Influenza Vaccination of Persons with Egg Allergy: Evidence to Recommendations Discussion and Work Group Considerations

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Background

Egg Allergy

- Affects approximately 1-3% of children by age 3 years.[1,2]
- Resolves for many during later childhood and adolescence.
  - In one study,[3]
    - 4% developed tolerance by age 4 years,
    - 12% by age 6 years,
    - 37% by age 10 years,
    - 68% by age 16 years.
- Reactions range from mild to life-threatening.
- Diagnosis:
  - Clear history of immediate allergic reaction to egg or egg-containing foods.[2]
  - Skin prick testing (SPT) or estimation of egg-specific IgE levels. [2]

1. *Eggesbo M et al. Allergy 2001;56(5):403-411*
2. *Erlewyn-Lajeunesse M et al. BMJ 2009;339:b3680.*
3. *Savage JH et al. J Allergy Clin Immunol 2007;120(6):1413-7.*

Ovalbumin Content of U.S. Influenza Vaccines, 2022-23

Vaccine (manufacturer)	Approved age indication	Ovalbumin, mcg/dose* (per package insert)
Egg-based		
Afluria Quadrivalent (Seqirus)	≥6 mos	<1
Fluarix Quadrivalent (GSK)	≥6 mos	≤0.05
FluLaval Quadrivalent (GSK)	≥6 mos	≤0.3
Fluzone Quadrivalent (Sanofi Pasteur)	≥6 mos	Not stated
FluMist Quadrivalent (AstraZeneca)	2 through 49 yrs	<0.024
Fluad Quadrivalent (Seqirus)	≥65 yrs	≤1
Fluzone High-Dose Quadrivalent (Sanofi Pasteur)	≥65 yrs	Not stated
Egg-free		
Flucelvax Quadrivalent (Seqirus)	≥6 mos	Egg-free
Flublok Quadrivalent (Sanofi Pasteur)	≥18 yrs	Egg-free

* 0.5 mL for injectable vaccines and 0.2 mL for LAIV

Current ACIP Recommendations[1]

- Persons with a history of egg allergy of any severity should receive influenza vaccine.
- Any licensed, recommended influenza vaccine (i.e., any IIV4, RIV4, or LAIV4) that is otherwise appropriate can be used.
- For persons with previous reactions to egg involving symptoms other than urticaria:
  - *"If a vaccine other than ccIIV4 or RIV4 is used, the selected vaccine should be administered in an inpatient or outpatient medical setting, including but not necessarily limited to hospitals, clinics, health departments, and physician offices. Vaccine administration should be supervised by a health care provider who is able to recognize and manage severe allergic reactions."*
- No specific observation period recommended.

1. CDC/ACIP. MMWR Recomm Rep 2022;71(No. RR-1):1–28.

IIV4= quadrivalent inactivated influenza vaccine
LAIV4=quadrivalent live attenuated influenza vaccine
ccIIV4=quadrivalent cell culture based inactivated influenza vaccine
RIV4=quadrivalent recombinant influenza vaccine

Influenza Vaccines and Egg Allergy: Other Guidance

- American Academy of Pediatrics
  - Since 2016-17, no additional measures recommended for persons with egg allergy.[1]
  - "*Children with egg allergy can receive any influenza vaccine without any additional precautions beyond those recommended for all vaccines.*"[2]
  - Measures related to use of specific vaccines, observation periods, or restricting vaccination to specific medical settings not warranted and constitute a barrier to vaccination.[3]
  - Not necessary to inquire about or screen for egg allergy prior to influenza vaccination. [3]

- Joint Task Force, AAAAI/ACAAI
  - "No special precautions beyond those recommended for the administration of any vaccine to any patient are necessary for administration of influenza vaccine to egg allergic individuals." [4]

1. Recommendations for Prevention and Control of Influenza in Children, 2016–2017 | Pediatrics | American Academy of Pediatrics (aap.org)
2. Recommendations for Prevention and Control of Influenza in Children, 2022–2023 | Pediatrics | American Academy of Pediatrics (aap.org).
3. *AAP. Technical Report for the 2022-23 Recommendations for the Prevention and Control of Influenza in Children, 2022-23*
4. *Greenhawt M et al. Ann Allergy Asthma Immunol 2018;120:49-52.*

General Best Practices Guidelines for Immunization[1]

- From chapter titled “Preventing and Managing Adverse Reactions”:
  - *“Although allergic reactions are a common concern for vaccine providers, these reactions are uncommon and anaphylaxis following vaccines is rare, occurring at a rate of approximately one per million doses for many vaccines. Epinephrine and equipment for managing an airway should be available for immediate use.”*

1. *Kroger AT et al.* https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/index.html

Past Approaches to Influenza Vaccination of Persons with Egg Allergy (Not Currently Recommended)

- Vaccine skin testing prior to vaccination.[1,2]
  - Skin prick and/or intradermal testing with dilution of vaccine
  - If positive, vaccination deferred or administered via alternative dosing protocol
- Graded administration of vaccine.[3]
  - Incrementally increasing volumes, often in 5 to 6 steps; sometimes with dilutions in early steps
  - E.g., 0.05 mL of 1:100 dilution→0.05 mL of 1:10 dilution→0.05 mL→0.1 mL→ 0.15 mL→0.2 mL, with observation periods after each dose (e.g., 15 minutes).
- Split dosing of vaccine.[4]
  - Most commonly 10% of dose volume→observation period→remaining 90% of dose volume, often with additional observation after final dose.

1. *Bierman CW et al. J Infect Dis 1977;136:S652-S655.*
2. *Miller JR et al. J Allergy Clin Immunol 1983;71:568-173.*
3. *Murphy KR et al. J Pediatr 1985;106(6):931-933.*
4. *James JM et al. J Pediatr 1998;133:624-628.*

Policy Question

- Whether to no longer recommend additional safety measures for persons with egg allergy of any severity, beyond what is recommended for any other persons presenting for influenza vaccination.

  - In the discussion that follows, the proposed intervention is to no longer make the recommendation regarding vaccination setting for those with a history of severe allergic reaction to egg.

EtR Domain 1: Public Health Importance

Is Vaccination of Egg-Allergic Persons an Issue of Public Health Importance?

- Egg allergy more common in younger children, and often co-exists with asthma:
  - In a cross-sectional survey of 38,408 children,[1]
    - Egg allergy prevalence was 0.9% overall; 1.3% for those <5 yrs.
    - Asthma prevalence higher with egg allergy (46.5%) with other 8 most common food allergies (33.2%).
- Younger children and people with asthma are at increased risk of severe influenza illness.

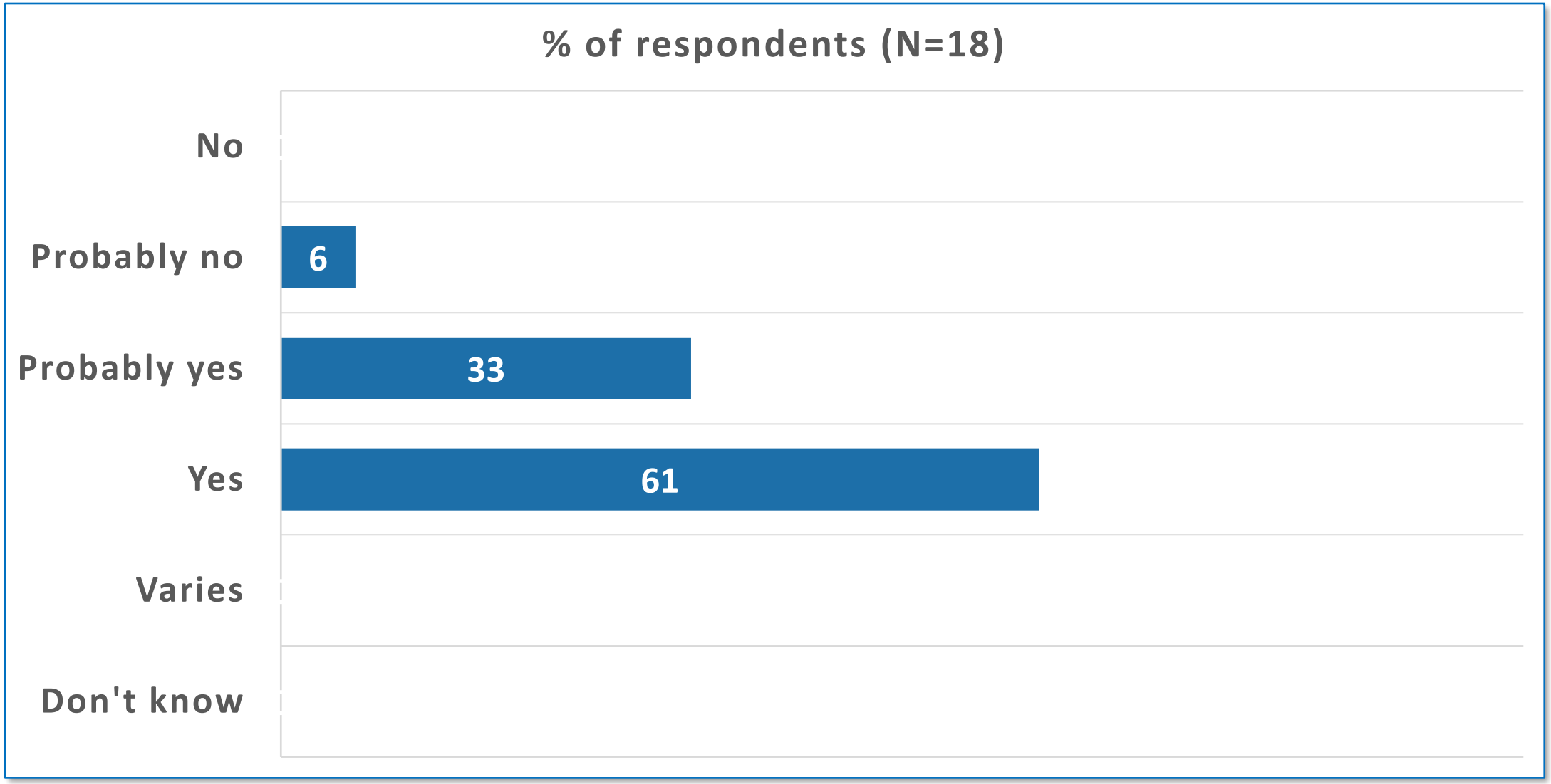
1. *Samady W, Warren C, Wang J, et al. Egg allergy in US children. J Allergy Clin Immunol Pract. 2020;8(9):3066-73.*

Public Health Importance: WG Considerations

- Current recommendations might be a real or perceived barrier to vaccination (e.g., by promoting hesitancy based on safety concerns, or providing a reason to decline vaccination).
  - No data specifically examining or confirming that current recommendations are a barrier found, but existence of real or perceived barriers is plausible.

- Current recommendations might be less of a barrier now, since cell-based (egg-free) inactivated vaccine is approved for ages ≥6 mos.
  - However, there is only one such vaccine licensed for children <18 years, compared with four egg-based vaccines available for this age group.

Is Vaccination of Egg-Allergic Persons an Issue of Public Health Importance?



EtR Domain 2: Benefits and Harms

Review Question

- Does the available evidence concerning the safety of influenza vaccines in persons with a history of egg allergy favor routine vaccination without additional safety measures, regardless of severity of previous allergic reaction to egg?

