

Allergie et vaccins anticoronavirus : les **connaissances** actuelles



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Sommaire

- Mécanismes d'infection de Sars-Cov2
- Les stratégies vaccinales en cours
- Allergie/anaphylaxie
- Diagnostic de l'allergie aux vaccins mRNA
- Induction de tolérance des personnes allergiques
- Feedback formulaires online coronavax

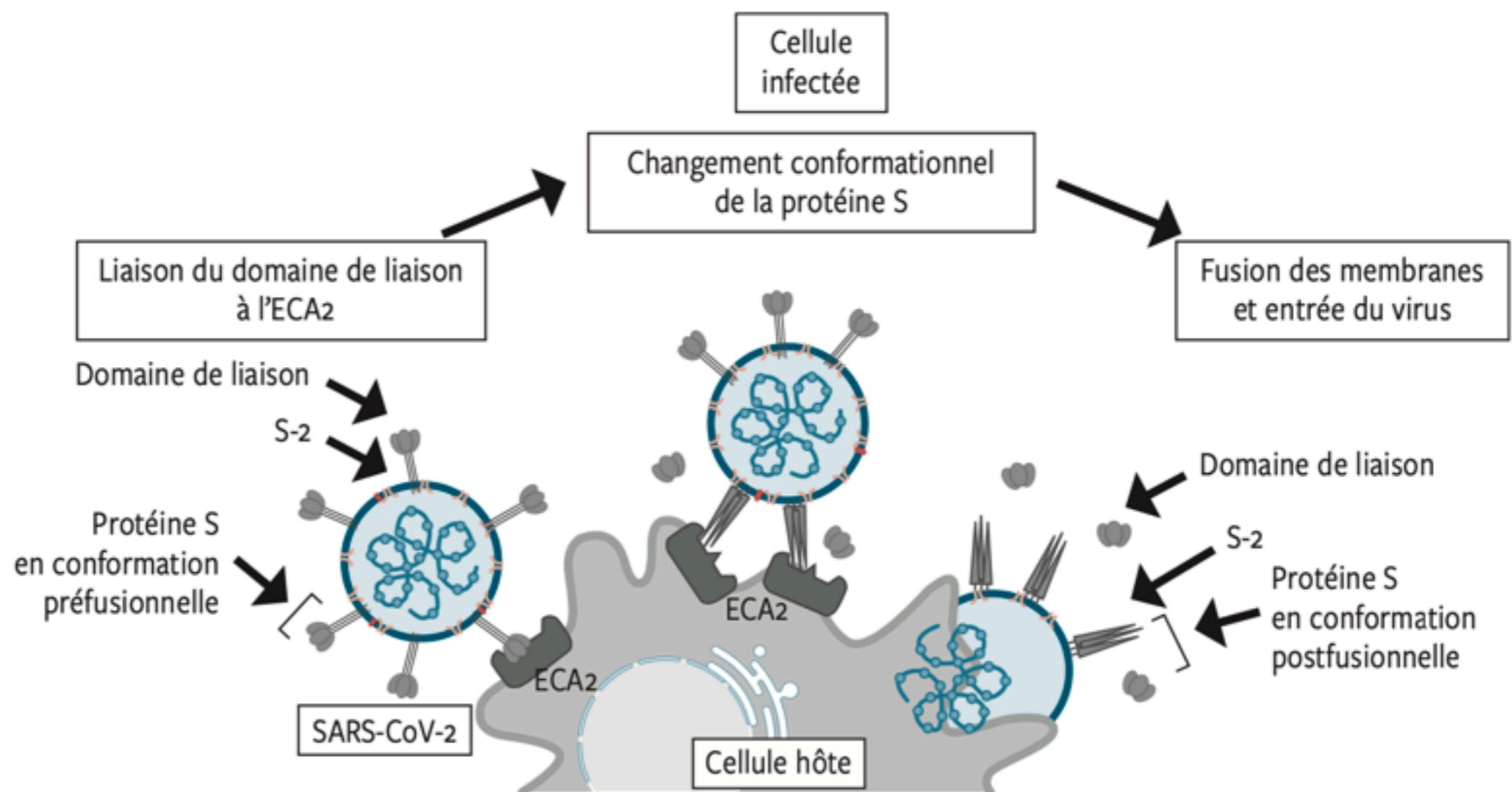
Coronavirus

FIG 1

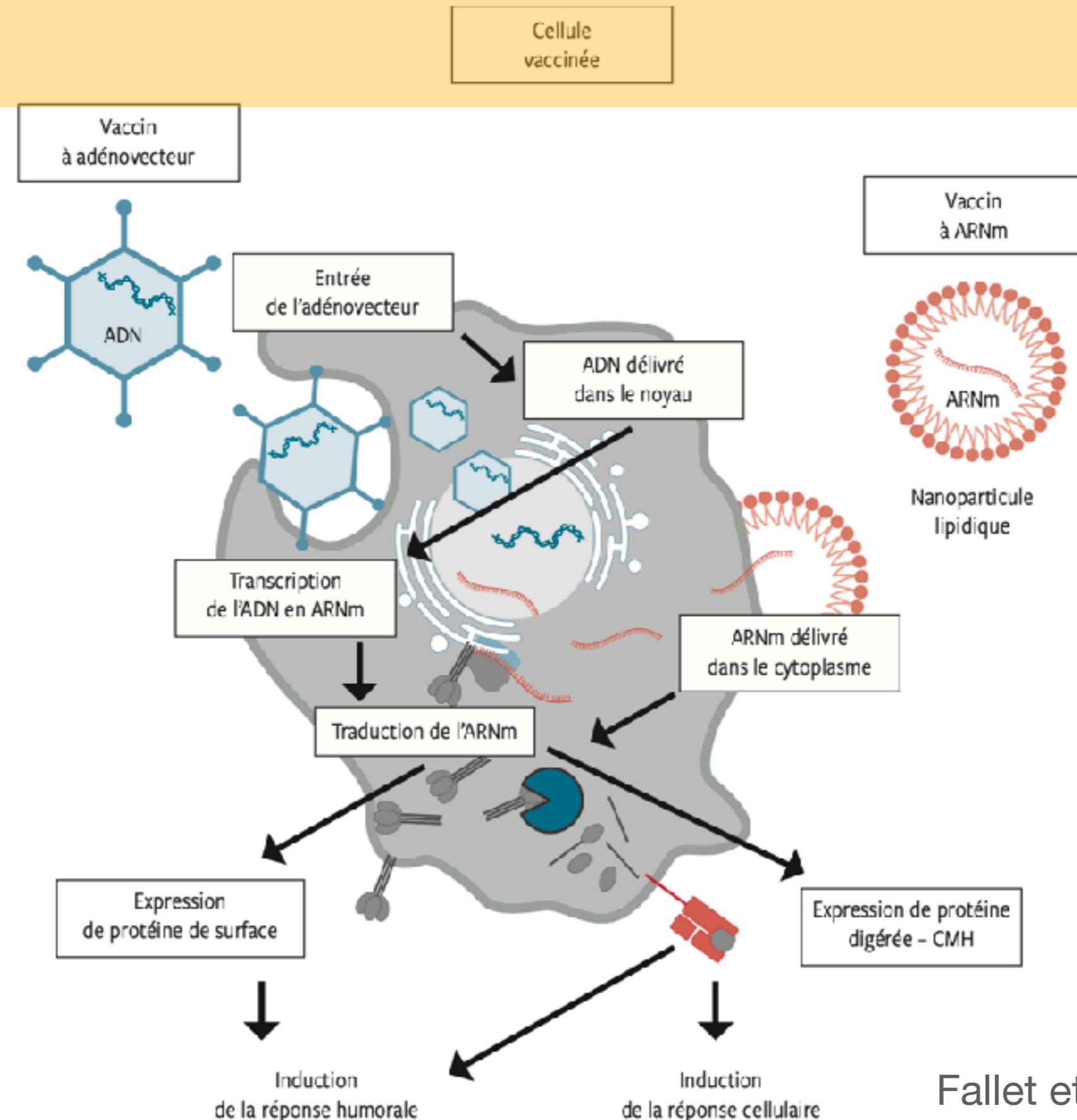
Infection d'une cellule hôte par le SARS-CoV-2

Les principales étapes de l'entrée du virus dans une cellule hôte sont schématisées.

