Evaluation and Management of Adverse Reactions to Vaccines

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Faculty Disclosure Information

- I have not had a significant financial interest or other relationship with the manufacturers of the products or providers of the services that will be discussed in my presentation.
- This presentation will not include discussion of pharmaceuticals or devices that have not been approved by the FDA.

Objectives

- Appreciate the nature of IgE-mediated and non-IgE-mediated adverse reactions to various vaccines, including those to COVID-19.
- Appropriately evaluate or refer patients who have had adverse reaction to vaccines.
- Provide advice to patients regarding the future administration of vaccines after an adverse reaction to a previously administered vaccine.

Task force report

Adverse reactions to vaccines practice parameter 2012 update

Chief Editors: John M. Kelso, MD, Matthew J. Greenhawt, MD, MBA, and James T. Li, MD, PhD

Task Force Reviewers: Richard A. Nicklas, MD, David I. Bernstein, MD, Joann Blessing-Moore, MD, Linda Cox, MD, David Khan, MD, David M. Lang, MD, John Oppenheimer, MD, Jay M. Portnoy, MD, Christopher R. Randolph, MD, Diane E. Schuller, MD, Sheldon L. Spector, MD, Stephen A. Tilles, MD, and Dana Wallace, MD

Kelso JM, Greenhawt MJ,
Li JT, et al.
Adverse reactions to vaccines practice parameter 2012 update.
J Allergy Clin Immunol 2012; 130:25-43.

Dreskin *et al. World Allergy Organization Journal* (2016) 9:32
DOI 10.1186/s40413-016-0120-5

World Allergy Organization Journal

CONSENSUS DOCUMENT Open Access

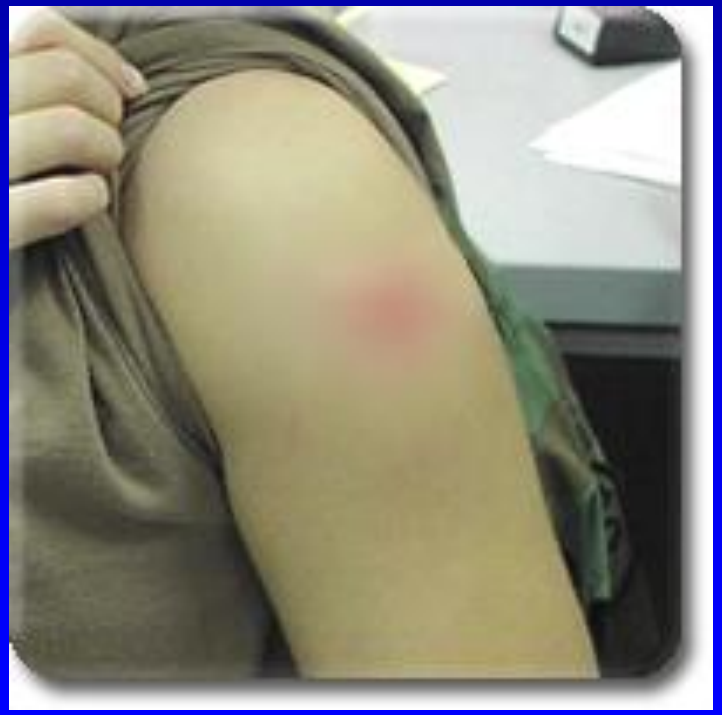
International Consensus (ICON): allergic reactions to vaccines

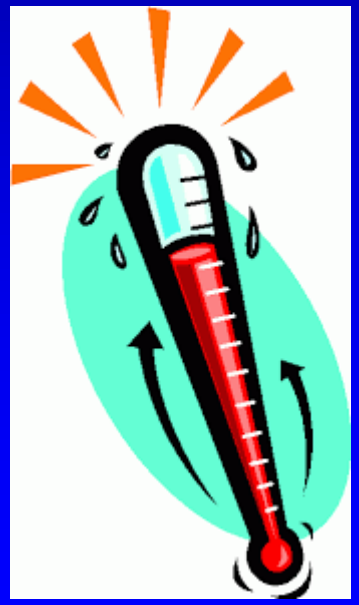
Stephen C. Dreskin[1*], Neal A. Halsey[2], John M. Kelso[3], Robert A. Wood[4], Donna S. Hummell[5], Kathryn M. Edwards[6], Jean-Christoph Caubet[7], Renata J. M. Engler[8], Michael S. Gold[9], Claude Ponvert[10], Pascal Demoly[11], Mario Sanchez-Borges[12], Antonella Muraro[13], James T. Li[14], Menachem Rottem[15] and Lanny J. Rosenwasser[16]

Dreskin SC, Halsey NA, Kelso JM, et al.
International Consensus (ICON): allergic reactions to vaccines.
WAO Journal 2016;9:1-21.

Common Reactions

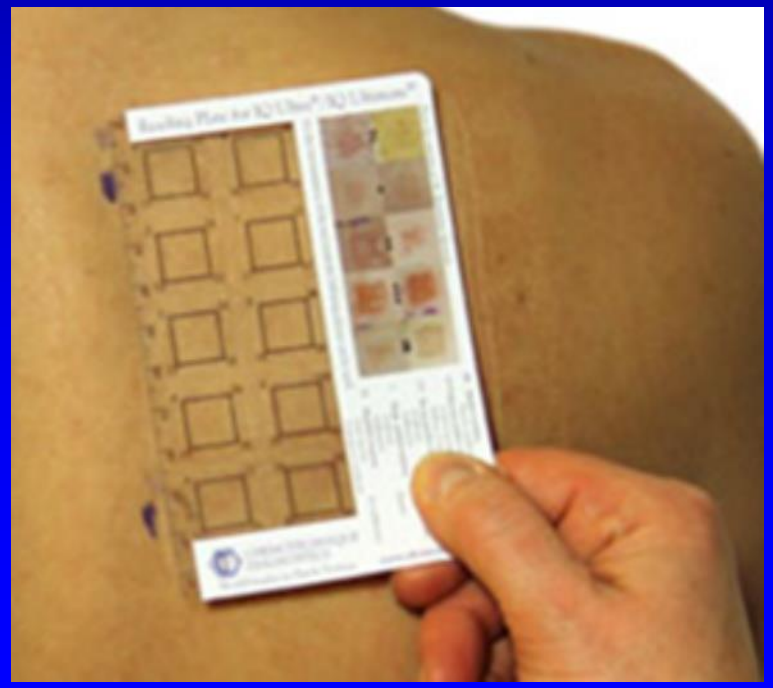
Mild local (injection site) reactions and constitutional symptoms, such as fever, after vaccinations are common and do not contraindicate future doses.





