



MASSACHUSETTS
GENERAL HOSPITAL

RHEUMATOLOGY, ALLERGY
AND IMMUNOLOGY



Adverse Reactions to COVID-19 Vaccines

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Learning Objectives

- Upon completion of this learning activity, participants should be able to assess patients with a history of reaction to COVID vaccines
- Upon completion of this learning activity, participants should be able to identify the epidemiology and clinical presentation of allergic reactions to COVID-19 vaccines
- Upon completion of this learning activity, participants should be able to describe the public health impact of reactions to COVID-19 vaccines

Anaphylaxis Day 1 of Worldwide Vaccination



- Anaphylaxis on December 9, 2020
- Up until December 30, 2020, UK guidance restricted access for those with history of anaphylaxis after vaccine, medicine or food

NEWS

Pregnant nurse, unborn baby die of COVID after refusing to get vaccinated

By Jesse O'Neill

August 24, 2021 | 9:05pm | Updated

COVID-19

Pfizer's vaccine raises allergy concerns

Polymer in mRNA's "packaging" may cause rare anaphylactic reactions

By Jop de Vrieze

Severe allergy-like reactions in at least 12 people who received the COVID-19 vaccine produced by Pfizer and BioNTech may be due to a compound in the packaging of the messenger RNA (mRNA) that forms the vaccine's main ingredient, scientists say. A similar mRNA

UK issues anaphylaxis warning on Pfizer vaccine after adverse reactions

By Alistair Smout

5 MIN READ



LONDON (Reuters) - Britain's medicine regulator said anyone with a history of anaphylaxis to a medicine or food should not get the Pfizer-BioNTech COVID-19 vaccine, giving fuller guidance on an earlier allergy warning about the shot.

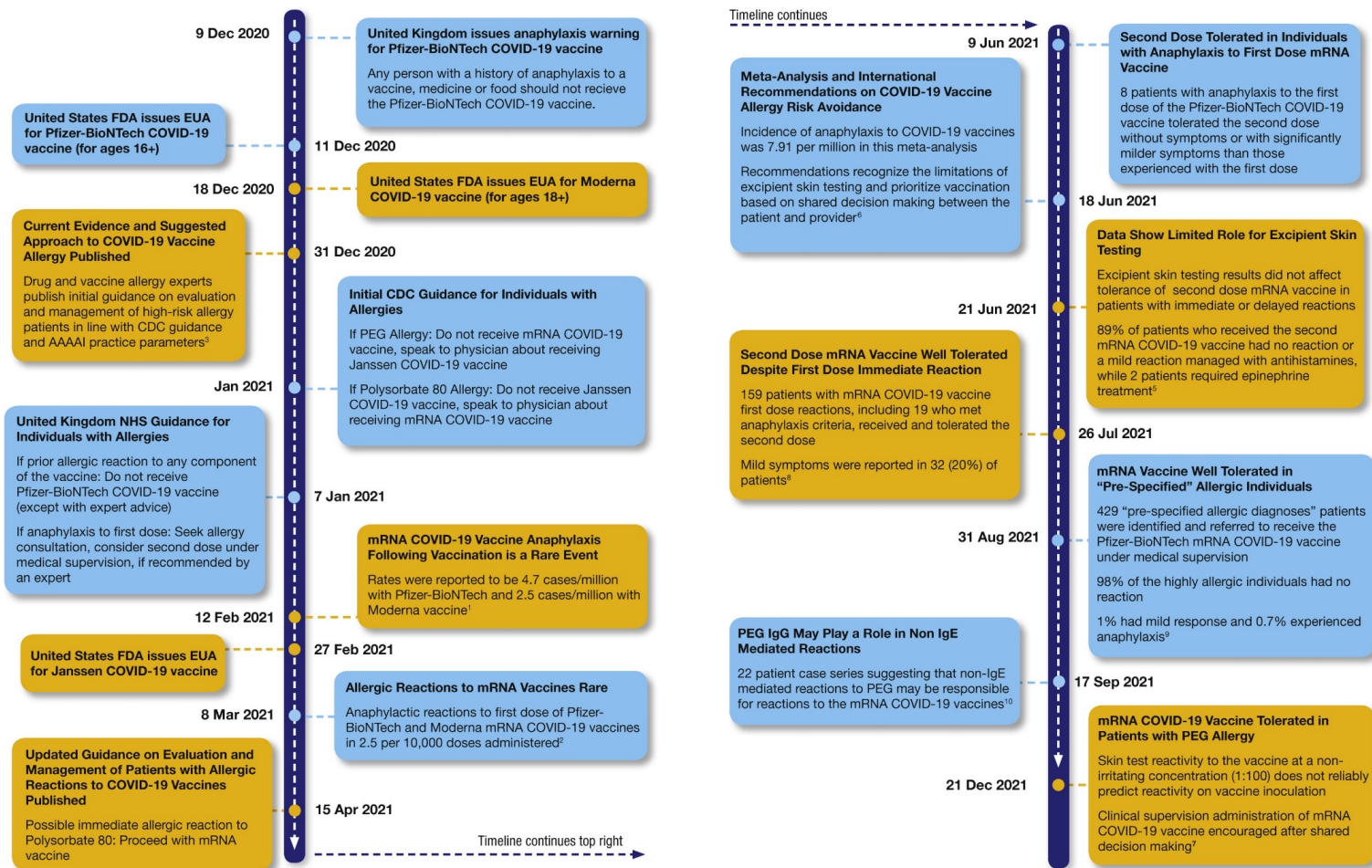
Here's What People With Allergies Should Know About Covid Vaccines

Four people so far have had allergic reactions after getting the Pfizer-BioNTech vaccine. Experts say that shouldn't deter most people from getting a jab.

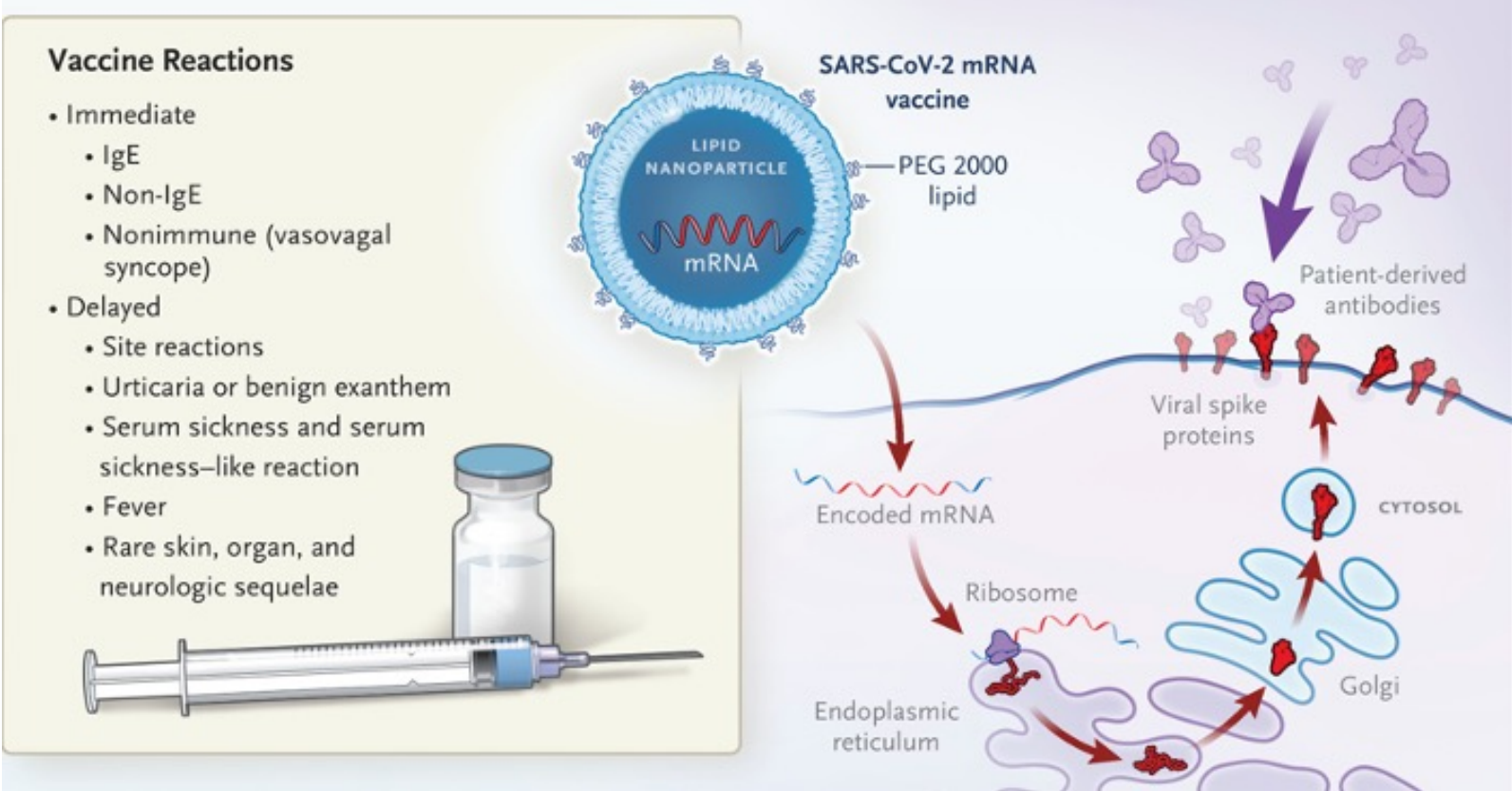
Boston Doctor Reports Serious Allergic Reaction After Getting Moderna's Covid Vaccine

The patient, who has a severe shellfish allergy, recovered quickly with treatment. Until now, reports of severe reactions had been linked to the Pfizer vaccine.

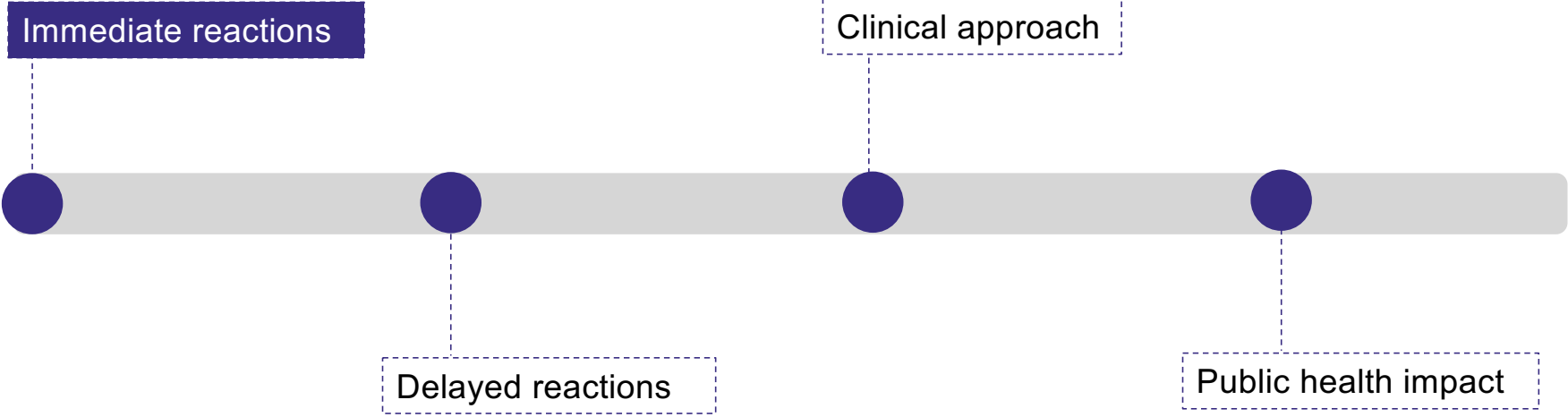
Rapid Progress in Our Understanding



COVID-19 Vaccine Reactions



Roadmap



Historically Vaccine Anaphylaxis is Rare

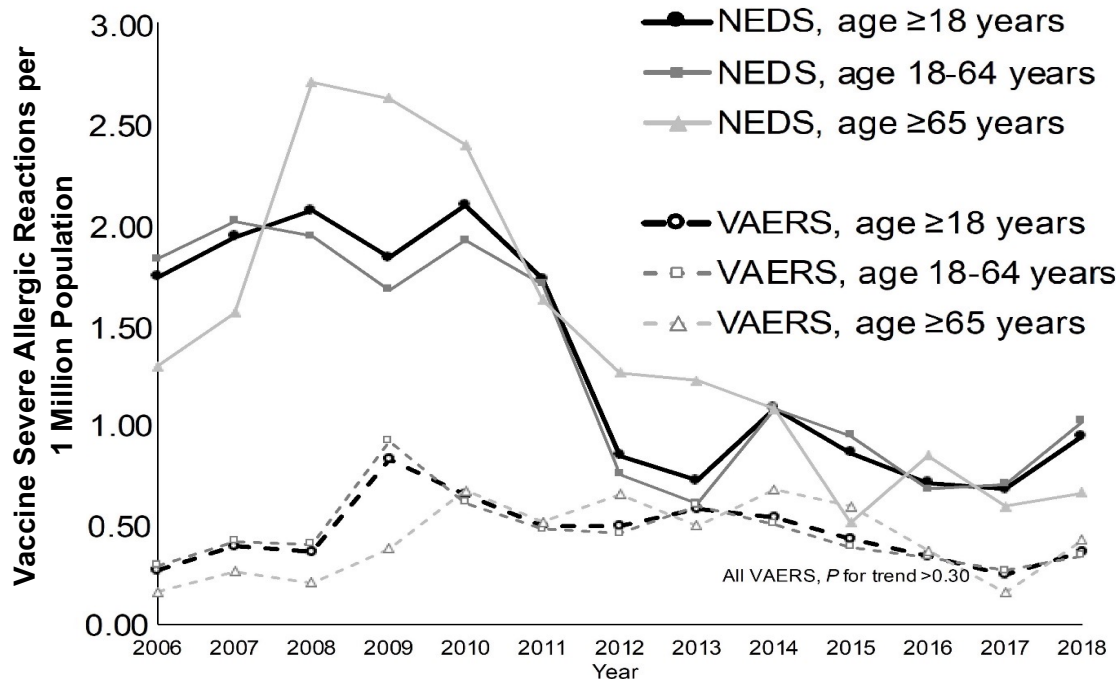
Overall, 1.31 (95% CI, 0.90-1.84) per million doses

