However, following the relaxation of these measures, influenza activity rebounded dramatically, increasing by 131.7% in winter and 161.2% in summer (*48*). These empirical observations highlight the critical importance of integrating NPIs with influenza vaccination programs: during the initial emergence of novel influenza strains or periods when vaccines remain unavailable, NPIs function as an essential barrier to slow transmission and provide crucial time for vaccine development and deployment. Once vaccines become widely accessible, NPIs continue to serve a vital complementary role by addressing gaps in vaccine-induced protection, thereby collectively strengthening immune defense systems. Furthermore, emergency vaccine supply capabilities must be enhanced by leveraging established industrial platforms for seasonal influenza vaccines to enable rapid production of pandemic influenza vaccines.

To prepare for future influenza pandemics, a comprehensive strategy must be implemented across three critical domains. First, global influenza surveillance networks require continuous strengthening to ensure the collection of accurate etiological data that supports evidence-based vaccine strain selection. China's national influenza surveillance network exemplifies this approach, encompassing 1,041 sentinel hospitals and 665 network laboratories that collectively test over one million samples annually through virus isolation and deep sequencing, thereby establishing a robust foundation for influenza prevention and control. Second, targeted research must address fundamental technical barriers in universal vaccine development, particularly those related to conserved antigen immunogenicity and scalable manufacturing processes, with the ultimate goal of eliminating dependence on strain prediction. Third, a coordinated framework that integrates vaccination programs with complementary interventions — specifically antiviral therapeutics and non-pharmaceutical measures — must be optimized to establish multilayered pandemic defense capabilities. Only through achieving synergistic integration of surveillance systems, vaccine research and development, and comprehensive control measures can we adequately prepare for the next influenza pandemic.

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REFERENCES

1. Keilman LJ. Seasonal influenza (flu). Nurs Clin N Am 2019;54(2):227 – 43. https://doi.org/10.1016/j.cnur.2019.02.009.
2. Nypaver C, Dehlinger C, Carter C. Influenza and influenza vaccine: a review. J Midwifery Wom Heal 2021;66(1):45 – 53. https://doi.org/10.1111/jmwh.13203.
3. Mokalla VR, Gundarapu S, Kaushik RS, Rajput M, Tummala H. Influenza vaccines: current status, adjuvant strategies, and efficacy. Vaccines 2025;13(9):962. https://doi.org/10.3390/vaccines13090962.
4. Neumann G, Kawaoka Y. Which virus will cause the next pandemic? Viruses 2023;15(1):199. http://dx.doi.org/10.3390/v15010199.
5. Shi JZ, Zeng XY, Cui PF, Yan C, Chen HL. Alarming situation of emerging H5 and H7 avian influenza and effective control strategies. Emerg Microbes Infec 2023;12(1):2155072. https://doi.org/10.1080/22221751.2022.2155072.
6. Li CJ, Chen HL. H7N9 influenza virus in China. Cold Spring Harb Perspect Med 2021;11(8):a038349. https://doi.org/10.1101/cshperspect.a038349.
7. Wang L, Gao GF. A brief history of human infections with H5Ny avian influenza viruses. Cell Host Microbe 2025;33(2):176 – 81. https://doi.org/10.1016/j.chom.2025.01.010.
8. World Health Organization. Cumulative number of confirmed human cases for avian influenza A(H5N1) reported to WHO, 2003-2023. Geneva: World Health Organization; 2023. https://www.who.int/publications/m/item/cumulative-number-of-confirmed-human-cases-for-avian-influenza-a(h5n1)-reported-to-who--2003-2023--3-october-2023.
9. Plaza PI, Gamarra-Toledo V, Euguí JR, Lambertucci SA. Recent changes in patterns of mammal infection with highly pathogenic avian influenza A(H5N1) virus worldwide. Emerg Infect Dis 2024;30(3):444 – 52. https://doi.org/10.3201/eid3003.231098.
10. Shi JZ, Kong HH, Cui PF, Deng GH, Zeng XY, Jiang YP, et al. H5N1 virus invades the mammary glands of dairy cattle through 'mouth-to-teat' transmission. Natl Sci Rev 2025;12(9):nwaf262. https://doi.org/10.1093/nsr/nwaf262.
11. Marchenko VY, Panova AS, Kolosova NP, Gudymo AS, Svyatchenko SV, Danilenko AV, et al. Characterization of H5N1 avian influenza virus isolated from bird in Russia with the E627K mutation in the PB2 protein. Sci Rep 2024;14(1):26490. https://doi.org/10.1038/s41598-024-78175-y.
12. Xiong JL, Ding SP, Zhou JT, Cui YQ, Chen XN, Huang LH, et al. Clade 2. 3.4.4b highly pathogenic H5N1 influenza viruses from birds

in China replicate effectively in bovine cells and pose potential public health risk. Emerg Microbes Infec 2025;14(1):2505649. https://doi.org/10.1080/22221751.2025.2505649.
