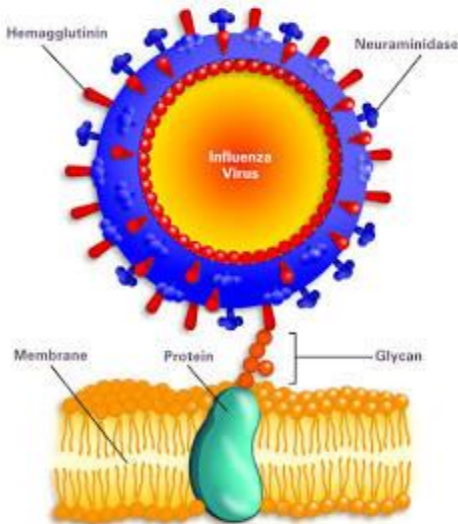
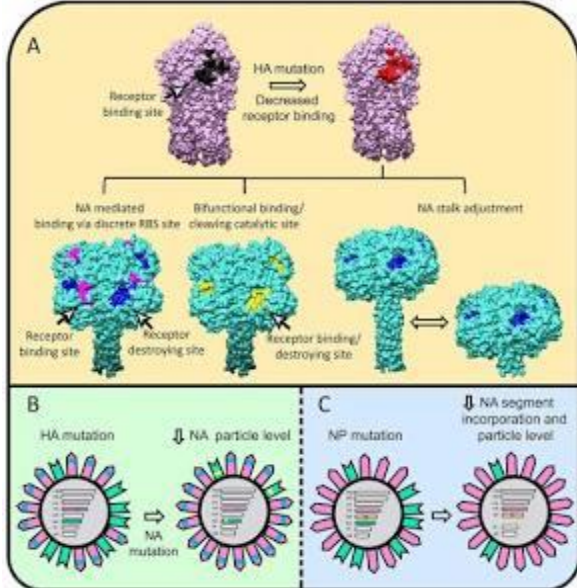


# Flu Vaccines

Hemagglutinin (HA) and Neuraminidase (NA) are the two major surface glycoproteins of the influenza virus, famously represented by the "H" and "N" in strain names like H1N1 or H3N2. They act as functional opposites that must be perfectly balanced for the virus to infect cells, replicate, and spread.

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## Key Functions and Differences

While both proteins interact with **sialic acid** (the receptor on host cell surfaces), they perform distinct roles in the viral life cycle:

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- **Hemagglutinin (HA): The "Key" to Entry**
  - **Function:** Acts as a binding agent that attaches the virus to host cells. It recognizes and binds to sialic acid on the cell membrane, triggering the cell to "swallow" the virus through endocytosis.
  - **Structure:** A trimer (three identical parts) consisting of a globular head for binding and a stalk for membrane fusion.
  - **Immune Response:** HA is the primary target of seasonal flu vaccines, which aim to produce antibodies that block this binding process.
- **Neuraminidase (NA): The "Scissors" for Exit**
  - **Function:** Acts as a receptor-destroying enzyme. After the virus has replicated inside a cell, NA cleaves the sialic acid bonds that tether new viral particles to the cell surface, allowing them to break free and infect other cells.
  - **Structure:** A tetramer (four identical parts) shaped like a mushroom, with a catalytic head that performs the "cutting".
  - **Medical Target:** Antiviral drugs like **Tamiflu (oseltamivir)** work by inhibiting NA, effectively "trapping" the virus on the surface of the already-infected cell to prevent further spread.

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## The "Yin-Yang" Balance

The relationship between HA and NA is often described as a competitive cooperation. If HA binding is too strong or NA activity is too weak, the virus gets stuck and cannot spread; conversely, if NA is too active, it may destroy receptors before HA has a chance to bind. This delicate balance is a major factor in determining how easily a virus can jump between species, such as from birds to humans.

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## Diversity and Subtypes

- **Subtypes:** There are **18 HA subtypes** (H1–H18) and **11 NA subtypes** (N1–N11) recognized in nature, mostly circulating in wild birds.
- **Antigenic Drift:** Both proteins frequently mutate to hide from the human immune system, which is why flu vaccines must be updated almost every year.

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Would you like to know more about how **antiviral drugs** specifically target these proteins, or perhaps how **vaccines** are designed to recognize them?