	Number of Cases (n=18)	Incidence Rate Per Million Doses (95% CI)
Tetanus, Diphtheria, and Pertussis	1	0.51 (0.01–2.86)
Trivalent Influenza Vaccine	10	1.35 (0.65–2.47)
Inactivated Influenza Vaccines	2	1.83 (0.22–6.63)
Pneumococcal 23	1	2.48 (0.06–13.80)
Hepatitis A Vaccine	1	3.38 (0.09–18.81)
Herpes Zoster Vaccine	2	9.60 (1.16–34.67)
Rabies Vaccine	1	86.1 (2.18–479.43)

Higher

- CDC Vaccine Safety Datalink
- 9 million adults and children, 2009 –2011
- Cases identified by ICD-9-CM code, validated by Brighton Collaboration Criteria

Vaccine Anaphylaxis Declined 2006-2018



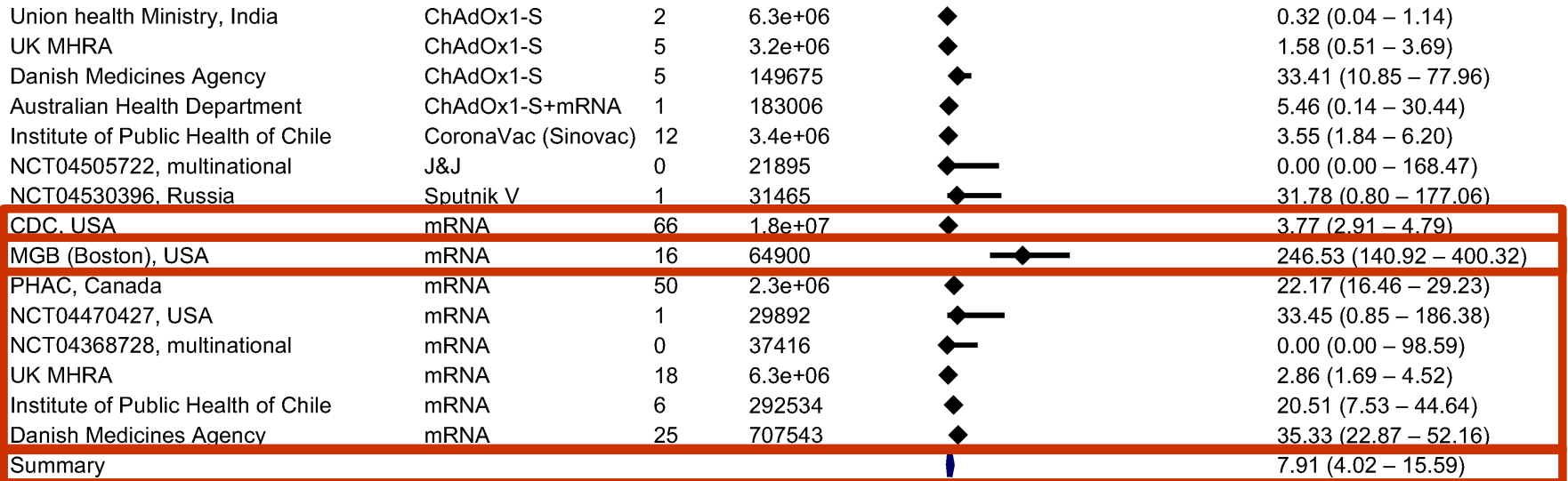
≥18 and 18-64 years, P for trend <0.001 , decrease
 ≥65 years, P for trend 2006-2008 = .22
 ≥65 years, P for trend 2009-2018 <0.001 , decrease

NEDs: Nationwide Emergency Department Sample
VAERS: Vaccine Adverse Event Reporting System

- Death was rare (1%)
- Severe reactions:
 - Age: OR 2.24 ≥65 years compared to age 18-24 years
 - Male sex: OR 1.56
 - Chronic condition: OR 14.36

COVID-19 Vaccine Anaphylaxis Incidence

Adjudicated



Test for interaction, $P < .0001$

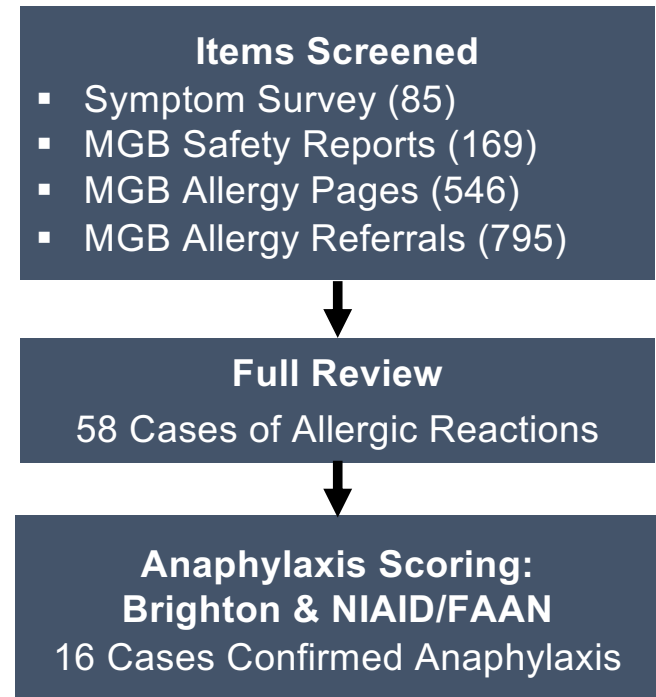
Incidence per million doses

0 100 500 1,000

- Adjudicated cases (Brighton)
- 7.91 per million doses (95% CI 4.02-15.59)
- No anaphylaxis-related fatalities

MGB Employee Vaccine Cohort

- ~65,000 vaccinated employees across northeastern US
- Sign-up for vaccination required answering a few **pre-vaccine questions** including:
 - History of anaphylaxis?
 - Allergy to injectable medications, vaccines, or inactive ingredients?
- After vaccination (each dose), **symptom survey** administered days 1, 2, and 3
 - At least one symptom survey completed by >80% of employees



Anaphylaxis in the MGB Employee Vaccine Cohort

	Both mRNA Vaccines (n=64,900)	Pfizer-BioNTech (n=25,929)	Moderna (n=38,971)	P-value
Confirmed anaphylaxis (either criteria)	16 (0.025; 0.014, 0.040)	7 (0.027; 0.011, 0.056)	9 (0.023; 0.011, 0.044)	0.76
Confirmed anaphylaxis (Brighton)	14 (0.022; 0.012, 0.036)	7 (0.027; 0.011, 0.056)	7 (0.018; 0.007, 0.037)	0.44
Confirmed anaphylaxis (NIAID/FAAN)	9 (0.014; 0.006, 0.026)	4 (0.015; 0.004, 0.040)	5 (0.012; 0.004, 0.030)	0.75
Confirmed anaphylaxis (both criteria)	7 (0.011; 0.004, 0.022)	4 (0.015; 0.004, 0.040)	3 (0.008; 0.002, 0.023)	0.45

NIAID/FAAN, National Institute of Allergy and Infectious Diseases/ Food Allergy and Anaphylaxis Network

- Anaphylaxis incidence mRNA COVID-19 vaccines: 1.1 to 2.5 per 10,000 vaccinations

110 to 250 per million first doses

Anaphylaxis Case Review

Anaphylaxis Cases (n=16)

Age	41 (13)
Female	15 (94)
Prior allergic reactions	10 (63)
Prior anaphylaxis	5 (31)
Symptoms	
Pruritus, urticaria, and/or angioedema	14 (88)
Throat tightness, cough, wheeze, and/or dyspnea	14 (88)
Nausea, vomiting, and/or diarrhea	8 (50)
Minutes onset, mean (SD), range	17 (28), 1-120
Symptoms ≤30 minutes	15 (94)
Received epinephrine	9 (56)
Highest treatment setting	
Emergency department	9 (56)
Hospitalization	1 (6)
Intensive care unit	1 (6)
Brighton Level	
Brighton 1	1 (6)
Brighton 2	13 (81)
NIAID FAAN criteria	9 (56)
Elevated tryptase (captured in 5 [32%])	1 (6)

[4.3ng/mL → 7.7ng/mL]



- All (n = 66) treated in healthcare settings
- 32 (48%) hospitalized (including 18 in ICU)
- 7 intubation

Treated Allergic Reactions: Kaiser

Reaction Type and Dose		%, Incidence	
Allergic reactions	Dose 1	0.028%	280 per million first doses
	Dose 2	0.014%	140 per million second doses
Anaphylaxis		0.00033%	3.3 per million

- Risk factors for treated allergic reactions:
 - Younger age ($p < .0001$)
 - Female sex ($p < .0001$)
 - Drug allergy history (2.11 ± 2.12 versus 1.02 ± 1.41 , $p < .0001$ for average recipients)

Pfizer vs Moderna

Pfizer-BioNTech, anaphylaxis rate per million doses, 95% CI		
Shimbakuro 2021	11.1	[6.3, 15.8[
Shimabukuro 2021	4.7	[3.4, 6.1[
Blumenthal 2021	270.0	[70.0, 469.9]
Mathioudakis 2021	3208.1	[835.4, 5580.8]
Ontario Public Health Agency 2021	19.0	[9.0, 28.9]
Combined	8.0	[0.0, 11.3]

Moderna, anaphylaxis rate per million doses, 95% CI		
Shimbakuro 2021	2.5	[1.4, 3.6]
Shimabukuro 2021	2.5	[0.9, 4.0]
Blumenthal 2021	230.9	[80.1, 381.8]
Kadali 2021	2314.8	[0.0, 6846.5]
Mathioudakis 2021	7067.1	[0.0, 16826.8]
Ontario Public Health Agency 2021	6.5	[0.0, 19.4]
Combined	2.8	[0.0, 5.7]



~8 per Million



~3 per Million

Immunization of Highly Allergic Individuals

Highly allergic
Individuals
(N=429)



Characteristic	N (%)
Age, mean (SD)	52 (16)
Female	304 (71%)
Prior allergies	429 (100)
Drug allergy	258 (60)
Injectable Drug allergy	118 (28)
Prior anaphylaxis	271 (63)

429 received dose 1 under medical supervision

- 420 (98%) had no allergic reaction
- 6 (1.4%) had mild allergic responses
- **3 (0.7%) had anaphylactic reactions**