Delayed Type Hypersensitivity

Rarely, delayed-type hypersensitivity (DTH) to a vaccine constituent, such as neomycin or thimerosal, may cause a temporary injection site nodule, but DTH to these constituents, or a history of such nodules is not a contraindication to subsequent vaccination.



Anaphylaxis

Anaphylactic reactions to vaccines are estimated to occur at a rate of approximately 1 per million doses.

Evaluation

All suspected anaphylactic reactions to vaccines should be evaluated in an attempt to determine the culprit allergen.

Evaluate before labeling

- When a patient experiences an apparently IgE-mediated reaction after an immunization, often labeled “allergic” and advised against future doses
- This approach should be avoided because it may leave patients inadequately immunized if they unnecessarily avoid vaccines to which they are not allergic or if the vaccine could be administered safely despite their allergy.
- In addition, not knowing the constituent of a vaccine to which the patient is allergic may pose a risk with future vaccinations that contain the same ingredient.

Excipients

IgE-mediated reactions to vaccines are more often caused by vaccine components such as gelatin, rather than the immunizing agent itself.

Vaccine Excipient Summary

Excipients Included in U.S. Vaccines, by Vaccine

www.cdc.gov/vaccines/pubs/pinkbook/appendix/appdx-b.html

Egg allergy and influenza vaccination

Egg allergy and influenza vaccines

- Most influenza vaccines contain measurable quantities of egg protein (ovalbumin)
- Does this cause systemic reactions when injected into egg-allergic patients?

Egg allergy and influenza vaccines

- 27 studies involving >4100 patients with egg allergy, including 513 with a history of anaphylaxis after egg ingestion, receiving inactivated influenza vaccine (IIV) without *any* serious reactions
- Reports describe 1129 patients with egg allergy, including 412 with history of anaphylaxis to egg ingestion, given live attenuated influenza vaccine (LAIV) without any immediate systemic reactions

Why are there no serious reactions being reported?

- Manufacturers of all influenza vaccines report the maximum amount of ovalbumin < 1 µg per 0.5 mL dose
- The measured amounts in independent laboratories are usually much lower than the claimed amounts
- Thus, the vaccine does not contain enough ovalbumin to cause a reaction

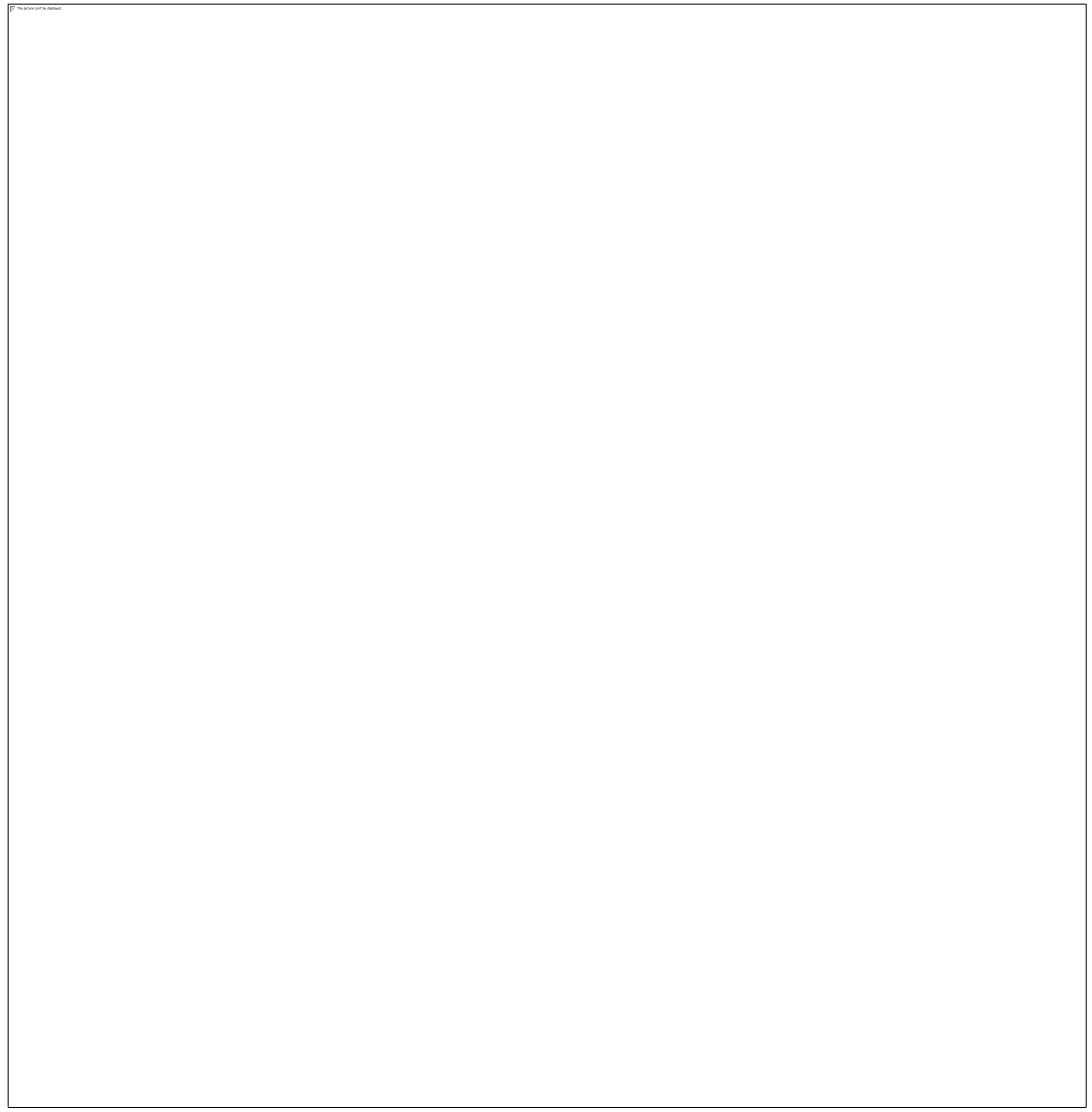
Recommendations for Prevention and Control of Influenza in Children, 2020-2021

Committee on Infectious Diseases

American Academy of Pediatrics

Pediatrics 2020

Egg allergy and influenza vaccine



Egg allergy and influenza vaccine

- “There is strong evidence that egg-allergic individuals can safely receive influenza vaccine without any additional precautions beyond those recommended for any vaccine.”
- “The presence of egg allergy in an individual is not a contraindication to receive IIV or LAIV.”
- “Vaccine recipients with egg allergy are at no greater risk for a systemic allergic reaction than those without egg allergy.”

