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IMMUNE IMPRINTING IN INFLUENZA: CELLULAR MECHANISMS, CLINICAL SIGNIFICANCE, AND PROSPECTS FOR NEXT – GENERATION VACCINE DEVELOPMENT

Influenza viruses remain a major cause of seasonal morbidity and mortality worldwide, while the effectiveness of current influenza vaccines depends not only on the antigenic match between vaccine and circulating strains but also on an individual's immunological history. One of the key mechanisms shaping both infection- and vaccine-induced immunity is immune imprinting, historically described as Original Antigenic Sin (OAS). The aim of this review was to summarize current knowledge on the cellular and molecular mechanisms of immune imprinting in influenza, evaluate its clinical and epidemiological significance, and discuss its implications for the development of next-generation influenza vaccines. This narrative review was based on publications retrieved from the PubMed, Scopus, and Web of Science databases. Particular attention was paid to the roles of memory B cells, long-lived plasma cells, germinal centers, and T follicular helper cells in the establishment and maintenance of immunological memory. The review also examines the influence of antigenic distance between sequential influenza strains on the effectiveness of naturally acquired and vaccine-induced immunity and highlights recent advances in antigen engineering aimed at reshaping pre-existing immune memory. Current evidence indicates that immune imprinting is a fundamental property of adaptive immunity that may either enhance broad cross-protective immunity or restrict the generation of novel immune specificities, depending on the antigenic context. Recent developments in vaccine engineering, systems immunology, and high-throughput immune profiling provide new opportunities for the design of universal influenza vaccines capable of rationally modulating immunological memory while inducing durable and broadly protective immune responses.

Key words: influenza, immune imprinting, Original Antigenic Sin, adaptive immunity, memory B cells, universal influenza vaccine, vaccination.

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ІМУННИЙ ІМПРИНТИНГ ПРИ ГРИПІ: КЛІТИННІ МЕХАНІЗМИ, КЛІНІЧНЕ ЗНАЧЕННЯ ТА ПЕРСПЕКТИВИ СТВОРЕННЯ ВАКЦИН НОВОГО ПОКОЛІННЯ

Віруси грипу залишаються однією з провідних причин сезонної захворюваності та смертності у світі, тоді як ефективність сучасних вакцин значною мірою залежить не лише від антигенної відповідності вакцинних і циркулюючих штамів, але й від індивідуального імунологічного досвіду. Одним із ключових механізмів, що визначає характер постінфекційної та поствакцинальної

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імуноної відповіді, є імунний імпринтинг, відомий також у класичній літературі як феномен Original Antigenic Sin. Метою роботи було узагальнення сучасних уявлень про клітинні й молекулярні механізми імунного імпринтування при грипі, аналіз його клінічного та епідеміологічного значення, а також оцінка перспектив використання цієї концепції у створенні вакцин нового покоління. Роботу виконано у форматі наративного огляду сучасної наукової літератури з використанням міжнародних наукометричних баз даних PubMed, Scopus і Web of Science. Проаналізовано роль В-клітин пам'яті, довгоживучих плазматичних клітин, гермінативних центрів і Т-фолікулярних хелперів у формуванні імунологічної пам'яті, висвітлено вплив антигенної дистанції між послідовними штамами вірусу на ефективність природного та вакцинального імунітету, а також розглянуто сучасні підходи до антигенної інженерії, спрямовані на модифікацію вже сформованої імунної пам'яті. Показано, що імунний імпринтинг є фундаментальною властивістю адаптивного імунітету, яка залежно від антигенного контексту може забезпечувати як широкий перехресний захист, так і обмежувати формування нових імунних специфічностей. Використання сучасних платформ вакцинальної інженерії, системної імунології та високопродуктивних технологій відкриває перспективи для створення універсальних вакцин проти грипу, здатних раціонально модифікувати імунологічну пам'ять і забезпечувати тривалий широкий захисний імунітет.