218 (50.8%) received dose 2 under medical supervision

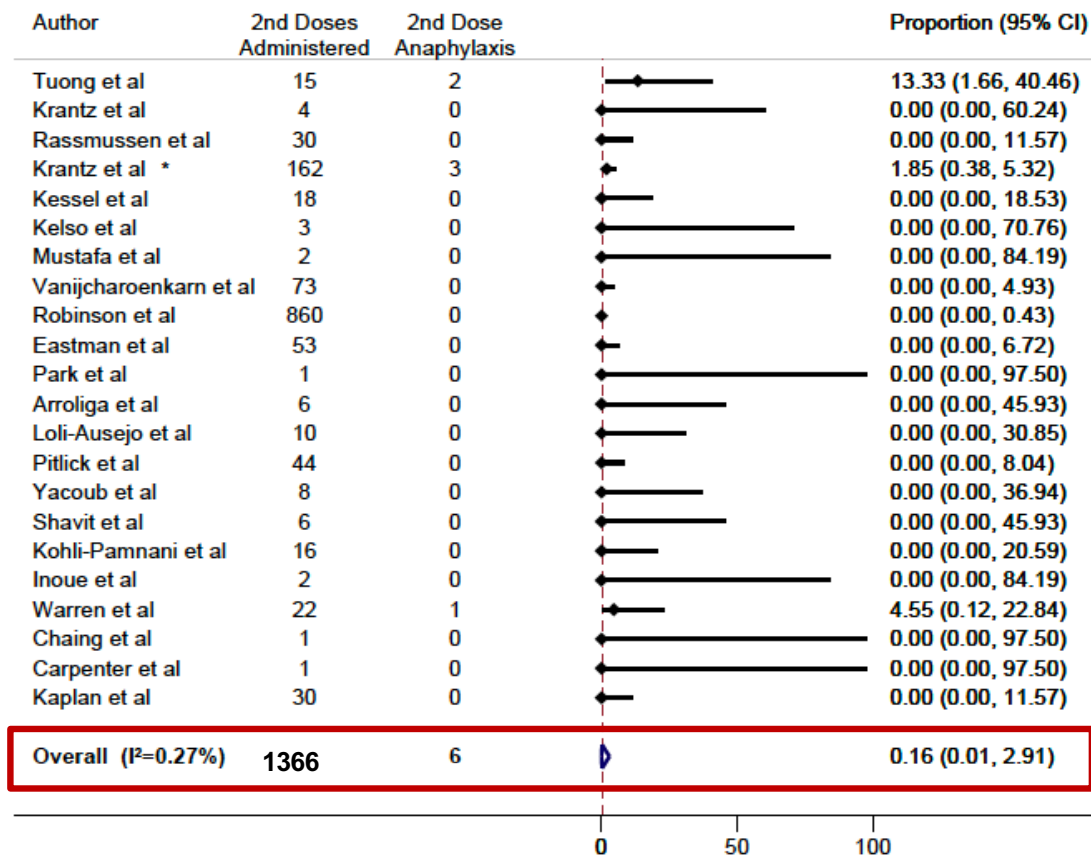
- 214 (98%) had no allergic reactions
- 4 (1.8%) had minor allergic reactions

Most First Dose Reactions Do Not Recur

- 84% tolerated the 2nd dose including 19 with first-dose anaphylaxis

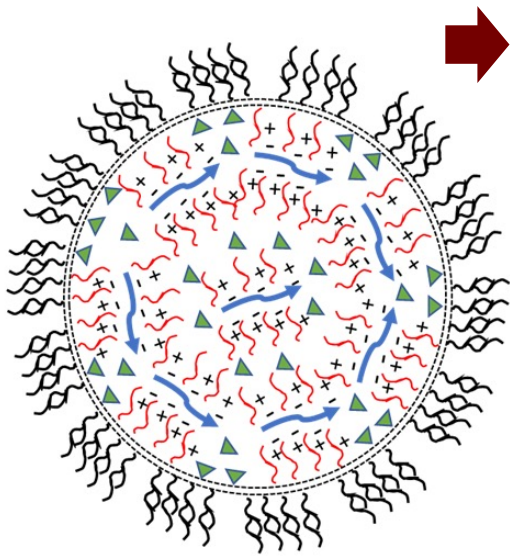
Site	n	Female	Age, Mean	Moderna	Pfizer	Anaphylaxis	Dose 2 Received	Dose 2 Immediate Reaction	Dose 2 Tolerance
Mass General	76	66 (87)	39.5	60 (79)	16 (21)	6(8)	65 (86)	8 (12)	65 (100)
Brigham	54	45 (83)	43.0	41 (76)	13 (24)	5(9)	50 (93)	7 (14)	50 (100)
Vanderbilt	27	22 (81)	49.8	6 (22)	21 (78)	8 (30)	19 (70)	7 (37)	19 (100)
Yale	25	23 (92)	46.3	20 (80)	5 (20)	7 (28)	18 (72)	7 (29)	18 (100)
UTSW	7	7 (100)	47.0	3 (43)	4 (57)	6 (86)	7 (100)	3 (43)	7 (100)
Pooled Values	189	163 (86)	43.2	130 (69)	59 (31)	32(17)	159 (84)	32 (20)	159 (100)






Severe Allergic Reactions to 2nd Dose Rare



- Risk of severe immediate allergic reactions after Dose 2: **6** (0.16% [95% CI 0.01% to 2.94%])
- Risk of mild symptoms after Dose 2: **232** (13.65% [95% CI 7.76% to 22.9%])
- No deaths reported

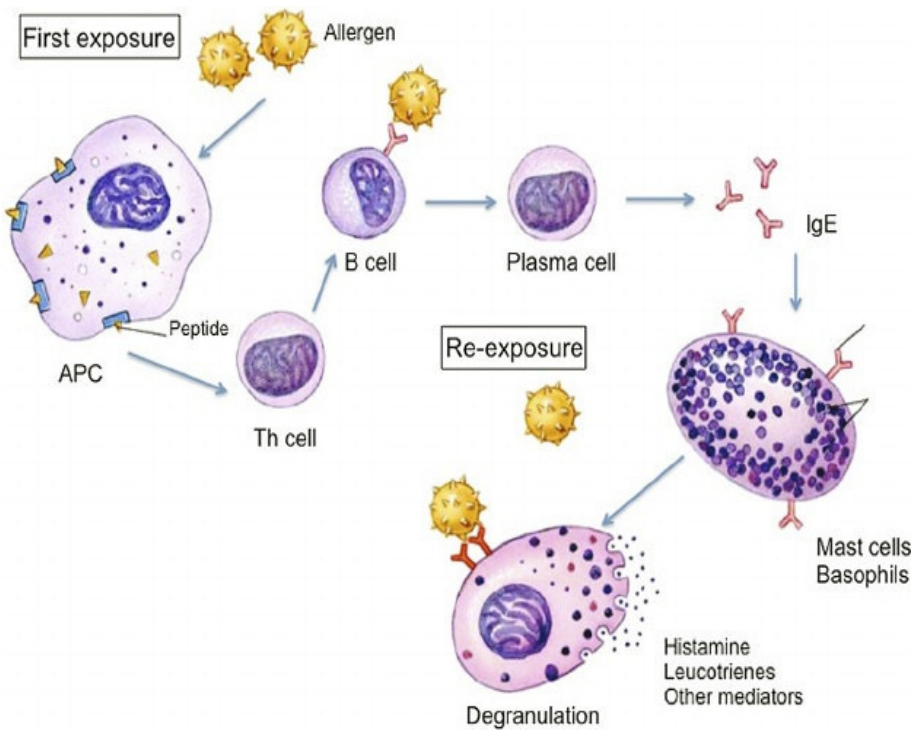
Lipid Nanoparticle



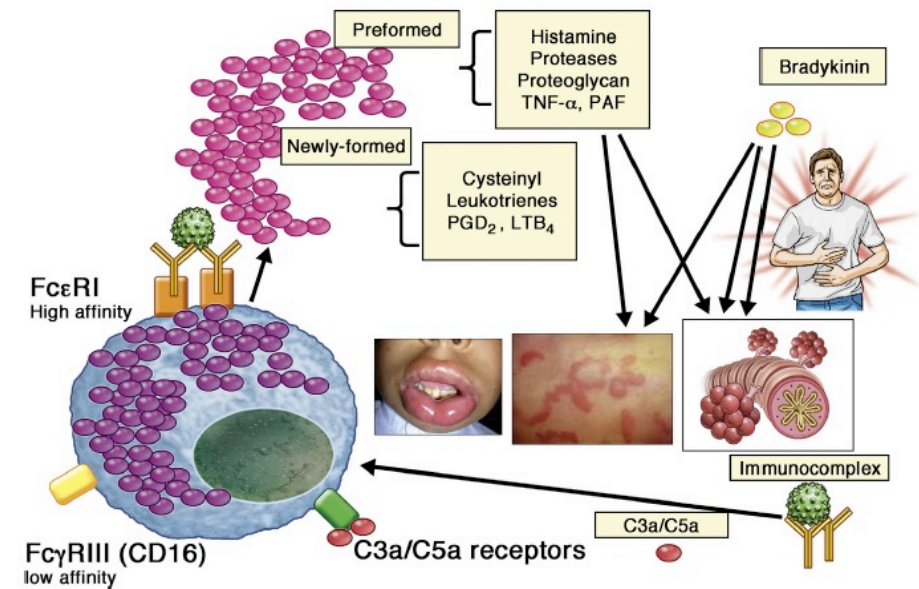
LNP component	Predicted Immunogenicity	mcg/dose Pfizer-BioNtech	mcg/dose Moderna
PEG-lipid 	Pre-existing Anti-PEG IgM, IgG and/or IgE	50 mcg	Total lipid dose is 1930 mcg
Ionizable lipid 	Pathogen associated molecular pattern receptors	430 mcg	
neutral lipid (DSPC) 	Complement activation	90 mcg	
cholesterol 		200 mcg	
mRNA 	Pathogen associated molecular pattern receptors and Factor XII activation	30 mcg	100mcg

Possible Mechanisms of Anaphylaxis

IgE-mediated (Rare)



Non IgE-Mediated (Multiple Mechanisms Possible)



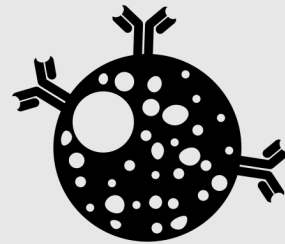
Vaccine Anaphylaxis: Differential Diagnosis



Anaphylaxis Due to Other



- Urticaria
- Angioedema
- Reactogenicity



- Mast cell disorders



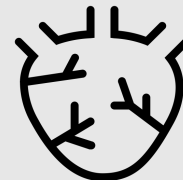
Flushing



Neurologic



Vocal cord dysfunction



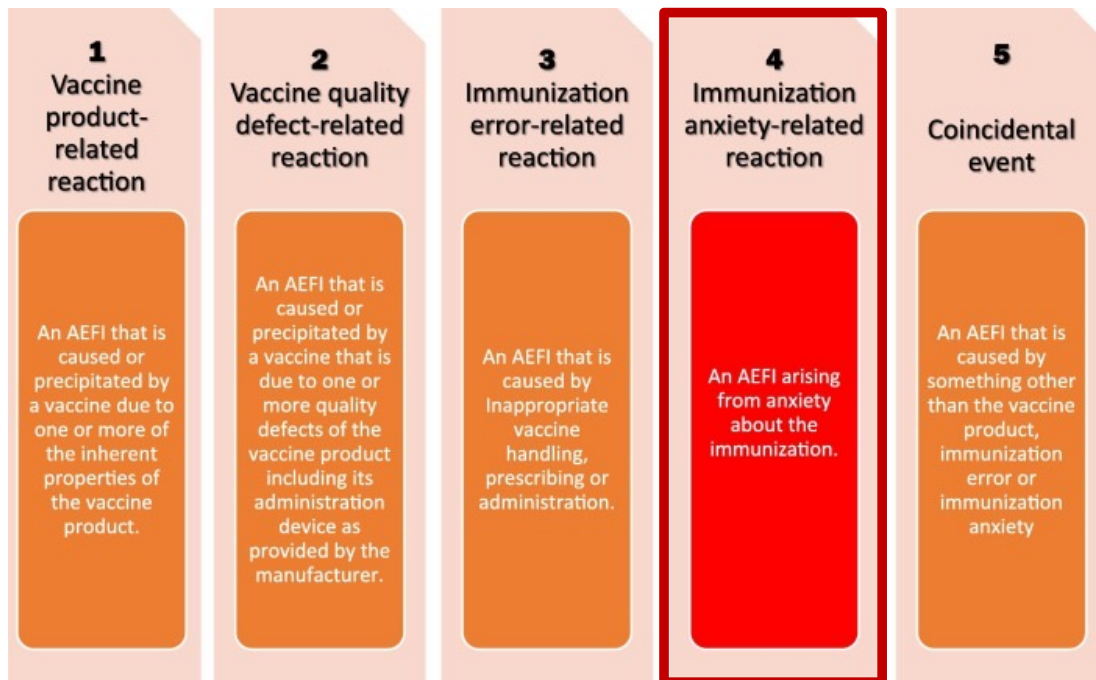
Cardiovascular



Stress

ISRR

Alternatives To Anaphylaxis: Immunization Stress-Related Response (ISRR)



- Symptoms (subjective) often predominate, without signs (objective) to support them:
 - Pruritus or tingling
 - Throat tightness
 - Shortness of breath
 - Lightheadedness

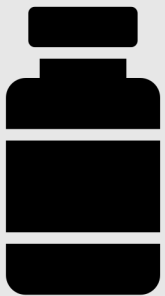
Anaphylaxis Versus Stress Related Response

	Anaphylaxis	Vasovagal	Stress Reaction (ISRR)
Onset	Shortly (5-60 min) after vaccination	Before, during or shortly (<5 min) after vaccination	Before, during or soon after vaccination
Skin	Hives, swollen eyes and face, generalized rash	Pale, sweaty, cold, clammy	Pale, sweaty, cold, clammy
Respiratory	Cough, wheezing, stridor	Normal to deep breathing	Rapid and shallow (hyperventilation)
Cardiovascular	Tachycardia, hypotension, dysrhythmias, arrest	Bradycardia, transient hypotension	Tachycardia, normotension or hypertension
Gastrointestinal	Nausea, vomiting, abdominal cramps	Nausea, vomiting	Nausea, vomiting
Neurologic	Uneasiness, restlessness, agitation, loss of consciousness, little response once supine	Transient loss of consciousness, good response once supine, tonic/clonic seizure	Fearful, lightheaded, weakness, numbness/tingling sensation on face, spasms extremities

Nocebo Effect

- The nocebo effect is the onset of untoward reactions following the administration of an indifferent substance.

