# Influenza Vaccine

- Clinical Policy Bulletins
- Medical Clinical Policy Bulletins

**Number: 0035**

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## Policy

### Scope of Policy

This Clinical Policy Bulletin addresses influenza vaccine.

1. **Medical Necessity**

   Aetna considers the following U.S. Food and Drug Administration (FDA)-approved influenza vaccines medically necessary according to the recommendations of the Centers for Disease Control and Prevention's (CDC) Advisory Committee on Immunization Practices (ACIP):

   1. FDA-approved standard or preservative-free trivalent influenza injectables (e.g., Afluria, Agriflu, Fluarix, Flucelvax, Fluzone) for members 6 months of age or older; *or*
   2. FDA-approved trivalent intranasal vaccine (e.g., FluMist) for members aged 2 through 49 years of age. **Note:** The CDC does not recommend use in individuals who are pregnant, immunocompromised, or have certain medical conditions (e.g., asthma).

2. **Related Policies**

   1. CPB 0476 - Influenza Rapid Diagnostic Tests

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## CPT Codes / HCPCS Codes / ICD-10 Codes

### CPT codes covered if selection criteria are met:

| Code | Code Description |
|---|---|
| 90630 | Influenza virus vaccine, quadrivalent (IIV4), split virus, preservative free, for intradermal use |
| 90637 | Influenza virus vaccine, quadrivalent (qIRV), mRNA; 30 mcg/0.5 mL dosage, for intramuscular use |
| 90638 | Influenza virus vaccine, quadrivalent (qIRV), mRNA; 60 mcg/0.5 mL dosage, for intramuscular use |
| 90653 | Influenza vaccine, inactivated (IIV), subunit, adjuvanted, for intramuscular use |
| 90654 | Influenza virus vaccine, trivalent (IIV3), split virus, preservative-free, for intradermal use |
| 90655 | Influenza virus vaccine, trivalent (IIV3), split virus, preservative free, 0.25 mL dosage, for intramuscular use |
| 90656 | Influenza virus vaccine, trivalent (IIV3), split virus, preservative free, 0.5 mL dosage, for intramuscular use |
| 90657 | Influenza virus vaccine, trivalent (IIV3), split virus, 0.25 mL dosage, for intramuscular use |
| 90658 | Influenza virus vaccine, trivalent (IIV3), split virus, 0.5 mL dosage, for intramuscular use |
| 90660 | Influenza virus vaccine, trivalent, live (LAIV3), for intranasal use |

| Code | Code Description |
|---|---|
| 90661 | Influenza virus vaccine (ccIIV3), derived from cell cultures, subunit, preservative and antibiotic free, 0.5 mL dosage, for intramuscular use |
| 90662 | Influenza virus vaccine (IIV), split virus, preservative free, enhanced immunogenicity via increased antigen content, for intramuscular use |
| 90672 | Influenza virus vaccine, quadrivalent, live (LAIV4), for intranasal use |
| 90673 | Influenza virus vaccine, trivalent (RIV3), derived from recombinant DNA, hemagglutinin (HA) protein only, preservative and antibiotic free, for intramuscular use |
| 90674 | Influenza virus vaccine, quadrivalent (ccIIV4), derived from cell cultures, subunit, preservative and antibiotic free, 0.5 mL dosage, for intramuscular use |
| 90682 | Influenza virus vaccine, quadrivalent (RIV4), derived from recombinant DNA, hemagglutinin (HA) protein only, preservative and antibiotic free, for intramuscular use |
| 90685 | Influenza virus vaccine, quadrivalent (IIV4), split virus, preservative free, 0.25 mL dosage, for intramuscular use |
| 90686 | Influenza virus vaccine, quadrivalent (IIV4), split virus, preservative free, 0.5 mL dosage, for intramuscular use |
| 90687 | Influenza virus vaccine, quadrivalent (IIV4), split virus, 0.25 mL dosage, for intramuscular use |
| 90688 | Influenza virus vaccine, quadrivalent (IIV4), split virus, 0.5 mL dosage, for intramuscular use |
| 90694 | Influenza virus vaccine, quadrivalent (aIIV4), inactivated, adjuvanted, preservative free, 0.5 mL dosage, for intramuscular use [over age 65] |
| 90695 | Influenza virus vaccine, H5N8, derived from cell cultures, adjuvanted, for intramuscular use |
| 90756 | Influenza virus vaccine, quadrivalent (ccIIV4), derived from cell cultures, subunit, antibiotic free, 0.5mL dosage, for intramuscular use |

## CPT codes not covered for indications listed in the CPB:

| | |
|---|---|
| 90664 | Influenza virus vaccine, live (LAIV), pandemic formulation, for intranasal use |

## Other CPT codes related to the CPB:

| | |
|---|---|
| 87275 | Infectious agent antigen detection by immunoflourescent technique; influenza B virus |
| 87276 | influenza A virus |
| 87400 | Infectious agent antigen detection by enzyme immunoassay technique, qualitative or semi quantitative, multiple step method; influenza A or B, each |
| 90460 | Immunization administration through 18 years of age via any route of administration, with counseling by physician or other qualified health care professional; first or only component of each vaccine or toxoid administered |
| 90461 | each additional vaccine or toxoid component administered (list separately in addition to code for primary procedure) |
| 90471 | Immunization administration (includes percutaneous, intradermal, subcutaneous, intramuscular injections); one vaccine (single or combination vaccine/toxoid) |
| + 90472 | each additional vaccine (single or combination vaccine/toxoid) (List separately in addition to code for primary procedure) |
| 90473 | Immunization administration by intranasal or oral route: one vaccine (single or combination vaccine/toxoid) |
| + 90474 | each additional vaccine (single or combination vaccine/toxoid) (List separately in addition to code for primary procedure) |
| 90666 | Influenza virus vaccine (IIV), pandemic formulation, split virus, preservative free, for intramuscular use |
| 90667 | Influenza virus vaccine (IIV), pandemic formulation, split virus, adjuvanted, for intramuscular use |
| 90668 | Influenza virus vaccine (IIV), pandemic formulation, split virus, for intramuscular use |

## HCPCS codes covered if selection criteria are met:

| | |
|---|---|
| G0008 | Administration of influenza virus vaccine |
| J3530 | Nasal vaccine inhalation |
| Q2034 | Influenza virus vaccine, split virus, for intramuscular use (agriflu) |
| Q2035 | Influenza virus vaccine, split virus, when administered to individuals 3 years of age and older, for intramuscular use (Afluria) |

| Code | Code Description |
|---|---|
| Q2036 | Influenza virus vaccine, split virus, when administered to individuals 3 years of age and older, for intramuscular use (Flulaval) |
| Q2037 | Influenza virus vaccine, split virus, when administered to individuals 3 years of age and older, for intramuscular use (Fluvirin) |
| Q2038 | Influenza virus vaccine, split virus, when administered to individuals 3 years of age and older, for intramuscular use (Fluzone) [also covered for Fluzone High-Dose for member's age 65 years of age or older when influenza immunization is recommended] |
| Q2039 | Influenza virus vaccine, split virus, not otherwise specified |