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If there are only 18 HA subtypes why does a new vaccine need to be developed every year? Shouldn't there be a maximum of 18 different vaccines?

While there are 18 main subtypes of Hemagglutinin, you need a new vaccine every year because of **antigenic drift**—a process where those 18 "master categories" constantly change their internal structure.

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Think of an HA subtype like a "car model." While there might only be 18 basic models (e.g., an H1 "Sedan" or an H3 "Truck"), the virus constantly changes the color, shape, and details of that model every season. Your immune system is like a security guard trained to recognize a **specific** red H1 sedan from last year; if this year's version is a blue H1 sedan with a different grille, the guard may not recognize it as a threat.

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## Why 18 Vaccines Aren't Enough

- **Constant Mutation (Antigenic Drift):** The flu is an RNA virus that replicates very quickly and lacks a "proofreading" mechanism to fix genetic errors. These tiny mutations accumulate specifically in the parts of the HA protein that your antibodies target. Over time, an H3N2 virus can look so different from the H3N2 virus of five years ago that your old antibodies no longer fit.
- **Waning Immunity:** Even if the virus didn't change, your body's immune protection from a flu shot naturally declines over several months. An annual "booster" ensures your antibody levels are high enough for the peak of the next season.
- **Targeting the Winners:** Scientists don't put all 18 subtypes in one shot because most (like H5 or H7) primarily circulate in birds and don't easily infect humans.

Instead, they use global surveillance to predict which specific **variants** of H1N1 and H3N2 (and Influenza B) will be the most dominant "winners" for the upcoming year.

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## Vaccine Composition for 2025–2026

For the **2025–2026 season**, the [U.S. FDA](#) and [CDC](#) have recommended a **trivalent** (three-strain) vaccine to match these specific circulating variants:

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- **A(H1N1):** An A/Victoria/4897/2022-like virus.
- **A(H3N2):** An A/Croatia/10136RV/2023-like virus.
- **Influenza B:** A B/Austria/1359417/2021 (Victoria lineage)-like virus.

U.S. Food and Drug Administration (.gov)

Even when the "match" isn't perfect—which occurred in the 2025–26 season when a drifted H3N2 clade emerged after the vaccine was finalized—the shot still significantly reduces the risk of **hospitalization and death**.

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Would you like to see how researchers are trying to develop a "**universal**" **flu vaccine** that would target the parts of the HA protein that never change?

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How are researchers trying to develop a "universal" flu vaccine that would target the parts of the HA protein that never change?

Researchers are developing a "universal" flu vaccine by shifting the immune system's focus from the rapidly mutating **head** of the Hemagglutinin (HA) protein to its highly conserved **stalk** (or stem). While the head changes annually, the stalk remains virtually identical across many different flu strains.

respiratory-therapy.com +3

As of early 2026, several key strategies are in clinical and preclinical development:

### 1. Chimeric HA (The "Head-Swap" Strategy)

This is currently one of the most advanced approaches.

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- **How it works:** Scientists create "chimera" proteins that pair a common, conserved stalk (like H1) with "exotic" heads from bird flu viruses (like H5 or H8) that humans have never encountered.
- **The Goal:** By giving a series of shots with the *same* stalk but *different* exotic heads, the immune system is "tricked" into ignoring the unfamiliar heads and focusing its defense on the one constant part: the stalk.

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## 2. Headless HA & Nanoparticles

- **Headless HA:** Some researchers try to remove the head entirely to expose the stalk. However, the stalk is structurally unstable on its own.
- **Nanoparticle Scaffolds:** To solve the stability issue, scientists attach the "headless" stalks to synthetic nanoparticles (like ferritin). This presents the stalk in a stable, recognizable shape to the immune system.

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## 3. Computational Design (COBRA & Mosaic)

- **COBRA (Computationally Optimized Broadly Reactive Antigen):** This uses algorithms to find the most common, unchanged sequences across thousands of flu strains to build a "consensus" version of the protein that covers as many variants as possible.
- **Mosaic HAs:** Similar to COBRA, these use "mosaic" head domains that combine pieces from many different strains, overwhelming the immune system so it defaults to targeting the shared, fixed parts.