Ключові слова: грип, імунний імпринтинг, Original Antigenic Sin, адаптивний імунітет, В-клітини пам'яті, універсальна вакцина, щеплення.

Introduction. Influenza viruses remain among the most important respiratory pathogens affecting humans, causing substantial morbidity, hospitalization, and mortality worldwide each year. Despite the widespread use of seasonal influenza vaccines for decades, vaccine effectiveness varies considerably depending on circulating viral strains, age, previous immunological experience, and other host – related factors. For many years, this variability was primarily attributed to the continuous antigenic drift of the viral surface glycoproteins-hemagglutinin (HA) and neuraminidase (NA)-which results in the emergence of novel antigenic variants capable of partially or completely escaping pre – existing immune responses [1–3].

However, accumulating experimental and clinical evidence indicates that viral antigenic variability is not the sole determinant of naturally acquired or vaccine – induced immunity. Increasing evidence suggests that the quality and magnitude of the immune response are strongly influenced by an individual's history of previous encounters with influenza viruses or their antigens. In particular, the first antigenic exposure establishes long – lasting immunological memory that shapes both the specificity and magnitude of immune responses to subsequent influenza infections or vaccinations [2, 4, 5].

This phenomenon, now widely referred to as immune imprinting, was originally described by Thomas Francis Jr. as the concept of Original Antigenic Sin (OAS), which refers to the preferential recall of immune responses directed against antigens encountered during the first exposure to influenza virus. Although initially regarded as an undesirable fixation of the primary immune response, the concept has evolved substantially over recent decades. Immune imprinting is now recognized as a fundamental property of adaptive immunity that can provide rapid cross – protection against antigenically related viral variants while simultaneously limiting the development of effective immune responses to antigenically distinct strains [4, 6, 7].

Despite considerable advances in understanding the cellular and molecular basis of immunological memory, many aspects of immune imprinting remain incompletely understood. In particular, the coordinated interactions among memory B cells, long – lived plasma cells, germinal centers, and T follicular helper (Tfh) cells during the establishment and maintenance of long – term humoral immunity continue to be actively investigated. Furthermore, the influence of antigenic distance between

primary and subsequent influenza strains on the strength of immune imprinting, vaccine effectiveness, and the level of natural protection remains an area of ongoing research [5–8].

Recent advances in systems immunology, single – cell sequencing, structural vaccinology, and bioinformatics have substantially expanded current knowledge of the mechanisms underlying immune imprinting. The integration of findings from fundamental and clinical studies has provided new insights into the role of previous immune experience in shaping protective immunity and has opened promising avenues for the development of universal or broadly protective influenza vaccines capable of minimizing the unfavorable consequences of pre – existing immunological memory [3, 7–9].

The aim of this review is to summarize current knowledge of the cellular and molecular mechanisms underlying immune imprinting in influenza, analyze its immunological, clinical, and epidemiological implications, and evaluate its significance for the development of next – generation influenza vaccines and future strategies toward universal influenza vaccination.

Methodology and Research Methods. This study was conducted as a narrative review of the scientific literature on immune imprinting in influenza, its cellular and molecular mechanisms, clinical and epidemiological implications, and relevance to the development of next-generation influenza vaccines.

The literature search was performed using the international bibliographic databases PubMed, Scopus, and Web of Science, supplemented by relevant World Health Organization (WHO) recommendations and documents concerning influenza prevention and vaccination. The search covered publications from 1960 to 2025, including seminal studies that established the concept of Original Antigenic Sin as well as recent experimental, clinical, epidemiological, and review studies addressing contemporary concepts of immune imprinting.

The search strategy included combinations of the following keywords and their related terms: “influenza”, “immune imprinting”, “Original Antigenic Sin”, “immunological memory”, “memory B cells”, “germinal centers”, “T follicular helper cells”, “antigenic drift”, “influenza vaccine effectiveness”, “universal influenza vaccine”, and “antigen engineering”.