  - Review focused on Harms (safety)—did not include review of effectiveness/efficacy data.

Population, Intervention, and Comparators

- **Population:** Persons of any age with a history of allergy to eggs, or who have had an allergic reaction to influenza vaccine believed to be secondary to egg allergy.

- **Intervention:** Any influenza vaccine.

- **Comparators:** Placebo, non egg-based influenza vaccine, non-influenza control vaccine, no vaccine, no comparator

Outcomes

Within 4 hours of vaccination:

Critical

- Death
- Anaphylaxis meeting Brighton criteria Levels 1-3*
- Anaphylaxis otherwise classified*
- Allergic symptoms requiring hospitalization

Important

- Allergic reaction symptoms requiring outpatient or emergency department medical attention†
- Allergic reaction including cardiovascular symptoms, respiratory symptoms, angioedema, or generalized urticaria

* These two outcomes are combined in the tables that follow.

† Includes instances treated with medications, without explicit mention of outpatient or emergency department care.

Study Designs, Vaccines, and Comparison Groups

- 47 reports describing 52 studies.
  - 1 randomized study (compared full-dose with 10%/90% split dose).
  - 1 VAERS report summary.
  - Remainder retrospective/prospective cohort studies and case series.
  - 2 involved only recombinant vaccine (egg-free).
- No studies include a relevant comparison group (e.g., an alternative or no vaccine).
- 14 abstracts only (no related paper found).
- All studies were reviewed descriptively.
- 28 reports (31 studies) included in GRADE:
  - Egg-based vaccines only (seasonal and monovalent).
  - Full-dose or split-dose administration.
    - For the randomized study, full- and split-dose groups combined; treated as a cohort study.
  - Data with unknown/unclear vaccine type, unspecified administration protocol, graded (≥3 steps) dosing, and/or unknown denominator excluded.
  - Since there are no comparators, data are summarized as frequencies.

Summary of Events by Vaccine Type: Egg Allergy of All severities

Outcome	Seasonal IIVs*	Monovalent IIVs*	LAIV	Importance	Certainty
Death	0/1591 (0%)	0/5235 (0%)	0/1129 (0%)	Critical	Very low
Anaphylaxis	0/1591 (0%)	0/5235 (0%)	0/1129 (0%)	Critical	Very low
Reaction requiring hospitalization	0/1591 (0%)	0/5235 (0%)	0/1129 (0%)	Critical	Very low
Reaction requiring outpatient/ED attention (includes those given symptomatic medications)	3/1591 (0.2%)	77/5235 (1.5%)	0/1129 (0%)	Important	Very low
Allergic reaction including cardiovascular symptoms, respiratory symptoms, angioedema, or generalized urticaria	5/1591 (0.3%)†	33/5235 (0.6%)	10/1129 (0.8%)	Important	Very low

*Includes several papers for which vaccine type not explicitly stated, but presumed based upon season, study location, and/or use of graded/split dosing. Seasonal IIV data include one paper describing a virosomal vaccine.

†One study reported 6 instances of reactions including “wheezing, eczema exacerbation, or hives on chest”, but not specifying number with each symptom. If assumed that all six included wheezing, frequency would be 11/1591=0.7%

Summary of Events by Vaccine Type: Persons with Anaphylaxis to Egg

Outcome	Seasonal IIVs*	Monovalent IIVs*	LAIV	Importance	Certainty
Death	0/322 (0%)	0/68 (0%)	0/412 (0%)	Critical	Very low
Anaphylaxis	0/322 (0%)	0/68 (0%)	0/412 (0%)	Critical	Very low
Reaction requiring hospitalization	0/322 (0%)	0/68 (0%)	0/412 (0%)	Critical	Very low
Reaction requiring outpatient/ED attention	0/295 (0%)	0/68 (0%)	0/412 (0%)	Important	Very low
Allergic reaction including cardiovascular symptoms, respiratory symptoms, angioedema, or generalized urticaria	0/291 (0%)	0/68 (0%)	0/27 (0%)	Important	Very low

*Includes several papers for which vaccine type not explicitly stated, but presumed to be IIV based upon season, study location, and/or use of graded/split dosing.

Summary of Evidence for Outcomes of Interest

Outcome	Importance	Included in profile	Certainty
Death	Critical	Yes	Very low
Anaphylaxis	Critical	Yes	Very low
Allergic reaction symptoms requiring hospitalization	Critical	Yes	Very low
Allergic reaction symptoms requiring outpatient or emergency department medical attention	Important	Yes	Very low
Allergic reaction including cardiovascular symptoms, respiratory symptoms, angioedema, or generalized urticaria	Important	Yes	Very low

Report of Brighton Level 1 Anaphylaxis

- One report of Brighton Level 1 anaphylaxis in person with “possible” egg allergy within 30 minutes of receiving monovalent vaccine.
  - In paper summarizing VAERS reports following monovalent pandemic influenza vaccine during 2009-10 season.[1]
  - Unclear from paper whether documented to be egg-allergic.
- Doses administered that season unknown
  - Reaction not included in counts in GRADE evidence profiles (as denominator undefined).
- Paper states approximately 127 million doses distributed that season.
- Other reactions:
  - 2 of respiratory hypersensitivity
  - 1 sensation of throat closure

1. Halsey NA, et al. Vaccine. 2013 Dec 9;31(51):6107-12. doi: 10.1016/j.vaccine.2013.09.066. Epub 2013 Oct 8. PMID: 24120547.

Descriptions Of Reactions Following Egg-free Vaccines

- Woo et al 2015, 2017: summaries of VAERS reports following recombinant influenza vaccine (RIV):
  - Reports of serious allergic reactions following RIV, some of which occurred among persons with egg allergy.
  - RIV is egg, gelatin, antibiotic, and preservative-free.
- Authors note that the occurrence of such reactions might reflect an underlying predisposition to atopy.
- Reports also highlight unpredictability of severe allergic reactions, and importance of being prepared in all vaccination settings, for all recipients, and with all vaccines.

Limitations and WG Considerations

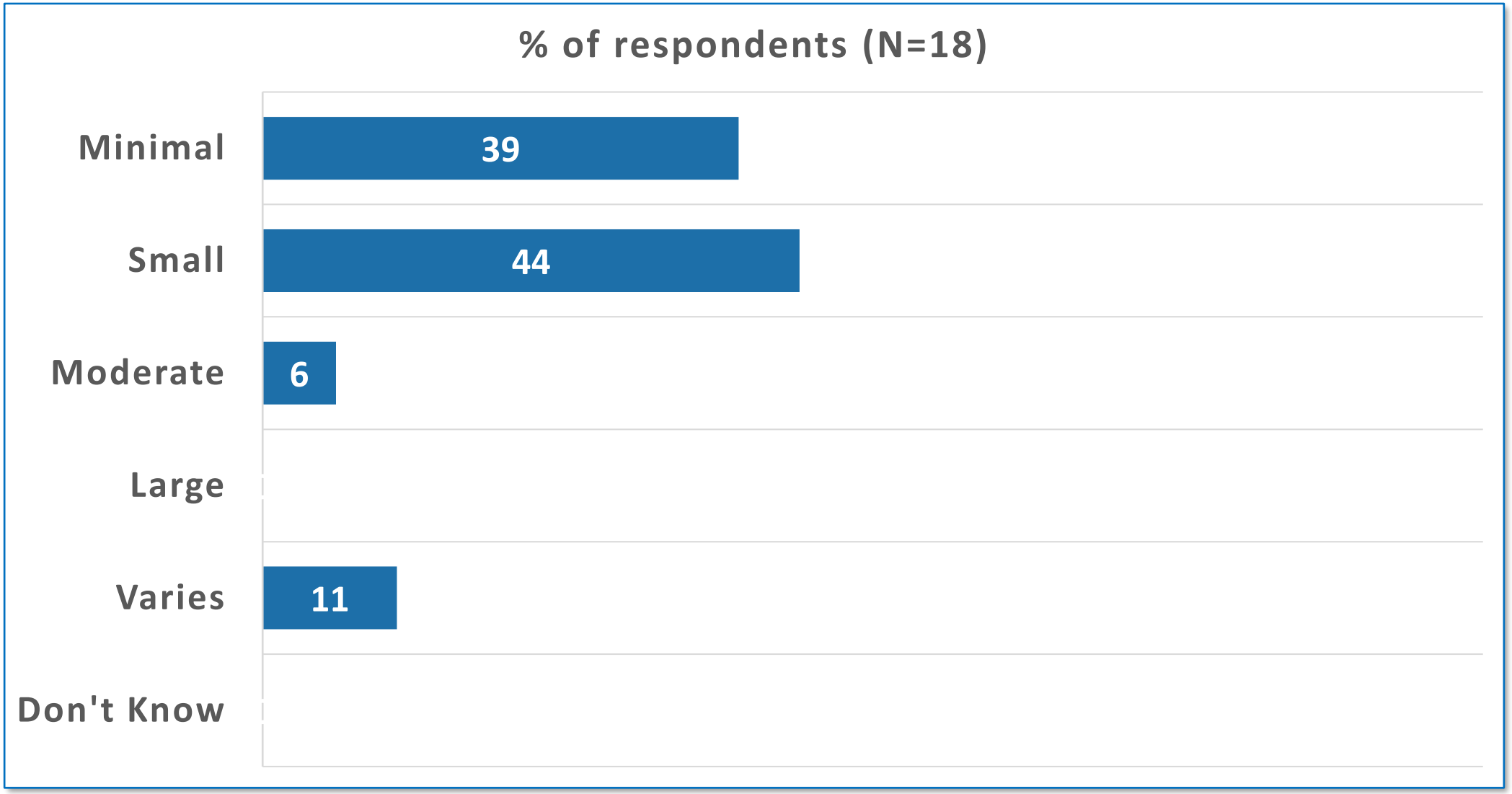
- Observational data with no comparator groups meeting criteria.
- Some data only available from abstracts.
- Many (particularly older) studies employed skin testing with egg proteins and/or vaccine prior to decision to vaccinate.
- Considerable variability in level of detail in which outcomes are described.
- Observation time post-vaccination varied; time elapsed post-vaccination not often reported for delayed reactions.
  - Observation for immediate reactions under 4 hours for most studies; generally 30 min to 2 hours.
- Ovalbumin content was not reported/unknown in most instances.
  - In most instances where noted, was <1µg/dose; in some cases substantially less.
  - Difficult to know how this compares with current vaccines, since expressed as an upper limit.
- Data specifically for persons with anaphylaxis to egg were limited.
  - Not all studies specified that persons with severe egg allergy were included.
  - Where included, not all studies reported reactions specifically for this subgroup.

Egg Allergy and Anaphylaxis Reports after IIVs in VAERS, 2017-2022

- 178 anaphylaxis reports after any IIV
- 18 had an egg allergy (based on VAERS report)
- Clinical review revealed 7 reports of anaphylaxis and egg allergy (all in 2017-18):
  - 4 in children (ages 2, 4, 9, 11 yrs); 3 in adults (ages 21, 52, 61 yrs)
  - 4 Brighton level 1; 1 Brighton level 3; 2 did not meet Brighton
  - Influenza vaccines:
    - Fluarix quadrivalent: 2
    - Fluzone quadrivalent: 2
    - Fluvirin trivalent: 1
    - Flucelvax quadrivalent: 1
    - Flublok quadrivalent: 1
- Difficult to assess if reaction was due to egg protein due to limited laboratory data.

