

U.S. Centers for Disease Control and Prevention
National Center for Immunization and Respiratory Diseases

Influenza Updates, Work Group Considerations, and Proposed Recommendations for the 2024-25 Influenza Season

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Acknowledgements

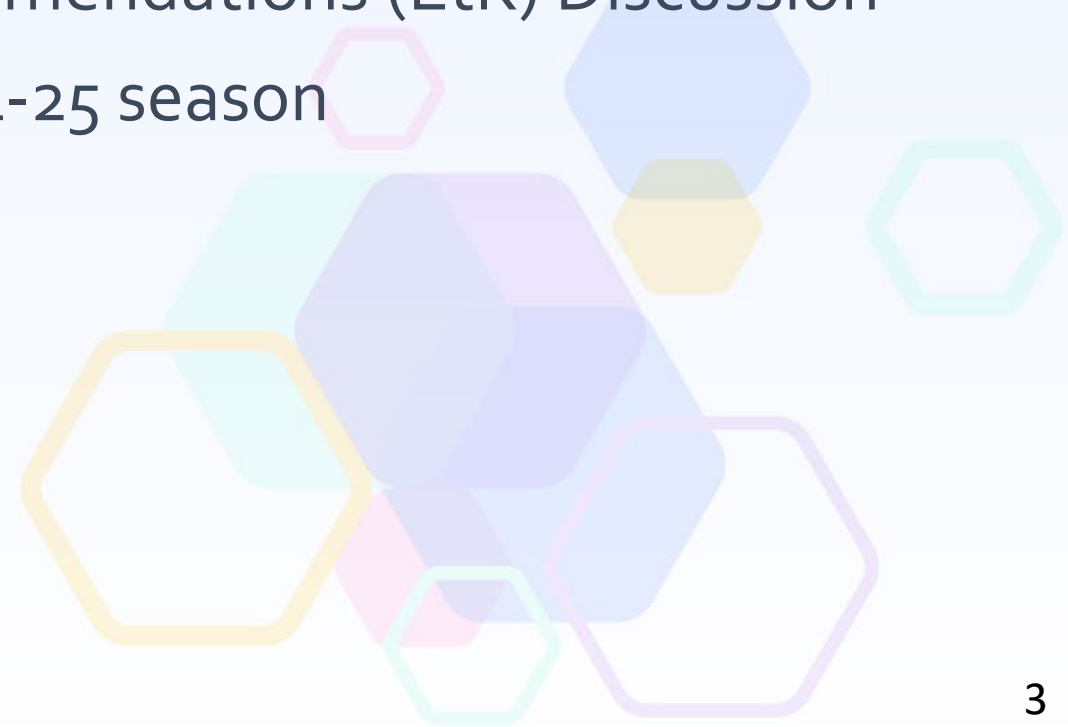
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Overview

- U.S. Influenza vaccine composition for the 2024-25 season
- Brief end-of-season influenza vaccine safety update
- Higher dose and adjuvanted influenza vaccines for solid organ transplant recipients: Evidence to Recommendations (EtR) Discussion
- Proposed recommendations for the 2024-25 season



Influenza Updates



U.S. Influenza Vaccine Composition for the 2024-25 Influenza Season

- All influenza vaccines marketed in the United States for the 2024-25 season will be trivalent
- There will be no influenza B/Yamagata component, following no confirmed detections of wild-type influenza B/Yamagata viruses since March 2020
- U.S. influenza vaccine composition for 2024-25 includes an update to the influenza A(H3N2) component:
 - An A/Victoria/4897/2022 (H1N1)pdm09-like virus for egg-based vaccines or an A/Wisconsin/67/2022 (H1N1)pdm09-like virus for cell and recombinant vaccines;
 - **An A/Thailand/8/2022 (H3N2)-like virus for egg-based vaccines or an A/Massachusetts/18/2022 (H3N2)-like virus for cell and recombinant vaccines;**
 - A B/Austria/1359417/2021 (B/Victoria lineage)-like virus