Priority was given to peer-reviewed systematic reviews, meta-analyses, experimental and clinical studies, epidemiological investigations, and authoritative scientific

reviews directly addressing the mechanisms or consequences of immune imprinting in influenza. Seminal publications were additionally included when they provided the conceptual or historical basis for understanding Original Antigenic Sin and immune imprinting.

Studies were selected according to their relevance to the objectives of the review, scientific significance, methodological quality, and contribution to understanding the cellular and molecular mechanisms of immune imprinting, its effects on influenza susceptibility and vaccine-induced immunity, and approaches to modulation of pre-existing immune memory. Publications that did not directly address the subject of the review or lacked sufficient scientific relevance were excluded.

The retrieved literature was analyzed using comparative, analytical, and synthesis approaches. The findings were integrated to provide a comprehensive overview of current understanding of immune imprinting and its implications for influenza prevention and vaccine development.

Presentation of the main research findings. General Principles of Immune Imprinting in Adaptive Immunity. Immune imprinting is a fundamental property of the adaptive immune system whereby the first encounter with an antigen establishes a long – lasting immunological memory pattern that shapes subsequent immune responses to antigenically related variants of the same pathogen. In influenza, this phenomenon is of particular importance because of the continuous antigenic drift of the viral surface glycoproteins-hemagglutinin (HA) and neuraminidase (NA)-which drives the emergence of sequential yet immunologically distinct viral variants [2, 10].

Rather than serving as a passive repository of information about previous infections, the adaptive immune system functions as a highly organized and dynamic network in which early antigenic encounters determine the subsequent selection and dominance of specific lymphocyte clones. This hierarchical organization is maintained through coordinated interactions among memory B cells, long – lived plasma cells, germinal centers, and antigen-specific T-cell populations, enabling the rapid restoration of protective immune responses upon re – exposure to related antigens [5, 6].

Accordingly, immune imprinting should not be viewed as a passive “imprint” of the primary immune response but rather as an active regulatory mechanism of adaptive immunity that determines lymphocyte activation thresholds, epitope immunodominance, and the overall direction of humoral immune responses [5].

Memory B cells play a central role in the establishment and maintenance of immune imprinting because of their capacity for rapid reactivation following repeated antigen exposure. Following primary infection or vaccination, a population of long – lived memory B cells is generated, predominantly recognizing the immunodominant epitopes of the influenza strain that initially elicited the immune response [4, 11].

Upon subsequent infection or vaccination with antigenically related influenza viruses, these memory B cells are reactivated much more rapidly than naïve B cells owing to their lower activation threshold, higher B – cell receptor affinity, and enhanced proliferative capacity. Con-

sequently, the humoral immune response develops more rapidly but becomes functionally biased toward conserved epitopes shared with the primary influenza strain [4, 12].

At the same time, the preferential activation of memory B cells suppresses the recruitment of naïve B cells that could otherwise recognize novel or substantially altered epitopes. As a result, the antibody repertoire remains focused on the antigenic characteristics of the original virus, potentially limiting the effectiveness of immune responses against antigenically divergent influenza variants [7, 11].

Long – lived plasma cells, located primarily in the bone marrow, also play an essential role in maintaining immune imprinting. These cells continuously secrete antibodies for many years, or even decades, thereby sustaining a stable serological profile that reflects an individual's primary antigenic exposure [13, 14].

Antibodies produced by long – lived plasma cells can further shape subsequent immune responses by masking specific epitopes and reducing antigen availability for naïve B cells. This process further favors the reactivation of pre – existing memory B – cell clones, thereby reinforcing the effects of immune imprinting [4, 5].

Another critical component of immune imprinting is the germinal center reaction occurring within secondary lymphoid organs, particularly the lymph nodes and spleen. Germinal centers provide the microenvironment in which somatic hypermutation, affinity maturation, and affinity – based selection of B – cell clones take place. These processes are tightly regulated by T follicular helper (Tfh) cells, which deliver essential signals for B – cell survival, proliferation, and differentiation [6, 15].