Vaccine Adverse Event Reporting System (VAERS) (hhs.gov)

How Substantial are the Undesirable Anticipated Effects?

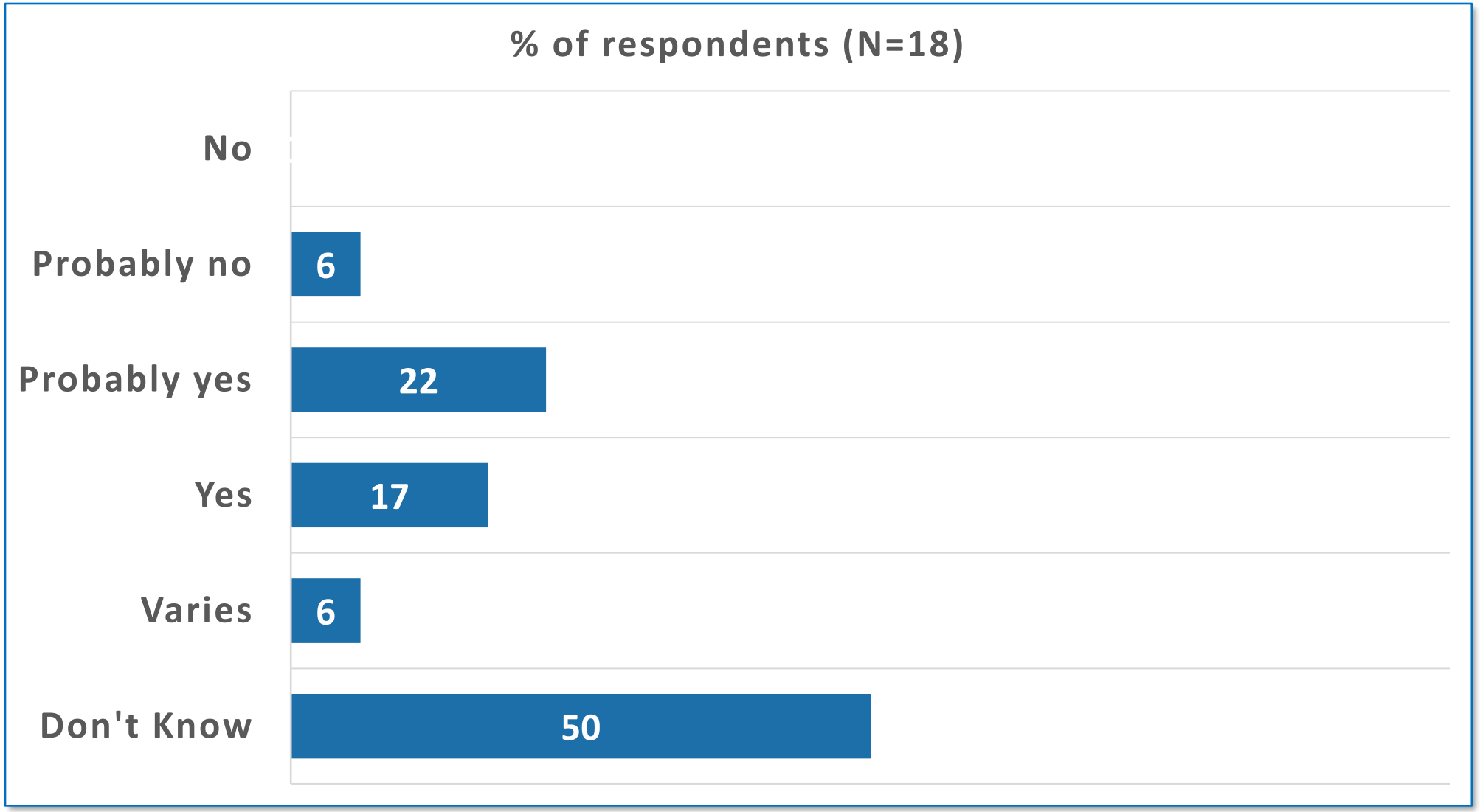


EtR Domain 3: Values

Does the Target Population Feel that the Desirable Effects are Large Relative To Undesirable Effects?

- No direct evidence found.
- Change in recommendations might be reassuring to some who have wanted to be vaccinated but were hesitant/perceived it is unsafe;
- Or might be source of concern.
  - WG member expressed that change might be viewed unfavorably if it is perceived as trade-off between safety vs. increasing coverage/reducing missed opportunities for vaccination.

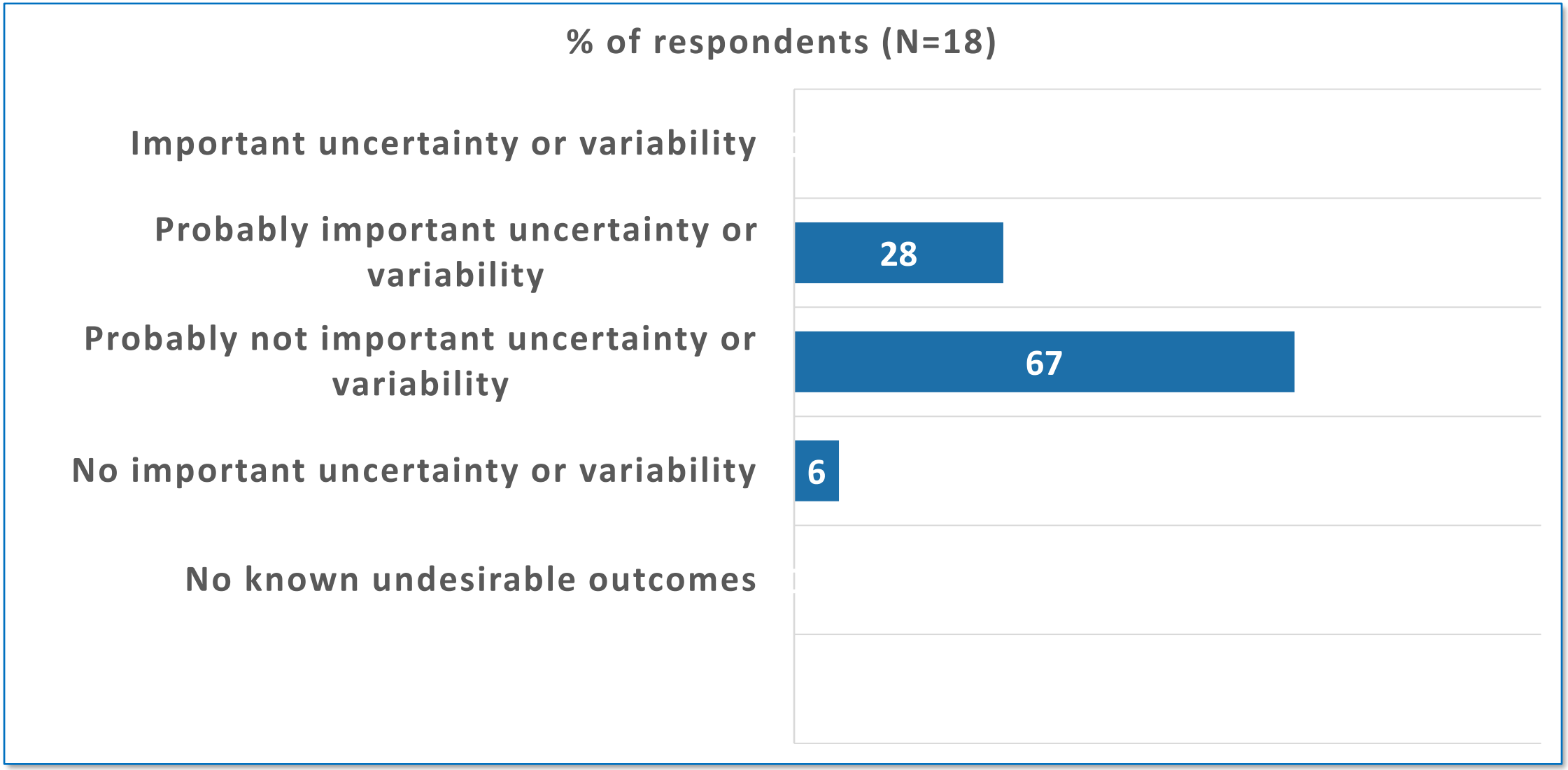
Does the Target Population Feel that the Desirable Effects are Large Relative To Undesirable Effects?



Is There Important Uncertainty About, or Variability In, How Much People Value the Main Outcomes?

- No direct evidence found.
  - Presumably, greater value attached to the more serious outcomes (death, anaphylaxis, hospitalization).

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



EtR Domain 4: Acceptability

Is the Intervention Acceptable to Key Stakeholders?

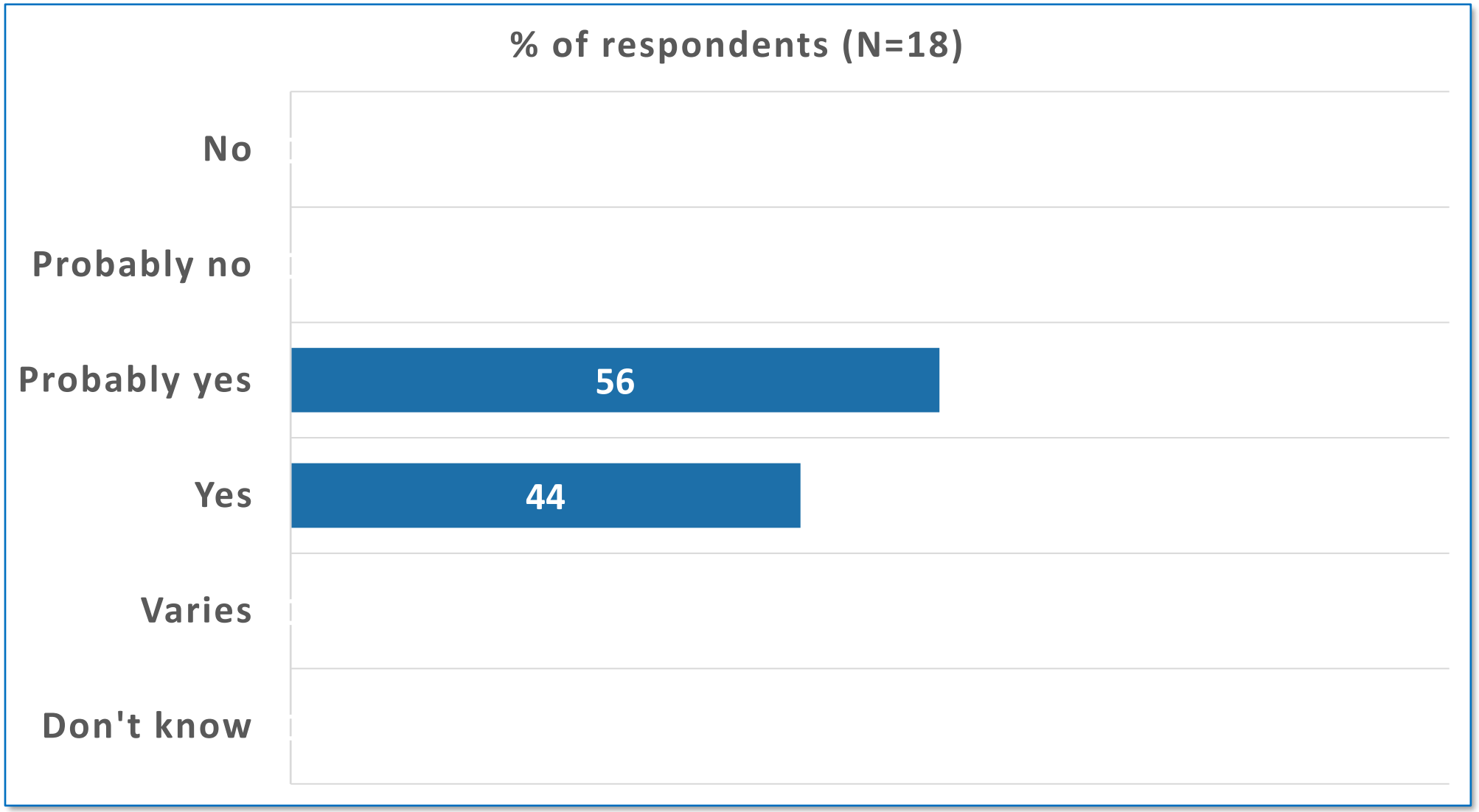
- No direct evidence found.
- Several US professional societies (AAP, AAAAI, ACAAI) already recommend no special measures (screening, observation periods, selection of specific vaccines, specific vaccination settings) for those with egg allergy.
- As of 2022-23, package inserts for egg-based vaccines continue to carry a contraindication of severe hypersensitivity reaction to any vaccine components.
  - However, ACIP has previously recommended influenza vaccination with any appropriate vaccine (egg-based or not), regardless of severity of reaction to egg.