End-of-Season Update: 2023-2024 Influenza Vaccine Safety Monitoring

Immunization Safety Office

Centers for Disease Control and Prevention

Vaccine Safety Update: 2023-2024 Influenza Season

- **~158 million doses of influenza vaccine distributed in United States***
- **Vaccine Adverse Event Reporting System (VAERS)** (co-managed by CDC and FDA)
 - No new safety concerns identified for influenza vaccines
- **Vaccine Safety Datalink (VSD)** (collaboration between CDC and 13 integrated healthcare organizations)
 - VSD monitors pre-specified outcomes using rapid cycle analysis (RCA)**
 - ~4.8 million doses of influenza vaccine administered in VSD through 5/31/2024
 - No new safety concerns identified in influenza vaccine monitoring

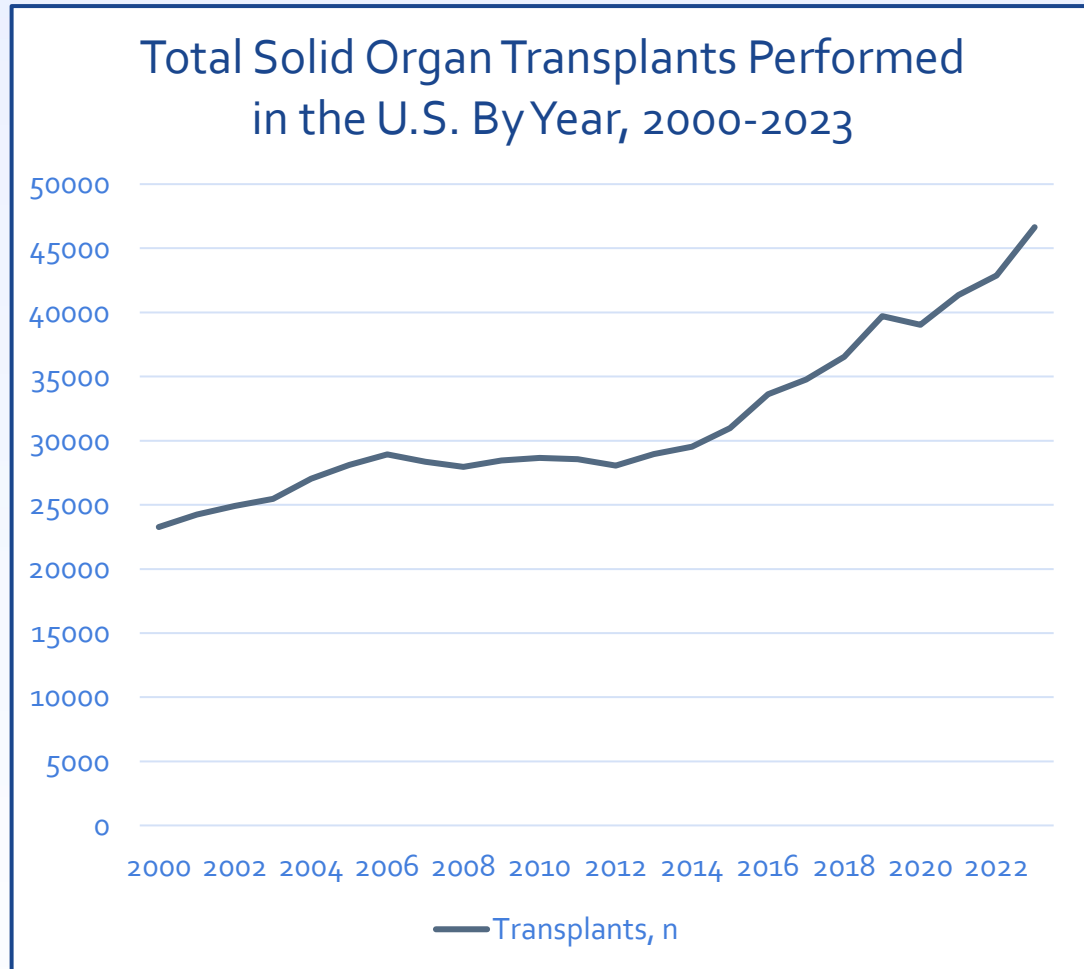
*As of March 9, 2024, [Weekly Flu Vaccination Dashboard](#) | [FluVaxView](#) | [Seasonal Influenza \(Flu\)](#) |

** Outcomes monitored in VSD for influenza vaccines: acute disseminated encephalomyelitis (ADEM), anaphylaxis (case counts), Bell's palsy, encephalitis, Guillain-Barré syndrome, seizures, and transverse myelitis; Li et al. [Post licensure surveillance of influenza vaccines in the Vaccine Safety Datalink in the 2013–2014 and 2014–2015 seasons \(wiley.com\)](#) *Pharmacoepidemiol Drug Saf.* 2016 Aug;25(8):928-34.