**Other HCPCS codes related to the CPB:**

| | |
|---|---|
| G0310 | Immunization counseling by a physician or other qualified health care professional when the vaccine(s) is not administered on the same date of service, 5 to 15 mins time (this code is used for Medicaid billing purposes) |
| G0311 | Immunization counseling by a physician or other qualified health care professional when the vaccine(s) is not administered on the same date of service, 16-30 mins time (this code is used for Medicaid billing purposes) |
| G0312 | Immunization counseling by a physician or other qualified health care professional when the vaccine(s) is not administered on the same date of service for ages under 21, 5 to 15 mins time (this code is used for Medicaid billing purposes) |
| G0313 | Immunization counseling by a physician or other qualified health care professional when the vaccine(s) is not administered on the same date of service for ages under 21, 16-30 mins time (this code is used for Medicaid billing purposes) |

**ICD-10 codes covered if selection criteria are met:**

| | |
|---|---|
| Z23 | Encounter for immunization |

***Trivalent intranasal vaccine (e.g., FluMist):***

**CPT codes covered if selection criteria are met:**

| | |
|---|---|
| 90660 | Influenza virus vaccine, trivalent, live (LAIV3), for intranasal use |

**ICD-10 codes not covered for indications listed in the CPB (not all-inclusive):**

| | |
|---|---|
| D80.0 - D89.839 | Disorders involving the immune mechanism |
| J45.20 – J45.998 | Asthma |
| O00.101 - O9A.519 | Pregnancy, childbirth and the puerperium |

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# Background

Influenza ("the flu") is a contagious respiratory illness caused by viruses that infect the nose, throat, and sometimes the lungs. Influenza can cause mild to severe illness, and at times can lead to death. Symptoms, which may appear suddenly, include fever, chills, cough, sore throat, runny or stuffy nose, muscle or body aches, headaches, and fatigue. It is important to note that not everyone with the flu will have a fever. In addition, some people may have vomiting and diarrhea, though this is more common in children than adults. Most experts believe that flu viruses spread mainly by tiny droplets made when people infected with the flu cough, sneeze or talk. Less often, a person might get the flu from contact with a contaminated surface or object and subsequently touch their own mouth, nose, or possibly their eyes. Influenza places a substantial health burden on the United States (U.S.) each year, sickening millions, hospitalizing hundreds of thousands and killing thousands to tens of thousands. Thus, the Centers for Disease Control and Prevention (CDC), Advisory Committee on Immunization Practices (ACIP), recommends individuals to get a flu vaccine each year in order to prevent contracting and spreading influenza viruses (CDC, 2019).

The composition of U.S. flu vaccines is reviewed annually. The vaccine imparts immunity against the influenza virus by stimulating production of antibodies that are specific to the disease. Persons who receive the vaccine will become immune only to those strains of the virus from which the vaccine was prepared.

Seasonal influenza epidemics are caused by influenza A and B virus types. The virus types are recognized by the surface antigens they carry, and two such antigens, hemagglutinin (H) and neuraminidase (N), have been identified and are used to

classify the various viruses. Subtypes of these strains (H1, H2, H3, N1, N2) have been associated with influenza A virus and have been recognized to cause disease in humans. Immunity to any of these surface antigens increases resistance to infection and decreases the severity of the disease if infection occurs. Influenza B viruses, classified into two lineages B/Yamagata and B/Victoria, have co-circulated with influenza A. Eventually, antigenic variation can occur, and immunity to one strain may no longer impart immunity to distantly related subtypes of the virus.

From the 1978-1979 through 2012-2013 seasons, U.S. flu vaccines were trivalent, meaning they included three vaccine viruses: an influenza A(H1N1), an A(H3N2), and a B-lineage vaccine virus (either from the B/Yamagata or B/Victoria lineage). From 2013-2014 through 2023-2024 flu seasons, quadrivalent flu vaccines were made available. The quadrivalent vaccine contained a fourth component—a second influenza B virus—in order to protect against both lineages of influenza B viruses. However, influenza B/Yamagata viruses have not been detected to be actively circulating in global surveillance after March 2020, and therefore, their inclusion in flu vaccines is no longer warranted (CDC, 2024; FDA, 2024; Paget et al, 2022).

In March 2024, the U.S. Food and Drug Administration (FDA) strongly recommended to influenza vaccine manufacturers the removal of the B/Yamagata lineage virus from seasonal influenza vaccines in the U.S. for the 2024-2025 influenza season. FDA and the manufacturers have been working together so that the move from quadrivalent to trivalent seasonal influenza vaccines occurs for the upcoming influenza season.

Trivalent flu vaccines are formulated to protect against three flu viruses (an A(H1N1) virus, an A(H3N2) virus, and a B/Victoria virus).

The recommended trivalent vaccines for use in the 2024-2025 season in the U.S. should contain the following:

- Egg-based vaccines
    - an A/Victoria/4897/2022 (H1N1)pdm09-like virus;
    - an A/Thailand/8/2022 (H3N2)-like virus; and
    - a B/Austria/1359417/2021 (B/Victoria lineage)-like virus;

- Cell culture- or recombinant-based vaccines
    - an A/Wisconsin/67/2022 (H1N1)pdm09-like virus;
    - an A/Massachusetts/18/2022 (H3N2)-like virus; and
    - a B/Austria/1359417/2021 (B/Victoria lineage)-like virus.

The CDC recommends everyone 6 months of age and older, with rare exceptions, to receive an updated 2024-2025 flu vaccine to reduce the risk of influenza and its potentially serious complications in the fall and winter. Updated 2024-2025 flu vaccines will all be trivalent and will protect against an H1N1, H3N2 and a B/Victoria lineage virus. The composition of this season's vaccine compared to last has been updated with a new influenza A(H3N2) virus. Moreover, The CDC reports that it is safe to receive the COVID-19 and flu vaccines at the same visit. Data continue to show the importance of vaccination to protect against severe outcomes of COVID-19 and flu, including hospitalization and death.

For individuals younger than 65 years, the CDC does not preferentially recommend any licensed, age-appropriate influenza (flu) vaccine over another. Options for this age group include inactivated influenza vaccines [IIVs], recombinant influenza vaccine [RIV], or live attenuated influenza vaccine (LAIV), with no preference for any flu vaccine over another. Everyone should get an age-appropriate vaccine (that is, one that is approved for their age), with the exception that individuals 18 through 64 years old who have had a solid organ transplant and are taking immunosuppressive medications may receive high-dose (HD-IIV3) or adjuvanted inactivated (aIIV3) influenza vaccines as acceptable options (without a preference over other age-appropriate IIV3s and RIV3).

For individuals 65 years and older, there are three flu vaccines that are preferentially recommended over standard-dose, unadjuvanted flu vaccines. These are Fluzone High-Dose flu vaccine, Flublok Recombinant flu vaccine and Fluad Adjuvanted flu vaccine. This recommendation was based on a review of available studies which suggests that, in this age group, these vaccines are potentially more effective than standard dose unadjuvanted influenza vaccines. However, if none of the three influenza vaccines is available at the time of administration, people in this age group should get any other age-appropriate influenza vaccine instead.

Each year CDC publishes recommendations for the use of flu vaccines in the U.S. based on input from the ACIP.