Acceptability: WG Considerations

- Alignment of recommendations among public health organizations and professional societies facilitates consistent messaging to providers and patients.

- Concern that some settings might not be prepared to manage severe reactions (e.g., retail).
- Acceptability will be severely impacted if anaphylaxis occurs in a setting unprepared to manage it.
  - Importance of stressing that ***every*** setting must be able to manage anaphylaxis, or should not administer any vaccines to any recipient.
- Concern for potential liability issues.

Is the Intervention Acceptable to Key Stakeholders?



EtR Domain 5: Resource Use

Is the Intervention a Reasonable and Efficient Allocation of Resources?

- No economic analysis was conducted.
  - The target population is small.
  - Lack of data for some factors.
    - No reliable estimate of the proportion of those with egg allergy who have had severe reaction to egg.
    - Proportions of individuals with egg allergy by age uncertain.
    - Proportions of persons receiving egg-based vs. egg-free vaccines uncertain.
- Primary emphasis of assessment was safety rather than cost.

Relative Costs of Egg-Based vs. Egg-Free Influenza Vaccines

- CMS payment allowances and VFC costs higher for egg-free vaccines that are approved for children (rounded to nearest dollar):

Vaccine (based on 0.5mL dose)	CMS Rate 2022-23[1]	VFC List 2023-24[2]
Egg-based		
Average for egg-based vaccines for ≥6 mos: Multidose	$20.00	$20.00
Average for egg-based vaccines for ≥6 mos: Preservative-free	$22.00 (IIV4s) $27.00 (LAIV4)	$21.00 (IIV4s) $24.00 (LAIV4)
Fluzone High-Dose Quadrivalent: Preservative-free (≥65 yrs only)	*$70.00*	-
Fluad Quadrivalent: Preservative-free (≥65 yrs only)	*$72.00*	-
Egg-free		
Flucelvax Quadrivalent: Multidose (≥6 mos)	$31.00	$29.00
Preservative-free (≥6 mos)	$32.00	$30.00
Flublok Quadrivalent Preservative-free (≥18 yrs only)	*$70.00*	-

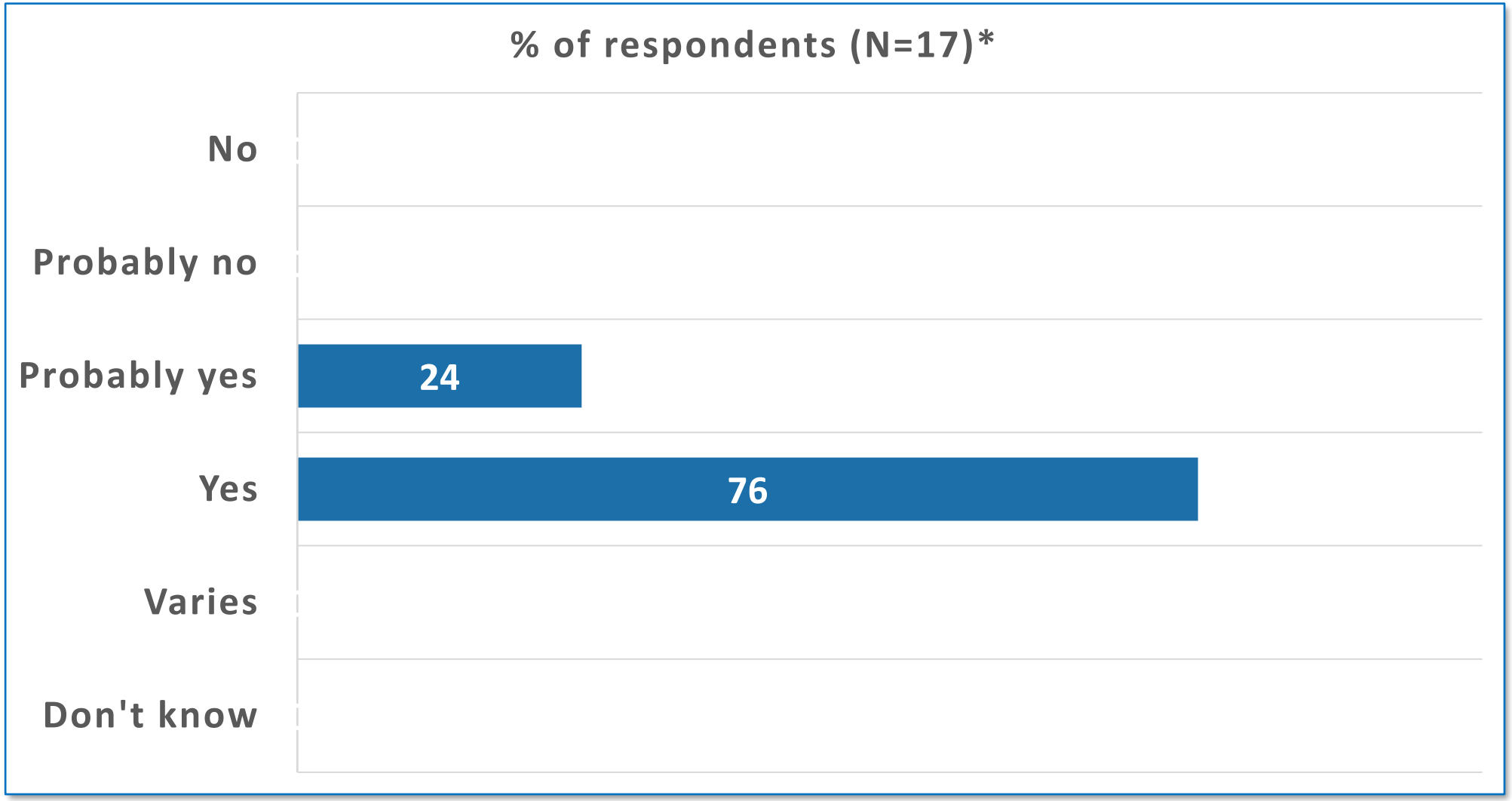
1. https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Part-B-Drugs/McrPartBDrugAvgSalesPrice/VaccinesPricing
2. CDC Vaccine Price List (Private sector cost per dose)

Resource Use: WG Considerations

- Removing existing restrictions could result more efficient allocation of resources, if data suggest no or minimal increase in adverse events.

- Change in recommendations and lower cost of egg-based vaccines might lead to their increased use, which might be associated with increased costs if these is an increase in reactions requiring medical attention.

Is the Intervention a Reasonable and Efficient Allocation of Resources?



* Answer from one respondent who selected “Probably yes” and “Yes” excluded

EtR Domain 6: Equity

What Would Be the Impact on Health Equity?

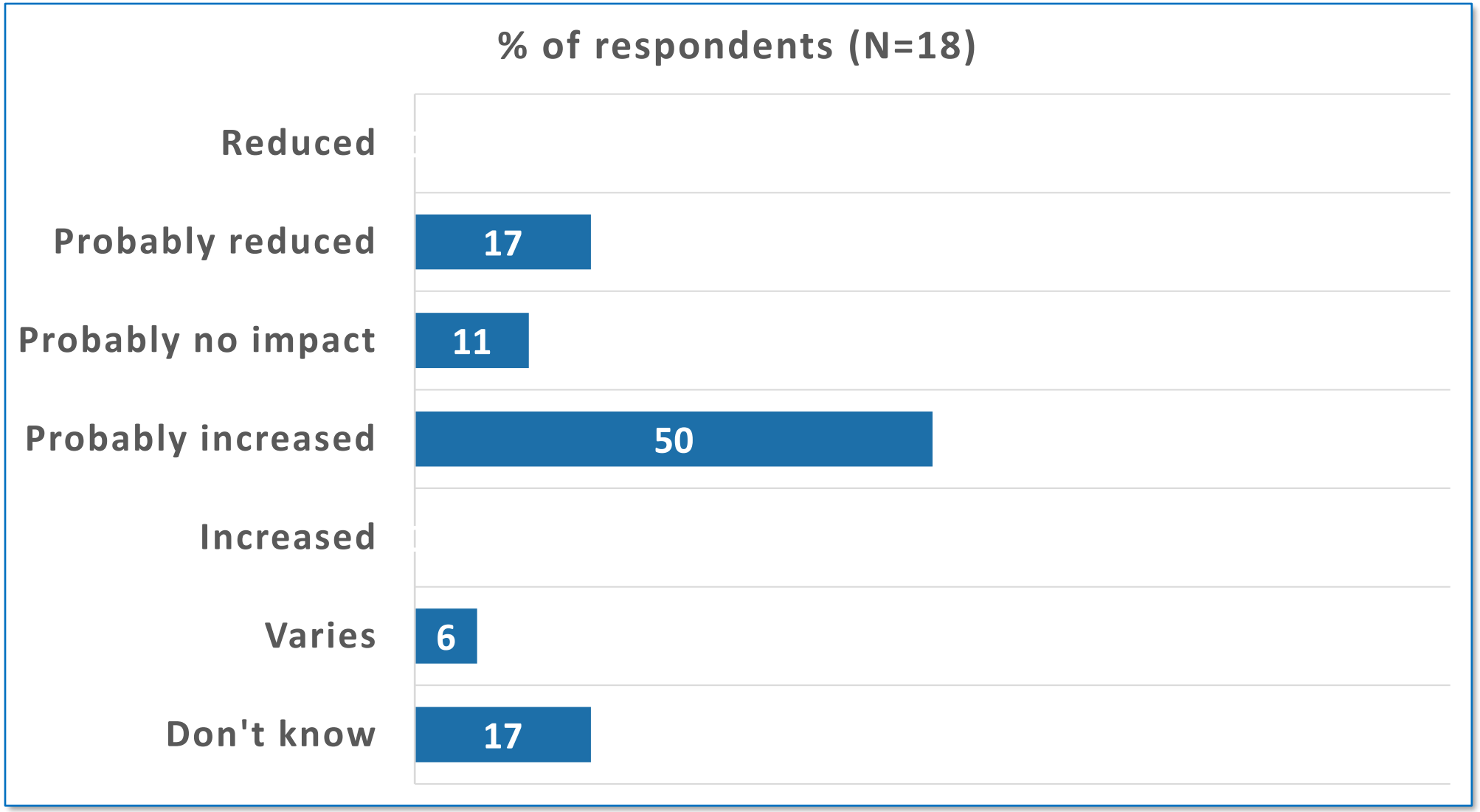
- No direct evidence found.
- Some racial/ethnic groups at increased risk for severe influenza illness, highlighting importance of vaccination:
  - Influenza associated hospitalization and ICU admission rates higher among Black, Hispanic, and American Indian/Alaska Native children <4 yrs of age compared with White children.[1]
  - Black children were disproportionately represented among children with egg allergy in one series (23.4%, relative to comprising 13.2% of the U.S. pediatric population).[2]
  - If current recommendations are a barrier to vaccination, the intervention could improve equity with regard to risk of severe influenza illness.