Higher Dose and Adjuvanted Influenza Vaccines for Solid Organ Transplant Recipients: EtR Discussion

Background

Solid Organ Transplantation in the United States



| U.S. Organ Transplants Performed, 2023 | |
|--|--------------|
| All | 46,632 (100) |
| By age group | |
| <18 years | 1,916 (4) |
| 18-64 years | 33,610 (72) |
| ≥65 years | 11,104 (24) |
| Organ(s) | |
| Kidney | 27,332 (59) |
| Liver | 10,660 (23) |
| Heart | 4,545 (10) |
| Lung | 3,026 (6) |
| Kidney/pancreas | 812 (2) |
| Pancreas | 102 (0.2) |
| Heart/lung | 54 (0.1) |

Recommendations for Influenza Vaccination of SOT Recipients

- Per ACIP recommendations, SOT recipients should receive an age-appropriate inactivated or recombinant influenza vaccine (i.e., an IIV or RIV)
 - Live attenuated influenza vaccine (LAIV) is not recommended for immunocompromised populations
- Immunosuppressive regimens might contribute to diminished response to vaccines
- High-dose (HD-IIV) and adjuvanted (aIIV) inactivated influenza vaccines have been studied in SOT recipients
- American Society for Transplantation (AST) states that high-dose or boosted dosing might be preferable post-transplant
- HD-IIV and aIIV are approved for ages ≥ 65 years, and might not be covered by insurance when administered to persons under age 65 years

Policy Question

- Should high-dose inactivated, adjuvanted inactivated, and/or recombinant influenza vaccines be recommended as an option for influenza vaccination of solid organ transplant recipients who are younger than the approved age indication?
 - <65 years for high-dose and adjuvanted influenza vaccines
 - <18 years for recombinant influenza vaccine



Public Health Importance

EtR Domain 1

Public Health Importance—Scope of Population

- The number of transplants performed each year, and post-transplant survival have increased

| Median recipient survival (years) | | |
|-----------------------------------|-----------|-----------|
| Organ | 1987-2012 | 1987-2021 |
| Kidney | 12.4 | 14.8 |
| Liver | 11.6 | 14.6 |
| Heart | 9.5 | 11.7 |
| Lung | 5.2 | 5.6 |
| Pancreas | 13.3 | 16.1 |

- Approximately 430,000 recipients alive in 2020
 - 0.1% of U.S. population

| Recipients alive, n | | |
|---------------------|-----------|-----------|
| Organ | June 2015 | June 2020 |
| Kidney | 200,000 | 255,738 |
| Liver | 74,945 | 98,842 |
| Heart | 29,172 | 37,419 |
| Lung | 12,100 | 17,500 |
| Pancreas | 14,161 | 19,458 |

*Considering recipients of the most commonly transplanted organs, for whom systemic immunosuppression is generally required

OPTN/SRTR 2015 Annual Data Report

OPTN/SRTR 2020 Annual Data Report [2020 ADR \(hrsa.gov\)](https://www.hrsa.gov/2020-adr)

Organ Transplant and Procurement Network (OPTN). [National data - OPTN \(hrsa.gov\)](https://www.hrsa.gov/national-data)

Rana et al, JAMA Surgery 2015; 150(3):252-259

Ferreira et al, Digestive Diseases and Sciences 2023;68:3810-3817

Public Health Importance—Disease Burden

- SOT recipients require lifelong immunosuppressive medications.
- Manifestations of influenza can be more severe
 - Lower respiratory tract disease, including pneumonia, occurs in 22-49% of SOT recipients
- In a 5-year cohort of SOT recipients with influenza (n=477):
 - 21% had lower respiratory tract disease on presentation
 - 69% were hospitalized
 - 11% admitted to an intensive care unit
 - 8% required mechanical ventilation
 - 3% died (all-causes) within 30 days



WG Judgement: Public Health Importance

Is influenza among solid organ transplant recipients a problem of public health importance?