## Intradermal Vaccine

On May 11, 2011, the FDA approved Sanofi Pasteur's supplemental Biologics License Application for licensure of Fluzone Intradermal (Influenza Virus Vaccine). Fluzone intradermal vaccine is indicated for active immunization of adults 18 through 64 years of age against influenza disease caused by influenza virus subtypes A and type B contained in the vaccine. The most common side effects observed with the administration of Fluzone Intradermal vaccine include injection-site reactions, erythema,

induration, swelling, pain, and pruritus. Erythema, induration, swelling, and pruritus occurred more frequently following Fluzone Intradermal than Fluzone. However, Sanofi Pasteur, the manufacturer of standard dose Intradermal IIV4, discontinued the production and supply of Fluzone Intradermal Quadrivalent vaccine at the conclusion of the 2017-2018 influenza season (MDedge, 2018).

Frenck and colleagues (2011) examined if reduced doses of trivalent inactivated influenza vaccine (TIV) administered by the intradermal (ID) route generated similar immune responses to standard TIV given intramuscularly (IM) with comparable safety profiles. Recent changes in immunization recommendations have increased the number of people for whom influenza vaccination is recommended. Thus, given this increased need and intermittent vaccine shortages, means to rapidly expand the vaccine supply are needed. Previously healthy subjects 18 to 64 years of age were randomly assigned to 1 of 4 TIV vaccine groups: standard 15 µg HA/strain TIV IM, either 9 µg or 6 µg HA/strain of TIV ID given using a new microinjection system (BD Soluvia™ Microinjection System(1)), or 3 µg HA/strain of TIV ID given by Mantoux technique. All vaccines contained A/New Caledonia (H1N1), A/Wyoming (H3N2) and B/Jiangsu strains of influenza. Sera were obtained 21 days after vaccination and hemagglutination inhibition (HAI) assays were performed and geometric mean titers (GMT) were compared among the groups. Subjects were queried immediately following vaccination regarding injection pain and quality of the experience. Local and systemic reactions were collected for 7 days following vaccination and compared. A total of 10 study sites enrolled 1,592 subjects stratified by age; 18 to 49 years (n = 814) and 50 to 64 years (n = 778). Among all subjects, for each of the 3 vaccine strains, the GMTs at 21 days post-vaccination for both the 9 µg and the 6 µg doses of each strain given ID were non- inferior to GMTs generated after standard 15 µg doses/strain IM. However, for the 3 µg ID dose, only the A/Wyoming antigen produced a GMT that was non-inferior to the standard IM dose. Additionally, in the subgroup of subjects 50 to 64 years of age, the 6 µg dose given ID induced GMTs that were inferior to the standard IM TIV for the A/H1N1 and B strains. No ID dose produced a GMT superior to that seen after standard IM TIV. Local erythema and swelling were significantly more common in the ID groups but the reactions were mild-to-moderate and short-lived. No significant safety issues related to intradermal administration were identified. Participants given TIV ID provided favorable responses to questions about their experiences with ID administration. The authors concluded that for the aggregated cohorts of adults 18 to 64 years of age, reduced doses (6 µg and 9 µg) of TIV delivered ID using a novel microinjection system stimulated comparable HAI antibody responses to standard TIV given IM. The reduced 3 µg dose administered ID by needle and syringe, as well as the 6 µg ID for subjects aged 50 to 64 years of age generated poorer immune responses as compared to the 15 µg IM dose.

Pileggi et al (2015) stated that the primary influenza prevention strategy is focused on annual vaccination according to the categories identified in the various countries as being at greatest risk of complications. Many studies were conducted in order to demonstrate that ID vaccine formulation represents a promising alternative to conventional IM formulation, especially in subjects with an impaired immune system. However, there is no consensus whether the safety and effectiveness of ID is equivalent to IM in these subjects. Therefore, these investigators performed a meta-analysis of RCTs to compare the immunogenicity and safety of ID and IM influenza vaccines in subjects with a depleted immune system. These researchers conducted a search strategy of medical literature published until November 2014 in order to identify RCTs that evaluated the immunogenicity and safety of ID compared with IM influenza vaccines in immuno-compromised patients. They identified a total of 269 citations through research in electronic databases and scanning reference lists. Of these, 6 articles were included in the meta-analysis, for a total of 673 subjects. The sero-protection rate induced by the ID vaccine is comparable to that elicited by the IM vaccine. The overall RR was 1.00 (95 % CI: 0.91 to 1.10) for A/H1N1 strain, 1.00 (95 % CI: 0.90 to 1.12) for A/H3N2 and 0.99 (95 % CI: 0.84 to 1.16) for B strain. No significant differences in the occurrence of systemic reactions were detected (17.7 % in the ID group versus 18.2 % in the IM group) with a pooled RR = 1.00 (95 % CI: 0.67 to 1.51), whereas ID administration caused significantly more injection site reactions with a mean frequency of 46 % in the ID group compared to 22 % in the IM group, with a pooled RR = 1.89 (95 % CI: 1.40 to 2.57). The authors concluded that ID influenza vaccine had shown a similar immunogenicity and safety to the IM influenza vaccine in immuno-compromised patients, and it may be a valid option to increase compliance to influenza vaccination in these populations.

## Intranasal

On September 20, 2024, The Food and Drug Administration (FDA) approved the nasal spray flu vaccine, FluMist (MedImmune, LLC), for self or caregiver administration. FluMist is sprayed into the nose and is approved for the prevention of influenza disease in individuals 2 through 49 years of age. FluMist is currently available for administration by a health care provider in a health care setting (including a pharmacy) only. The option for self or caregiver administration is not expected to be available until next flu season (2025-2026). When self or caregiver administration becomes available, it will be possible for people to administer the vaccine to themselves (if they are 18 through 49 years old) or for it to be administered by a caregiver who is age 18 years or older (if the recipient is 2 through 17 years old). FluMist contains weakened live influenza viruses. FluMist has the same vaccine virus components as other flu vaccines and will protect against an H1N1 virus, and an H3N2 virus, and an influenza B virus (CDC, 2024a).

The effectiveness of FluMist has not been studied in immunocompromised persons. Data on safety and shedding of vaccine virus after administration of FluMist in immunocompromised persons are limited to 173 persons with HIV infection and 10 mild to moderately immunocompromised children and adolescents with cancer.

The CDC does not recommend the nasal spray flu vaccine for pregnant people, but does recommend the vaccine injection (CDC, 2024b).

FluMist is contraindicated in children and adolescents through 17 years of age who are receiving aspirin therapy or aspirin-containing therapy and persons who have had a severe allergic reaction (e.g., anaphylaxis) to any component of the vaccine including egg protein, or after a previous dose of any influenza vaccine.

The most common solicited adverse reactions (10% or more in vaccine recipients and at least 5% greater than in placebo recipients) reported after FluMist were runny nose or nasal congestion (ages 2 years through 49 years), fever over 100°F (children ages 2 years through 6 years), and sore throat (adults ages 18 years through 49 years).

