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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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

Vaccines and Related Biological Products Advisory Committee March 5, 2024 Meeting Announcement - 03/05/2024 | FDA

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

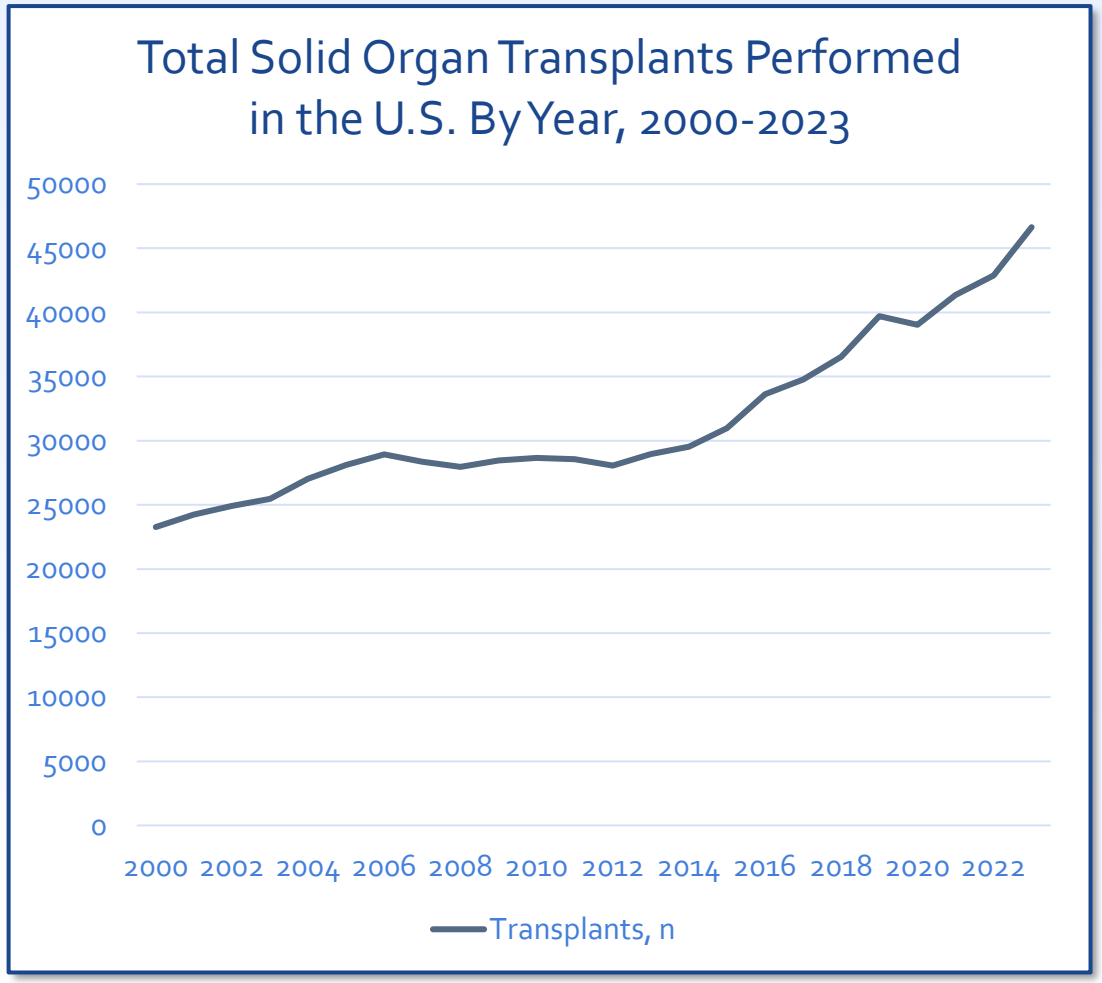
*As of March 9, 2024, Weekly Flu Vaccination Dashboard | FluVaxView | Seasonal Influenza (Flu) |

** 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	N (%)
<18 years	1,916 (4)
18-64 years	33,610 (72)
≥65 years	11,104 (24)
Organ(s)	N (%)
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)

National Data, Organ Transplant and Procurement Network (OPTN). National data - OPTN (hrsa.gov)

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

ACIP, Prevention and Control of Seasonal Influenza with Vaccines, 2023-24. https://www.cdc.gov/mmwr/volumes/72/rr/rr7202a1.htm
Danziger-Isakov L et al, Clin Transplant 2019;33(9):e13563

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

Organ Transplant and Procurement Network (OPTN). National data - OPTN (hrsa.gov)
Rana et al, JAMA Surgery 2015; 150(3):252-259
Ferreira et al, Digestive Diseases and Sciences 2023;68:3810-3817

OPTN/SRTR 2015 Annual Data Report
OPTN/SRTR 2020 Annual Data Report 2020 ADR (hrsa.gov)

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

Mombelli et al, Exp Rev Anti-infect Ther 2020;18:103-112
Kumar et al, Cin Infect Dis 2018;67:1322-1329

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

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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	Primary outcomes Benefits: • Medically-attended influenza (Critical) • Influenza-associated hospitalization (Critical) • Laboratory-confirmed influenza—immunogenicity data acceptable (Important) Harms: • 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: aIIV3 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 H1N1	2 (554)	**2.46 (1.86, 3.27)**	Moderate	Important
Seroconversion to H3N2	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 H1N1	2 (554)	1.03 (0.95, 1.11)	Low	Important
Seroprotection to H3N2	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: aIIV3 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(H1N1)	Important	3	Yes	aIIV3	Low
Seroconversion to A(H3N2)	Important	3	Yes	aIIV3	Low
Seroconversion to B	Important	3	Yes	aIIV3	Low
Seroprotection to A(H1N1)	Important	3	Yes	Neither	Very Low
Seroprotection to A(H3N2)	Important	3	Yes	aIIV3	Low
Seroprotection to B	Important	3	Yes	aIIV3	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-IIV$_3$ 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(H1N1)	Important	3	Yes	HD-IIV$_3$	Moderate
Seroconversion to A(H3N2)	Important	3	Yes	HD-IIV$_3$	Moderate
Seroconversion to B	Important	3	Yes	HD-IIV$_3$	Moderate
Seroprotection to A(H1N1)	Important	3	Yes	Neither	Low
Seroprotection to A(H3N2)	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
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- 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

Danziger-Isakov L et al, Clin Transplant 2019;33(9):e13563
COVID-19 and Flu Vaccination Information for Transplant Patients - Penn Medicine

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)

Influenza Vaccine Pricing (2023-24), CMS.gov (https://www.cms.gov/medicare/payment/part-b-drugs/vaccine-pricing)

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

Mahmud et al, Lancet Healthy Longevity 2021;2:e143-e153

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

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.