- No
- Probably no
- Probably yes
- Yes
- Varies
- Don't know



Benefits and Harms

EtR Domain 2

Population, Intervention, Comparator, and Outcomes

| | |
|----------------------|---|
| Population | Solid organ transplant recipients aged ≥ 6 months |
| Interventions | High-dose (HD-IIV), MF59-djuvanted (aIIV), or recombinant (RIV) trivalent or quadrivalent influenza vaccines |
| Comparator | Single intramuscular dose of trivalent or quadrivalent unadjuvanted standard dose influenza vaccines |
| Outcomes | <p>Primary outcomes</p> <p>Benefits:</p> <ul style="list-style-type: none">• Medically-attended influenza (Critical)• Influenza-associated hospitalization (Critical)• Laboratory-confirmed influenza—immunogenicity data acceptable (Important) <p>Harms:</p> <ul style="list-style-type: none">• Transplant rejection or graft failure (Critical)• Neuroinflammatory conditions , e.g. GBS, ADEM (Critical)• Other immune-related adverse events, including new onset or exacerbation of an autoimmune condition (Critical) |



Study Characteristics (n=9)

- 9 papers describing 9 studies:
 - 8 randomized; 1 cohort
- Vaccines and comparisons:
 - HD-IIV₃ vs. SD-IIV₃ 2
 - Double-dose vs. single-dose SD-IIV₃ 2
 - aIIV₃ vs. SD-IIV₃ 3
 - aIIV₃ vs. HD-IIV₃ vs. SD-IIV₄ 1
 - aIIV₃ (most participants, no comparator) 1
 - No papers examining RIV
- Transplant populations:
 - Kidney 4
 - Heart 1
 - Mixed 4 (40-80% kidney)
- No papers reported on medically-attended influenza, neuroinflammatory conditions, or immune-mediated adverse events (all critical outcomes)
- Only one pediatric study (omitted from meta-analysis/GRADE)
- Cohort study excluded from GRADE given small size, lack of a comparison group, and availability of randomized studies
- 7 papers included in GRADE

Summary—Benefits: aIV3 vs SD-IIV

| Outcome | N studies (n participants) | Pooled RR (95% CI) | GRADE Certainty | Importance |
|--------------------------------------|-------------------------------|--------------------------|-----------------|------------|
| Influenza-associated hospitalization | 1 (403) | 2.90 (0.12, 70.71) | Low | Critical |
| Medically-attended influenza | 0 | - | - | Critical |
| Lab-confirmed influenza | 1 (403) | 0.97 (0.43, 2.18) | Moderate | Important |
| Seroconversion to H1N1 | 3 (558) | 1.37 (1.09, 1.72) | Low | Important |
| Seroconversion to H3N2 | 3 (558) | 1.51 (1.25, 1.82) | Low | Important |
| Seroconversion to B | 3 (558) | 1.64 (1.28, 2.11) | Low | Important |
| Seroprotection to H1N1 | 3 (558) | 1.06 (0.98, 1.14) | Very low | Important |
| Seroprotection to H3N2 | 3 (558) | 1.20 (1.07, 1.33) | Low | Important |
| Seroprotection to B | 3 (558) | 1.17 (1.01, 1.34) | Low | Important |

Summary—Benefits: HD-IIV₃ vs SD-IIV

| Outcome | N studies (n participants) | Pooled RR (95% CI) | GRADE Certainty | Importance |
|---|-------------------------------|--------------------------|-----------------|------------|
| Influenza-associated hospitalization | 1 (393) | 3.05 (0.12, 74.32) | Low | Critical |
| Medically-attended influenza | 0 | - | - | Critical |
| Lab-confirmed influenza | 2 (565) | 1.09 (0.52, 2.27) | Moderate | Important |
| Seroconversion to H ₁ N ₁ | 2 (554) | 2.46 (1.86, 3.27) | Moderate | Important |
| Seroconversion to H ₃ N ₂ | 2 (554) | 1.67 (1.38, 2.02) | Moderate | Important |
| Seroconversion to B | 2 (554) | 1.90 (1.46, 2.46) | Moderate | Important |
| Seroprotection to H ₁ N ₁ | 2 (554) | 1.03 (0.95, 1.11) | Low | Important |
| Seroprotection to H ₃ N ₂ | 2 (554) | 1.13 (1.01, 1.26) | Moderate | Important |
| Seroprotection to B | 2 (554) | 1.22 (1.08, 1.38) | Moderate | Important |