## Booster Dose of Influenza Vaccine

Liao and colleagues (2016) noted that booster influenza vaccination has been recommended for patients with chronic renal disease in order to enhance the immune response to the influenza vaccine; however, the effectiveness of a booster influenza vaccination is a matter of controversy. These investigators performed a meta-analysis to determine the effectiveness in patients with hemodialysis (HD), peritoneal dialysis (PD) and renal transplant recipient (RT). The sero-protection rate was used as a serologic parameter to describe the immune response to the vaccine. Statistical analysis was performed to calculate the pooled rate difference (RD) and 95 % CI. The pooled RD for the H1N1, H3N2 and B influenza vaccines was 0.02 (95 % CI: -0.02 to 0.06), 0.05 (95 % CI: -0.01 to 0.11), 0.04 (95 % CI: -0.02 to 0.10), respectively. The authors concluded that a booster dose of the influenza vaccine did not effectively enhance immunogenicity. Therefore, a booster dose of vaccine is not recommended for patients with hemodialysis, peritoneal dialysis and renal transplant recipients.

## Does Repeated Influenza Vaccination Attenuate Effectiveness

Jones-Gray et al (2023) noted that influenza vaccines require annual re-administration; however, several reports have suggested that repeated vaccination might attenuate the vaccine's effectiveness. In a systematic review and meta-analysis, these researchers estimated the reduction in vaccine effectiveness associated with repeated influenza vaccination. They searched Medline, Embase, and CINAHL Complete databases for studies published from January 1, 2016, to June 13, 2022, and Web of Science for studies published from database inception to June 13, 2022. For studies published before January 1, 2016, these investigators consulted published systematic reviews. Two reviewers independently screened, extracted data using a data collection form, assessed studies' risk of bias using the Risk Of Bias In Non-Randomized Studies of Interventions (ROBINS-I) and evaluated the weight of evidence by the GRADE approach. They included observational studies and RCTs that reported vaccine effectiveness against influenza A(H1N1)pdm09, influenza A(H3N2), or influenza B using 4 vaccination groups: current season; previous season; current and previous seasons; and neither season (reference). For each study, these investigators calculated the absolute difference in vaccine effectiveness (ΔVE) for current season only and previous season only versus current and previous season vaccination to estimate attenuation associated with repeated vaccination. Pooled vaccine effectiveness and ΔVE were calculated by season, age group, and overall. These researchers identified 4,979 studies, selected 681 for full review, and included 83 in the systematic review and 41 in meta-analyses. ΔVE for vaccination in both seasons compared with the current season was -9 % (95 % CI: -16 to -1, I2 = 0%; low certainty) for influenza A(H1N1)pdm09, -18 % (-26 to -11, I2 = 7%; low certainty) for influenza A(H3N2), and -7 % (-14 to 0, I2 = 0%; low certainty) for influenza B, indicating lower protection with consecutive vaccination. However, for all types, A subtypes and B lineages, vaccination in both seasons afforded better protection than not being vaccinated. The authors concluded that their estimates suggested that, although vaccination in the previous year reduced vaccine effectiveness, vaccination in 2 consecutive years provided better protection than no vaccination. These researchers stated that the estimated effects of vaccination in the previous year are concerning and warrant further investigations; however, are not consistent or severe enough to support an alternative vaccination regimen at this time.

## Dual COVID-19 and Seasonal Influenza Vaccination

Xie et al (2023) stated that the clinical guideline states that COVID-19 vaccination can be administered concurrently with Influenza (flu) vaccination (dual vaccination). Using data from the 2021 National Health Interview Survey (NHIS), these investigators carried out descriptive analysis and multi-variate logistic regressions to examine the association between dual vaccination status and self-reported COVID-19 infection and severity. Among 21,387 (weighted 185,251,310) U.S. adults, approximately 22 % did not receive either the flu or COVID-19 vaccine, 6.0 % received the flu vaccine only, 29.1 % received the COVID-19 vaccine only, and 42.5 % received both vaccines. In the multi-variate analysis, individuals with dual vaccination (OR, 0.65, 95 % CI: 0.56 to 0.75) and COVID-19 vaccine only (OR, 0.71, 95 % CI: 0.61 to 0.82) were significantly less likely to report COVID-19 infection when compared with those unvaccinated. There was no significant difference in self-reported COVID-19 symptom severity by vaccination status. The authors concluded that the findings of this study suggested that dual vaccination may be an effective strategy to reduce the contagious respiratory disease burden.

Nguyen et al (2023) noted that despite recommendations for influenza and COVID-19 vaccines, studies have documented gaps and disparities in vaccination coverage for adults and adolescents. Understanding the proportion and demographics of those unvaccinated against influenza and/or COVID-19 is important for tailoring appropriate messaging and strategies to increase confidence and uptake. Using the 2021 NHIS, these researchers examined the prevalence of 4 vaccination patterns (exclusive influenza vaccination, exclusive COVID-19 vaccination, dual influenza and COVID-19 vaccination, and neither vaccination) by sociodemographic and other characteristics among adults and adolescents aged 12 to 17 years. Adjusted multi-variable regression analyses were carried out to examine factors associated with each of the 4 vaccination categories among adults and

adolescents. In 2021, 42.5 % of adults and 28.3 % of adolescents received both influenza and COVID-19 vaccines, while approximately a quarter (22.4 %) of adults and a third (34.0 %) of adolescents did not receive either vaccine. Among adults and adolescents, 6.0 % and 11.4 % were exclusively vaccinated against influenza; and 29.1 % and 26.4 % were exclusively vaccinated against COVID-19, respectively. Among adults, exclusive COVID-19 or dual vaccination was more likely to be associated with older age, non-Hispanic multi/other race, and having a college degree compared to their respective counterparts. Exclusive influenza or neither vaccination was more likely to be associated with younger age, having a high school diploma or less, living below the poverty level, and having a previous COVID-19 diagnosis. The authors concluded that during the COVID-19 pandemic, approximately 2/3 of adolescents and 3/4 of adults received exclusive influenza or COVID-19 vaccines or both vaccines in 2021. Vaccination patterns differed by sociodemographic and other characteristics. Promoting confidence in vaccines and reducing barriers to access is needed to protect individuals and families from severe health consequences of vaccine-preventable diseases. Being up-to-date with all recommended vaccinations can prevent a future resurgence of hospitalizations and cases.

## Effect of Influenza Vaccine in Reducing the Severity of Clinical Outcomes in Patients with COVID-19

Almadhoon et al (2022) stated that recent evidence suggested that vaccination against influenza may reduce the clinical outcomes of COVID-19. In a systematic review and meta-analysis, these researchers examined the link between influenza vaccination and the severity of COVID-19 infection. They searched 5 databases until August 2021; and included studies that reported the relationship between influenza vaccination and COVID-19 outcomes. These investigators pooled the data as RR or mean difference (MD), with 95 % CIs, the data pooled using fixed and random effects models according to the heterogeneity of results. A total of 16 observational studies with 191,496 COVID-19 patients were included. In terms of mechanical ventilation, this analysis showed a significant favor for the influenza vaccinated group over the non-vaccinated group (RR = 0.72, 95 % CI: 0.54 to 0.96, p = 0.03). However, the analysis indicated no statistically significant differences between vaccinated and non-vaccinated groups in the term of mortality rate (RR = 1.20, 95 % CI: 0.71 to 2.04], p = 0.50), hospital admissions (RR = 1.04, 95 % CI: 0.84 to 1.29, p = 0.75), intensive care unit (ICU) admissions (RR = 0.84, 95 % CI: 0.44 to 1.62, p = 0.60). The authors concluded that the analysis showed a significant favor for mechanical ventilation in influenza vaccinated COVID-19 patients over the non-vaccinated ones, on the other hand, there were no significant differences between influenza vaccinated and the non-vaccinated groups among COVID-19 patients in the mortality rate, hospital admission, hospitalization time, ICU admission, ICU time, and appearance of symptoms. However, the study was limited by the heterogeneity of data and the inclusion of retrospective studies, besides that most of the included studies have not examined viral infections other than COVID-19. Furthermore, this should not overlook the importance of influenza vaccination, especially during the COVID-19 pandemic. These researchers stated that future research of high-quality RCTs are needed to examine the effectiveness of the influenza vaccine in COVID-19 patients. The regular updating of the influenza vaccine should also be put into consideration. Other possible important confounding factors should also be taken into consideration, such as patient's health literacy, and socioeconomic status.