1. *O'Halloran et al JAMA Netw Open. 2021 Aug 2;4(8):e2121880*
2. *Samady W et al. J Allergy Clin Immunol Pract. 2020 Oct;8(9):3066-3073.e6. doi: 10.1016/j.jaip.2020.04.058.*

Equity: WG Considerations

- Issues related to trust in the healthcare system, from the patient's perspective:
  - A change in recommendations might mean vaccination occurs more widely in more settings than previously, and perhaps increased use of egg-based vaccines rather than egg-free vaccines in some settings.
  - The fact that egg-based vaccines are less expensive might reinforce belief that providers/healthcare systems do not care to use the necessary resources to provide a potentially safer vaccine.

What Would Be the Impact on Health Equity?



EtR Domain 7: Feasibility

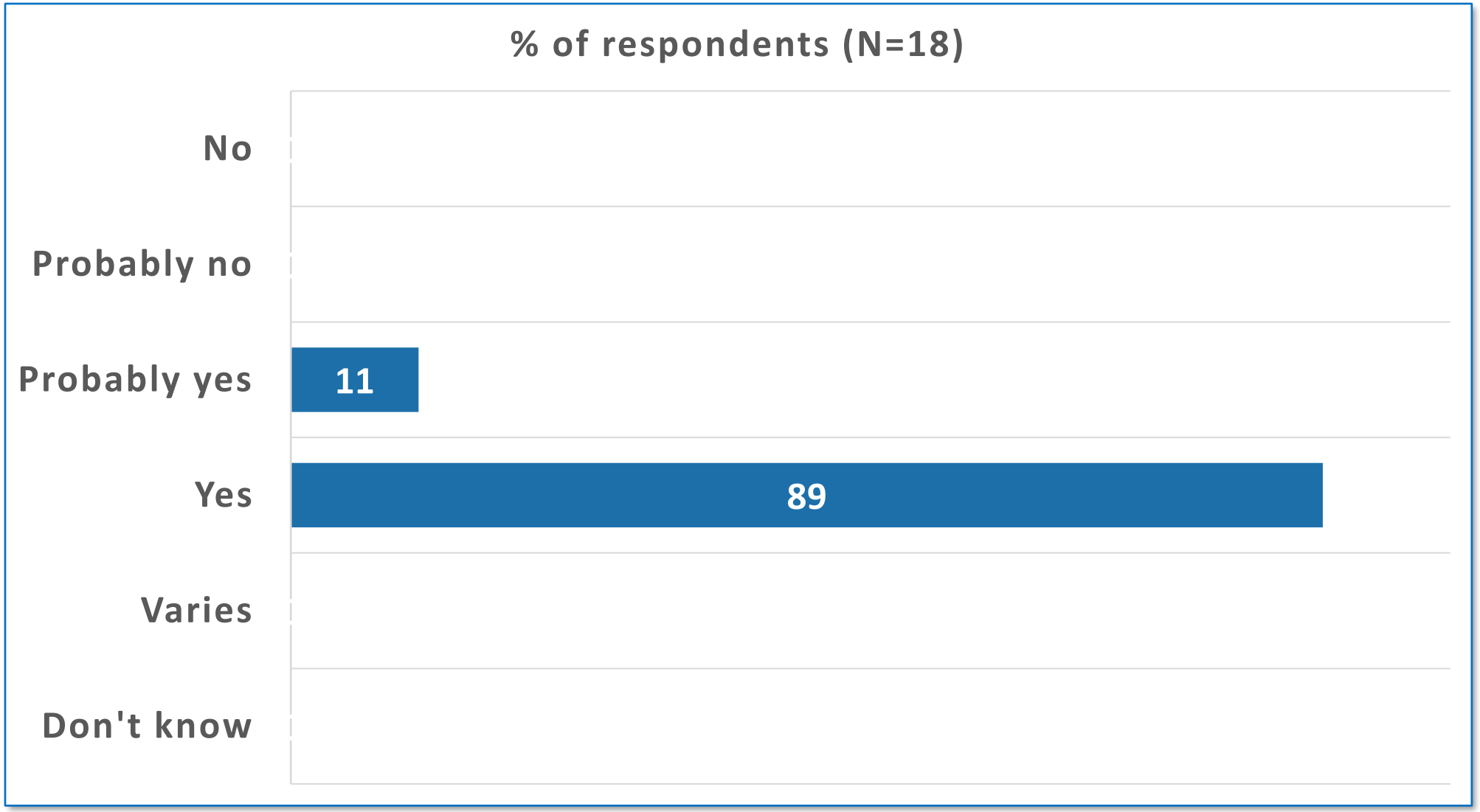
Is the Intervention Feasible to Implement?

- Considerations favoring feasibility:
  - The proposed change is a simplification of the previous recommendation.
  - It does not specify particular vaccines.
  - It does not change recommendations for emergency equipment and resources.
    - › The General Best Practices indicate that epinephrine and equipment to manage an airway should be available in all vaccination settings.[1]

- Consideration against feasibility:
  - Vaccination settings not already prepared to manage severe allergic reactions would need to address these needs.
    - › However, all settings are already recommended to be prepared for severe allergic reactions when administering any vaccine to any recipient.[1]

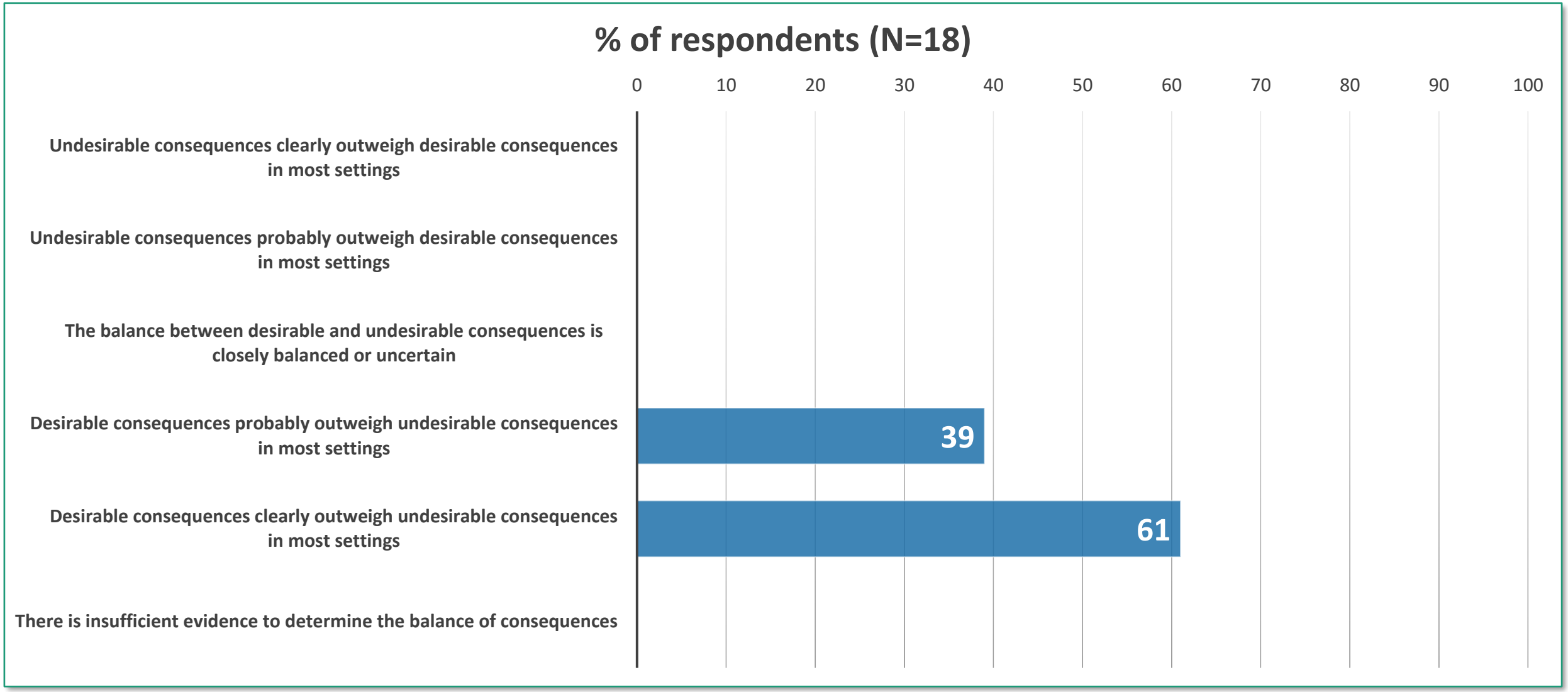
1. *Kroger AT et al. https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/index.html.*

Is the Intervention Feasible to Implement?



Balance of Consequences and Sufficiency of Information

Balance of Consequences



Is There Sufficient Information to Move Forward With a Recommendation?

- Of 18 respondents,
  - 18 responded “Yes”
  - 0 responded “No”

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

Literature Search, Inclusion/Exclusion Criteria

Search

- First search 03-14-2019; updated search 10-26-2022.
- Medline, Embase, PsycInfo, CINAHL, NTIS, Scopus, Cochrane Library, ClinicalTrials.gov; no date or language restriction.