Summary—Harms

| Outcome | Studies (N) | Pooled RR (95% CI) | GRADE Certainty | Importance |
|-------------------------------------|-------------|--------------------|-----------------|------------|
| aIIV₃ vs SD-IIV | | | | |
| Graft rejection | 3 (517) | 0.28 (0.06, 1.34) | Moderate | Critical |
| Neuroinflammatory events | 0 | - | - | Critical |
| Other autoimmune events | 0 | - | - | Critical |
| HD-IIV₃ vs SD-IIV | | | | |
| Graft rejection | 3 (579) | 1.00 (0.32, 3.06) | Moderate | Critical |
| Neuroinflammatory events | 0 | - | - | Critical |
| Other autoimmune events | 0 | - | - | Critical |



Summary of Evidence: aIV₃ vs SD-IIV

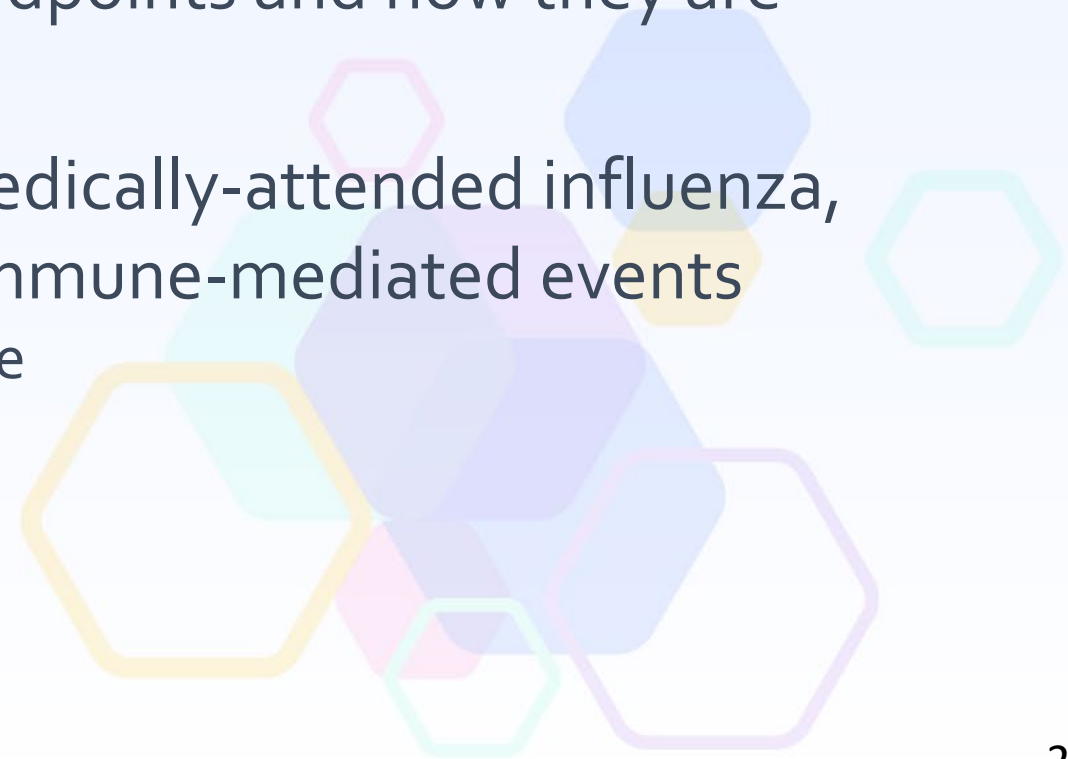
| Outcome | Importance | No. studies | Included in profile | Favored vaccine | Certainty |
|---|------------|-------------|---------------------|------------------|-----------|
| Benefits | | | | | |
| Medically-attended influenza | Critical | 0 | - | - | - |
| Influenza-associated hospitalization | Critical | 1 | Yes | Neither | Low |
| Laboratory-confirmed influenza | Important | 1 | Yes | Neither | Moderate |
| Immunogenicity (surrogate outcome) | | | | | |
| Seroconversion to A(H ₁ N ₁) | Important | 3 | Yes | aIV ₃ | Low |
| Seroconversion to A(H ₃ N ₂) | Important | 3 | Yes | aIV ₃ | Low |
| Seroconversion to B | Important | 3 | Yes | aIV ₃ | Low |
| Seroprotection to A(H ₁ N ₁) | Important | 3 | Yes | Neither | Very Low |
| Seroprotection to A(H ₃ N ₂) | Important | 3 | Yes | aIV ₃ | Low |
| Seroprotection to B | Important | 3 | Yes | aIV ₃ | Low |
| Harms | | | | | |
| Transplant rejection/graft failure | Critical | 3 | Yes | Neither | Moderate |
| Neuroinflammatory conditions | Critical | 0 | - | - | - |
| Other immune-mediated adverse events | Critical | 0 | - | - | - |