The authors stated that the drawbacks of this review were the inclusion of retrospective studies that were liable to bias. In addition, the results showed heterogeneity that sometimes could not be resolved. There has been a wide variety of included populations, as some studies included all COVID 19 patients, others included only hospitalized ones; 1 study only included pregnant patients, and another study only included pediatrics population. Furthermore, there were different follow-up periods.

Su et al (2022) noted that the association between influenza vaccination and COVID-19 remains controversial. In a meta-analysis , these investigators examined if influenza vaccination could reduce the susceptibility and severity of SARS-CoV-2 infection. They carried out a systematic literature search of PubMed, Web of Science, the Cochrane Library, Embase, China National Knowledge Infrastructure, SinoMed, Wanfang Data Knowledge Service Platform, and China Science and Technology Journal VIP Database from database inception to August 2021. The pooled RR with 95 % CI was used to estimate the effect of influenza vaccination on COVID-19. The I2 value was used to examine heterogeneity. If I2 were greater than 50 %, the random-effects model was used as the pooling method. A total of 23 published articles with 1,037,445 subjects were identified. This meta-analysis showed that influenza vaccination was associated with reduced risk of COVID-19 infection (RR = 0.83, 95 % CI: 0.76 to 0.90) and hospitalization (RR = 0.71, 95 % CI: 0.59 to 0.84), although not significantly associated with ICU admission and death (risk of ICU admission: RR = 0.93, 95 % CI: 0.64 to 1.36; risk of death: RR = 0.83, 95 % CI: 0.68 to 1.01). Further analysis suggested that the tetra-valent influenza vaccine may be associated with a reduced risk of COVID-19 infection (RR = 0.74, 95 % CI: 0.65 to 0.84). The authors concluded that the findings of this review suggested that influenza vaccination was associated with reduced susceptibility to; or disease severity of COVID-19 and that influenza vaccination may reduce the risk of COVID-19 and improve clinical outcomes. Moreover, these researchers stated that further investigation is needed to confirm and further clarify this study's preliminary findings, and more in-depth studies are needed to explain the potential mechanisms by which influenza vaccines could reduce the risk of COVID-19 infection and disease severity.

The authors stated that this meta-analysis had several drawbacks. First, the evidence of the correlation between influenza vaccination and COVID-19 was mainly based on observational studies, which only generated hypotheses. Thus, further studies with more appropriate designs are still needed to verify this study's findings. Second, the small number of studies included in this meta-analysis on influenza vaccination and the risk of hospitalization, ICU admission, and death in patients with COVID-19 lacked sufficient data to conduct subgroup and sensitivity analyses. Third, considering the completeness of the data and inappropriate statistical methods, this study was not included in the gray literature database in the search strategy, which may have caused some bias to the findings. Fourth, owing to the limited authority of the retrieval system used in this study, literature

other than Chinese and English could not be obtained. This study focused only on the findings of the literature on influenza vaccines and COVID-19 in both Chinese and English; thus, there may be a potential language bias in the study results. A more comprehensive study will be carried out when more literature is available in other languages. Fifth, although most of the studies included in this meta-analysis controlled for the underlying confounders, this study was unable to adjust for all potential and unrecognized confounders, which may have an impact on the associations this study observed.

## Egg Allergy

Egg allergy may be confirmed by a consistent medical history of adverse reactions to eggs and egg-containing foods, plus a skin and/or blood testing for IgE antibodies to egg proteins.

There are now influenza vaccine options for persons with an egg allergy.

No post-vaccination observation period is recommended specifically for egg-allergic persons. However, ACIP recommends that vaccine providers consider observing patients (seated or supine) for 15 minutes after administration of any vaccine to decrease the risk for injury should syncope occur.

## H1N1 (Swine Flu)

According to the CDC, H1N1 (swine flu) is an influenza virus that was first detected in people in the U.S. in April 2009. It spreads from person-to-person in much the same way that regular seasonal influenza viruses spread (i.e., through coughing or sneezing by people with influenza). This virus was originally referred to as "swine flu" because laboratory testing showed that many of the genes in this new virus were very similar to influenza viruses that normally occur in pigs (swine) in North America. However, studies have shown that this new virus is very different from what normally circulates in North American pigs. It has two genes from flu viruses that normally circulate in pigs in Europe and Asia as well as genes from bird (avian) flu and human influenza strains. It is referred to as a "quadruple reassortant" virus. Symptoms are similar to seasonal influenza (e.g., fever and chills, cough, sore throat, muscle aches, headache, and extreme fatigue). The CDC, however, reported that there is little 2009 H1N1 virus currently circulating in the U.S. and the Department of Health and Human Services has declared the end of the H1N1 influenza public health emergency as of June 23, 2010. With 2009 H1N1, approximately 90 % of estimated hospitalizations and 87 % of estimated deaths from April 2009 through January 16, 2010 occurred in people younger than age 65 years. In contrast, with seasonal influenza, about 60 % of seasonal flu-related hospitalizations and 90 % of flu-related deaths occur in people aged 65 years and older. These data confirm that the 2009 H1N1 impacted younger adults and children more than older adults compared to seasonal flu. However, people in all age groups can develop severe illness from either seasonal flu or from 2009 H1N1.

## Population-Specific

Nichol and colleagues (2007) examined the effectiveness of influenza vaccine in seniors over the long-term. Data were pooled from 18 cohorts of community-dwelling elderly members of 1 U.S. health maintenance organization (HMO) for 1990 to 1991 through 1999 to 2000 and of 2 other HMOs for 1996 to 1997 through 1999 to 2000. Logistic regression was used to estimate the effectiveness of the vaccine for the prevention of hospitalization for pneumonia or influenza and death after adjustment for important co-variates. Additional analyses explored for evidence of bias and the potential effect of residual confounding. There were 713,872 person-seasons of observation. Most high-risk medical conditions that were measured were more prevalent among vaccinated than among unvaccinated persons. Vaccination was associated with a 27 % reduction in the risk of hospitalization for pneumonia or influenza (adjusted odds ratio, 0.73; 95 % confidence interval [CI]: 0.68 to 0.77) and a 48 % reduction in the risk of death (adjusted odds ratio, 0.52; 95 % CI: 0.50 to 0.55). Estimates were generally stable across age and risk subgroups. In the sensitivity analyses, these researchers modeled the effect of a hypothetical unmeasured confounder that would have caused over-estimation of vaccine effectiveness in the main analysis; vaccination was still associated with statistically significant -- though lower -- reductions in the risks of both hospitalization and death. The authors concluded that during 10 seasons, influenza vaccination was associated with significant reductions in the risk of hospitalization for pneumonia or influenza and in the risk of death among community-dwelling elderly persons. They noted that vaccine delivery to this high-priority group should be improved.