In addition to T follicular helper cells, other memory T – cell populations contribute to the establishment of immune imprinting. In particular, CD4⁺ T cells coordinate humoral immune responses and support germinal center activity, whereas CD8⁺ cytotoxic T lymphocytes recognize more conserved internal viral proteins and can provide cross – reactive cellular immunity despite substantial antigenic variation in viral surface glycoproteins [6-8].

Previous antigenic experience profoundly alters the functional organization of germinal centers. Upon re – exposure to antigenically related influenza viruses, Tfh cells preferentially support pre – existing memory B – cell clones, whereas the participation of naïve B cells in generating novel antigen specificities is substantially reduced. This selective support represents one of the principal cellular mechanisms underlying immune imprinting [5, 7].

At the cellular level, immune imprinting is mediated through clonal competition. Compared with naïve B lymphocytes, memory B cells possess a substantial selective advantage owing to their greater precursor frequency, higher receptor affinity, and more rapid reactivation following repeated antigen exposure [5].

As a consequence of this competition, immune responses become increasingly focused on epitopes shared with the primary influenza strain. The magnitude of this effect largely depends on the antigenic distance between the primary strain and subsequent antigenically related viruses. When antigenic differences are relatively small,

immune imprinting promotes efficient cross – protection. In contrast, increasing antigenic distance may limit the generation of novel immune specificities, thereby reducing the effectiveness of adaptive immune responses against emerging influenza variants [7, 12, 16].

Clinical and Epidemiological Implications of Immune Imprinting. One of the most striking manifestations of immune imprinting is the emergence of birth cohort-specific differences in susceptibility to influenza virus infection. Individuals born during different periods of influenza virus circulation exhibit distinct profiles of immune protection and infection risk, determined not only by subsequent viral exposures but, more importantly, by their primary antigenic encounter during early childhood [17, 18]. Consequently, cohort – specific heterogeneity of immunity develops, whereby susceptibility to particular influenza virus subtypes and strains is strongly influenced by the year of birth and the epidemiological landscape at the time of the initial infection [12].

Immune imprinting influences not only susceptibility to infection but also the clinical course of influenza. When the primary infecting strain and subsequently encountered antigenically related viruses share sufficient antigenic similarity, pre – existing immunity may provide partial cross – protection, resulting in reduced viral load, shorter disease duration, and a lower risk of severe clinical outcomes [5]. In contrast, substantial antigenic distance between viral variants may favor the production of cross – reactive but weakly neutralizing antibodies, thereby limiting antiviral protection, promoting prolonged viral persistence, and contributing to more severe disease manifestations [7, 12].

One of the most important practical consequences of immune imprinting is the variability in the effectiveness of seasonal influenza vaccines. Because vaccination is usually administered in individuals with pre – existing immunological memory, repeated antigen exposure frequently reactivates established memory B-cell clones rather than inducing *de novo* immune responses against newly emerged viral variants [10, 11]. Consequently, the breadth of the antibody response is reduced, leading to diminished protection against antigenically drifted influenza strains, particularly among older adults with a long history of natural infections and repeated vaccinations [19].

An additional factor that may further exacerbate the effects of immune imprinting is the manufacturing process used for conventional influenza vaccines. In particular, adaptation of vaccine strains for propagation in embryonated chicken eggs can introduce mutations in the hemagglutinin molecule, altering the antigenic properties of the vaccine virus and reducing its antigenic match with circulating influenza strains [20, 21].

At the population level, immune imprinting contributes to the formation of a complex landscape of herd immunity that is largely determined by the age structure of the population, the historical circulation of influenza viruses, and previous vaccination programs. Such immunological heterogeneity considerably complicates the prediction of epidemic dynamics and the modeling of influenza transmission. Traditional epidemiological models, which generally assume a relatively homogeneous

immune status within the population, often fail to account for the profound influence of primary antigenic exposure on subsequent immune responses [17].