Summary of Evidence: HD-IIV₃ vs SD-IIV

| Outcome | Importance | No. studies | Included in profile | Favored vaccine | Certainty |
|---|------------|-------------|---------------------|---------------------|-----------|
| Benefits | | | | | |
| Medically-attended influenza | Critical | 0 | - | | - |
| Influenza-associated hospitalization | Critical | 1 | Yes | Neither | Low |
| Laboratory-confirmed influenza | Important | 2 | Yes | Neither | Moderate |
| Immunogenicity (surrogate outcome) | | | | | |
| Seroconversion to A(H ₁ N ₁) | Important | 3 | Yes | HD-IIV ₃ | Moderate |
| Seroconversion to A(H ₃ N ₂) | Important | 3 | Yes | HD-IIV ₃ | Moderate |
| Seroconversion to B | Important | 3 | Yes | HD-IIV ₃ | Moderate |
| Seroprotection to A(H ₁ N ₁) | Important | 3 | Yes | Neither | Low |
| Seroprotection to A(H ₃ N ₂) | Important | 3 | Yes | HD-IIV ₃ | Moderate |
| Seroprotection to B | Important | 3 | Yes | HD-IIV ₃ | Moderate |
| Harms | | | | | |
| Transplant rejection/graft failure | Critical | 3 | Yes | Neither | Moderate |
| Neuroinflammatory conditions | Critical | 0 | - | | - |
| Other immune-mediated adverse events | Critical | 0 | - | | - |

Limitations

- Few studies; most are small (4 of 7 have <100 participants)
- No direct evidence of relative benefit or either HD-iiv3 or aIIV3 vs SD-IIV
 - Only indirect evidence (immunogenicity)
- Variability in timing of immunogenicity endpoints and how they are reported
- No information for critical outcomes of medically-attended influenza, neuroinflammatory conditions, or other immune-mediated events
 - Given study sizes, power probably not adequate
- No evaluations of RIV



WG Judgement: Benefits and Harms

How substantial are the desirable anticipated effects?

- Minimal

- Small

- Moderate

- Large

- Varies

- Don't know



WG Judgement: Benefits and Harms

How substantial are the undesirable anticipated effects?

▪ Minimal

▪ Small

▪ Moderate

▪ Large

▪ Varies

▪ Don't know



WG Judgement: Benefits and Harms

Do desirable effects outweigh undesirable effects?

- Favors intervention

- Favors comparison

- Favors both

- Favors neither

- Varies

- Don't know



Benefits and Harms: Certainty of Evidence

What is the overall certainty of the evidence for the critical outcomes?

Benefits of the intervention

- No studies found
- Very low
- Low
- Moderate
- High

Harms of the intervention

- No studies found
- Very low
- Low
- Moderate
- High

Values and Preferences

EtR Domain 3

Values and Preferences for Influenza Vaccine Types

- No direct evidence was identified reflecting values or preferences for specific influenza vaccine types among SOT recipients
- There might be a healthcare provider preference for HD-IIV, evidenced by the recommendations of the American Society for Transplantation and various transplant programs



WG Judgement: Values

Does the target population feel that the desirable effects are large relative to undesirable effects?

- No
- Probably no
- Probably yes

▪ Yes

▪ Varies

▪ Don't know



WG Judgement: Values

Is there important uncertainty about or variability in how much people value the main outcomes?