In an editorial that accompanied the afore-mentioned study, Treanor (2007) stated that these findings support the current policy of vaccinating the elderly but also demonstrate that the inactivated influenza vaccine is by itself a relatively mediocre means for controlling flu in this population. Until more immunogenic vaccines are developed, routine vaccination of children as well as health care workers could limit transmission and play an important role in controlling the development of influenza in the elderly.

Maternal influenza immunization is a strategy with substantial benefits for both mothers and infants. Zaman et al (2008) evaluated the clinical effectiveness of inactivated influenza vaccine administered during pregnancy in Bangladesh. In this randomized study, a total of 340 mothers were assigned to receive either inactivated influenza vaccine (influenza-vaccine group) or the 23-valent pneumococcal polysaccharide vaccine (control group). Mothers were interviewed weekly to assess illnesses until 24 weeks after birth. Subjects with febrile respiratory illness were assessed clinically, and ill infants were tested for influenza antigens. These researchers estimated the incidence of illness, incidence rate ratios, and vaccine effectiveness. Mothers and infants were observed from August 2004 through December 2005. Among infants of mothers who received

influenza vaccine, there were fewer cases of laboratory-confirmed influenza than among infants in the control group (6 cases and 16 cases, respectively), with a vaccine effectiveness of 63 % (95 % CI: 5 to 85). Respiratory illness with fever occurred in 110 infants in the influenza-vaccine group and 153 infants in the control group, with a vaccine effectiveness of 29 % (95 % CI: 7 to 46). Among the mothers, there was a reduction in the rate of respiratory illness with fever of 36 % (95 % CI: 4 to 57). The authors concluded that inactivated influenza vaccine reduced proven influenza illness by 63 % in infants up to 6 months of age and averted about one-third of all febrile respiratory illnesses in mothers and young infants.

Guidelines for preventing infections in hematopoietic cell transplant (HCT) recipients by the Center for International Blood and Marrow Transplant Research, National Marrow Donor Program, European Group for Blood and Marrow Transplantation, American Society for Blood and Marrow Transplantation, Canadian Blood and Marrow Transplant Group, Infectious Diseases Society of America, Society for Healthcare Epidemiology of America, Association of Medical Microbiology and Infectious Disease, and the CDC (Ljungman et al, 2009) indicated that intranasal influenza vaccine (live) should not be given to HCT recipients since an effective, inactivated alternative exist.

Available evidence shows that two doses of influenza vaccine does not improve antibody response in persons with hematologic malignancies. In a randomized controlled study (n = 70), Ljungman and associates (2005) examined if 2 doses of influenza vaccine were more effective than one to elicit an immune response in patients with hematological malignancies. These investigators found that responses were not improved by 2 doses compared with 1 (influenza A virus serotypes H1/N1 18 % versus 22 % and H3/N2 26 % versus 14 %; influenza B 25 % versus 22 %). The results were similar in patients with ongoing and discontinued therapy. Patients treated with monoclonal antibodies for lymphoma had very poor responses. These researchers concluded that 2 doses of influenza vaccine do not improve the antibody response in patients with hematological malignancies.

Madhi et al (2014) conducted 2 double-blind, randomized, placebo-controlled trials of trivalent IIV (IIV3) in South Africa during 2011 in pregnant women infected with HIV and during 2011 and 2012 in pregnant women who were not infected. The immunogenicity, safety, and efficacy of IIV3 in pregnant women and their infants were evaluated until 24 weeks after birth. Immune responses were measured with a HAI assay, and influenza was diagnosed by means of reverse-transcriptase-polymerase-chain-reaction (RT-PCR) assays of respiratory samples. The study cohorts included 2,116 pregnant women who were not infected with HIV and 194 pregnant women who were infected with HIV. At 1 month after vaccination, sero-conversion rates and the proportion of participants with HAI titers of 1:40 or more were higher among IIV3 recipients than among placebo recipients in both cohorts. Newborns of IIV3 recipients also had higher HAI titers than newborns of placebo recipients. The attack rate for RT-PCR-confirmed influenza among both HIV-uninfected placebo recipients and their infants was 3.6 %. The attack rates among HIV-uninfected IIV3 recipients and their infants were 1.8 % and 1.9 %, respectively, and the respective vaccine-efficacy rates were 50.4 % (95 % CI: 14.5 to 71.2) and 48.8 % (95 % CI: 11.6 to 70.4). Among HIV-infected women, the attack rate for placebo recipients was 17.0 % and the rate for IIV3 recipients was 7.0 %; the vaccine-efficacy rate for these IIV3 recipients was 57.7 % (95 % CI: 0.2 to 82.1). The authors concluded that influenza vaccine was immunogenic in HIV-uninfected and HIV-infected pregnant women and provided partial protection against confirmed influenza in both groups of women and in infants who were not exposed to HIV.

In a Cochrane review, Dharmaraj and Smyth (2014) evaluated the effectiveness of influenza vaccination for people with cystic fibrosis (CF). These investigators searched the Cochrane Cystic Fibrosis and Genetic Disorders Group Trials Register which comprises of references identified from comprehensive electronic database searches and hand-searching of relevant journals and abstract books of conference proceedings. They also contacted the companies which market the influenza vaccines used in the trials to obtain further information about RCTs. Date of the most recent search of the Cochrane Cystic Fibrosis and Genetic Disorders Group's Cystic Fibrosis Trials Register: July 8, 2013. All randomized and quasi-randomized trials (published or unpublished) comparing any influenza vaccine with a placebo or with another type of influenza vaccine were selected for analysis. Two authors independently assessed study quality and extracted data. Additional information was obtained by contacting the investigators when it was indicated. A total of 4 studies enrolling a total of 179 participants with CF (143 (80 %) were children aged 1 to 16 years) were included in this review. There was no study comparing a vaccine to a placebo or a whole virus vaccine to a subunit or split virus vaccine. Two studies compared an intra-nasal applied live vaccine to an intra-muscular inactivated vaccine and the other 2 studies compared a split virus to a subunit vaccine and a virosome to a subunit vaccine (all intra-muscular). The incidence of all reported adverse events was high depending on the type of influenza vaccine. The total adverse event rate ranged from 48 out of 201 participants (24 %) for the intra-nasal live vaccine to 13 out of 30 participants (43 %) for the split virus vaccine. With the limitation of a statistical low power there was no significant difference between the study vaccinations. None of the events was severe. All study influenza vaccinations generated a satisfactory serological antibody response. No study reported other clinically important benefits. The authors concluded that there is currently no evidence from randomized studies that influenza vaccine given to people with CF is of benefit to them. They stated that there remains a need for a well-constructed clinical study, that assesses the effectiveness of influenza vaccination on important clinical outcome measures.