DRUGS



8-27%

- Beta-lactam challenge, ~200 patients in US, **8%** reacted to placebo
- Oral challenge, ~600 patients in Spain, **27%** reacted to placebo
- Placebo reactors commonly female and with more drug allergy labels

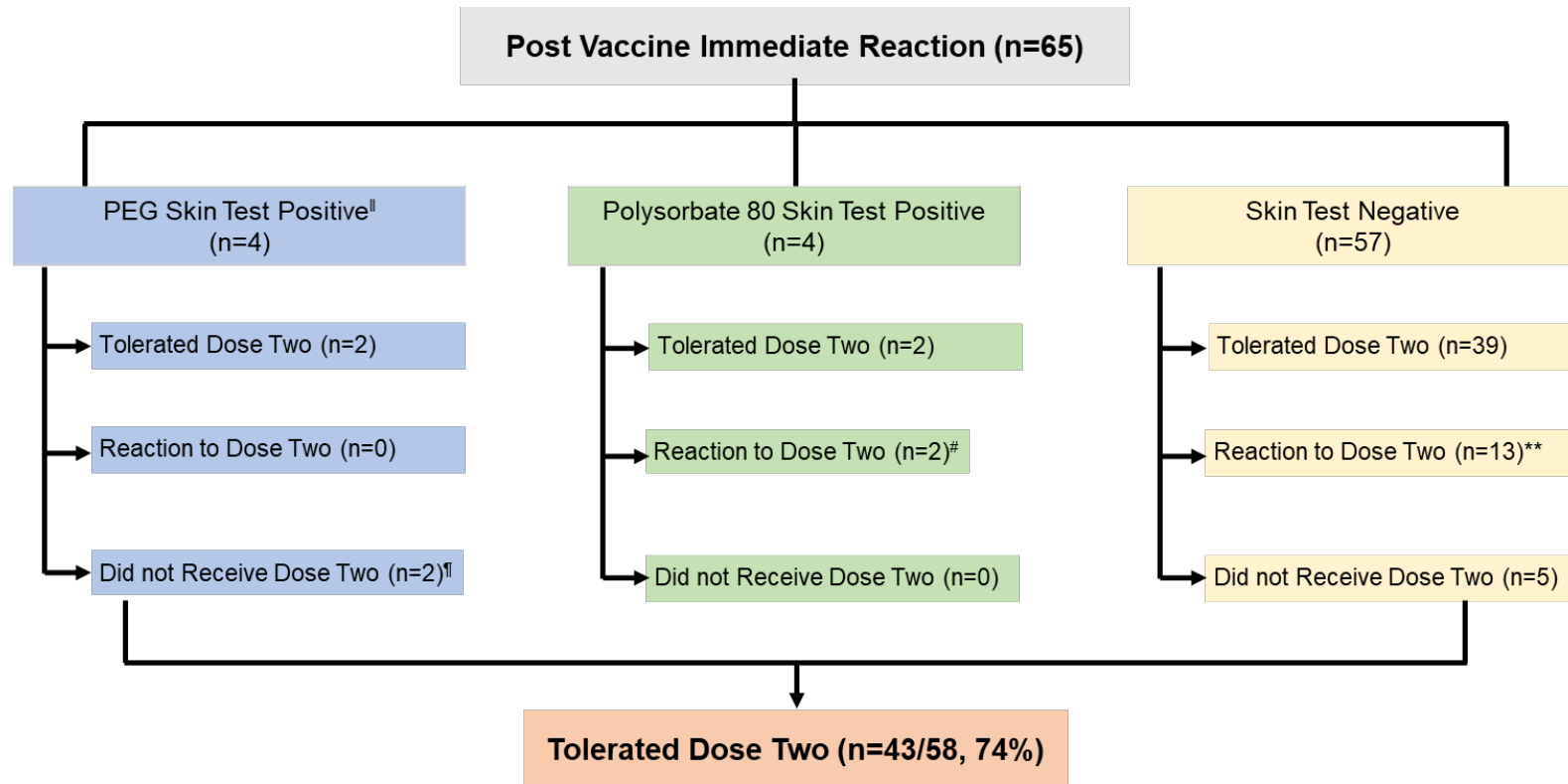
VACCINES






32-35%

- Meta analysis from 12 clinical trials
- mRNA vaccine systemic nonallergic reaction, systemic and local
- Systemic adverse events **35%** after dose 1 and **32%** after dose 2
- Nocebo responses accounted for 76% of systemic and 24% of local adverse events

Excipients PEG/PS80 Not Particularly Helpful



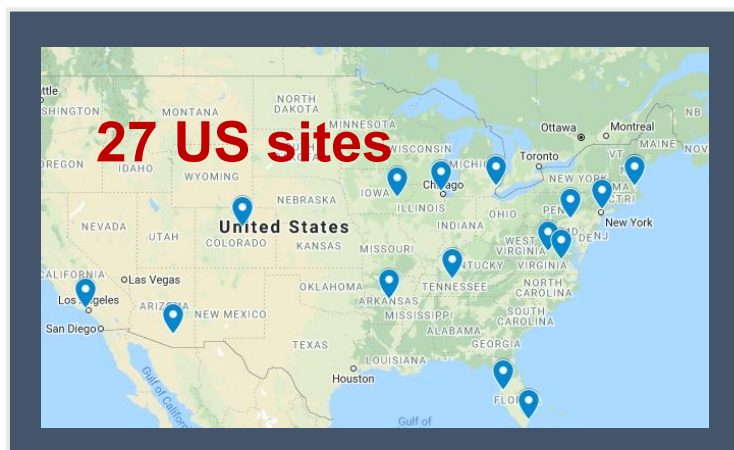
PEG Allergic Individuals Do Not Have Reactions to mRNA COVID-19 Vaccines

PEG or Derivative	Study, n, clinical detail	mRNA Vaccines	Reactions
PEG 11 PEG 3350 	Picard (n=12; 6 with +ST/DPT)	10	None
Pegasparginase Derived from PEG 5000 	<ol style="list-style-type: none"> Koo (n=19, 16 prior PEG exposure/tolerance, none ST positive to PEG 3350) Rush (n=31, 25 prior PEG exposure/tolerance) Mark (n=32, 22 prior PEG exposure/tolerance) 	1. 19 2. 29 3. 32	None
Paclitaxel Polyoxyl-35 castor oil 	Banerji (n=17, 52% reactions occurred in last 4 years)	12	None

Picard *J Allergy Clin Immunol Pract.* 2021; Koo *J Allergy Clin Immunol Pract.* 2022; Rush *J Allergy Clin Immunol Pract.* 2021; Mark *Pediatr Blood Cancer.* 2021; Banerji *Allergy.* 2021

Immunization of Highly Allergic Individuals

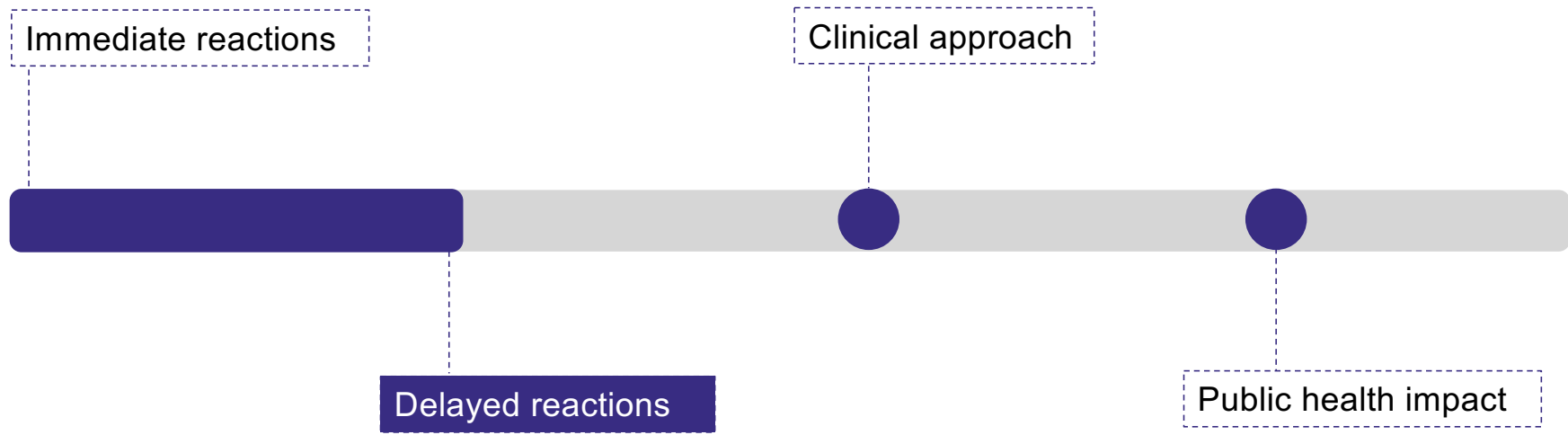
Systemic Allergic Reactions to SARS-CoV-2 Vaccination (SARS Vaccination; NCT04761822)



Enrollment To Date (Age ≥ 18)		
	High Allergy (n=345)	Comparison (n=267)
Allergy History	All	None
Drug allergy	70%	
Food allergy	66%	
Mast cell disorder	21%	

- Pfizer-BioNTech, Moderna (adults only), initial placebo
- Primary outcome: Proportion of participants with a systemic allergic reaction
- Exploratory mechanistic studies

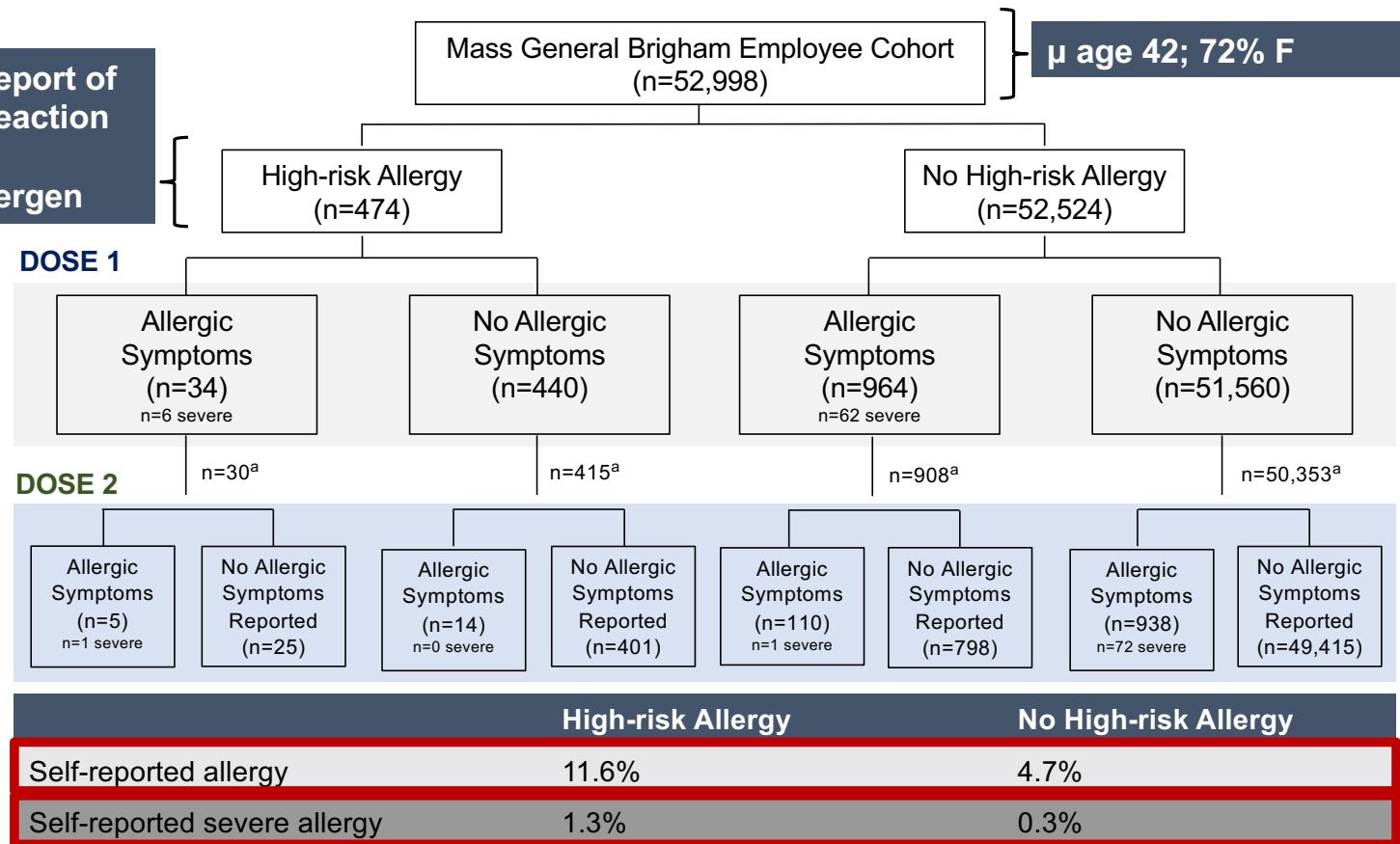
Roadmap



Immunization of Highly Allergic Individuals

High-risk allergy: Self-report of a prior severe allergic reaction to a vaccine, injectable medication, or other allergen