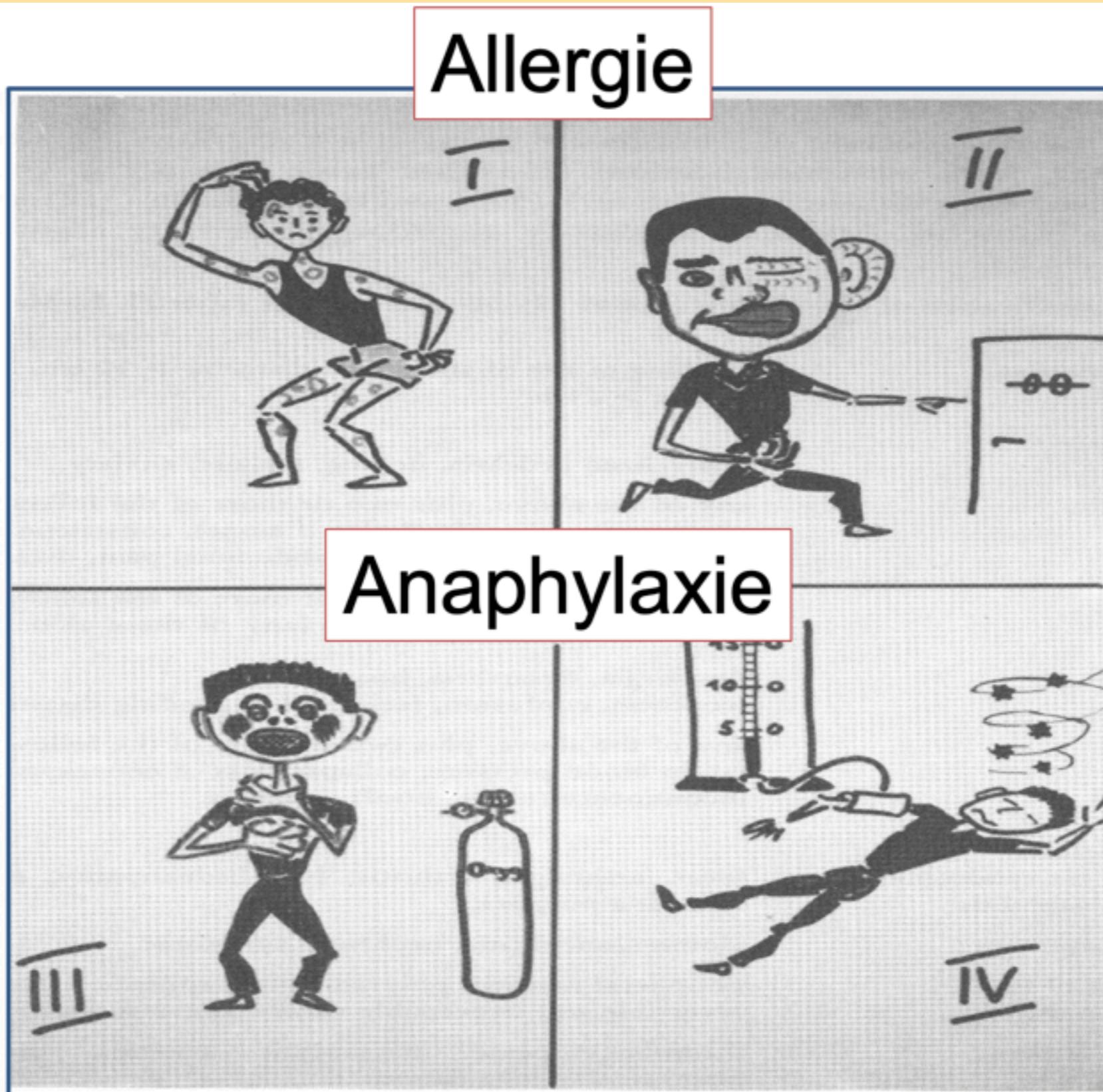
ECA2: enzyme de conversion de l'angiotensine 2; protéine S: protéine de surface; S-2: sous-unité S-2 de la protéine de surface.