Remschmidt et al (2015) noted that patients with diabetes are at increased risk of severe influenza disease; influenza vaccination for these patients is therefore recommended by the World Health Organization (WHO) and several National Immunization Technical Advisory Groups. However, no systematic review has evaluated the effects of influenza vaccines for patients with diabetes. These researchers conducted a systematic review and meta-analysis by searching Medline, Embase, Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov from inception until November 2014. They included all types of studies reporting on the efficacy, effectiveness, and/or safety of influenza vaccination in patients with type 1 and type 2

diabetes mellitus of all ages. They used the Newcastle-Ottawa scale to assess risk of bias in observational studies. Residual confounding was addressed by comparing estimates of vaccine effectiveness (VE) during influenza seasons to those obtained during off-seasons. Quality of the evidence for each outcome was assessed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology. Following review of 1,444 articles, 11 observational studies with a total of 170,924 participants were included. In diabetic patients of working-age (18 to 64 years), influenza vaccination prevented all-cause hospitalization with a pooled VE of 58 % (95 % CI: 6 to 81 %) and hospitalization due to influenza or pneumonia (VE 43 %; 95 % CI: 28 to 54 %), whereas no effects on all-cause mortality and influenza-like illness (ILI) were observed. In the elderly (65+), influenza vaccination prevented all-cause mortality (VE 38 %; 95 % CI: 32 to 43 %), all-cause hospitalization (VE 23 %; 95 % CI: 1 to 40 %), hospitalization due to influenza or pneumonia (VE 45 %; 95 % CI: 34 to 53 %), and ILI (VE 13 %; 95 % CI: 10 to 16 %). However, significant off-season estimates for several outcomes indicated residual confounding, particularly in elderly patients. Quality of the evidence was low to very low for all outcomes. Laboratory-confirmed influenza infections were not reported. The authors concluded that due to strong residual confounding in most of the identified studies, the available evidence is insufficient to determine the magnitude of benefit that diabetic people derive from seasonal influenza vaccination. They stated that adequately powered RCTs or quasi-experimental studies using laboratory-confirmed influenza-specific outcomes are urgently needed.

In a Cochrane review, Norhayati et al (2015) stated that acute otitis media (AOM) is one of the most common infectious diseases in children. It has been reported that 64 % of infants have an episode of AOM by the age of 6 months and 86 % by 1 year. Although most cases of AOM are due to bacterial infection, it is commonly triggered by a viral infection. In most children it is self-limiting, but it does carry a risk of complications. Since antibiotic treatment increases the risk of antibiotic resistance, influenza vaccines might be an effective way of reducing this risk by preventing the development of AOM. These investigators evaluated the effectiveness of influenza vaccine in reducing the occurrence of AOM in infants and children. They searched CENTRAL (2014, Issue 6), MEDLINE (1946 to Week 1, July 2014), EMBASE (2010 to July 2014), CINAHL (1981 to July 2014), LILACS (1982 to July 2014), Web of Science (1955 to July 2014) and reference lists of articles to July 2014. Randomized controlled trials comparing influenza vaccine with placebo or no treatment in infants and children aged younger than 6 years old. These researchers included children of either sex and of any ethnicity, with or without a history of recurrent AOM. Two review authors independently screened studies, assessed trial quality and extracted data. They performed statistical analyses using the random-effects and fixed-effect models and expressed the results as RR, risk difference (RD) and number needed to treat to benefit (NNTB) for dichotomous outcomes, with 95 % CI. These investigators included 10 trials (6 trials in high-income countries and 4 multi-center trials in high-, middle- and low-income countries) involving 16,707 children aged 6 months to 6 years. Eight trials recruited participants from a healthcare setting; 9 trials (and all 5 trials that contributed to the primary outcome) declared funding from vaccine manufacturers. Four trials reported adequate allocation concealment and 9 trials reported adequate blinding of participants and personnel. Attrition was low for all trials included in the analysis. The primary outcome showed a small reduction in at least 1 episode of AOM over at least 6 months of follow-up (5 trials, 4,736 participants: RR 0.80, 95 % CI: 0.67 to 0.96; RD -0.04, 95 % CI: -0.07 to -0.02; NNTB 25, 95 % CI: 15 to 50). The subgroup analyses (i.e., number of courses, settings, seasons or types of vaccine administered) showed no differences. There was a reduction in the use of antibiotics in vaccinated children (2 trials, 1,223 participants: RR 0.70, 95 % CI: 0.59 to 0.83; RD -0.15, 95 % CI: -0.30 to -0.00). There was no significant difference in the utilization of health care for the 1 trial that provided sufficient information to be included. The use of influenza vaccine resulted in a significant increase in fever (6 trials, 10,199 participants: RR 1.15, 95 % CI: 1.06 to 1.24; RD 0.02, 95 % CI: -0.00 to 0.05) and rhinorrhea (6 trials, 10,563 children: RR 1.17, 95 % CI: 1.07 to 1.29; RD 0.09, 95 % CI: 0.01 to 0.16) but no difference in pharyngitis. No major adverse events were reported. Compared to the protocol, the review included a subgroup analysis of AOM episodes by season, and changed the types of influenza vaccine from a secondary outcome to a subgroup analysis. The authors concluded that influenza vaccine results in a small reduction in AOM. The observed reduction with the use of antibiotics needs to be considered in the light of current recommended practices aimed at avoiding antibiotic overuse. Safety data from these trials are limited. They stated that the benefits may not justify the use of influenza vaccine without taking into account the vaccine efficacy in reducing influenza and safety data. The quality of the evidence was high-to-moderate; additional research is needed.

## Prevention of Cardiovascular Diseases (e.g., e Acute Myocardial Infarction)

There is evidence to suggest that influenza vaccination improves the clinical course of coronary artery disease (CAD) and reduces the frequency of coronary ischemic events. In a randomized, double-blind, placebo-controlled trial, Ciszewski et al (2008) assessed the effect of influenza vaccination on the coronary events in patients with confirmed CAD. This study included 658 optimally treated CAD patients (477 men, mean age of 59.9 +/- 10.3 years). A total of 325 patients received the influenza vaccine, and 333 patients received a placebo. Median follow-up was 298 days (inter-quartile range of 263 to 317). Primary end-point was cardiovascular death. Its estimated 12-month cumulative event rate was 0.63 % in the vaccine versus 0.76 % in controls (HR 1.06; 95 % CI: 0.15 to 7.56, p = 0.95). There were 2 secondary composite end-points:

1. the MACE (cardiovascular death, myocardial infarction, coronary re-vascularization) tended to occur less frequently in the vaccine group versus placebo with the event rate 3.00 % and 5.87 %, respectively (HR 0.54; 95 % CI: 0.24 to 1.21, p = 0.13),
2. coronary ischemic event (MACE or hospitalization for myocardial ischemia) estimated 12-month event rate was significantly lower in the vaccine group 6.02 % versus 9.97 % in controls (HR 0.54; 95 % CI: 0.29 to 0.99, p = 0.047).

The authors concluded that in optimally treated CAD patients, influenza vaccination improves the clinical course of CAD and reduces the frequency of coronary ischemic events. They stated that large-scale studies are needed to evaluate the effect of influenza vaccination on cardiovascular mortality.

A Cochrane review concluded that despite the significant effects noted in available randomized controlled clinical trials, that there are not enough data to evaluate the effect of influenza vaccination on coronary heart disease (Keller et al, 2008).