51,706 (97.6%)
Received Dose 2

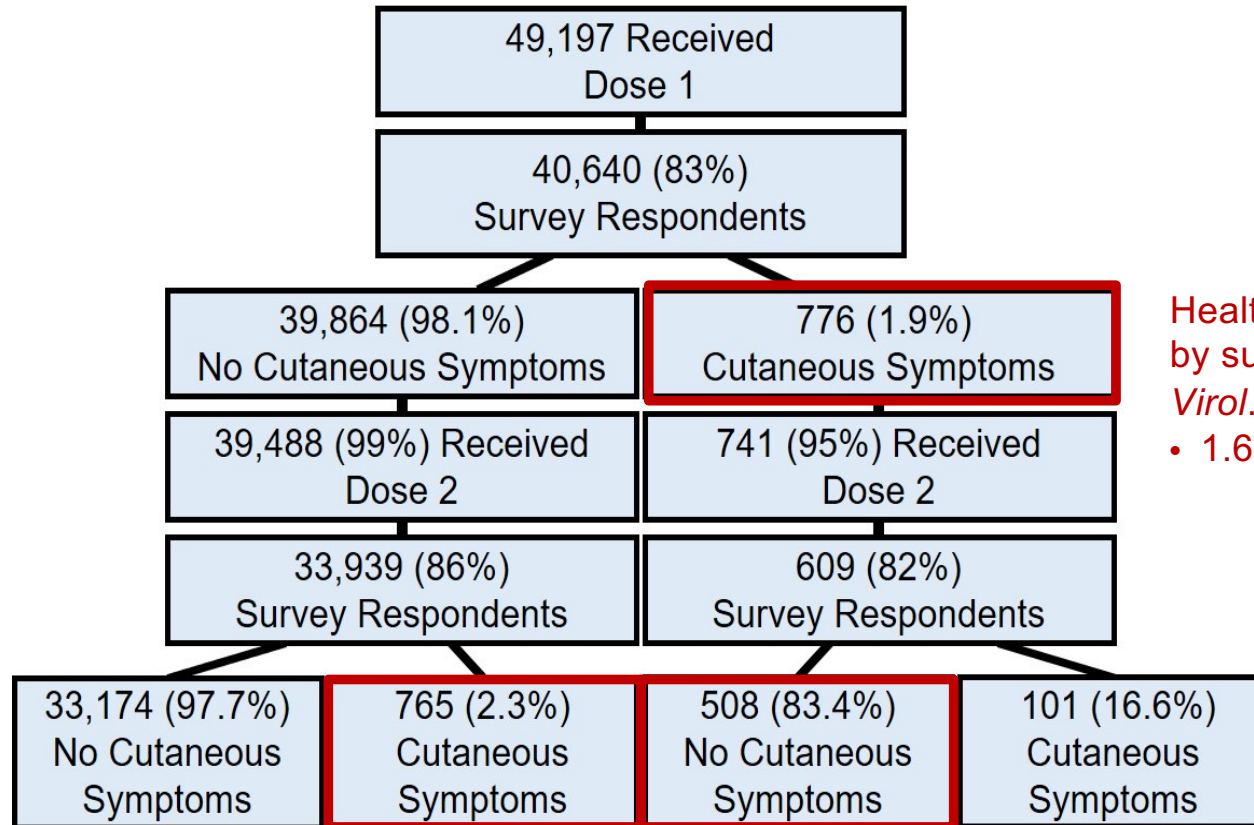


Increased Allergic Reactions

	High-risk Allergy History (n=474)	No High-risk Allergy History (n=52,524)	Adjusted Relative Risk (95%CI)
Allergic Reaction - Either Dose 1 or Dose 2	55 (11.6)	2,461 (4.7)	2.46 (1.92, 3.16)
Itching or rash	32 (6.8)	1,390 (2.7)	2.46 (1.76, 3.45)
Hives	16 (3.4)	460 (0.9)	3.81 (2.33, 6.22)
Respiratory Symptoms	10 (2.1)	677 (1.3)	1.76 (0.95, 3.27)
Angioedema	13 (2.7)	329 (0.6)	4.36 (2.52, 7.54)
Allergic Reaction - Dose 1	34 (7.2)	964 (1.8)	3.66 (2.63, 5.10)
Itching or rash	22 (4.6)	714 (1.4)	3.16 (2.09, 4.79)
Hives	11 (2.3)	211 (0.4)	5.47 (3.00, 9.99)
Respiratory Symptoms	9 (1.9)	306 (0.6)	3.24 (1.68, 6.26)
Angioedema	10 (2.1)	169 (0.3)	6.33 (3.35, 11.95)
Allergic Reaction - Dose 2	19 (4.3)	1,048 (2.0)	2.10 (1.35, 3.28)
Itching or rash	14 (3.2)	755 (1.5)	2.15 (1.28, 3.62)
Hives	6 (1.4)	258 (0.5)	2.81 (1.26, 6.28)
Respiratory Symptoms	3 (0.7)	385 (0.8)	1.05 (0.34, 3.25)
Angioedema	3 (0.7)	170 (0.3)	2.15 (0.69, 6.72)

Higher ←

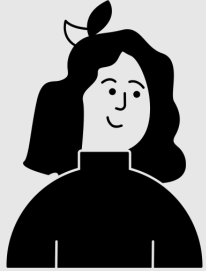
Skin Reactions: Incidence & Recurrence Risk



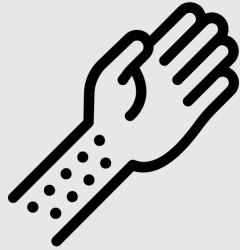
Healthcare worker study by survey (Kadali *J Med Virol.* 2021)
 • 1.6% hives

Urticaria/Angioedema Reports

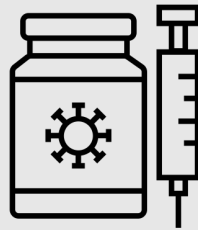
- 58 patients with urticaria or angioedema



Mean age 42
88% Female
82% White



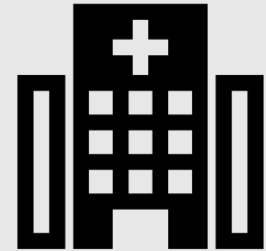
17% chronic
urticaria history



50% Pfizer
50% Moderna
74% 1st Dose



5% epinephrine IM
18% oral steroids



26% Home
24% Emergency
3% Hospitalization

Urticaria Post mRNA COVID-19 Vaccination



Chronic Spontaneous Urticaria After COVID-19 Vaccine Support Group >

Private group · 3.2K members → **6.5K members**

Join group

About

DISCLAIMER: this is NOT an antivaccine facebook group.

... See More

Urticaria and/or Angioedema after Vaccination



35 y/o M, Day +18 s/p
Moderna Booster



27 y/o F Day +15 s/p
Moderna Booster



47 y/o F, Moderna dose 2,
urticaria 3 weeks later, Day
+12 s/p Moderna Booster

Skin Reactions after mRNA COVID-19 Vaccines

Local site reaction



-92% Moderna
-94% Female

Urticaria



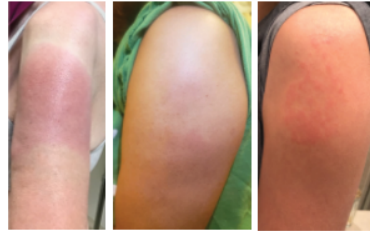
-57% Moderna
-89% Female

Morbilliform



-65% Moderna
-88% Female

Delayed hypersensitivity

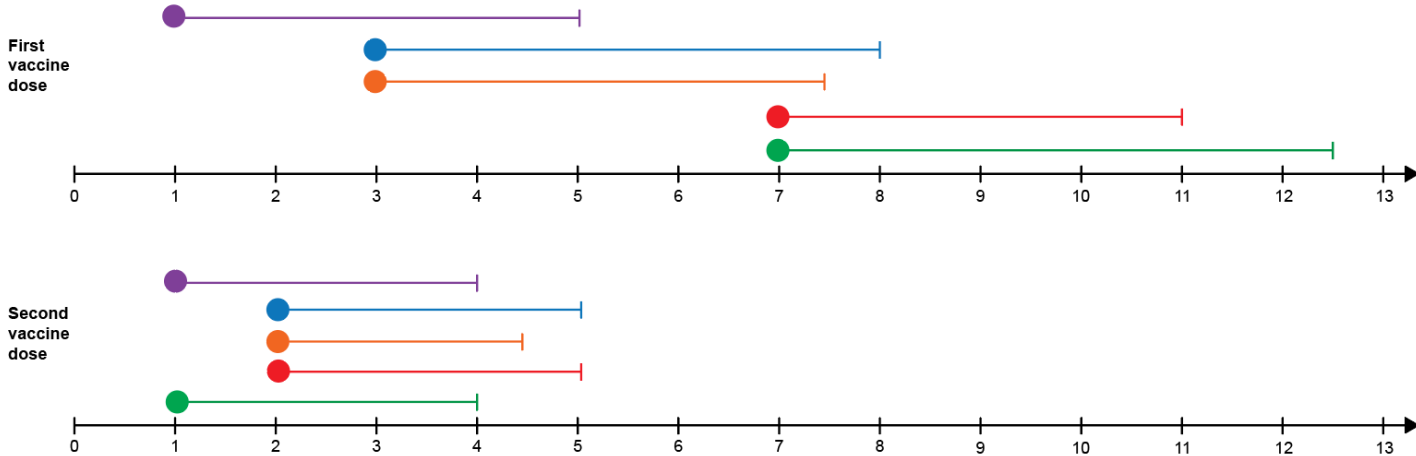


-94% Moderna
-93% Female

Erythromelalgia



-77% Moderna
-92% Female



Days after vaccination

Morbilliform Rash after mRNA COVID-19 Vaccines



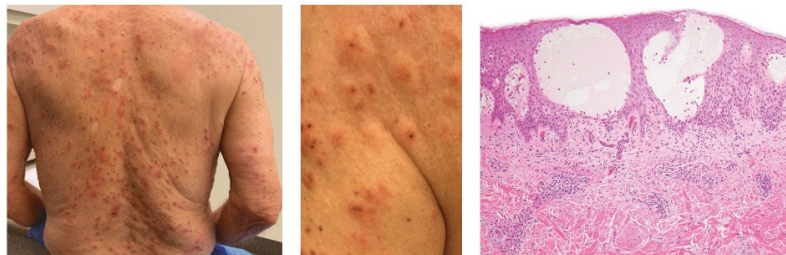
23 y/o M patient hospitalized day #8 after Moderna dose #1 with MP rash, AEC>1K/L



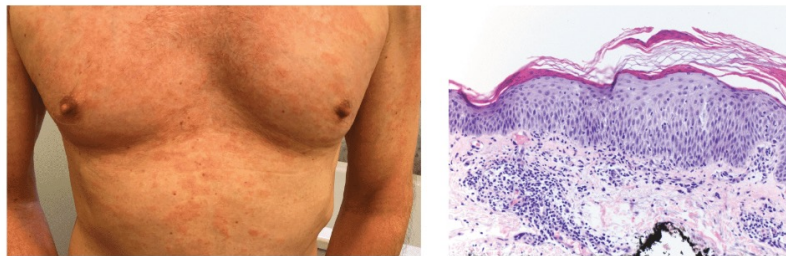
32 y/o F day 2 after Moderna dose #2 LLR then day #4 MP rash with ALT 41 U/L with lower baseline