Included reports

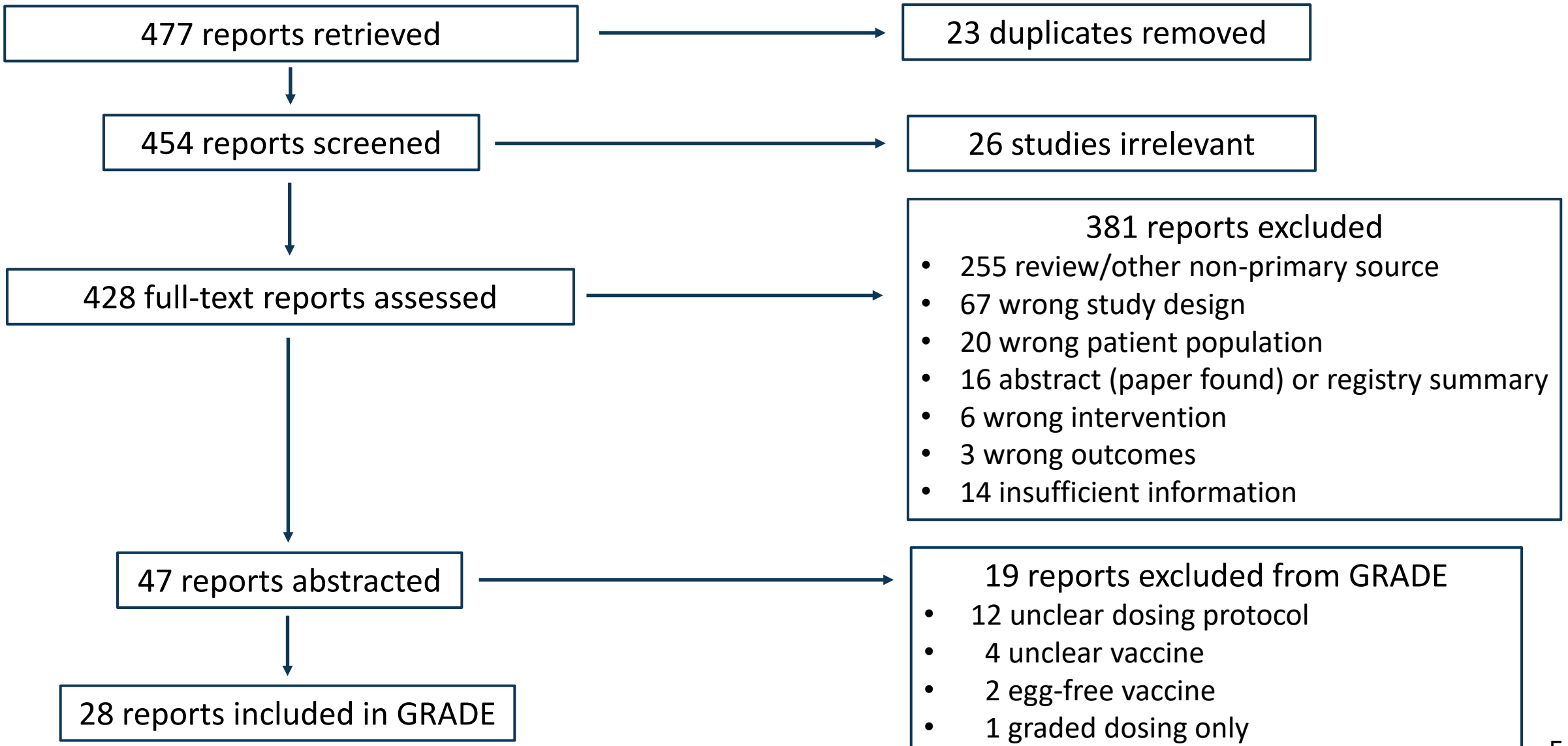
- Randomized Controlled trials, Observational studies, Case reports, Case series, Safety surveillance system reports (including Vaccine Adverse Event Reporting System and other safety surveillance system reports).
- Abstracts for which no papers found were included.

Excluded reports

- Animal studies, duplicate reports, reviews*, clinical trial registry summaries.*

* Used to help identify other potentially relevant reports

PRISMA Diagram



1. Question and PICO

Policy question:	Whether available evidence concerning safety of influenza vaccines in persons with a history of egg allergy favors routine vaccination without additional safety measures, regardless of severity of previous allergic reaction to egg.
Population	Persons of any age with a history of allergy to eggs, or who have had an allergic reaction to influenza vaccine believed to be secondary to egg allergy.
Intervention	Receipt of any influenza vaccine.
Comparison	Placebo, nonegg-based influenza vaccine, non-influenza control vaccine, no vaccine, no comparator.
Outcomes	***Critical:*** • Death • Anaphylaxis meeting Brighton criteria Levels 1-3* • Anaphylaxis otherwise classified* • Allergic reaction symptoms requiring hospitalization ***Important:*** • Allergic reaction symptoms requiring outpatient or emergency department medical attention† • Allergic reaction including cardiovascular symptoms, respiratory symptoms, angioedema, or generalized urticaria

*These outcomes are combined in the evidence profile tables.

†Includes instances treated with medications, without explicit mention of outpatient or emergency department care.

2. Outcomes and Rankings

Outcome	Importance	Included in evidence profile
Death	Critical	Yes
Anaphylaxis meeting Brighton criteria Levels 1-3*	Critical	Yes
Anaphylaxis otherwise classified*	Critical	Yes
Allergic reaction symptoms requiring hospitalization	Critical	Yes
Allergic reaction symptoms requiring outpatient or emergency department medical attention†	Important	Yes
Allergic reaction including cardiovascular symptoms, respiratory symptoms, angioedema, or generalized urticaria	Important	Yes

*These outcomes are combined in the evidence profile tables.

†Includes instances treated with medications, without explicit mention of outpatient or emergency department care.

3a. Summary of Studies and Outcomes—Seasonal IIV (1)

Author Publication year	Age/other characteristics	N	Comparator	Events by outcome	Methodological quality concern*
Anvari 2011	Not specified	86	None	None	Unclear
Chung 2010	Skin test group: Average 6.2 (95%CI 5.1-7.2) yrs Non-skin test group: Average 3.9 (95%CI 3.3-4.5) yrs	171	None	None	Moderate
Comeau 2016†	Not specified	88	None	None	Serious
Des Roches 2012-1	<2 yrs: 27 2-4 yrs: 83 5-11 yrs: 82 >12 yrs: 37	230	None	None	Low
DesRoches 2012-2	<2 yrs: 29 2-4 yrs: 53 5-11 yrs: 51 >12 yrs: 4	137	None	None	Low
Erlewyn-Lajeunesse 2010†	Not specified	16 doses	None	Cardiovascular, respiratory, angioedema, or generalized urticaria: 1	Moderate

*Adapted from Murad MH et al, BMJ Evid Based Med 2018;23(2):60-62. Domains assessed included Selection, Ascertainment, Causality (excluding items pertaining to alternative causes and dose-response effect), and Reporting

†Abstract only.

3a. Summary of Studies and Outcomes—Seasonal IIV (2)

Author Publication year	Age/other characteristics	N	Comparator	Events by outcome	Methodological quality concern
Esposito 2008	6.03 +/- 3.33 yrs	44	Non-allergic group	Outpatient or emergency department medical attention: 1 Cardiovascular, respiratory, angioedema, or generalized urticaria: 1	Low
Greenhawt 2012-1	Median 11-12 mos	31	Comparison of full- vs. split-dose (combined in this review)	None	Low
Greenhawt 2012-2	Median 12 mos at diagnosis	112	None	None	Low
Hotte 2008†	Not provided	115	None	None	Unclear
Howe 2011	Not specified	69	Non-allergic group	None	Unclear
James 1998	Median 3 (1-46) yrs	83	Non-allergic group	Outpatient or emergency department medical attention: 2 Cardiovascular, respiratory, angioedema, or generalized urticaria: 3	Low
Leo 2010†	Not provided	31	None	None	Unclear
Park 2008†	Mean 36.1 +/- 19.1 (11 to 105 mos)	45	None	None	Unclear
Paschall 2011†	Mean 3.8 yrs	65 doses	None	None	Unclear
Shimizu 2016	Median 15 (IQR 13-20) mos	17	None	None	Low
Thanik 2010	Not specified	214 doses	None	None	Unclear

*Adapted from Murad MH et al, BMJ Evid Based Med 2018;23(2):60-62. Domains assessed included Selection, Ascertainment, Causality (excluding items pertaining to alternative causes and dose-response effect), and Reporting

†Abstract only.

3b. Summary of Studies and Outcomes—Monovalent IIV (1)

Author Publication year	Age/other characteristics	N	Comparator	Events by outcome	Methodological quality concern*
Didenko 2010	median 4 (2-11) yrs	6	None	None	Moderate
Forsdahl 2012	Mean 6.25 yrs (10 mos-16.5 yrs)	80	None	Outpatient or emergency department medical attention: 1 Cardiovascular, respiratory, angioedema, or generalized urticaria: 1	Moderate
Gagnon 2010-1	173 <2 yrs 280 2-4 yrs 277 5-11 yrs 100 ≥12 yrs	830	Non-allergic group	Outpatient or emergency department medical attention: 4 Cardiovascular, respiratory, angioedema, or generalized urticaria: 6	Low
Gagnon 2010-2	Not specified	3460	None	Outpatient or emergency department medical attention: 68 Cardiovascular, respiratory, angioedema, or generalized urticaria: 26	Unclear
Greenhawt 2010	Mean 5.5 (range 0.4-20.4) yrs	105	Non-allergic group	None	Low

*Adapted from Murad MH et al, BMJ Evid Based Med 2018;23(2):60-62. Domains assessed included Selection, Ascertainment, Causality (excluding items pertaining to alternative causes and dose-response effect), and Reporting.

3b. Summary of Studies and Outcomes—Monovalent IIV (2)

Author Publication year	Age/other characteristics	N	Comparator	Events by outcome	Methodological quality concern*
Leo 2010†	Not specified	50	None	None	Unclear
Paschall 2011†	Mean 3.8 yrs	66	None	None	Unclear
Pien 2010	Mean 3.7 +/- 3.0 yrs	59	None	None	Moderate
Pitt 2011	Mean 5.6 (1-27) yrs	59	None	None	Moderate
Schuler 2011	Mean 4.5 yrs (10 mos-16 yrs)	62	None	Outpatient or emergency department medical attention: 4	Moderate
Siret-Alatrista 2010†	Unclear	53	None	None	Unclear
Spiegel 2010†	Range 1-56 yrs	150	None	None	Unclear
Upton 2012	3-5 yrs:12 6-9 yrs:24 10-13 yrs:28 14+ yrs:10	75	None	None	Moderate

*Adapted from Murad MH et al, BMJ Evid Based Med 2018;23(2):60-62. Domains assessed included Selection, Ascertainment, Causality (excluding items pertaining to alternative causes and dose-response effect), and Reporting

†Abstract only.

3c. Summary of Studies and Outcomes—LAIV

Author Publication year	Age/other characteristics	N	Comparator	Events by outcome	Methodological quality concern*
Des Roches 2015	2-16 yrs	68	Non-allergic group	None	Low
Turner 2015a	Median 4.9 yrs (2-17 yrs)	282	None	Cardiovascular symptoms, respiratory symptoms, angioedema, or generalized urticaria: 6	Low
Turner 2015b	Median 5.3 yrs (2-18 yrs)	779	None	Cardiovascular symptoms, respiratory symptoms, angioedema, or generalized urticaria: 4	Low

*Adapted from Murad MH et al, BMJ Evid Based Med 2018;23(2):60-62. Domains assessed included Selection, Ascertainment, Causality (excluding items pertaining to alternative causes and dose-response effect), and Reporting

†Abstract only.

4a: Seasonal IIV administered full- or split-dose, egg allergy of all severities (1)

Certainty Assessment							Impact	Certainty	Importance
No. of studies	Study Design	Method-ological Quality*	Inconsistency	Indirectness	Imprecision	Other considerations			
1. Death									
17	Observa-tional	Serious[a]	Not serious	Serious[b]	Serious[c]	None	0/1591 (0%) instances	Very Low	CRITICAL
2. Anaphylaxis									
17	Observa-tional	Serious[a]	Not serious	Serious[b]	Serious[c]	None	0/1591 (0%) instances	Very Low	CRITICAL
3. Allergic reaction symptoms requiring hospitalization									
17	Observa-tional	Serious[a]	Not serious	Serious[b]	Serious[c]	None	0/1591 (0%) instances	Very Low	CRITICAL

*Adapted from Murad MH et al, Methodological quality and synthesis of case series and case reports, BMJ Evid Based Med 2018;23(2):60-62 [51]. Domains assessed included Selection, Ascertainment, Causality (excluding items pertaining to alternative causes and dose-response effect), and Reporting.

a. All are cohort studies without comparator interventions, with the exception of one randomized study which compared administration of full dose vs split dose. Full dose and split dose administration are treated as equivalent in this review, and so this study is treated as a cohort study. Six of 17 are of unclear methodological quality. Six of 17 are abstracts.

b. Most studies did not report data specifically for persons with a history of anaphylaxis to egg.

c. Cannot assess imprecision as these are proportions with no confidence intervals. However, some degree of imprecision should be assumed.