Barnes and associates (2015) stated that acute myocardial infarction (AMI) is the leading cause of death and disability globally. There is increasing evidence from observational studies that influenza infection is associated with AMI. In patients with known coronary disease, influenza vaccination is associated with a lower risk of cardiovascular events. However, the effect of influenza vaccination on incident AMI across the entire population is less well established. In a systematic review of case-control studies, these investigators

1. estimated the association between influenza infection and AMI, and
2. estimated the association between influenza vaccination and AMI.

Cases included those conducted with first-time AMI or any AMI cases. Studies were appraised for quality and meta-analyses using random effects models for the influenza exposures of infection, and vaccination were conducted. A total of 16 studies (8 on influenza vaccination, 10 on influenza infection and AMI) met the eligibility criteria, and were included in the review and meta-analysis. Recent influenza infection, influenza-like illness or respiratory tract infection was significantly more likely in AMI cases, with a pooled odds ratio (OR) of 2.01 (95 % CI: 1.47 to 2.76). Influenza vaccination was significantly associated with AMI, with a pooled OR of 0.71 (95 % CI: 0.56 to 0.91), equating to an estimated vaccine effectiveness of 29 % (95 % CI: 9 % to 44 %) against AMI. The authors concluded that the findings of this meta-analysis of case-control studies found a significant association between recent respiratory infection and AMI. The estimated vaccine effectiveness against AMI was comparable with the effectiveness of currently accepted therapies for secondary prevention of AMI from clinical trial data. They stated that al large-scale RCT is needed to provide robust evidence of the protective effect of influenza vaccination on AMI, including as primary prevention.

In a Cochrane review, Clar and colleagues (2015) evaluated the potential benefits of influenza vaccination for primary and secondary prevention of cardiovascular diseases. These investigators searched the following electronic databases on October 18, 2013: The Cochrane Library (including Cochrane Central Register of Controlled Trials (CENTRAL), Database of Abstracts of Reviews of Effects (DARE), Economic Evaluation Database (EED) and Health Technology Assessment database (HTA)), Medline, Embase, Science Citation Index Expanded, Conference Proceedings Citation Index - Science and ongoing trials registers (www.controlled-trials.com/ and www.clinicaltrials.gov). They examined reference lists of relevant primary studies and systematic reviews, and performed a limited PubMed search on February 20, 2015, just before publication. Randomized controlled trials of influenza vaccination compared with placebo or no treatment in participants with or without cardiovascular diseases, assessing cardiovascular death or non-fatal cardiovascular events. These researchers used standard methodological procedures as expected by the Cochrane Collaboration; they performed meta-analyses only for cardiovascular death, as other outcomes were reported too infrequently. They expressed effect sizes as RRs and used random-effects models. The authors included 8 trials of influenza vaccination compared with placebo or no vaccination, with 12,029 participants receiving at least 1 vaccination or control treatment. They included 6 new studies (n = 11,251), in addition to the 2 included in the previous version of the review; 4 of these trials (n = 10,347) focused on prevention of influenza in the general or elderly population and reported cardiovascular outcomes among their safety analyses; 4 trials (n = 1,682) focused on prevention of cardiovascular events in patients with established coronary heart disease. These populations were analyzed separately; follow-up continued between 42 days and 1 year; 5 RCTs showed deficits in at least 3 of the risk of bias criteria assessed. When reported (7 studies), vaccination provided adequate immunogenicity or protection against influenza. Cardiovascular mortality was reported by 4 secondary prevention trials and was significantly reduced by influenza vaccination overall (RR of 0.45, 95 % CI: 0.26 to 0.76; p value of 0.003) with no significant heterogeneity between studies, and by 3 trials reporting cardiovascular mortality as part of their safety analyses when the numbers of events were too small to permit conclusions. In studies of patients with coronary heart disease, composite outcomes of cardiovascular events tended to be decreased with influenza vaccination compared with placebo. Generally no significant difference was found between comparison groups regarding individual outcomes such as MI. The authors concluded that in patients with cardiovascular disease, influenza vaccination may reduce cardiovascular mortality and combined cardiovascular events. However, studies had some risk of bias, and results were not always consistent, so additional higher-quality evidence is needed to confirm these findings. They stated that not enough evidence was available to establish whether influenza vaccination has a role to play in the primary prevention of cardiovascular diseases.

## Vaccine Preservatives

Some researchers have raised concern over the preservative added to vaccines, such as thimerosal which contains mercury. Thimerosal prevents the growth of microbes and contamination in the multi-dose vial when individual doses are drawn from it. Receiving a vaccine contaminated with bacteria can be deadly. However, there were public concerns on the risk of thimerosal to children and the possible link to autism. Although standard thimerosal-preserved influenza vaccines contain trace amounts of mercury, the American Academy of Pediatrics, the American Academy of Family Physicians, the Advisory Committee on Immunization Practices and the U.S. Public Health Service had issued a joint statement advising the removal of thimerosal-containing vaccines from vaccines routinely recommended for infants (AAP, 2000; CDC, 2015). The joint statement explains that

"[w]hile there was no evidence of any harm caused by low levels of thimerosal in vaccines and the risk was only theoretical, this goal was established as a precautionary measure. There is public concern about the health effects of mercury exposure of any sort, and the elimination of mercury from vaccines was judged a feasible means of reducing an infant's total exposure to mercury in a world where other environmental sources of exposure are more difficult or impossible to eliminate (e.g., certain foods)." Other persons who are sensitive to thimerosal should avoid vaccines containing this preservative. Furthermore, the U.S. Public Health Service recommended efforts be made to eliminate or reduce the thimerosal content in vaccines as part of an over-all strategy to reduce mercury exposures from all sources and ACIP and other federal agencies and professional medical organizations continue to support efforts to provide thimerosal preservative-free vaccine options (ACIP, 2008).

There has been no evidence of harm caused by low doses of thimerosal in vaccines, except for minor reactions like redness and swelling at the injection site (CDC, 2015). Nonetheless, except for some flu vaccines in multi-dose vials, no recommended childhood vaccines contain thimerosal as a preservative (CDC, 2013). There are single-dose influenza vaccines on the market that do not contain thimerosal (e.g., Fluzone Quadrivalent, (Sanofi Pasteur Inc); Afluria Quadrivalent, (Seqirus Inc); Fluarix Quadrivalent, Flulaval Quadrivalent (GSK).

The American College of Obstetricians and Gynecologists (ACOG) and the American Academy of Family Physicians (AAFP) recommend routine vaccination of all pregnant women. Although some researchers have raised concerns that thimerosal, a mercury-containing preservative used in multi-dose vials of the influenza vaccine, may be unsafe, there is no scientific evidence that thimerosal-containing vaccines cause health or developmental problems in children born to women who received vaccines with thimerosal during pregnancy. Although thimerosal-free formulations of the influenza vaccine are available, the CDC's Advisory Committee on Immunization Practices does not indicate a preference for thimerosal-containing or thimerosal-free vaccines for pregnant women (ACOG, 2018).

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## Policy History

- Last Review  01/10/2025

  Effective: 10/06/1995

  Next Review: 07/24/2025

- Review History
- Definitions

## Additional Information

- Clinical Policy Bulletin Notes