13. Elsmo EJ, Wunschmann A, Beckmen KB, Broughton-Neiswanger LE, Buckles EL, Ellis J, et al. Highly pathogenic avian influenza A(H5N1) virus clade 2.3.4.4b infections in wild terrestrial mammals, United States, 2022. Emerg Infect Dis 2023;29(12):2451-60. http://dx.doi.org/10.3201/eid2912.230464.
14. Yang JY, Zhang Y, Yang L, Li XY, Bo H, Liu J, et al. Evolution of avian influenza virus (H3) with spillover into humans, China. Emerg Infect Dis 2023;29(6):1191 – 201. https://doi.org/10.3201/eid2906.221786.
15. Zhu WF, Yang L, Han X, Tan M, Zou SM, Li XY, et al. Origin, pathogenicity, and transmissibility of a human isolated influenza A (H10N3) virus from China. Emerg Microbes Infec 2025;14(1): 2432364. https://doi.org/10.1080/22221751.2024.2432364.
16. Shi JR, Shen AL, Cheng Y, Zhang C, Yang XM. 30-year development of inactivated virus vaccine in China. Pharmaceutics 2023;15(12):2721. https://doi.org/10.3390/pharmaceutics15122721.
17. Zhang JY, Nian XX, Li XD, Huang SH, Duan K, Li XG, et al. The epidemiology of influenza and the associated vaccines development in China: a review. Vaccines 2022;10(11):1873. https://doi.org/10.3390/vaccines10111873.
18. Information on the delivery of pharmaceutical approval certification documents (October 10, 2025). National Medical Products Administration; 2025. https://www.nmpa.gov.cn/zwfw/sdxx/sdxxyp/yppjfb/20251010153004185.html.
19. Shi H, Ross TM. Inactivated recombinant influenza vaccine: the promising direction for the next generation of influenza vaccine. Expert Rev Vaccines 2024;23(1):409 – 18. https://doi.org/10.1080/14760584.2024.2333338.
20. Xu H, Zhu SY, Govinden R, Chenia HY. Multiple vaccines and strategies for pandemic preparedness of avian influenza virus. Viruses 2023;15(8):1694. https://doi.org/10.3390/v15081694.
21. Parvez S, Pathrathota A, Uppar AL, Yadagiri G, Mudavath SL. Influenza virus: global health impact, strategies, challenges, role of nanotechnolgy in influenza vaccine development. Vaccines 2025;13(9): 890. https://doi.org/10.3390/vaccines13090890.
22. Khudainazarova NS, Granovskiy DL, Kondakova OA, Ryabchevskaya EM, Kovalenko AO, Evtushenko EA, et al. Prokaryote- and eukaryote-based expression systems: advances in post-pandemic viral antigen production for vaccines. Int J Mol Sci 2024;25(22):11979. https://doi.org/10.3390/ijms252211979.
23. Chen JJ, Chen JZ, Xu QB. Current developments and challenges of mRNA vaccines. Annu Rev Biomed Eng 2022;24:85 – 109. https://doi.org/10.1146/annurev-bioeng-110220-031722.
24. Rudometov AP, Litvinova VR, Gudymo AS, Ivanova KI, Rudometova NB, Kisakov DN, et al. Dose-dependent effect of DNA vaccine pVAX-H5 encoding a modified hemagglutinin of influenza A (H5N8) and its cross-reactivity against A (H5N1) influenza viruses of clade 2. 3.4.4b. Viruses 2025;17(3):330. https://doi.org/10.3390/v17030330.
25. Patel N, Rehman A, Trost JF, Flores R, Longacre Z, Guebre-Xabier M, et al. Single-dose avian influenza A(H5N1) clade 2. 3.4.4b hemagglutinin-Matrix-M* nanoparticle vaccine induces neutralizing responses in nonhuman primates. Nat Commun 2025;16(1):6625. https://doi.org/10.1038/s41467-025-61964-y.
26. CTV. Safety, reactogenicity, and immunogenicity study of a self-amplifying mRNA influenza vaccine in healthy adults. 2025. https://ctv.veeva.com/study/safety-reactogenicity-and-immunogenicity-study-of-a-self-amplifying-mrna-influenza-vaccine-in-heal. [2025-10-10].
27. CTV. A study of mRNA-1018 pandemic influenza candidate vaccines in healthy adults. 2025. https://ctv.veeva.com/study/a-study-of-mrna-1018-pandemic-influenza-candidate-vaccines-in-healthy-adults. [2025-10-10].
28. A study to find and confirm the dose and assess safety, reactogenicity and immune response of a vaccine against pandemic H5N1 influenza virus in healthy younger and older adults. 2025. https://trial.medpath.com/clinical-trial/6af52e87e7b65ce9/nct06382311-randomized-observer-blind-dose-finding-dose-confirmation-mrna-based-pandemic. [2025-10-10].