4a: Seasonal IIV administered full- or split-dose, egg allergy of all severities (2)

Certainty Assessment							Impact	Certainty	Importance
No. of studies	Study Design	Method-ological Quality*	Inconsistency	Indirectness	Imprecision	Other considerations			
4. Allergic reaction symptoms requiring outpatient or emergency department medical attention									
17	Observa-tional	Serious[a]	Not serious	Serious[b]	Serious[c]	None	3/1591 (0.2%) instances	Very Low	IMPORTANT
5. Allergic reaction including cardiovascular symptoms, respiratory symptoms, angioedema, or generalized urticaria									
17	Observa-tional	Serious[a]	Not Serious	Serious[b]	Serious[c]	None	5/1591 (0.3%)† instances	Very Low	IMPORTANT

*Adapted from Murad MH et al, Methodological quality and synthesis of case series and case reports, BMJ Evid Based Med 2018;23(2):60-62 [51]. Domains assessed included Selection, Ascertainment, Causality (excluding items pertaining to alternative causes and dose-response effect), and Reporting.

† One study reported 6 instances of reactions included "wheezing, eczema exacerbation, or hives on chest", but not specifying number with each symptom. These are excluded here. If assumed that all six included wheezing, frequency would be 10/1591=0.6%

a. All are cohort studies without comparator interventions, with the exception of one randomized study which compared administration of full dose vs split dose. Full dose and split dose administration are treated as equivalent in this review, and so this study is treated as a cohort study. Six of 17 are of unclear methodological quality. Six of 17 are abstracts.

b. Most studies did not report data specifically for persons with a history of anaphylaxis to egg.

c. Cannot assess imprecision as these are proportions with no confidence intervals. However, some degree of imprecision should be assumed.

4b: Seasonal IIV administered full- or split-dose, persons with anaphylaxis to egg (1)

Certainty Assessment							Impact	Certainty	Importance
No. of studies	Study Design	Method-ological Quality*	Inconsistency	Indirectness	Imprecision	Other considerations			
1. Death									
10[a]	Observa-tional	Serious[b]	Not serious	Not serious	Serious[c]	None	0/322 (0%) instances	Very Low	CRITICAL
2. Anaphylaxis									
10[a]	Observa-tional	Serious[b]	Not serious	Not serious[b]	Serious[c]	None	0/322 (0%) instances	Very Low	CRITICAL
3. Allergic reaction symptoms requiring hospitalization									
10[a]	Observa-tional	Serious[b]	Not serious	Not serious	Serious[c]	None	0/322 (0%) instances	Very Low	CRITICAL

*Adapted from Murad MH et al, Methodological quality and synthesis of case series and case reports, BMJ Evid Based Med 2018;23(2):60-62 [51]. Domains assessed included Selection, Ascertainment, Causality (excluding items pertaining to alternative causes and dose-response effect), and Reporting

a. Includes only studies which explicitly mentioned inclusion of egg-anaphylactic patients for whom data are specifically reported.

b. All are cohort studies without comparator intervention groups, including administration via either full dose or split-dose (2-step) protocols. Two of 10 studies are abstracts, and 3 of 10 have uncertain methodological quality.

c. Cannot assess imprecision as these are proportions with no confidence intervals. However, some degree of imprecision should be assumed.

d. Studies removed from denominator which included persons with a history of anaphylaxis to egg and reported event(s), but which did not indicate whether these occurred in a person with a history of anaphylaxis to egg.

4b: Seasonal IIV administered full- or split-dose, persons with anaphylaxis to egg (2)

Certainty Assessment							Impact	Certainty	Importance
No. of studies	**Study Design**	**Method-ological Quality***	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**			
4. Allergic reaction symptoms requiring outpatient or emergency department medical attention									
9[a]	Observa-tional	Serious[b]	Not serious	Not serious	Serious[c]	None	0/295 (0%) instances[d]	Very Low	IMPORTANT
5. Allergic reaction including cardiovascular symptoms, respiratory symptoms, angioedema, or generalized urticaria									
8[a]	Observa-tional	Serious[b]	Not serious	Not serious	Serious[c]	None	0/291 (0%) instances[d]	Very Low	IMPORTANT

*Adapted from Murad MH et al, Methodological quality and synthesis of case series and case reports, BMJ Evid Based Med 2018;23(2):60-62 [51]. Domains assessed included Selection, Ascertainment, Causality (excluding items pertaining to alternative causes and dose-response effect), and Reporting

a. Includes only studies which explicitly mentioned inclusion of egg-anaphylactic patients for whom data are specifically reported.

b. All are cohort studies without comparator intervention groups, including administration via either full dose or split-dose (2-step) protocols. Two of 10 studies are abstracts, and 3 of 10 have uncertain methodological quality.

c. Cannot assess imprecision as these are proportions with no confidence intervals. However, some degree of imprecision should be assumed.

d. Studies removed from denominator which included persons with a history of anaphylaxis to egg and reported event(s), but which did not indicate whether these occurred in a person with a history of anaphylaxis to egg.

4c: Monovalent IIV administered full- or split-dose, egg allergy of all severities (1)

Certainty Assessment							Impact	Certainty	Importance
No. of studies	Study Design	Method-ological Quality*	Inconsistency	Indirectness	Imprecision	Other considerations			
1. Death									
13	Observa-tional	Very serious[a]	Not serious	Serious[b]	Serious[c]	None	0/5235 (0%) instances	Very Low	CRITICAL
2. Anaphylaxis									
13	Observa-tional	Very serious[a]	Not serious	Serious[b]	Serious[c]	None	0/5235 (0%) instances [d]	Very Low	CRITICAL
3. Allergic reaction symptoms requiring hospitalization									
13	Observa-tional	Very serious[a]	Not serious	Serious[b]	Serious[c]	None	0/5235 (0%) instances	Very Low	CRITICAL

*Adapted from Murad MH et al, Methodological quality and synthesis of case series and case reports, BMJ Evid Based Med 2018;23(2):60-62 [51]. Domains assessed included Selection, Ascertainment, Causality (excluding items pertaining to alternative causes and dose-response effect), and Reporting.

a. All were cohort studies without comparator intervention groups, including administration via either full dose or split-dose (2-step) protocols. Concerns regarding methodological quality were "Low" for only two studies, moderate for 6, and unclear for 4. History of egg allergy was by self report only for the largest study (n=3640).

b. Most studies did not report data specifically for persons with a history of anaphylaxis to egg.

c. Cannot assess imprecision as these are proportions without confidence intervals; however some degree of imprecision must be assumed.

d. One instance of Brighton Level 1 anaphylaxis was reported in a VAERS surveillance data summary from the 2009-10 influenza season. This instance is not represented in the table as no denominator is available for this paper. However, it was reported that 127,075,320 doses of monovalent influenza vaccine were distributed in the United States for the season.

4c: Monovalent IIV administered full- or split-dose, egg allergy of all severities (2)

Certainty Assessment							Impact	Certainty	Importance
No. of studies	**Study Design**	**Method-ological Quality***	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**			
4. Allergic reaction symptoms requiring outpatient or emergency department medical attention									
13	Observa-tional	Very serious[a]	Not serious	Serious[b]	Serious[c]	None	77/5235 (1.5%) instances	Very Low	IMPORTANT
5. Allergic reaction including cardiovascular symptoms, respiratory symptoms, angioedema, or generalized urticaria									
13	Observa-tional	Serious[a]	Not serious	Serious[b]	Serious[c]	None	33/5235 (0.6%) instances	Very Low	IMPORTANT

*Adapted from Murad MH et al, Methodological quality and synthesis of case series and case reports, BMJ Evid Based Med 2018;23(2):60-62 [51]. Domains assessed included Selection, Ascertainment, Causality (excluding items pertaining to alternative causes and dose-response effect), and Reporting.

a. All were cohort studies without comparator intervention groups, including administration via either full dose or split-dose (2-step) protocols. Concerns regarding methodological quality were "Low" for only two studies, moderate for 6, and unclear for 4.

b. Only 143 of total participants reported to have a history of anaphylaxis to egg.

c. Cannot assess imprecision as these are proportions without confidence intervals; however some degree of imprecision must be assumed.

d. One instance of Brighton Level 1 anaphylaxis was reported in a VAERS surveillance data summary from the 2009-10 influenza season. This instance is not represented in the table as no denominator is available for this paper. However, it was reported that 127,075,320 doses of monovalent influenza vaccine were distributed in the United States for the season.

4d: Monovalent IIV administered full- or split- dose, persons with anaphylaxis to egg (1)

Certainty Assessment							Impact	Certainty	Importance
No. of studies	**Study Design**	**Method-ological Quality***	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**			
1. Death									
3	Observa-tional	Very Serious[a]	Not Serious	Not Serious	Serious[b]	None	0/68 (0%) Instances	Very Low	CRITICAL
2. Anaphylaxis									
3	Observa-tional	Very Serious[a]	Not Serious	Not Serious	Serious[b]	None	0/68 instances	Very Low	CRITICAL
3. Allergic reaction symptoms requiring hospitalization									
3	Observa-tional	Very Serious[a]	Not Serious	Not Serious	Serious[b]	None	0/68 instances	Very Low	CRITICAL

*Adapted from Murad MH et al, Methodological quality and synthesis of case series and case reports, BMJ Evid Based Med 2018;23(2):60-62 [51]. Domains assessed included Selection, Ascertainment, Causality (excluding items pertaining to alternative causes and dose-response effect), and Reporting.

a. Cohort studies without comparator intervention groups, including administration via either full dose or split-dose (2-step) protocols.

b. Cannot assess imprecision as these are proportions with no confidence intervals. However, some degree of imprecision should be assumed.

4d: Monovalent IIV administered full- or split- dose, persons with anaphylaxis to egg (2)

Certainty Assessment							Impact	Certainty	Importance
No. of studies	**Study Design**	**Method-ological Quality***	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**			
4. Allergic reaction symptoms requiring outpatient or emergency department medical attention									
3	Observa-tional	Very Serious[a]	Not Serious	Not Serious	Serious[b]	None	0/68 instances	Very Low	IMPORTANT
5. Allergic reaction including cardiovascular symptoms, respiratory symptoms, angioedema, or generalized urticaria									
3	Observa-tional	Very Serious[a]	Not Serious	Not Serious	Serious[b]	None	0/68 instances	Very Low	IMPORTANT

*Adapted from Murad MH et al, Methodological quality and synthesis of case series and case reports, BMJ Evid Based Med 2018;23(2):60-62 [51]. Domains assessed included Selection, Ascertainment, Causality (excluding items pertaining to alternative causes and dose-response effect), and Reporting.

a. Cohort studies without comparator intervention groups, including administration via either full dose or split-dose (2-step) protocols.

b. Cannot assess imprecision as these are proportions with no confidence intervals. However, some degree of imprecision should be assumed.