Incorporating parameters related to immune imprinting into contemporary epidemiological models substantially improves the prediction of age – specific, cohort – specific, and seasonal patterns of influenza incidence, while also providing more accurate estimates of the potential effectiveness of vaccination strategies. Nevertheless, the application of such models requires large – scale seroepidemiological studies and detailed information regarding previous influenza exposures within the population, which remains one of the principal limitations to their widespread implementation [17, 18].

Taken together, the clinical and epidemiological consequences of immune imprinting demonstrate that previous antigenic experience is one of the major determinants of both naturally acquired and vaccine – induced immunity against influenza. A comprehensive understanding of this phenomenon is therefore essential for improving influenza surveillance, enhancing the prediction of seasonal epidemics, and guiding the development of next – generation influenza vaccines.

Controversies and the Dual Nature of Immune Imprinting. The concept of Original Antigenic Sin (OAS) was historically introduced to describe the phenomenon whereby the first encounter with influenza virus establishes a persistent immunological bias that shapes subsequent immune responses to antigenically related viral variants. In its classical interpretation, OAS was viewed primarily as a potentially detrimental feature of immunological memory that could limit the effectiveness of protective immune responses during subsequent infections or following vaccination [10, 11].

However, contemporary research has substantially broadened our understanding of this phenomenon. The term immune imprinting, now increasingly adopted in the scientific literature, more accurately reflects the complex, dynamic, and context – dependent nature of adaptive immunity. Within this framework, the primary antigenic exposure is no longer regarded as an “error” of the immune system but rather as an evolutionarily conserved mechanism that enables rapid recognition of antigenically related pathogens and accelerates the development of protective immune responses [4, 5].

Accordingly, immune imprinting exhibits a dual functional nature. When successive influenza virus strains are moderately antigenically related, immune imprinting promotes the rapid reactivation of memory B cells, accelerates antibody production, and enhances cross – protective immunity, thereby reducing the risk of severe disease [5]. Conversely, when the antigenic distance between the primary and newly encountered viral variants is substantial, immune responses may remain predominantly focused on previously established antigenic specificities. Under these circumstances, the production of cross – reactive but poorly neutralizing antibodies predominates, potentially limiting viral clearance and diminishing protective immunity [7, 12]. Therefore, immune imprinting should be viewed as a dynamic balance between the rapidity of secondary immune

responses and their capacity to adapt to novel antigenic variants.

The magnitude of immune imprinting varies considerably among individuals. Its development is influenced by multiple factors, including the age at primary exposure, the nature of the initial infection, the antigenic distance between sequential viral strains, host genetic background, and the cumulative history of previous influenza infections and vaccinations [6, 18]. Equally important is the quality of the primary germinal center response. Efficient germinal center formation and the generation of high – affinity memory B – cell clones establish a stronger and more dominant immunological imprint, whereas a less robust primary response may preserve greater flexibility of the adaptive immune system during subsequent antigenic exposures [5].

Despite the traditional view that immune imprinting is irreversible, accumulating evidence indicates that immunological memory retains a certain degree of plasticity. Repeated infections or vaccination with antigenically updated influenza strains may progressively broaden the antibody repertoire and reshape the overall architecture of the immune response [7, 19].

Nevertheless, available experimental and clinical evidence suggests that complete “reprogramming” of primary immune imprinting is unlikely. Rather, immune imprinting appears to represent a semi – stable immunological memory state that gradually adapts to new antigenic stimuli while retaining key features established during the primary antigenic exposure throughout life. This persistent imprint underlies both the protective potential and the inherent limitations of adaptive immunity to influenza.