29. Hardenberg G, Brouwer C, van Gemerden R, Jones NJ, Marriott AC, Rip J. Polymeric nanoparticle-based mRNA vaccine is protective against influenza virus infection in ferrets. Mol Ther Nucl Acids 2024;35(1): 102159. https://doi.org/10.1016/j.omtn.2024.102159.
30. Yi DR, Liu Q, Guo SS, Li QJ, Zhang YX, Li N, et al. Chimeric hemagglutinin and M2 mRNA vaccine for broad influenza subtype protection. npj Vaccines 2025;10(1):113. https://doi.org/10.1038/s41541-025-01178-x.
31. Hao MC, Wang YH, Yang WX, Xu M, Guan YW, Zhang Y, et al. Epitope-optimized influenza hemagglutinin nanoparticle vaccine provides broad cross-reactive immunity against H9N2 influenza virus. ACS Nano 2025;19(22):20824 – 40. https://doi.org/10.1021/acsnano.5c03199.
32. Styles TM, Akhtar A, Gu CY, Neumann G, Muramatsu H, McPartlan JS, et al. Chimeric hemagglutinin-based universal influenza mRNA vaccine induces protective immunity and bone marrow plasma cells in rhesus macaques. Cell Rep Med 2025;6(10):102369. https://doi.org/10.1016/j.xcrm.2025.102369.
33. Center For Drug Evaluation. Detailed information of CTR20241054. http://www.chinadrugtrials.org.cn/clinicaltrials.searchlistdetail.dhtml.
34. Center For Drug Evaluation. Detailed infoormation of CTR20241413. 2024. http://www.chinadrugtrials.org.cn/clinicaltrials.searchlistdetail.dhtml.
35. Center for Drug Evaluation. Detailed information of CTR20233159. 2023. http://www.chinadrugtrials.org.cn/clinicaltrials.searchlistdetail.dhtml?id=743a5631d4df4fd5a296777c87db0f1c. [2025-10-10].(In Chinese).
36. Center for Drug Evaluation. Detailed information of CTR20240729. 2023. https://www.yscro.com/index.php/cde/313ad820a3b87848355b390ce7c0c9ba.html. [2025-10-10]. (In Chinese).
37. Center for Drug Evaluation. Detailed information of CTR20250319. 2024. https://www.yscro.com/index.php/cde/87dd818ebf96472d8b486d3cee6f6d79.html.[2025-10-10]. (In Chinese).
38. Center For Drug Evaluation. Detailed information of CTR20254267. 2025. http://www.chinadrugtrials.org.cn/clinicaltrials.searchlistdetail.dhtml.
39. Center for Drug Evaluation. Detailed information of CTR20250309. 2025. http://www.chinadrugtrials.org.cn/clinicaltrials.searchlistdetail.dhtml?id=d06ff57863454e2dbd871b726768b746. [2025-10-10].(In Chinese).
40. Center for Drug Evaluation. Drug Clinical Trial Registration and Information Disclosure. 2024. https://www.cde.org.cn/main/xxgk/listpage/9f9c74c73e0f8f56a8bfbc646055026d.
41. Center for Drug Evaluation. Detailed information of CTR20254229. 2025. http://www.chinadrugtrials.org.cn/clinicaltrials.searchlistdetail.dhtml. (In Chinese).
42. Wang DY, Shu YL. History and reflection of pandemic influenza. Sci Sin Vitae 2018;48(12):1247 – 51. https://doi.org/10.1360/N052018-00205.
43. Roepke KC, Howard KP. Conformation and membrane topology of the N-terminal ectodomain of influenza A M2 protein. Membranes 2025;15(2):40. https://doi.org/10.3390/membranes15020040.
44. Kim H, Webster RG, Webby RJ. Influenza virus: dealing with a drifting and shifting pathogen. Viral Immunol 2018;31(2):174 – 83. https://doi.org/10.1089/vim.2017.0141.
45. Wang WC, Sayedahmed EE, Sambhara S, Mittal SK. Progress towards the development of a universal influenza vaccine. Viruses 2022;14(8): 1684. https://doi.org/10.3390/v14081684.
46. Facciolà A, Visalli G, Laganà A, Di Pietro A. An overview of vaccine adjuvants: current evidence and future perspectives. Vaccines 2022;10 (5):819. https://doi.org/10.3390/vaccines10050819.
47. Taaffe J, Ostrowsky JT, Mott J, Goldin S, Friede M, Gsell P, et al. Advancing influenza vaccines: a review of next-generation candidates and their potential for global health impact. Vaccine 2024;42(26): 126408. https://doi.org/10.1016/j.vaccine.2024.126408.
48. Chen L, Guo YC, López-Güell K, Ma J, Dong YH, Xie JQ, et al. Immunity debt for seasonal influenza after the COVID-19 pandemic and as a result of nonpharmaceutical interventions: an ecological analysis and cohort study. Adv Sci 2025;12(20):2410513. https://doi.org/10.1002/advs.202410513.