Vaccin mRNA de quoi on parle?



Allergie/Anaphylaxie



Adapté de:

Ulrich R. Mueller
Insect Sting Allergy: Clinical Picture, Diagnosis and Treatment

Gustav Fischer
Stuttgart, New York, 1990

Vaccin et allergie : épidémiologie

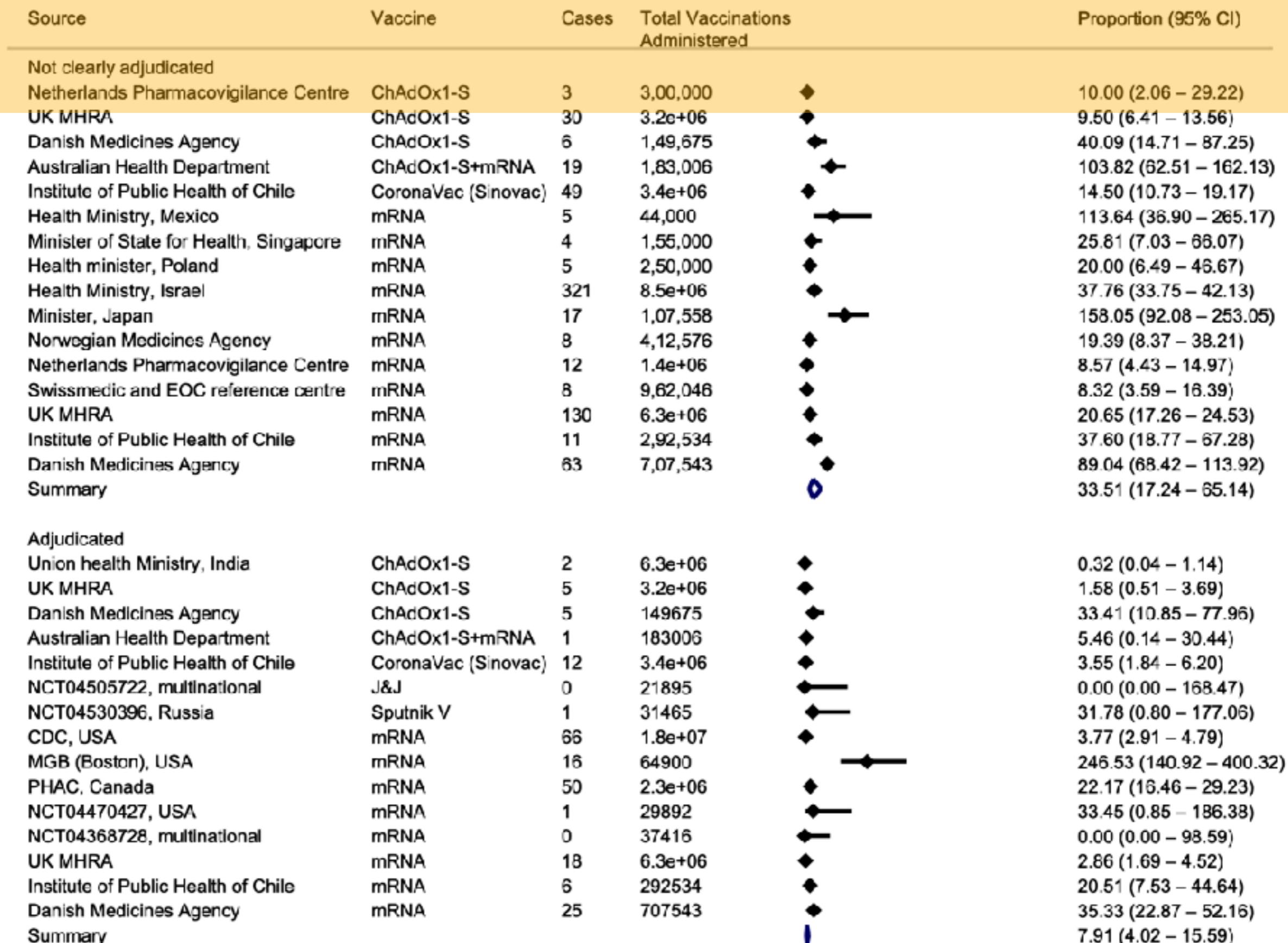
Table. Characteristics of Reported Cases of Anaphylaxis Following Receipt of Pfizer-BioNTech (9 943 247 Doses) and Moderna (7 581 429 Doses) COVID-19 Vaccines—Vaccine Adverse Events Reporting System (VAERS), US, December 14, 2020-January 18, 2021