PubMed Central (PMC) (.gov) +2

## 4. mRNA and "Signal Mimicry"

- **mRNA Platforms:** Companies like Moderna are using mRNA to deliver instructions for these conserved regions, allowing for faster production and potentially stronger immune responses.
- **Integrated Immunity:** New research in 2026 is exploring vaccines that mimic natural immune signals (cytokines) to "awaken" generalist immune cells

(macrophages) in the lungs, providing a broad, temporary shield against multiple respiratory viruses simultaneously.



## Current Status (2026)

While seasonal vaccines for the **2025–2026 season** remain traditional trivalent shots, several universal candidates have reached human trials:

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- **Centivax** launched a Phase 1 trial in February 2026 for a vaccine designed to protect against over 20 flu strains at once.
- The **NIAID** is currently testing "stabilized stem" ferritin nanoparticles in Phase 1 trials.
- **WHO** reports that as of February 2026, there are **46 next-generation influenza vaccines** in clinical development.

Vax-Before-Travel +3

Would you like to explore the **clinical trial results** for a specific vaccine candidate, or see how these strategies differ for **Influenza B** versus Influenza A?

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Describe the clinical trial results for a specific vaccine candidate, and how these strategies differ for Influenza B versus Influenza A?

Current universal flu vaccine research is characterized by shifting from the highly variable "head" of the hemagglutinin (HA) protein to its stable "stalk"

. As of early 2026, several candidates have reached critical human trial milestones.

Nature +1

## Clinical Trial Results: NIAID H1ssF & H10ssF

The [National Institute of Allergy and Infectious Diseases \(NIAID\)](#) has pioneered **stabilized stem ferritin nanoparticle** vaccines, which use a self-assembling scaffold to display the HA stalk.

National Institute of Allergy and Infectious Diseases (NIAID) (.gov) +1

- **H1ssF (Group 1 Vaccine):**
  - **Results:** In a Phase 1 trial of 52 healthy adults, the vaccine was safe and well-tolerated. It elicited **broadly neutralizing antibodies** against various

Group 1 viruses (like H1N1, H2N2, and H5N1) that remained elevated for more than a year.

- **Significance:** It successfully bypassed "antigenic imprinting," where the body normally only responds to the variable "head" it has seen before.
- **H10ssF (Group 2 Vaccine):**
  - **Results:** Phase 1 results published in [Nature Communications](#) (September 2024) showed this candidate was also safe but had **more limited neutralization breadth** compared to the Group 1 version.
  - **Outcome:** While it significantly increased binding antibodies for Group 2 strains (H3, H7, H10), it did not induce potent neutralization against H3N2 viruses, suggesting Group 2 stalks may be more difficult to target.
- **FluMos-v2:** A newer multivalent candidate displaying HA from **six different strains** (four Influenza A and two Influenza B) entered trials in late 2023 to further broaden this protection.

National Institute of Allergy and Infectious Diseases (NIAID) (.gov) +4

## Influenza A vs. Influenza B Strategies

The strategies for these two types differ primarily due to their genetic diversity and evolutionary patterns:

Feature	Influenza A Strategy	Influenza B Strategy
<b>Phylogenetic Groups</b>	Divided into two distinct groups (Group 1 and Group 2), requiring separate stalk designs or a <b>bivalent</b> cocktail.	Less diverse than Type A; it has two main lineages ( <b>Victoria</b> and <b>Yamagata</b> ), allowing for a more unified approach.
<b>Primary Target</b>	Focuses on the <b>highly conserved stalk</b> to protect against numerous "H" subtypes (H1–H18), including those with pandemic potential (H5, H7).	Focuses on broadly reactive antigens that cover both lineages, often included alongside Type A in <b>trivalent</b> universal designs like <b>FluMos-v2</b> .
<b>Pandemic Focus</b>	Heavy emphasis on preventing "jumps" from avian or swine reservoirs (e.g., H5N1).	Primarily focuses on improving seasonal durability, as Type B does not have significant animal reservoirs.

## Emerging Candidates (2026)

- **Centivax (Centi-Flu 01):** Dosing for a Phase 1a trial began in **February 2026**. This vaccine uses an "epitope-focusing" platform designed to outperform standard seasonal shots by targeting conserved regions shared across **24 different flu strains**.
- **FLU-v:** A synthetic peptide vaccine that targets internal, conserved viral proteins to trigger **T-cell responses** rather than just antibodies.

PR Newswire +5

Would you like to see a comparison of **Phase 1 vs. Phase 2** success rates for these next-generation technologies?

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