Egg allergy and influenza vaccine

- So if it doesn't matter if the patient is egg allergic, why do we ask?
- "It is not necessary to inquire about egg allergy before the administration of any influenza vaccine, including on screening forms."
- "Patients who have had a previous allergic reaction *to the influenza vaccine*, should be evaluated by an allergist to determine whether future receipt of the vaccine is appropriate."

Yellow Fever Vaccine

- A history of allergy after the ingestion of egg should be sought prior to the administration of yellow fever vaccine
- Persons with positive histories should be skin tested with yellow fever vaccine prior to administration
  - If negative, give in usual manner but observe for 30 minutes afterward.
  - If positive, give vaccine in graded doses

Yellow Fever Vaccine

Yellow Fever Vaccine

Anaphylaxis to measles, mumps, and rubella vaccine mediated by IgE to gelatin

Kelso JM, Jones RT, Yunginger JW

Journal of Allergy & Clinical Immunology
1993;91:867-72.

IgE-mediated systemic reactions to gelatin included in the varicella vaccine

Sakaguchi M, Yamanaka T, Ikeda K, Sano Y, Fujita H, Miura T, Inouye S.

Journal of Allergy & Clinical Immunology 1997;99:263-4.

None in Stamaril

None in SHINGRIX

Reactions to Gelatin in Vaccines

- Persons who react to gelatin on ingestion should be evaluated by an allergist prior to administration of gelatin-containing vaccines.
- If the history is consistent with an immediate-type allergic reaction to gelatin confirmed by skin tests or serum specific IgE, skin test with vaccines prior to administration.
  - If negative, give in usual manner but observe for 30 minutes afterward.
  - If positive, give vaccine in graded doses

Yeast

- Hepatitis B vaccines are grown in *Saccharomyces cerevisiae* (baker's yeast or brewer's yeast) and contain residual yeast protein (up to 25 mg per dose)
- Human papillomavirus vaccine also contains residual yeast protein (less than 7 mcg per dose)
- However, allergic reactions yeast in vaccines, are rare or nonexistent

Yeast

- Yeast allergy itself is very rare but, if a patient has a history of clinical reactivity to Baker's or Brewer's yeast and a positive skin test to *Saccharomyces cerevisiae*, skin test them with yeast-containing vaccines prior to administration.
  - If negative, give in usual manner but observe for 30 minutes afterward.
  - If positive, give vaccine in graded doses

Latex

- The “rubber” in vaccine vial stoppers or syringe plungers may be dry natural rubber (DNR) latex or synthetic rubber.
- Those made with DNR pose a theoretical risk to the latex allergic, however reports of reactions possibly due to latex are exceedingly rare

Latex

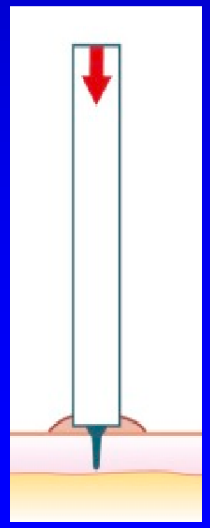
- Patients with latex allergy can safely receive vaccines from vials with non-DNR stoppers.
- If the only available preparation has a latex stopper, if feasible, consider removal of stopper and drawing vaccine up directly from the vial without passing the needle through the stopper.
- If the only available vaccine contains latex in the packaging that cannot be avoided, such as in a prefilled syringe, the vaccine can still be administered but consider observation for 30 minutes after.

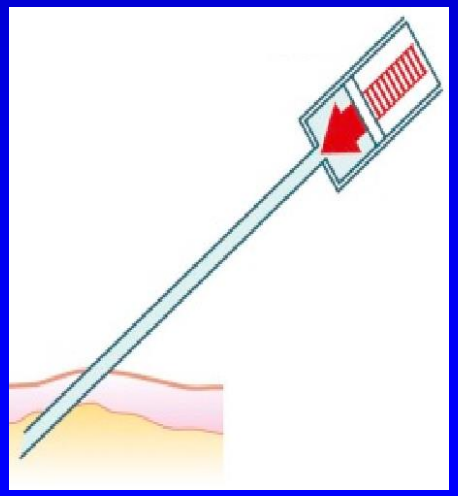
Latex in vaccine packaging

https://www.cdc.gov/vaccines/pubs/pinkbook/appendix/appdx-b.html

Vaccine skin tests

- Patients who have had an apparent anaphylactic reaction after immunization should undergo immediate-type allergy skin testing to help confirm that the reaction was IgE-mediated and determine the responsible component of the vaccine.





Vaccine skin tests

- To determine whether a vaccine was responsible for an apparent allergic reaction, skin test with the vaccine
  - first by prick method (full-strength unless history truly life-threatening)
  - If negative, ID 1:100
- As with any (especially non-standardized) skin test reagent, false positive (irritant) and clinically irrelevant positive results may occur
- Likewise, false-negatives also possible

Vaccine skin tests

- No formal studies to evaluate the positive and negative predictive values for vaccine skin tests
- Dilutions of vaccines of 1:100 have been demonstrated to be nonirritating for intradermal testing
- No reports of patients with negative intradermal skin test reacting to subsequent administration of vaccine

Component Skin Tests

- If the suspect vaccine contains gelatin, egg, latex or yeast, skin test for these
- Egg and yeast extracts commercially available
- In vitro assays for specific IgE antibody commercially available for gelatin, egg, latex and yeast

Vaccine hx +, skin tests -

If the intradermal skin test result is negative, the chance that the patient has IgE antibody to any vaccine constituent is negligible, and the vaccine can be administered in the usual manner. It is prudent nonetheless, in a patient with a history suggestive of an anaphylactic reaction, to administer the vaccine under observation with epinephrine and other treatment available.

Vaccine hx +, skin tests +

In patients with histories and skin test results consistent with an IgE-mediated reaction to a vaccine, who require additional doses of the suspect vaccine or other vaccines with common ingredients, consideration can be given to administering the vaccine in graded doses under observation.