4e. Seasonal LAIV, egg allergy of all severities (1)

Certainty Assessment							Impact	Certainty	Importance
No. of studies	**Study Design**	**Method-ological Quality***	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**			
1. Death									
3	Observa-tional	Serious[a]	Not serious	Serious[b]	Serious[c]	None	0/1129 instances	Very Low	CRITICAL
2. Anaphylaxis									
3	Observa-tional	Serious[a]	Not serious	Serious[b]	Serious[c]	None	0/1129 instances	Very Low	CRITICAL
3. Allergic reaction symptoms requiring hospitalization									
3	Observa-tional	Serious[a]	Not serious	Serious[b]	Serious[c]	None	0/1129 instances	Very Low	CRITICAL

*Adapted from Murad MH et al, Methodological quality and synthesis of case series and case reports, BMJ Evid Based Med 2018;23(2):60-62 [51]. Domains assessed included Selection, Ascertainment, Causality (excluding items pertaining to alternative causes and dose-response effect), and Reporting.

a. All are cohort studies without a comparison intervention.

b. Most studies did not report data specifically for persons with a history of anaphylaxis to egg.

c. Cannot assess imprecision as these are proportions with no confidence intervals. However, some degree of imprecision should be assumed.

4e. Seasonal LAIV, egg allergy of all severities (2)

Certainty Assessment							Impact	Certainty	Importance
No. of studies	**Study Design**	**Method-ological Quality***	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**			
4. Allergic reaction symptoms requiring outpatient or emergency department medical attention									
3	Observa-tional	Serious[a]	Not serious	Serious[b]	Serious[c]	None	0/1129 instances	Very Low	IMPORTANT
5. Allergic reaction including cardiovascular symptoms, respiratory symptoms, angioedema, or generalized urticaria									
3	Observa-tional	Serious[a]	Not serious	Serious[b]	Serious[c]	None	10/1129 (0.8%) instances	Very Low	IMPORTANT

*Adapted from Murad MH et al, Methodological quality and synthesis of case series and case reports, BMJ Evid Based Med 2018;23(2):60-62 [51]. Domains assessed included Selection, Ascertainment, Causality (excluding items pertaining to alternative causes and dose-response effect), and Reporting.

a. All are cohort studies without a comparison intervention.

b. Majority of persons in each study did not have history of anaphylaxis to egg.

c. Cannot assess imprecision as these are proportions with no confidence intervals. However, some degree of imprecision should be assumed.

4f. Seasonal LAIV, persons with anaphylaxis to egg (1)

Certainty Assessment							Impact	Certainty	Importance
No. of studies	Study Design	Method-ological Quality*	Inconsistency	Indirectness	Imprecision	Other considerations			
1. Death									
3	Observa-tional	Serious[a]	Not serious	Not serious	Serious[b]	None	0/412 instances	Very Low	CRITICAL
2. Anaphylaxis									
3	Observa-tional	Serious[a]	Not serious	Not serious	Serious[b]	None	0/412 instances	Very Low	CRITICAL
3. Allergic reaction symptoms requiring hospitalization									
3	Observa-tional	Serious[a]	Not serious	Not serious	Serious[b]	None	0/412 instances	Very Low	CRITICAL

*Adapted from Murad MH et al, Methodological quality and synthesis of case series and case reports, BMJ Evid Based Med 2018;23(2):60-62 [51]. Domains assessed included Selection, Ascertainment, Causality (excluding items pertaining to alternative causes and dose-response effect), and Reporting.

a. All are cohort studies with no comparison groups.

b. Cannot assess imprecision as these are proportions with no confidence intervals. However, some degree of imprecision should be assumed.

c. Cannot assess imprecision as these are proportions with no confidence intervals. However, some degree of imprecision should be assumed. Very low denominator count.

4f. Seasonal LAIV, persons with anaphylaxis to egg (2)

Certainty Assessment							Impact	Certainty	Importance
No. of studies	**Study Design**	**Method-ological Quality***	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**			
4. Allergic reaction symptoms requiring outpatient or emergency department medical attention									
3	Observa-tional	Serious[a]	Not serious	Not serious	Serious[b]	None	0/412 instances	Very Low	IMPORTANT
5. Allergic reaction including cardiovascular symptoms, respiratory symptoms, angioedema, or generalized urticaria									
1	Observa-tional	Serious[a]	Not serious	Not serious	Very serious[c]	None	0/27 instances	Very Low	IMPORTANT

*Adapted from Murad MH et al, Methodological quality and synthesis of case series and case reports, BMJ Evid Based Med 2018;23(2):60-62 [51]. Domains assessed included Selection, Ascertainment, Causality (excluding items pertaining to alternative causes and dose-response effect), and Reporting.

a. All are cohort studies with no comparison groups.

b. Cannot assess imprecision as these are proportions with no confidence intervals. However, some degree of imprecision should be assumed.

c. Cannot assess imprecision as these are proportions with no confidence intervals. However, some degree of imprecision should be assumed. Very low denominator count.

d. Studies removed from denominator which included persons with a history of anaphylaxis to egg and reported event(s), but which did not indicate whether these occurred in a person with a history of anaphylaxis to egg.

Appendix 1. Event Summary: Death

Author Publication year	Age	N egg allergic	N anaphylaxis to egg	Events
No studies reported this outcome.				

Appendix 2. Event Summary: Anaphylaxis

Author Publication year	Age	N egg allergic	N anaphylaxis to egg	Events
No studies reported this outcome.				

Appendix 3. Event Summary: Hospitalization

Author Publication year	Age	N egg allergic	N anaphylaxis to egg	Events
No studies reported this outcome.				

Appendix 4. Event Summary: Outpatient/Emergency Care (1)

Author Publication year	Age	Vaccine	N egg allergic	N anaphylaxis to egg	Events
Esposito 2008	Mean 6.03 +/-3.33	Seasonal virosomal	44	11	• 1 bronchospasm in mildly allergic child, treated with bronchodilator and steroid.
James 1998	Mean 6.25 (10mos-16.5 years)	Seasonal IIV	83	27	• 1 delayed (>1 hour post-vaccination) emesis, mild cough, wheeze treated with nebulizer.* • 1 delayed (>1 hour post-vaccination) erythema at injection site treated.*

*Uncertain whether occurred in individual with anaphylaxis to egg.

Appendix 4. Event Summary: Outpatient/Emergency Care (2)

Author Publication year	Age	Vaccine	N egg allergic	N anaphylaxis to egg/severe allergy	Events
Forsdahl 2012	Mean 6.25 yrs (10 mos-16.5 yrs)	Monovalent IIV	80	19	• 1 wheal on lip, diffuse rash, and loose stools a few minutes after 90% step; treated with antihistamine.
Gagnon 2010-1	173 <2 yrs 280 2-4 yrs 277 5-11 yrs 100 ≥12 yrs	Monovalent IIV	830	-	• 1 wheeze treated with bronchodilator. • 1 hives treated with antihistamines • 1 ocular pruritis treated with antihistamines • 1 angioedema treated with antihistamines.

Appendix 4. Event Summary: Outpatient/Emergency Care (3)

Author Publication year	Age	Vaccine	N egg allergic	N anaphylaxis to egg/severe allergy	Events

Gagnon 2010-2	Not provided	Monovalent IIV	3460	-	• 1 mouth/throat tingling 10-15 min post-vaccination; received two doses epinephrine and observed in emergency department; recovered.
					• 1 continuous crying with wheezing 30 min post-vaccination. Received epinephrine and bronchodilator (6 treatments), observed 4 hours, recovered.
					• 66 skin and respiratory symptoms, treated with antihistamines
					  • 42 with skin involvement
					  • 17 with throat tingling/tightening
					  • 7 with cough (4 also treated with bronchodilator)

Appendix 4. Event Summary: Outpatient/Emergency Care (4)

Author Publication year	Age	Vaccine	N egg allergic	N anaphylaxis to egg/severe allergy	Events
Schuler 2011	Mean 4.5 yrs (10 mos-16 yrs)	Monovalent IIV	62	-	• 1 vasovagal response requiring symptomatic management. • 1 hyporesponsive episode; referred to emergency department. • 2 hives treated with antihistamines.

Appendix 5. Event Summary: Cardiovascular, Respiratory, Angioedema, or Generalized Urticaria (1)

Author Publication year	Age	Vaccine	N egg allergic	N anaphylaxis to egg/severe allergy	Events
Erlewyn-Lajeunesse 2010	Children	Seasonal IIV	16 doses	4	• 1 instance subjective wheeze*
Esposito 2008	Mean 6.03 +/-3.33	Seasonal IIV	44	11	• 1 instance bronchospasm in mildly allergic child, treated with bronchodilator and steroid.
James 1998	Mean 6.25 (10mos-16.5 years)	Seasonal IIV	83	27	• 1 with mild throat itching, cough, and wheeze.* • 1 delayed (>1 hour post-vaccination) emesis, mild cough, wheeze treated with nebulizer.* • 1 mild URI symptoms.*

*Uncertain whether occurred in individual with anaphylaxis to egg.

Appendix 5. Event Summary: Cardiovascular, Respiratory, Angioedema, or Generalized Urticaria (2)

Author Publication year	Age	Vaccine	N egg allergic	N anaphylaxis to egg/severe allergy	Events
Forsdahl 2012	Mean 6.25 yrs (10 mos-16.5 yrs)	Monovalent IIV	80	19	• 1 sneezing without bronchospasm.
Gagnon 2010-1	173 <2 yrs 280 2-4 yrs 277 5-11 yrs 100 ≥12 yrs	Monovalent IIV	830	-	• 1 sensation of throat closure • 1 hoarse voice • 1 angioedema • 1 bilateral wheeze • 2 generalized urticaria

Appendix 5. Event Summary: Cardiovascular, Respiratory, Angioedema, or Generalized Urticaria (3)

Author Publication year	Age	Vaccine	N egg allergic	N anaphylaxis to egg/severe allergy	Events
Gagnon 2010-2	Not provided	Monovalent IIV	3460	-	• 1 mouth/throat tingling 10-15 min post-vaccination; received two doses epinephrine and observed in emergency department; recovered. • 1 continuous crying with wheezing 30 min post-vaccination. Received epinephrine and bronchodilator (6 treatments), observed 4 hours, recovered. • 17 with throat tingling/tightening • 7 with cough (4 also treated with bronchodilator)

Appendix 5. Event Summary: Cardiovascular, Respiratory, Angioedema, or Generalized Urticaria (4)

Author Publication year	Age	Vaccine	N egg allergic	N anaphylaxis to egg/severe allergy	Events
Turner 2015a	Median 4.9 yrs (2-17 yrs)	LAIV3	282	115	• 6 rhinitis within 30 min post-vaccination.
Turner 2015b	Median 5.3 yrs (2-18 yrs)	LAIV4	779	157	• 4 rhinitis within 2 hours post-vaccination.

Summary of Evidence for Outcomes of Interest

Outcome	Importance	Included in profile	Certainty
Death	Critical	Yes	Very low
Anaphylaxis	Critical	Yes	Very low
Allergic reaction symptoms requiring hospitalization	Critical	Yes	Very low
Allergic reaction symptoms requiring outpatient or emergency department medical attention	Important	Yes	Very low
Allergic reaction including cardiovascular symptoms, respiratory symptoms, angioedema, or generalized urticaria	Important	Yes	Very low

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