- Important uncertainty or variability
- Probably important uncertainty or variability
- Probably not important uncertainty or variability
- No important uncertainty or variability
- No known undesirable outcomes



Acceptability

EtR Domain 4

Acceptability Considerations

- Acceptability of a recommendation for high-dose vaccine is possibly evidenced by recommendations of the AST and some transplant programs for high-dose vaccine
- Acceptability might be limited among healthcare and public health systems and insurers by need for changes in standing orders, immunization information systems, and electronic medical record platforms



WG Judgement: Acceptability

Is the intervention acceptable to key stakeholders?

- No
- Probably no

- Probably yes

- Yes

- Varies

- Don't know



Resource Use

EtR Domain 5

Is the Intervention a Reasonable and Efficient Allocation of Resources?

- No economic analysis was conducted:
 - Population ~430,000 as of 2020
 - Insufficient data concerning relative effectiveness of influenza vaccines in SOT populations
 - Insufficient data indicating extent to which use of these vaccines is already occurring among off-label age group SOT recipients
- HD-IIV₃ and aIIV₃ more costly (\$73-77) than unadjuvanted influenza vaccines (\$21-34)

WG Judgement: Resource Use

Is the intervention a reasonable and efficient allocation of resources?

- No
- Probably no

- Probably yes

- Yes

- Varies

- Don't know



Equity

EtR Domain 6

Equity

- No literature was found concerning use of enhanced influenza vaccines among transplant recipients
- Among Medicare beneficiaries aged ≥ 65 years in a single-season (2015-16), Black, Asian, and Hispanic persons were 26% to 32% less likely to receive HD-IIV₃ than White persons
- A WG member noted other potential barriers for SOT recipients:
 - SOT recipients face barriers to receiving newer influenza vaccines as they are usually excluded from clinical trials, and there are few data for this population
 - Transplant programs with greater financial resources might be able to purchase vaccines for their patients, whereas those less well-resourced might not

WG Judgement: Equity

What would be the impact on health equity?

- Reduced

- Probably reduced

- Probably no impact

- Probably increased

- Increased

- Varies

- Don't know



Feasibility

EtR Domain 7

Feasibility

Factors favoring feasibility

- The recommendation might improve access, if more likely to be covered by insurance.
- If covered, insurance and reimbursement concerns should be minimal.
- Vaccination should be easily implementable in office and retail settings that serve adults.
- The vaccines are licensed and routinely stocked.

Factors not favoring feasibility

- A recommendation stating that vaccines are acceptable options (as opposed to a preferential recommendation) might not compel insurers to cover them.
- Use of vaccine in a new age group might require changes in standing orders, Electronic Medical Record programming, and immunization information systems.

WG Judgement: Balance of Consequences

Is the intervention feasible to implement?

- No
- Probably no
- **Probably yes**
- Yes
- Varies
- Don't know



Balance of Consequences and Sufficiency of Information



WG Judgement: Balance of Consequences

- Undesirable consequences *clearly outweigh* desirable consequences in most settings
- Undesirable consequences *probably outweigh* desirable consequences in most settings

▪ The balance between desirable and undesirable consequences *is closely balanced or uncertain*

▪ Desirable consequences *probably outweigh* undesirable consequences in most settings

▪ Desirable consequences *clearly outweigh* undesirable consequences in most settings

▪ There is insufficient evidence to determine the balance of consequences

WG Judgement: Sufficiency of Information

Is there sufficient evidence to move forward with a recommendation

▪ Yes

▪ No



Proposed Recommendations



Proposed Recommendations for Influenza Vaccination, 2024-25 (For Vote)

- Routine annual influenza vaccination is recommended for all persons aged ≥ 6 months without contraindications.
 - *Same as previously*
- All persons should receive an age-appropriate influenza vaccine (i.e., one approved for their age), with the following exception: solid organ transplant recipients aged 18 through 64 years on immunosuppressive medication regimens may receive either HD-IIV₃ or aIIV₃ as an acceptable option (without a preference over other age-appropriate IIV₃s or RIV₃).

For more information, contact CDC
1-800-CDC-INFO (232-4636)
TTY: 1-888-232-6348 www.cdc.gov

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