Graded Dosing

- If vaccine or vaccine component skin test results are positive, the vaccine may still be administered, if necessary, in graded doses

Administration of Vaccines in Graded Doses
For a vaccine for which the full normal-dose volume is 0.5 mL, give the following doses at 15-minute intervals as tolerated
0.05 mL, 1:10 dilution
0.05 mL, full strength
0.1 mL, full strength
0.15 mL, full strength
0.2 mL, full strength

Already “protected”?

- Measuring levels of IgG antibody to the immunizing agent in a vaccine suspected of causing a serious adverse reaction to determine if they are at protective levels can help determine whether or not subsequent doses are required.
- However, it is not clear that , even if serology is positive, not receiving fewer than the usual number of doses leads to the same level or duration of protection.

Table 1. Levels of antibody associated with protection from vaccine-preventable diseases

Vaccine	Protective level of IgG antibody ≥:
Diphtheria	0.1 IU/mL
Haemophilus influenzae b	0.15 µg/mL
Hepatitis A	10 mIU/mL
Hepatitis B Surface Antibody	10 mIU/mL
Measles (Rubeola)	120 PRN titer
Polio (Inactivated)	1:8 neutralizing antibody titer
Rabies	0.5 IU VNA/mL
Rubella	10 IU/mL
Tetanus	0.1 IU/mL
Yellow fever	0.7 IU/mL

Abbreviations: IU, international units; mIU, milli-international units;

PRN, plaque reduction neutralization; VNA, virus-neutralizing antibodies

Non-allergic Vaccine Reactions

Some more serious, and less common, reactions to vaccines require evaluation, but only a few are absolute contraindications to future doses.

Guillain-Barre´ syndrome

- “Swine flu” vaccine administered in 1976 associated with increased risk GBS (1 additional case per 100,000 over background rate of 1 to 2 cases per 100,000)
- Subsequent years influenza vaccines have shown no consistent increased risk (If any, 1 per million)
- Specific attention was paid to the potential for GBS after the 2009 pandemic influenza A (H1N1) vaccine campaign and no increased rate was found

Guillain-Barre´ syndrome

- GBS continues to be reported in temporal association with influenza infection itself
- Previous GBS has risk of a recurrence
- Persons who developed GBS within 6 weeks of influenza vaccination should avoid subsequent immunization
- However, individuals with a history of GBS unrelated to influenza infection or vaccination who would benefit from immunization can be vaccinated

Interval between Td and Tdap

- The recommended interval between doses of Td had been 10 years, with shorter intervals thought to be associated with increased rates of Arthus reactions.

Table 1: Guide to Use of Tetanus and Diphtheria Toxoids Adsorbed (Td) and Tetanus Immune Globulin (TIG) (Human) for Tetanus Prophylaxis in Routine Wound Management for Persons 7 Years of Age and Older

History of Adsorbed Tetanus Toxoid (doses)	Clean, Minor Wounds		All Other Wounds[a]	
	Td	TIG	Td	TIG
Unknown or <three	Yes	No	Yes	Yes
≥three[b]	No[c]	No	No[d]	No

[a] Such as, but not limited to, wounds contaminated with dirt, feces, soil, and saliva; puncture wounds; avulsions; and wounds resulting from missiles, crushing, burns, and frostbite.

[b] If only three doses of fluid tetanus toxoid have been received, then a fourth dose of toxoid, preferably, an adsorbed toxoid should be given.

[c] Yes, if ≥10 years since the last tetanus toxoid-containing vaccine dose.

[d] Yes, if ≥5 years since the last tetanus toxoid-containing vaccine dose. (More frequent boosters are not needed and can accentuate side effects.)

Interval between Td and Tdap

- However, two studies:
  - the rates of injection site reactions to Tdap were no different in those vaccinated with Td < 2 years vs >2 years earlier
  - no higher rates of injection site reactions whether Tdap was given one *month* after a Td or placebo