V-REPP: Vaccine-Related Eruption of Papules and Plaques

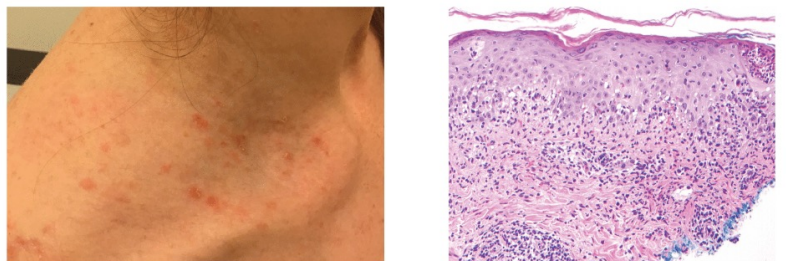
Robust
Papulovesicular



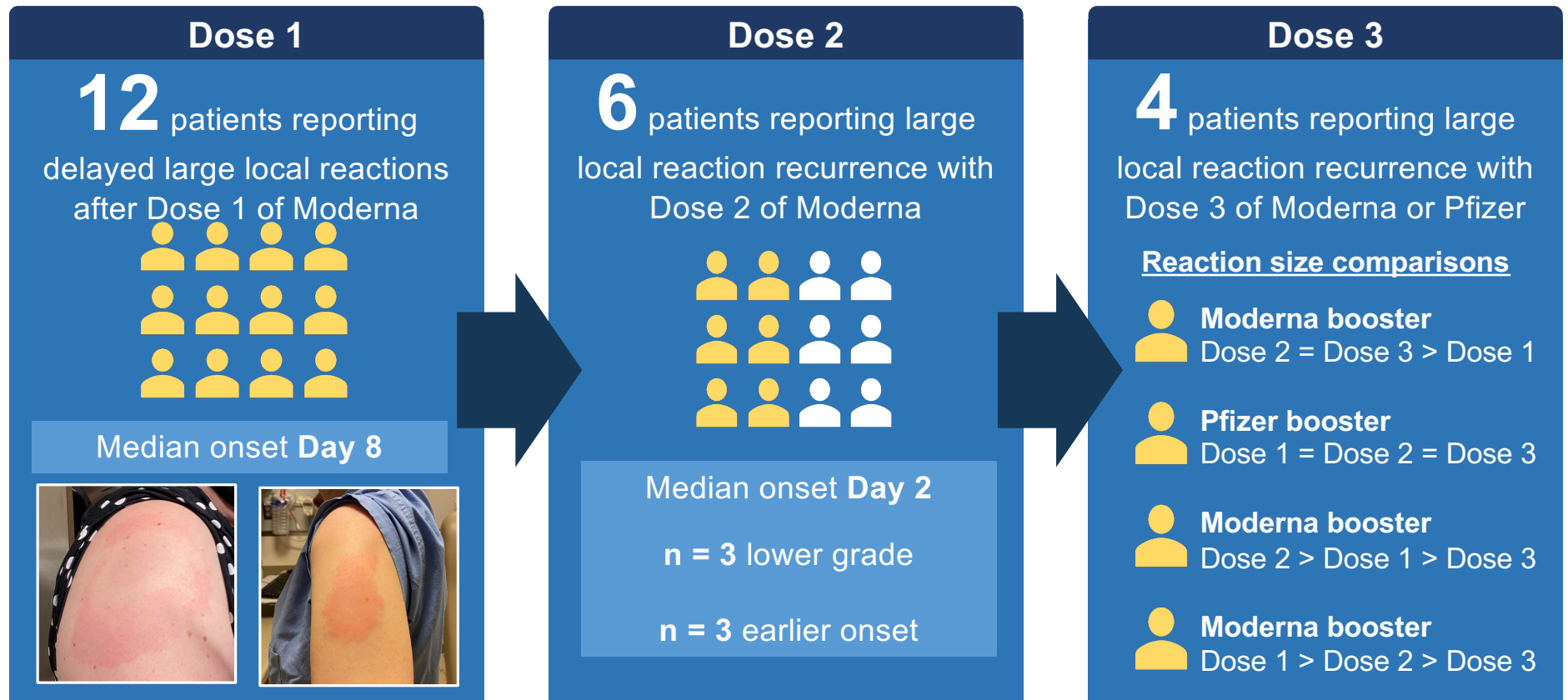
Moderate
Pityriasis rosea-like



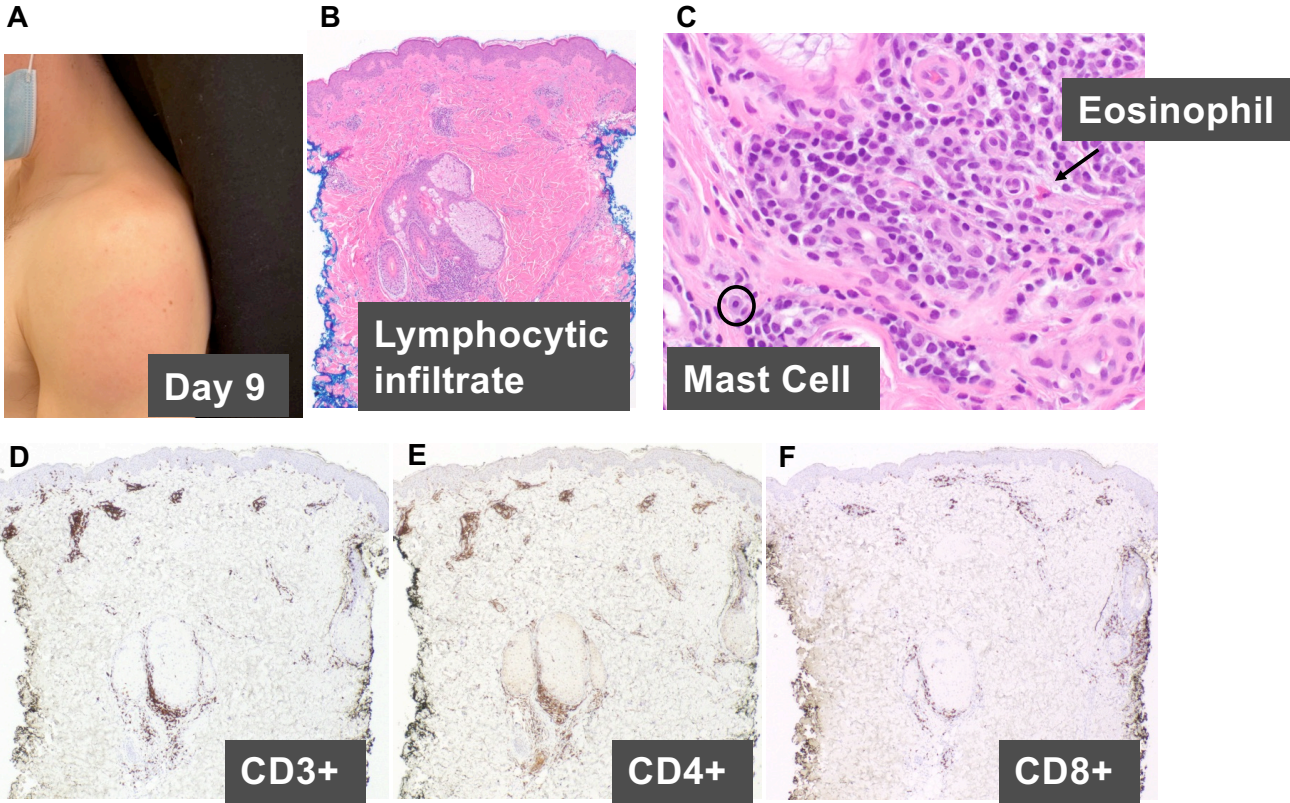
Mild
Papulosquamous



Delayed Large Localized Reactions (DLLR) after Moderna Vaccine



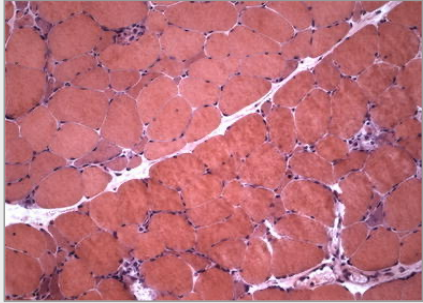
DLLR after mRNA COVID-19 Vaccines



More than “Moderna Arm”



52 y/o F day 8 s/p Moderna dose #1

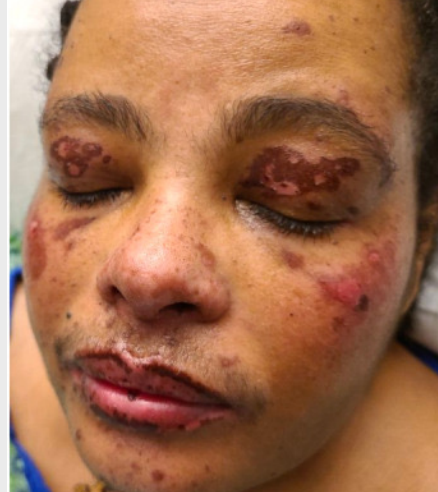


57 y/o M with severe pain and swelling day +8 after Moderna booster
Tm 102.5, elevated inflammatory markers, leukocytosis

SJS/TEN from mRNA COVID-19 Vaccine

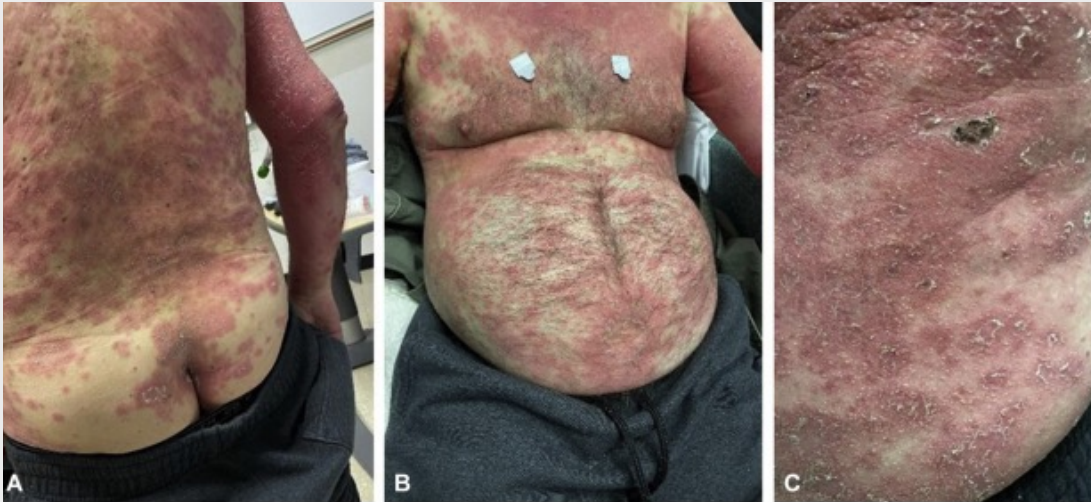


Middle aged Saudi Arabian F 5 days after Pfizer vaccine
Associated fever, no mention of labs other than d-dimer, no mention of rash, no biopsy



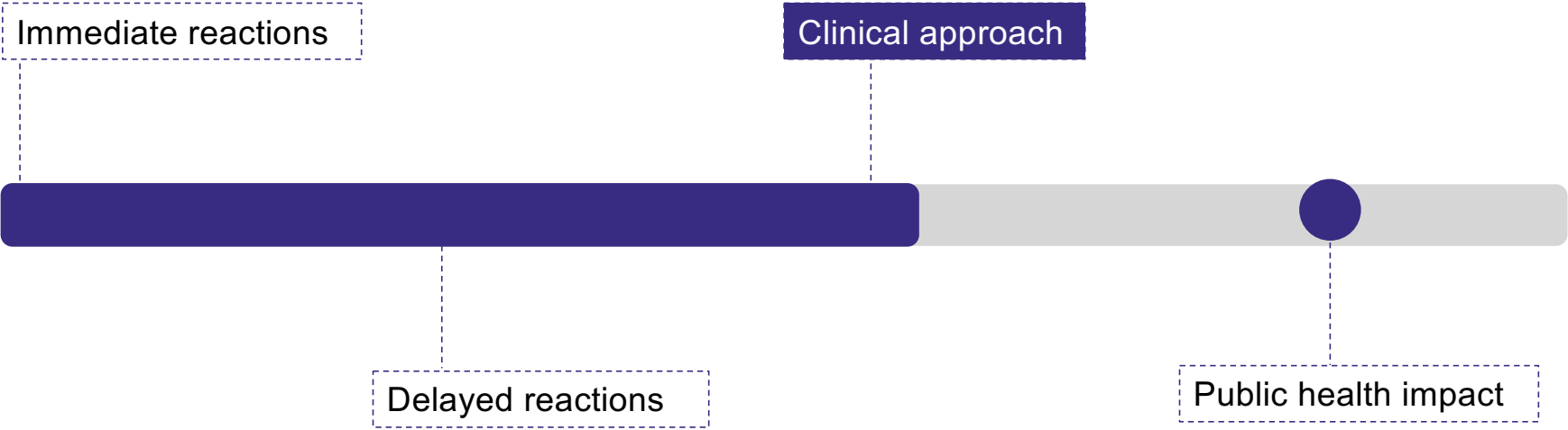
46 y/o Ethiopian F 2 days after Moderna vaccination with erosions of mucous membranes and pink-purple plaques ~20% BSA, biopsy with full-thickness necrosis of the epidermis with a basket weave-type stratum corneum, sparse mild perivascular infiltrate of lymphocytes in the dermis