Taken together, the modern concept of immune imprinting extends far beyond the classical notion of Original Antigenic Sin. Accumulating experimental and clinical evidence indicates that immune imprinting is an intrinsic property of adaptive immunity that, depending on the antigenic context, may either enhance cross – protective immunity or constrain the generation of novel immune specificities. A deeper understanding of this dual nature is essential for the rational design of vaccination strategies and the development of universal influenza vaccines.

Prospects for Applying the Concept of Immune Imprinting to the Development of Next – Generation Influenza Vaccines. Immune imprinting is now recognized as one of the major challenges in contemporary influenza vaccinology, as previous antigenic experience can profoundly influence both the quality and specificity of vaccine – induced immune responses. In most individuals, vaccination does not induce *de novo* generation of new B – cell clones but instead preferentially reactivates pre – existing memory B cells established during previous influenza infections or vaccinations. As a consequence, the breadth of the antibody response is reduced, limiting protection against antigenically drifted influenza virus variants [10, 11].

At the same time, current insights into immune imprinting are reshaping strategies for influenza vaccine development. Whereas earlier approaches focused primarily on overcoming or minimizing the influence of pre – existing immunological memory, increasing atten-

tion is now being directed toward its deliberate modulation. Within this emerging framework, immune imprinting is viewed not as an obstacle but as a potential tool for vaccine engineering that can be exploited to redirect immune responses toward conserved viral antigenic determinants [4].

One of the most promising directions in contemporary influenza vaccinology is the development of a universal influenza vaccine. This concept is based on eliciting immune responses against highly conserved viral regions, particularly the stem domain of hemagglutinin (HA), which exhibits substantially greater sequence conservation than the immunodominant globular head domain. By targeting these conserved epitopes, universal vaccines aim to induce broad cross – protective immunity regardless of seasonal antigenic drift [5, 12].

Nevertheless, translating this concept into effective vaccines remains challenging. Pre – existing immunological memory frequently continues to direct immune responses toward variable immunodominant epitopes, even when these epitopes are partially modified or masked within vaccine constructs. Consequently, the success of universal influenza vaccines will largely depend on their ability to reshape established immunological hierarchies and recruit previously naïve B – cell clones capable of recognizing conserved antigenic determinants [7].

To achieve this goal, several innovative antigen – engineering strategies are currently being explored. Among the most promising are chimeric hemagglutinins, sequential immunization strategies, nanoparticle – based antigen delivery platforms, epitope – masking approaches, and rational antigen design. Collectively, these approaches seek to remodel immunodominance hierarchies, promote the activation of novel B – cell clones, and broaden the repertoire of broadly neutralizing antibodies [7, 22, 23].

Particular attention has recently been devoted to the possibility of modulating immune imprinting through the regulation of germinal center reactions. It has been proposed that controlling B – cell selection and T follicular helper (T_{fh}) cell – mediated interactions within germinal centers may facilitate the recruitment of naïve B cells into ongoing immune responses, thereby progressively expanding the repertoire of neutralizing antibodies beyond the specificities established during primary antigenic imprinting [5, 6].

Systems immunology is expected to play an increasingly important role in advancing this field. High-throughput technologies-including single-cell sequencing, B-cell receptor repertoire analysis, antibody repertoire profiling, and high-dimensional flow cytometry-now enable detailed reconstruction of individual antigen exposure histories and provide unprecedented insights into the lifelong evolution of immunological memory [6, 7]. These approaches offer new opportunities to predict individual responses to vaccination, optimize vaccine design and immunization strategies, and improve the accuracy of epidemiological models.

Taken together, accumulating experimental and clinical evidence indicates that immune imprinting is not a defect of adaptive immunity but rather one of its fundamental biological properties, ensuring the long – term

maintenance of immunological memory while shaping subsequent immune responses throughout life. A deeper understanding of the molecular and cellular mechanisms underlying this phenomenon will facilitate the development of next – generation influenza vaccines capable not only of inducing protective immunity but also of rationally modulating pre – existing immunological memory. Such an approach is likely to become one of the defining directions of influenza vaccine research and development in the coming decades.