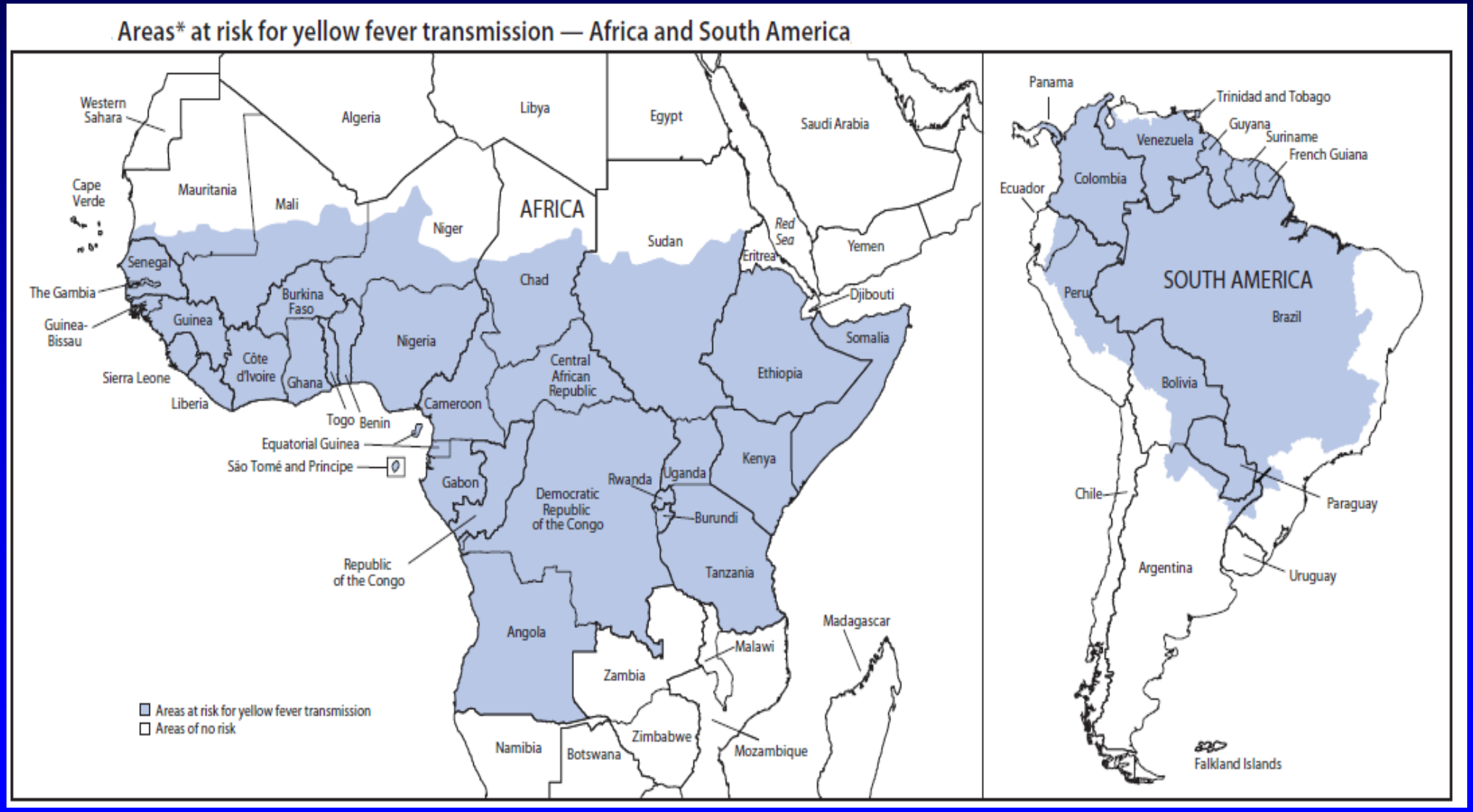
Interval between Td and Tdap

- Pertussis disease burden continues to be substantial
- Now recommended that Tdap be given to all adolescents and adults *regardless of interval* since the last Td and to pregnant women with each pregnancy
- After receipt of Tdap, persons should continue to receive a dose of Td or Tdap for routine booster immunization against tetanus and diphtheria every 10 years

Yellow Fever vaccine sequelae

- YF vaccine associated with a rare, but very severe illness in adults, yellow fever vaccine-associated viscerotropic disease (YEL-AVD), resulting in fatalities from multi-system disease strikingly similar to yellow fever itself
- Has occurred in patients who are not known to be immunocompromised, but history of a thymus disorder and age >60 years risk factors
- Cause unknown

- Vaccine should not be given to patients unless they are at risk of acquiring yellow fever, typically by traveling to an area where the disease is endemic.



Yellow Fever vaccine: no booster

عربي 中文 English

World Health Organization

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International travel and health

New yellow fever vaccination requirements for travellers

Amendment to the period of validity of the international certificate of vaccination against yellow fever, which is now extended to the life of the person vaccinated

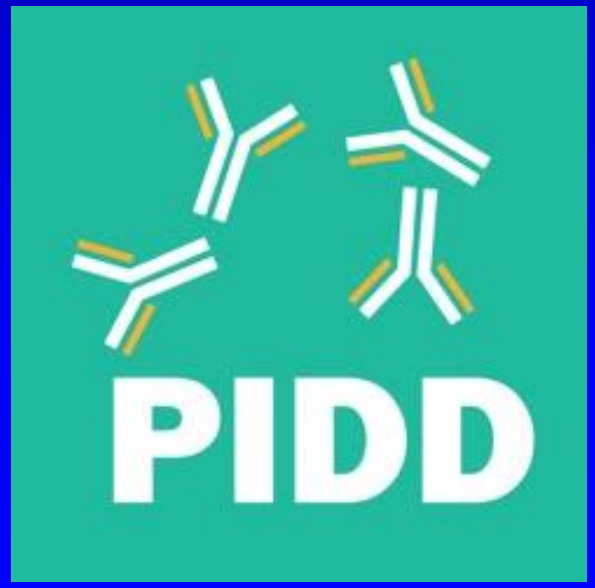
27 July 2016

Vaccines in Pregnancy

Pregnant women should not be vaccinated with live vaccines. However, pregnant women should be given inactivated influenza vaccine, as well as Tdap and hepatitis B vaccine if otherwise indicated.

Vaccines and Immunodeficiency

In general, live vaccines should not be given to persons who are immune compromised because of a risk of generalized infection with the immunizing agent.



LIVE VERSUS NON-LIVE VACCINES

Live Attenuated Vaccines	Non-Live (Killed, Subunit, Toxoid) Vaccines
Adenovirus	Anthrax
Bacille Calmette-Guérin (BCG)	Diphtheria, tetanus, acellular pertussis (DTaP, Tdap)
Cholera	Diphtheria-tetanus (DT, Td)
Influenza (intranasal)	Haemophilus influenzae type b (Hib) conjugates
Measles-mumps-rubella (MMR)	Hepatitis A
Oral poliovirus (OPV)	Hepatitis B
Rotavirus	Human papillomavirus (HPV)
Typhoid (oral)	Inactivated poliovirus (IPV)
Vaccinia (smallpox)	Influenza (injectable)
Varicella	Japanese encephalitis
Yellow fever	Meningococcal
Zoster (live)	Meningococcal conjugate
	Pneumococcal
	Pneumococcal conjugate
	Rabies
	Typhoid (injectable)
	Zoster (recombinant)

Vaccines: Long-term Consequences

Specific vaccines or vaccination in general have been purported to have long-term consequences including atopy, autism and multiple sclerosis. Epidemiologic studies have not supported such associations.

Vaccine 39 (2021) 865–867

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Commentary

Anaphylactic reactions to novel mRNA SARS-CoV-2/COVID-19 vaccines

John M. Kelso

Division of Allergy, Asthma and Immunology, Scripps Clinic, 3811 Valley Centre Drive, San Diego, CA 92130, United States

Anaphylactic reactions to mRNA COVID vaccines

- None reported in clinical trials, but small number reported after authorization
- 2.5-10 per million doses

JAMA Insights

Reports of Anaphylaxis After Receipt of mRNA COVID-19 Vaccines in the US—December 14, 2020-January 18, 2021

Tom T. Shimabukuro, MD, MPH, MBA; Matthew Cole, MPH; John R. Su, MD, PhD, MPH

JAMA. 2021;325(11):1101-2.