DRESS vs AGEP after J&J COVID Vaccine

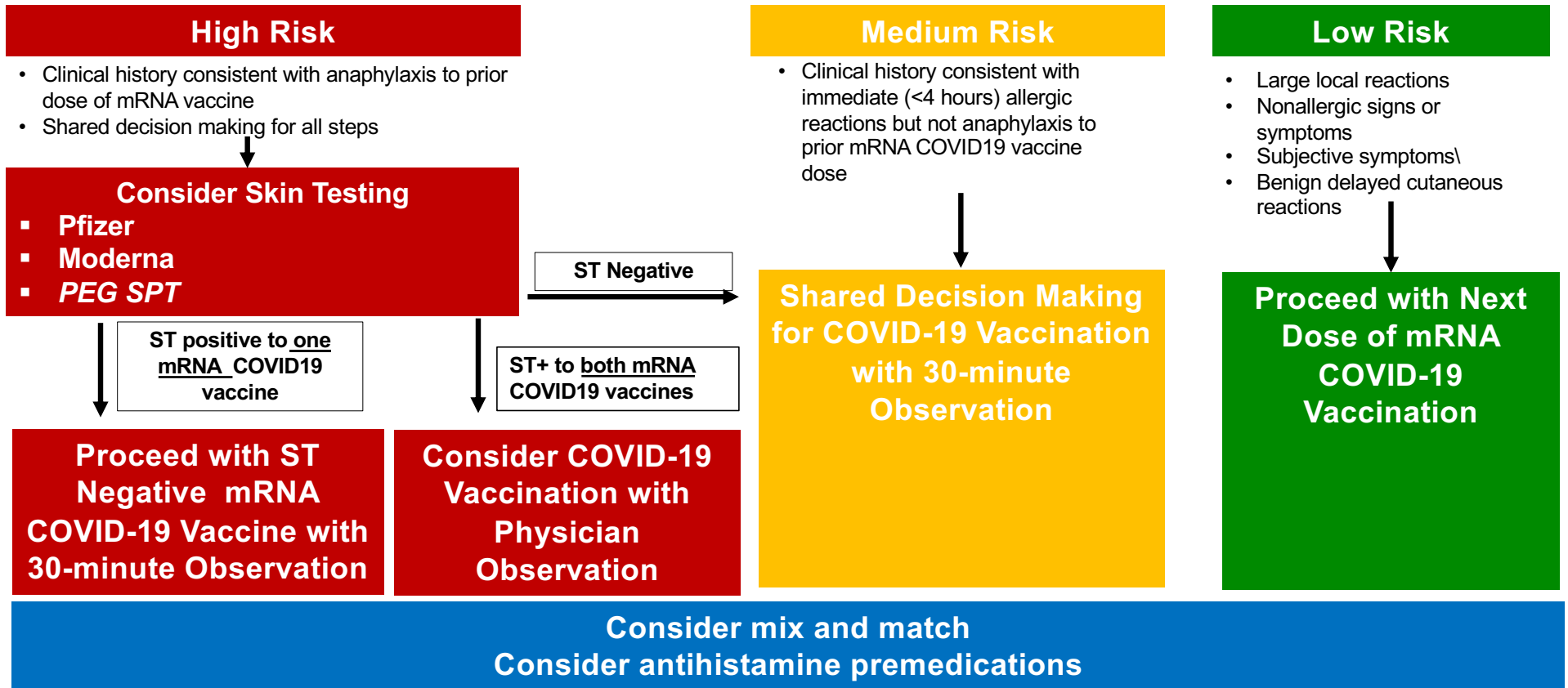


- 74 y/o M
 - Day 3 s/p Janssen vaccine
 - 50% BSA erythematous plaques (A and B) and non-follicular pustules (C)
 - Rash despite prednisone 5mg daily (adrenal insufficiency) and increase to 20 mg by outside dermatologist
 - AEC 600/L; Cr bump/recovery
- Skin biopsy: Epidermal spongiosis with focal, occasional, neutrophilic pustules and dermal neutrophilic inflammation with eosinophils, consistent with a spongiotic and pustular drug eruption

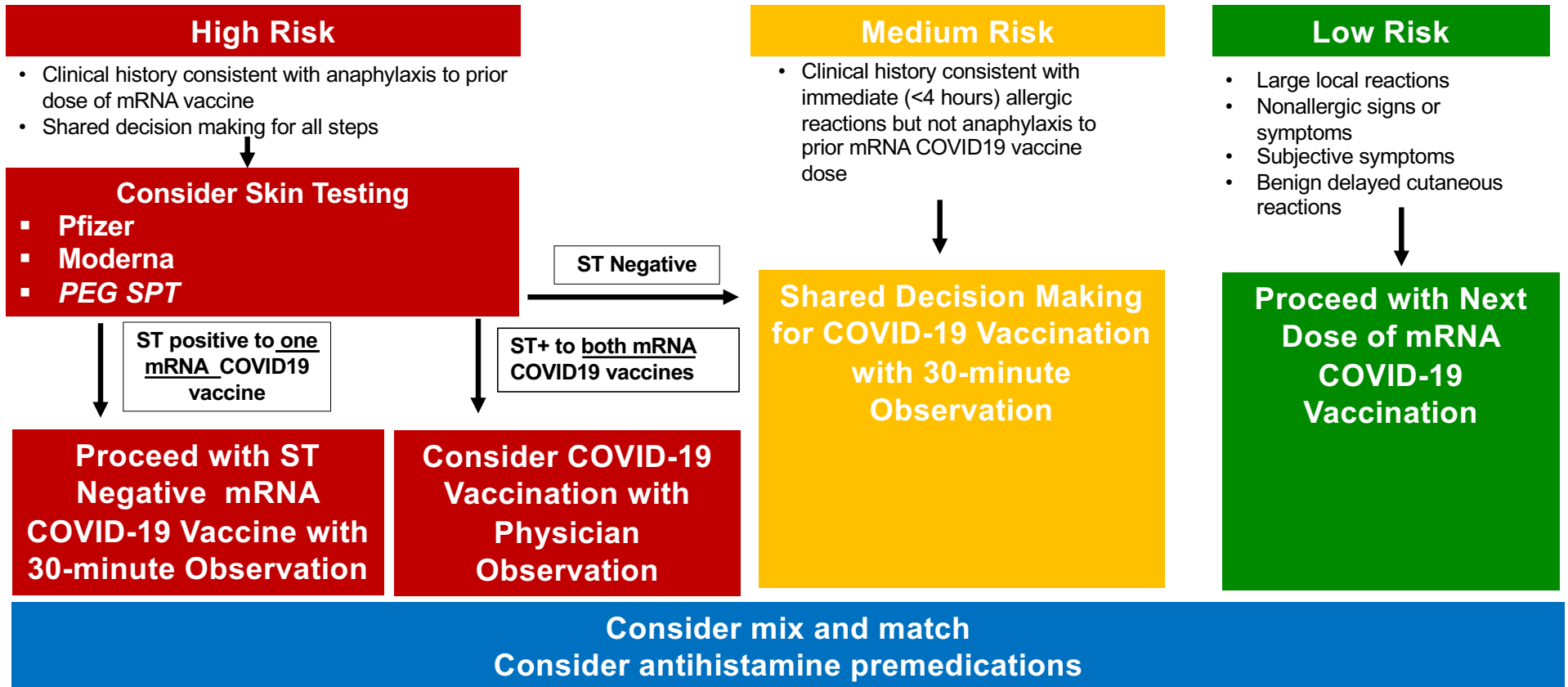
Roadmap



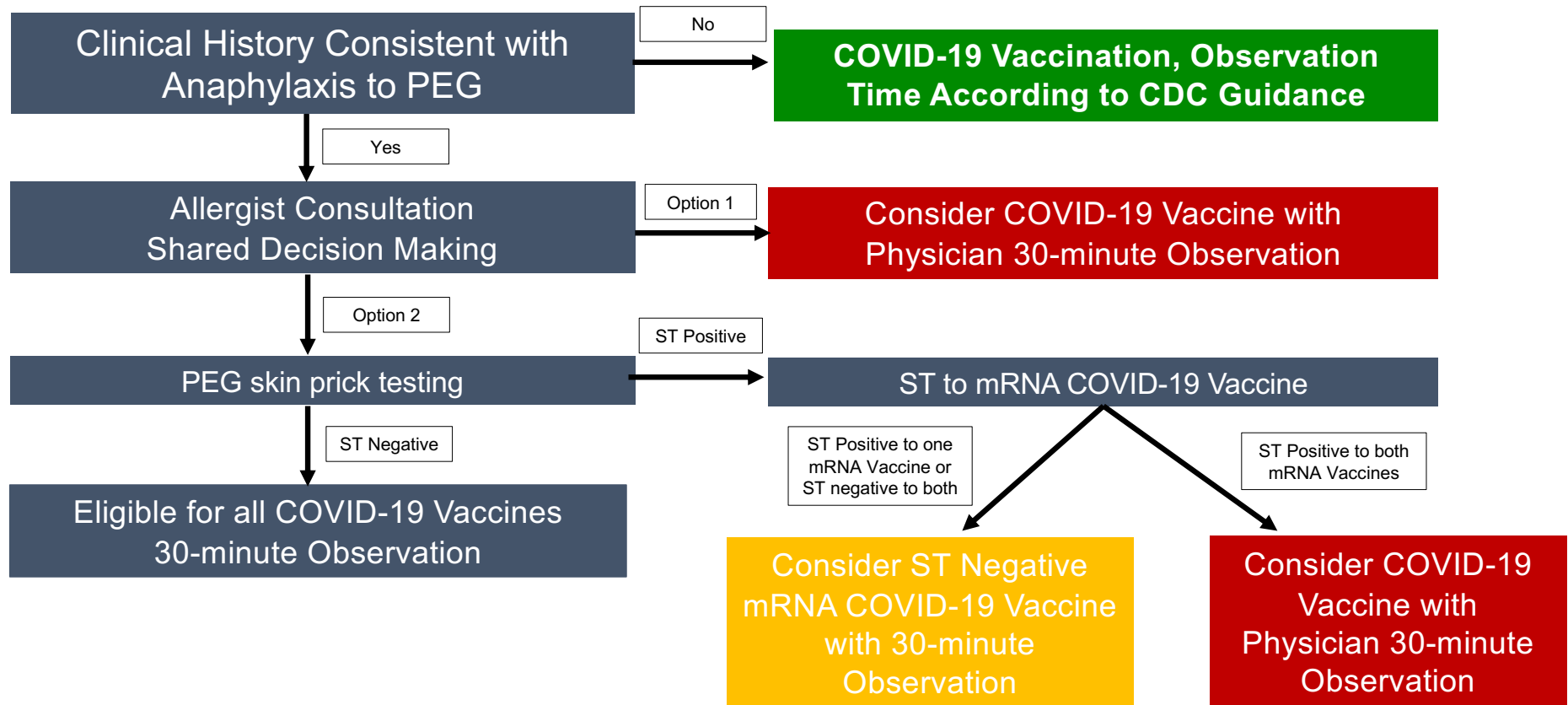
Clinical Approach to mRNA Vaccine Allergy