Research findings. Immune imprinting is a fundamental property of adaptive immunity established during the first encounter with an antigen, shaping both humoral and cellular immune responses throughout life. Unlike the classical concept of Original Antigenic Sin (OAS), the contemporary understanding of immune imprinting no longer regards it as a defect of the immune system but rather as an evolutionarily conserved mechanism that may either confer rapid cross – protection or limit the generation of novel immune specificities, depending on the antigenic context.

Accumulating experimental, clinical, and epidemiological evidence indicates that immune imprinting is one of the principal determinants of individual differences in influenza susceptibility, disease severity, vaccine effectiveness, and the heterogeneity of population immunity. Memory B cells, long-lived plasma cells, germinal centers, and T follicular helper (T_{fh}) cells play central roles in this process by establishing and maintaining stable immunological hierarchies that shape subsequent immune responses.

At the same time, recent studies demonstrate that immune imprinting is not an entirely immutable process. Although primary immunological memory is remarkably stable, repeated antigenic exposures can gradually broaden the antibody repertoire and partially reshape immune response profiles. These findings provide a scientific basis for the rational modulation of immunological memory through next-generation vaccine platforms.

These advances are particularly significant for the development of universal influenza vaccines. Rational antigen design, innovations in antigen engineering, systems immunology, and high-throughput immune profiling technologies are creating new opportunities to develop vaccines capable not only of inducing broad protective immunity but also of selectively reshaping pre-existing immunological memory.

In conclusion, the contemporary concept of immune imprinting represents a new paradigm for understanding the interactions between influenza viruses and the human immune system. Further elucidation of the molecular and cellular mechanisms underlying this phenomenon will provide a critical foundation for improving influenza prevention strategies, enhancing the effectiveness of both seasonal and universal influenza vaccines, and advancing personalized approaches to immunoprophylaxis.

Further research should focus on elucidating the mechanisms of immune imprinting and developing personalized influenza vaccination strategies that take an individual's prior immunological history into account.

REFERENCES

1. Iuliano AD, Roguski KM, Chang HH, Muscatello DJ, Palekar R, Tempia S, et al. Estimates of global seasonal influenza-associated respiratory mortality: a modelling study. *Lancet*. 2018;391:1285-1300. [https://doi.org/10.1016/S0140-6736\(17\)33293-2](https://doi.org/10.1016/S0140-6736(17)33293-2)
2. Petrova VN, Russell CA. The evolution of seasonal influenza viruses. *Nat Rev Microbiol*. 2018;16:47-60. <https://doi.org/10.1038/nrmicro.2017.118>
3. Krammer F. The human antibody response to influenza A virus infection and vaccination. *Nat Rev Immunol*. 2019;19:383-397. <https://doi.org/10.1038/s41577-019-0143-6>
4. Cobey S, Hensley SE. Immune history and influenza virus susceptibility. *Curr Opin Virol*. 2017;22:105-111. <https://doi.org/10.1016/j.coviro.2016.12.004>
5. Mesin L, Ersching J, Victora GD. Germinal center B cell dynamics. *Immunity*. 2016;45:471-482. <https://doi.org/10.1016/j.immuni.2016.09.001>
6. Victora GD, Nussenzweig MC. Germinal centers. *Annu Rev Immunol*. 2022;40:413-442. <https://doi.org/10.1146/annurev-immunol-120419-022408>
7. Han AX, de Jong SPJ, Russell CA. Co-evolution of immunity and seasonal influenza viruses. *Nat Rev Microbiol*. 2023;21:805-817. <https://doi.org/10.1038/s41579-023-00945-8>
8. Zhang M, Ma J, Li M. Original antigenic sin in CD4⁺ T cells. *Immunology*. 2025;175:165-179. <https://doi.org/10.1111/imm.13916>
9. Nachbagauer R, Palese P. Is a universal influenza virus vaccine possible? *Annu Rev Med*. 2020;71:315-327. <https://doi.org/10.1146/annurev-med-120617-041310>
10. Francis T. On the doctrine of original antigenic sin. *Proc Am Philos Soc*. 1960;104:572-578.
11. Kim JH, Skountzou I, Compans R, Jacob J. Original antigenic sin responses to influenza viruses. *J Immunol*. 2009;183:3294-3301. <https://doi.org/10.4049/jimmunol.0900398>
12. Arevalo P, McLean HQ, Belongia EA, Cobey S. Earliest infections predict the age distribution of seasonal influenza A cases. *Elife*. 2020;9. <https://doi.org/10.7554/eLife.50060>
13. Slifka MK, Antia R, Whitmire JK, Ahmed R. Humoral immunity due to long-lived plasma cells. *Immunity*. 1998;8:363-372. [https://doi.org/10.1016/S1074-7613\(00\)80541-5](https://doi.org/10.1016/S1074-7613(00)80541-5)
14. Amanna IJ, Slifka MK. Mechanisms that determine plasma cell lifespan and the duration of humoral immunity. *Immunol Rev*. 2010;236:125-138. <https://doi.org/10.1111/j.1600-065X.2010.00912.x>
15. Crotty S. T follicular helper cell biology: a decade of discovery and diseases. *Immunity*. 2019;50:1132-1148. <https://doi.org/10.1016/j.immuni.2019.04.011>