- All (n = 66) were treated in health care settings; 34 (52%) ED, 32 (48%) hospitalized (including 18 in ICU)
- 7 required endotracheal intubation
  - Of these 7, median time to symptom onset: 6 minutes (range, <1-45 minutes), all but one within 11 minutes

TABLE 1. Characteristics of reported cases of anaphylaxis (n = 21) after receipt of Pfizer-BioNTech COVID-19 vaccine — Vaccine Adverse Events Reporting System (VAERS), United States, December 14–23, 2020

Age (yrs)	Sex	Past history		Onset after receipt (mins)	Signs and symptoms	Treatment setting†	Epi received	Brighton level§	Outcome or disposition¶
		Allergies or allergic reactions*	Anaphylaxis						
27	F	Tropical fruit	No	2	Diffuse erythematous rash, sensation of throat closure	ED	Yes	2	Recovered at time of report
35	M	No	No	5	Diffuse erythematous rash, swollen tongue	ED	Yes	1	Discharged home
55	F	Rabies vaccine	Yes, rabies vaccine	5	Generalized urticaria, wheezing	Inpatient	Yes	1	Discharged home
52	F	Sulfa drugs	Yes, sulfa drugs	7	Wheezing, stridor, nausea	Inpatient	Yes	1	Discharged home
30	F	Bee sting	No	8	Generalized urticaria, wheezing	Inpatient	Yes	1	Recovered at time of report
32	F	No	No	10	Diffuse erythematous rash, difficulty breathing	Inpatient	Yes	2	Discharged home
60	F	Eggs, milk, sulfa drugs, jellyfish sting	Yes, jellyfish sting	10	Diffuse erythematous rash, hoarseness	ED	Yes	2	Recovered at time of report
29	F	Shellfish, eggs	No	10	Generalized urticaria, swollen lips and tongue	ED	Yes	1	Discharged home
52	F	Metoprolol, clarithromycin	No	10	Generalized urticaria, stridor, wheezing	ED	Yes	1	Recovered at time of report
49	F	Iodinated contrast media	No	13	Generalized urticaria, swollen throat	ED	Yes	1	Recovered at time of report

MMWR Morb Mortal Wkly Rep 2021;70:46–51.

Misdiagnosis of systemic allergic reactions to mRNA COVID-19 vaccines

Letters / Ann Allergy Asthma Immunol 127 (2021) 131–151

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Scripps Clinic
San Diego, California

- 4 cases characterized and treated as anaphylaxis
- 4/4 vaccine skin tests negative
- 3/4 received second doses uneventfully (1 refused due to fear of epinephrine to treat a reaction should one occur)

Anaphylaxis DDx

- Anaphylaxis typically involves urticaria with respiratory and/or cardiovascular symptoms.
- Other reactions can mimic anaphylaxis:
  - vasovagal reactions which can also cause syncope but are preceded by bradycardia and pallor as opposed to the tachycardia and flushing that would be typical of anaphylaxis
  - vocal cord spasm can cause stridor and dyspnea
  - panic attacks can cause a globus sensation, palpitations, dyspnea and other symptoms

Anaphylaxis DDx

- Embarrassment can cause obvious flushing (vasodilatation) triggered only by a thought
- After local anesthesia at the dentist, patients often have the distinct sensation that their lip or tongue is swollen, but looking the mirror reveals that it is not

Anaphylactic reactions to mRNA COVID vaccines

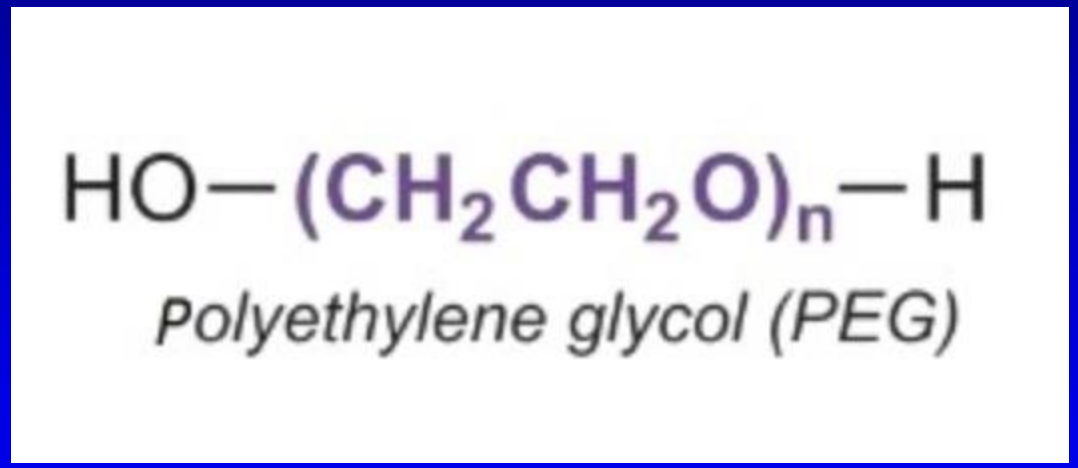
- IgE-mediated reactions:
  - almost all to proteins
  - require prior exposure
- mRNA COVID vaccines
  - do not contain proteins
  - reactions reported after first dose

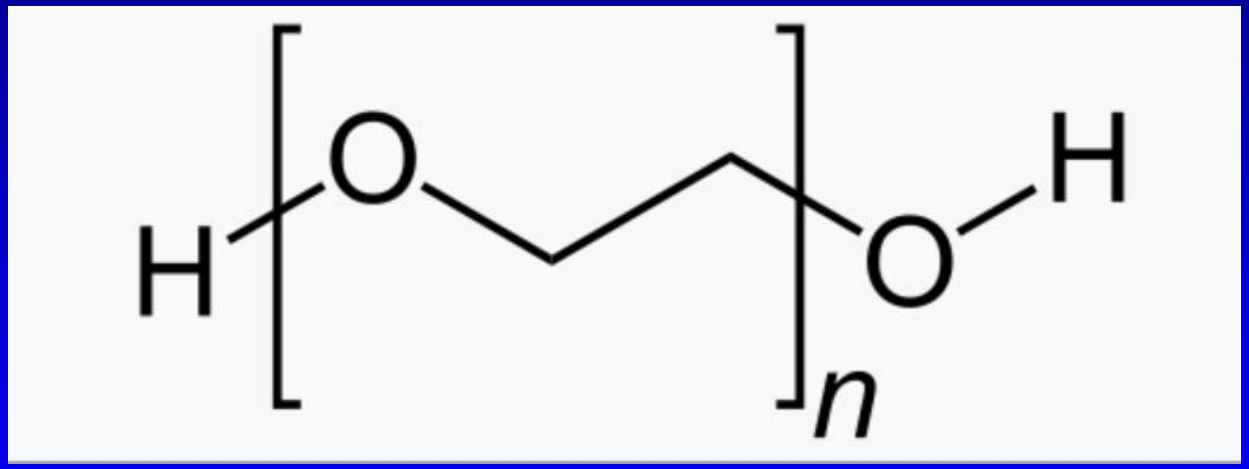
Description	Pfizer-BioNTech COVID-19 vaccine	Moderna COVID-19 vaccine
mRNA	Nucleoside-modified mRNA encoding the viral spike (S) glycoprotein of SARS-CoV-2	Nucleoside-modified mRNA encoding the viral spike (S) glycoprotein of SARS-CoV-2
Lipids	2[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide	PEG2000-DMG: 1,2-dimyristoyl-rac-glycerol, methoxypolyethylene glycol
	1,2-distearoyl-sn-glycero-3-phosphocholine	1,2-distearoyl-sn-glycero-3-phosphocholine
	Cholesterol	Cholesterol
	(4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate)	SM-102: heptadecan-9-yl 8-((2-hydroxyethyl) (6-oxo-6-(undecyloxy) hexyl) amino) octanoate
Salts, sugars, buffers	Potassium chloride	Tromethamine
	Monobasic potassium phosphate	Tromethamine hydrochloride
	Sodium chloride	Acetic acid
	Dibasic sodium phosphate dihydrate	Sodium acetate
	Sucrose	Sucrose