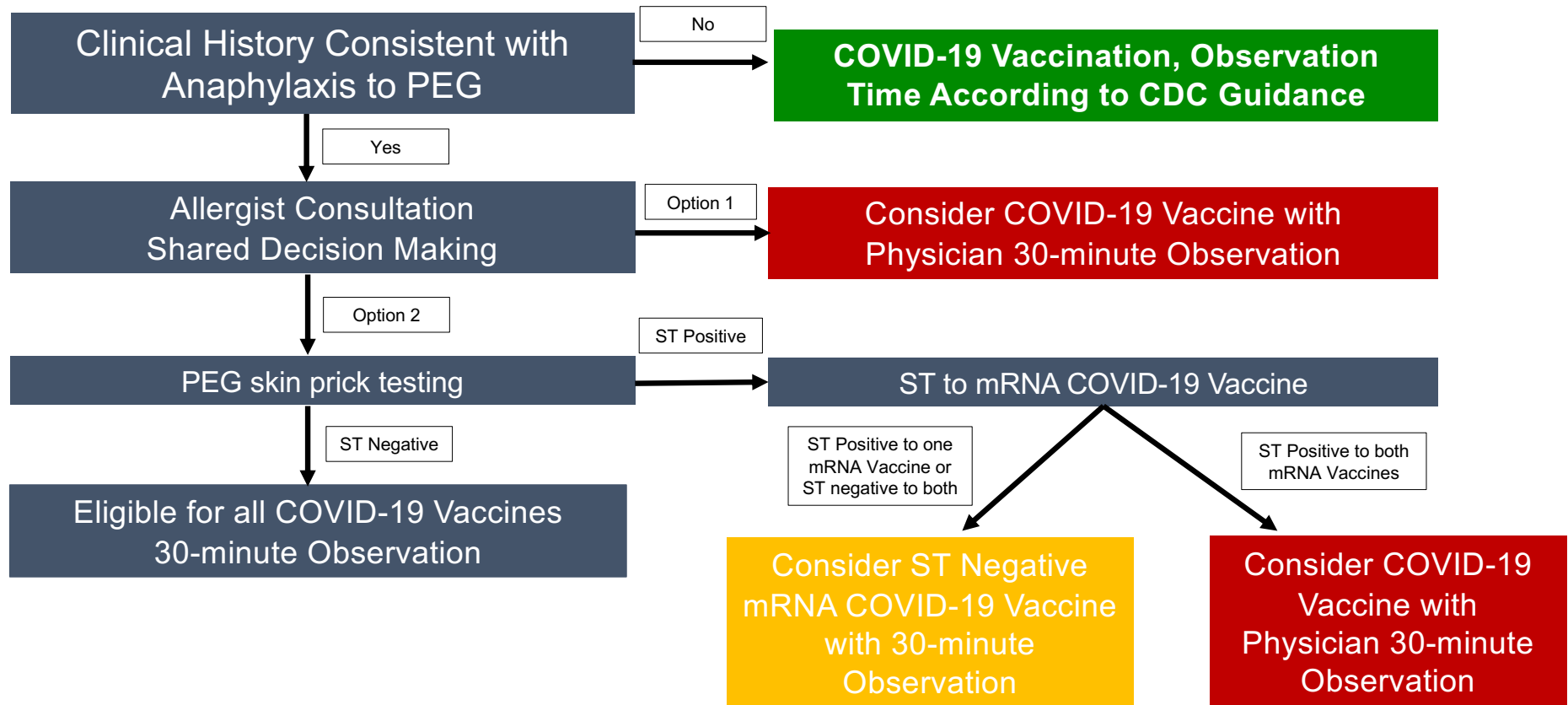
Clinical Approach to mRNA Vaccine Allergy



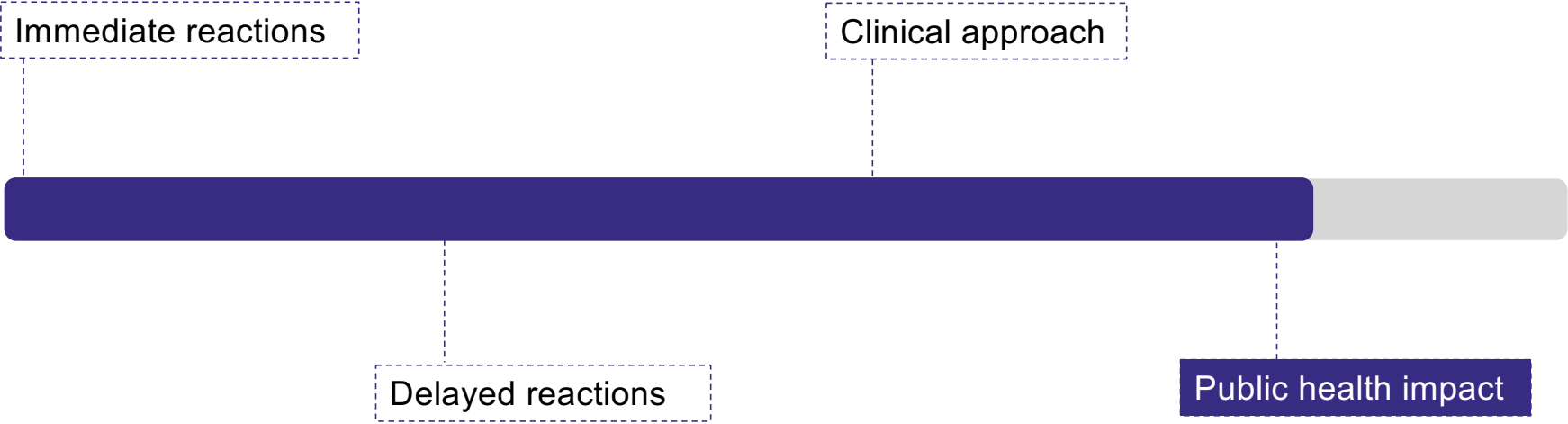
Clinical Approach to PEG Allergy



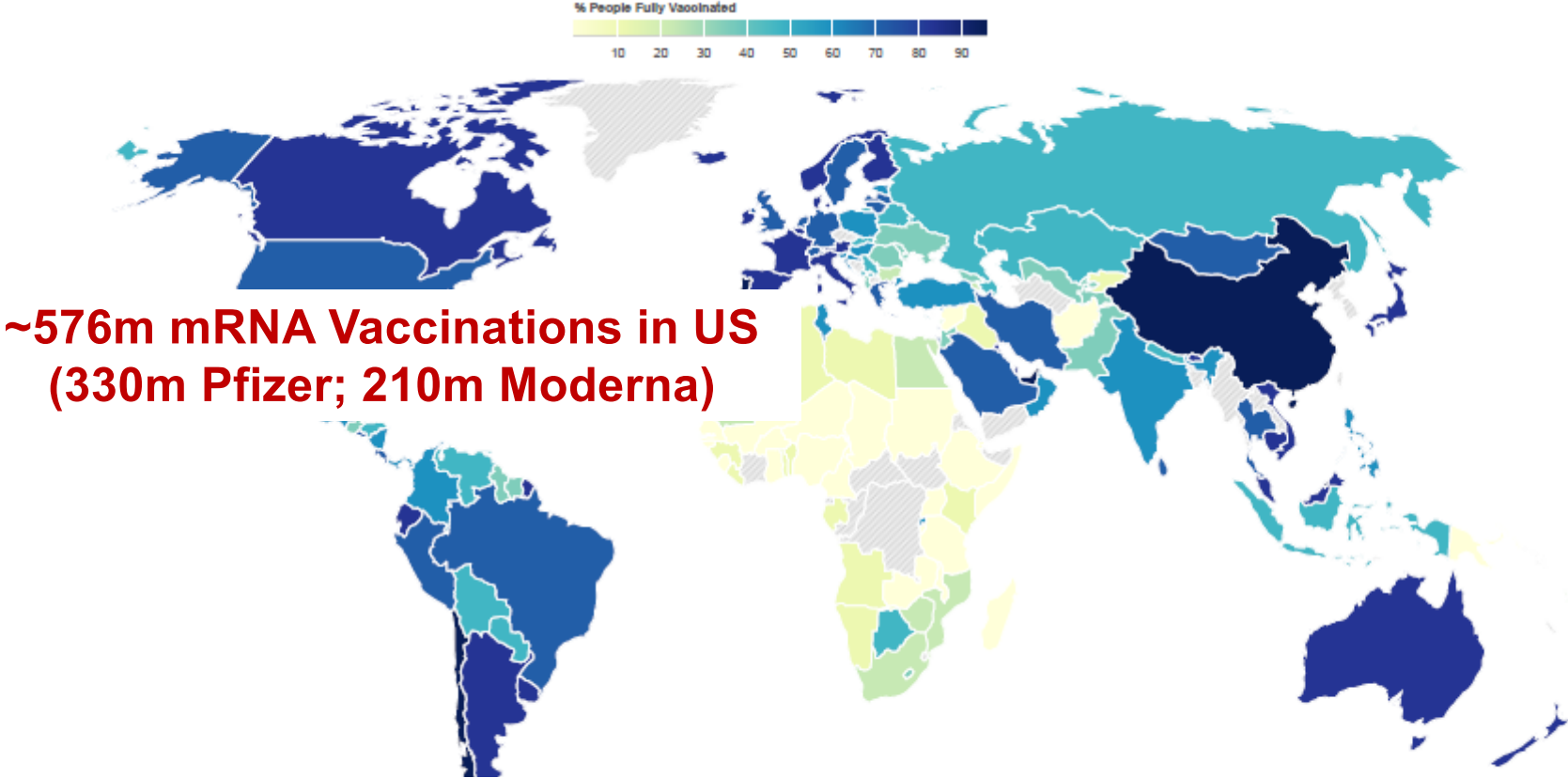
Clinical Approach to PEG Allergy



Roadmap



COVID-19 Vaccinations: >1 Billion Doses



<https://coronavirus.jhu.edu/vaccines/international>; https://covid.cdc.gov/covid-data-tracker/#vaccinations_vacc-total-admin-rate-total, as of March 22, 2022

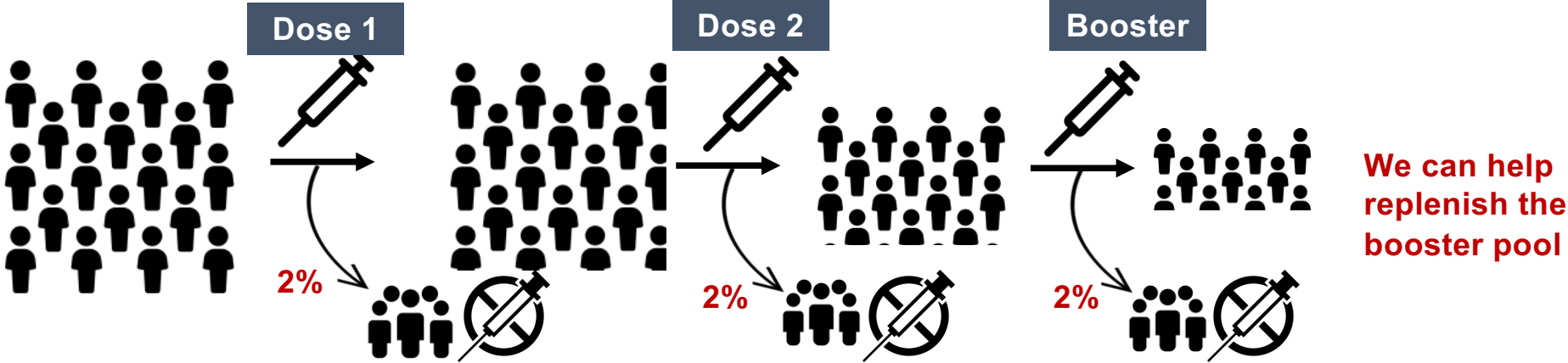
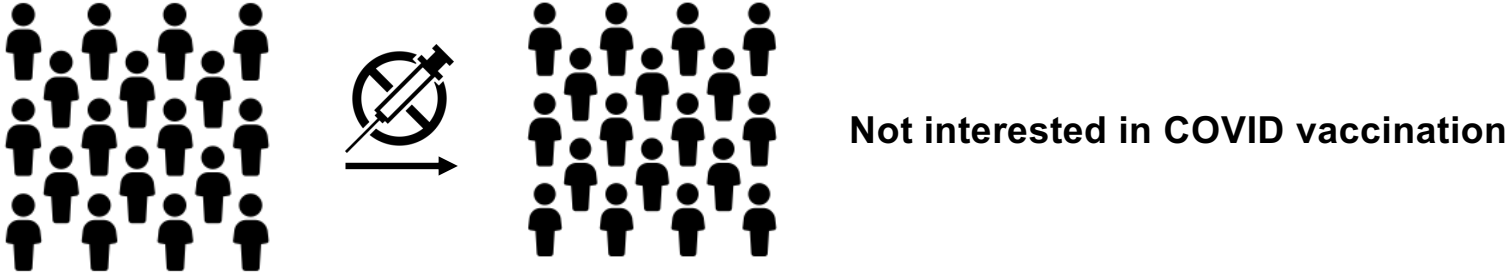
Allergic Symptoms & Incomplete Vaccination

- Incomplete vaccination in 348 (0.7%) MGB employees

Incomplete vaccination	No reported allergic symptoms	Allergic symptoms (Any)	Allergic symptoms (Severe)
Number of events (%)	305 (0.6%)	43 (3%)	6 (1.7%)
Unadjusted	1.00 (ref)	5.68 (4.11-7.85)	23.2 (9.7-55.2)
Adjusted	1.00 (ref)	5.15 (3.75-7.06)	--

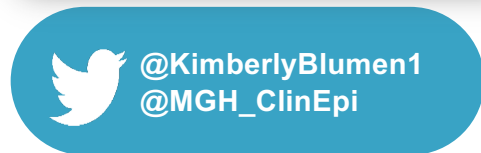
- Healthcare workers, 576 (46%) received allergy/immunology consultation → “best case” scenario
- 21% of individuals with treated allergic reactions at Kaiser failed to get a second dose

Diminishing Pool Eligible for Booster Vaccination



Robinson JAMA Dermatol 2021; Macy J Allergy Clin Immunol Pract 2021

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