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16. Smith DJ, Forrest S, Ackley DH, Perelson AS. Variable efficacy of repeated annual influenza vaccination. *Proc Natl Acad Sci U S A*. 1999;96:14001-14006. <https://doi.org/10.1073/pnas.96.24.14001>
 17. Lewnard JA, Cobey S. Immune history and influenza vaccine effectiveness. *Vaccines (Basel)*. 2018;6:28. <https://doi.org/10.3390/vaccines6020028>
 18. Gostic KM, Ambrose M, Worobey M, Lloyd-Smith JO. Potent protection against H5N1 and H7N9 influenza via childhood hemagglutinin imprinting. *Science*. 2016;354:722-726. <https://doi.org/10.1126/science.aag1322>
 19. Skowronski DM, Chambers C, Sabaiduc S, De Serres G, Winter AL, Dickinson JA, et al. Beyond antigenic match: possible agent-host and immuno-epidemiological influences on influenza vaccine effectiveness during the 2015-2016 season in Canada. *J Infect Dis*. 2017;216:1487-1500. <https://doi.org/10.1093/infdis/jix526>
 20. Zost SJ, Parkhouse K, Gumina ME, Kim K, Diaz Perez S, Wilson PC, et al. Contemporary H3N2 influenza viruses have a glycosylation site that alters binding of antibodies elicited by egg-adapted vaccine strains. *Proc Natl Acad Sci U S A*. 2017;114:12578-12583. <https://doi.org/10.1073/pnas.1712377114>
 21. Gouma S, Anderson EM, Hensley SE. Challenges of making effective influenza vaccines. *Annu Rev Virol*. 2020;7:495-512. <https://doi.org/10.1146/annurev-virology-010320-044746>
 22. Impagliazzo A, Milder F, Kuipers H, Wagner MV, Zhu X, Hoffman RMB, et al. A stable trimeric influenza hemagglutinin stem as a broadly protective immunogen. *Science*. 2015;349:1301-1306. <https://doi.org/10.1126/science.aac7263>
 23. Boyoglu-Barnum S, Ellis D, Gillespie RA, Hutchinson GB, Park YJ, Moin SM, et al. Quadrivalent influenza nanoparticle vaccines induce broad protection. *Nature*. 2021;592:623-628. <https://doi.org/10.1038/s41586-021-03365-x>

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