* Neither vaccine contain eggs, gelatin, latex, or preservatives

www.cdc.gov/vaccines/covid-19/info-by-product/clinical-considerations.html

Potential culprit: polyethylene glycol (PEG)





Potential culprit: polyethylene glycol (PEG)

- PEG allergy is rare
- PEG widely used in medications and bowel preps, and also in cosmetics and foods
- Not an ingredient in any non-COVID vaccine
- Such exposure could *potentially* explain how a patient may be sensitized to PEG prior to COVID vaccination but…

Potential culprit: polyethylene glycol (PEG)

- The amount of PEG in injected medications associated with potential allergic reactions is considerably higher than that contained in the vaccine
  - Methylprednisolone acetate injectable suspension contains 29.1 mg PEG 3350 per 1 mL dose
  - The Pfizer COVID vaccine contains 0.05 mg PEG 2000 per 0.3 mL dose
- To date, no confirmation of any case with positive vaccine skin test and positive skin test or serum specific IgE assay to PEG

Anaphylactic reactions to mRNA COVID vaccines

- Need to determine if IgE-mediated and if so, search for culprit allergen

mRNA COVID Vaccine Skin Testing

- The stability of any potential allergens in vaccines is not known so skin testing should be performed using vaccine within the same six-hour timeframe from reconstitution used for vaccine administration
- Some residual volume remains in multidose vials from both vaccines that can be used for skin testing, so as not to waste doses
- For many other vaccines, prick full strength and intradermal diluted 1:100 have proved to be nonirritating concentrations
- Prick and intradermal testing with full strength Pfizer mRNA COVID-19 vaccine has been reported to be non-irritating

SARS-CoV-2 Serology

- Alternative: assess for the presence of anti-SARS-CoV-2 IgG antibody as evidence of immune reactivity to the first dose
- Requires assay for IgG to spike protein specifically, not nucleocapsid protein
- If titers to the spike protein were positive and the risk of a reaction to a second dose were judged sufficiently high, second dose could be withheld, but no data to suggest single dose provides the same level or duration of protection from disease

mRNA COVID Vaccine Skin Testing

- Negative skin tests argue reaction not IgE-mediated
  - consider giving second dose in the usual manner under observation

mRNA COVID Vaccine Skin Testing

- Positive skin test results argue reaction was IgE-mediated:
  - consider giving second dose in graded doses under close observation

Annals of Internal Medicine

OBSERVATION: CASE REPORT

Administration of a Second Dose of the Moderna COVID-19 Vaccine After an Immediate Hypersensitivity Reaction With the First Dose: Two Case Reports

S. Shahzad Mustafa, MD
Allison Ramsey, MD
Rochester Regional Health and University of Rochester, Rochester, New York

Mary L. Staicu, PharmD
Rochester Regional Health, Rochester, New York

Ann Intern Med. 2021 Apr 6:L21-0104.

mRNA COVID Vaccine Skin Testing

- Positive skin test results argue reaction was IgE-mediated:
  - Could consider PEG skin tests to assess PEG as a potential culprit allergen, however…

Original Article J Allergy Clin Immunol Pract 2021

First-Dose mRNA COVID-19 Vaccine Allergic Reactions: Limited Role for Excipient Skin Testing

Anna R. Wolfson, MD[a,b], Lacey B. Robinson, MD, MPH[a,b], Lily Li, MD[a,c], Aubree E. McMahon, BA[b], Amelia S. Cogan, MPH[b], Xiaoqing Fu, MS[b], Paige Wickner, MD, MPH[a,c], Upeka Samarakoon, MS, PhD[b], Rebecca R. Saff, MD, PhD[a,b], Kimberly G. Blumenthal, MD, MSc[a,b,d,*], and Aleena Banerji, MD[a,b,*] *Boston, Mass*

- 65 patients with immediate reactions (≤ 4 hours) to a first dose of an mRNA COVID-19 vaccine had PEG skin testing
  - Only 4 positive:
    - 2 received second dose without reaction
    - 1 tolerated a dose of the Janssen vaccine as a substitute
    - 1 did not receive the second dose

- Among 61 negative:
  - 43 received second dose without reaction
  - 5 did not receive a second dose
  - 13 had immediate reaction to second dose (most mild, cutaneous reactions treated with antihistamines, 2 received epinephrine for itching/rash, cough and throat tightness)
- Thus, is this and other studies, PEG skin testing has demonstrated limited specificity and sensitivity
- Skin testing with the vaccine itself, although also of uncertain sensitivity and specificity, may yield the most clinically relevant information

mRNA COVID Vaccines: 2nd doses in patients with 1st dose reactions

- Administering second doses requires shared decision-making with the patient, weighing the risk of a vaccine reaction against the risk of remaining inadequately vaccinated against COVID-19
- Alternatively, administer second dose with another type of vaccine, e.g. Janssen (J&J) viral vector vaccine, although unknown safety and effectiveness of this approach

CONTRAINDICATION TO VACCINATION	PRECAUTION TO VACCINATION	MAY PROCEED WITH VACCINATION
History of the following: • Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to component of the vaccine† • Immediate allergic reaction* of any severity after a previous dose or known (diagnosed) allergy to a component of the vaccine†	**Among people without a contraindication, a history of:** • Any immediate allergic reaction* to other vaccines or injectable therapies‡ Note: people with a contraindication to mRNA COVID-19 vaccines have a precaution to Janssen COVID-19 vaccine, and vice versa. See footnote for additional information on additional measures to take in these people.#	**Among people without a contraindication or precaution, a history of:** • Allergy to oral medications (including the oral equivalent of an injectable medication) • History of food, pet, insect, venom, environmental, latex, etc., allergies • Family history of allergies
Actions: • Do not vaccinate. • Consider referral to allergist-immunologist. • Consider other vaccine alternative.†	**Actions:** • Risk assessment • Consider referral to allergist-immunologist • 30-minute observation period if vaccinated	**Actions:** • 30-minute observation period: people with history of anaphylaxis (due to any cause) • 15-minute observation period: all other people

www.cdc.gov/vaccines/covid-19/info-by-product/clinical-considerations.html

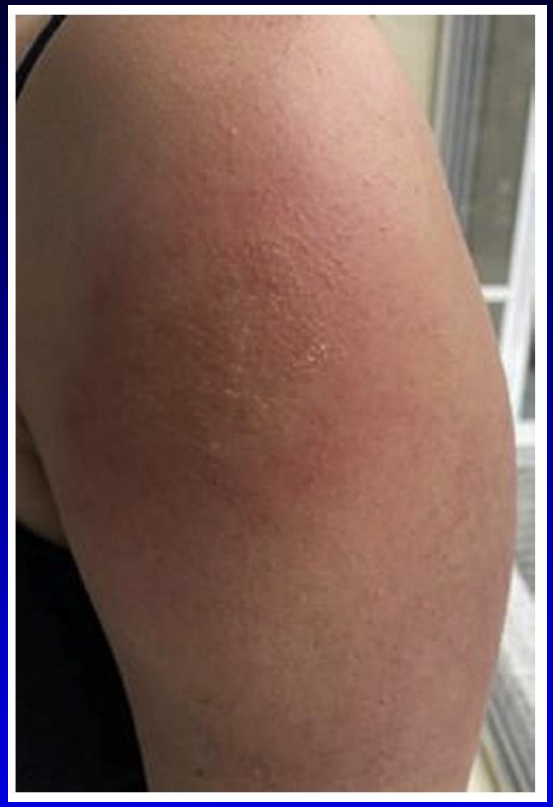
Clinical Communications

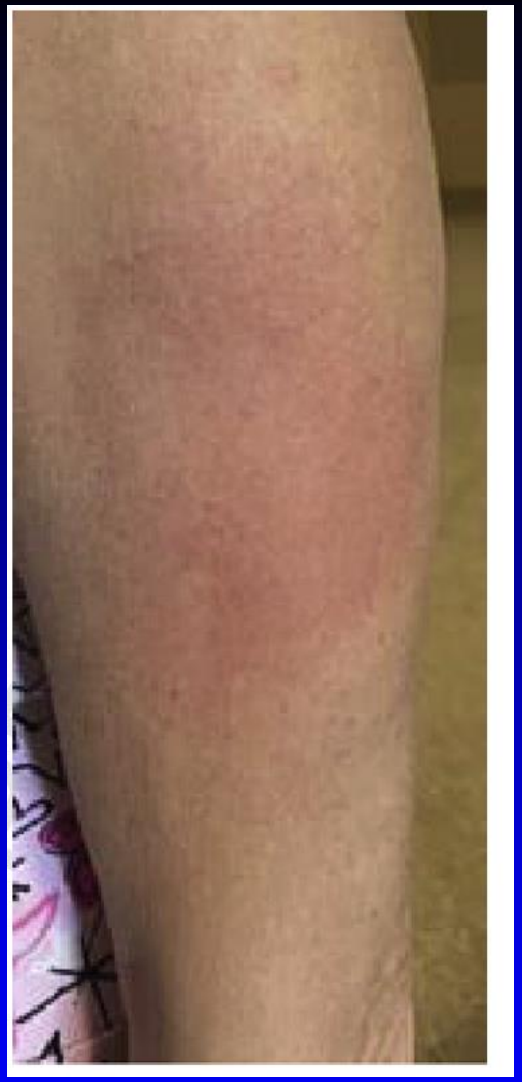
"COVID Arm": Very delayed large injection site reactions to mRNA COVID-19 vaccines

Courtney L. Ramos, DO, and John M. Kelso, MD

Clinical Implications

- Atypical very delayed large injection site reactions to the mRNA COVID vaccines appear fairly frequently. They begin about a week after vaccination, persist for several days, resolve without treatment, and have not recurred with second doses.





Ramos CL, Kelso JM.
"COVID Arm": very delayed large injection site reactions to mRNA COVID-19 vaccines.
J Allergy Clin Immunol Pract. 2021;9:2480-2481.

Changes you may wish to make in practice

- Stop asking about egg allergy prior to the administration of influenza vaccines
- Administer a single Tdap dose to all adolescents and adults regardless of interval since the last Td
- Administer injectable (inactivated) influenza vaccine and Tdap to pregnant patients

Changes you may wish to make in practice

- Encourage your colleagues overseeing vaccination clinics to:
  - recognize and treat anaphylaxis after vaccine administration, but to know there is a differential diagnosis
  - carefully record vital signs and physical exam findings (including skin, oropharynx and lungs), including photographs of skin findings if possible
  - obtain a blood sample within 4 hours of an apparent anaphylactic episode for mast cell tryptase
  - refer patients with histories of possible allergic reactions after immunization to allergy rather than simply labeling them “allergic”

Changes you may wish to make in practice

- Carefully review the nature and timing of reported immediate reactions to assess the likelihood (or not) of their being mast cell mediated
- For patients who have experienced mild immediate vaccine reactions to the first dose of an mRNA COVID-19 vaccine, consider giving second dose in the usual manner but under observation, without additional prior evaluation, because most will go on to tolerate the second dose uneventfully

Changes you may wish to make in practice

- For patients who have experienced more severe, potentially anaphylactic reactions to an mRNA COVID-19 vaccine, perform skin tests with the suspect vaccine
  - If negative, administer second dose in usual manner under observation
  - If positive, consider administration of second dose in graded doses under observation
- Weigh whatever risk there is to receiving a second dose against the risk of remaining inadequately vaccinated or using an alternate vaccine