Characteristics	No. (%) of cases	
	Pfizer-BioNTech (n = 47)	Moderna (n = 19)
Age, median (range), y	39 (27-63) ^a	41 (24-63)
Female sex	44 (94)	19 (100)
Minutes to symptom onset, median (range)	10 (<1-1140 [19 h]) ^b	10 (1-45)
Symptom onset, min		
≤15	34 (76) ^b	16 (84)
≤30	40 (89) ^b	17 (89)
Reported history ^c		
Allergies or allergic reactions	36 (77)	16 (84)
Prior anaphylaxis	16 (34)	5 (26)
Vaccine dose		
First	37	17
Second	4	1
Unknown	6	1
Brighton Collaboration case definition level ^d		
1	21 (45)	10 (52)
2	23 (49)	8 (43)
3	3 (6)	1 (5)
Anaphylaxis reporting rate (cases per million doses administered)	4.7	2.5

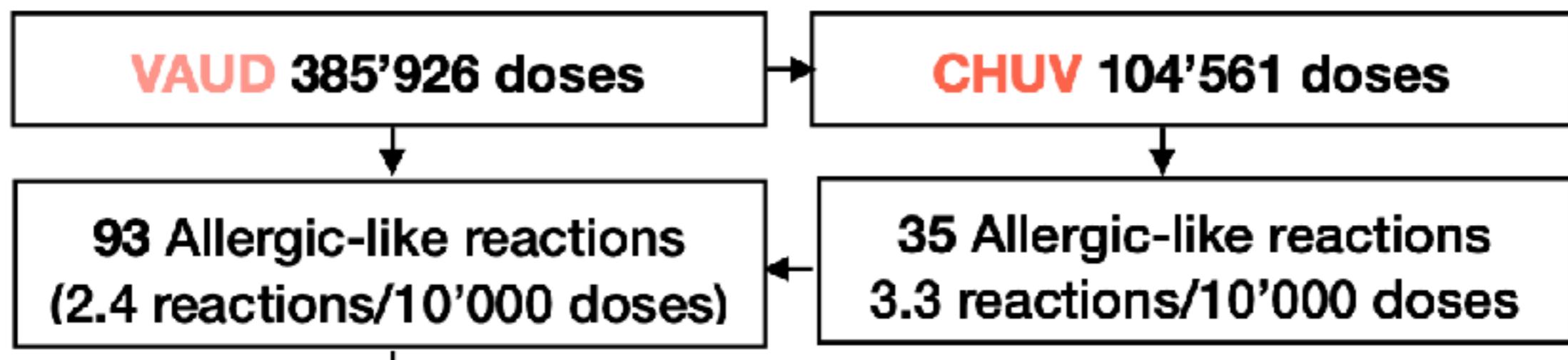
JAMA Insights

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

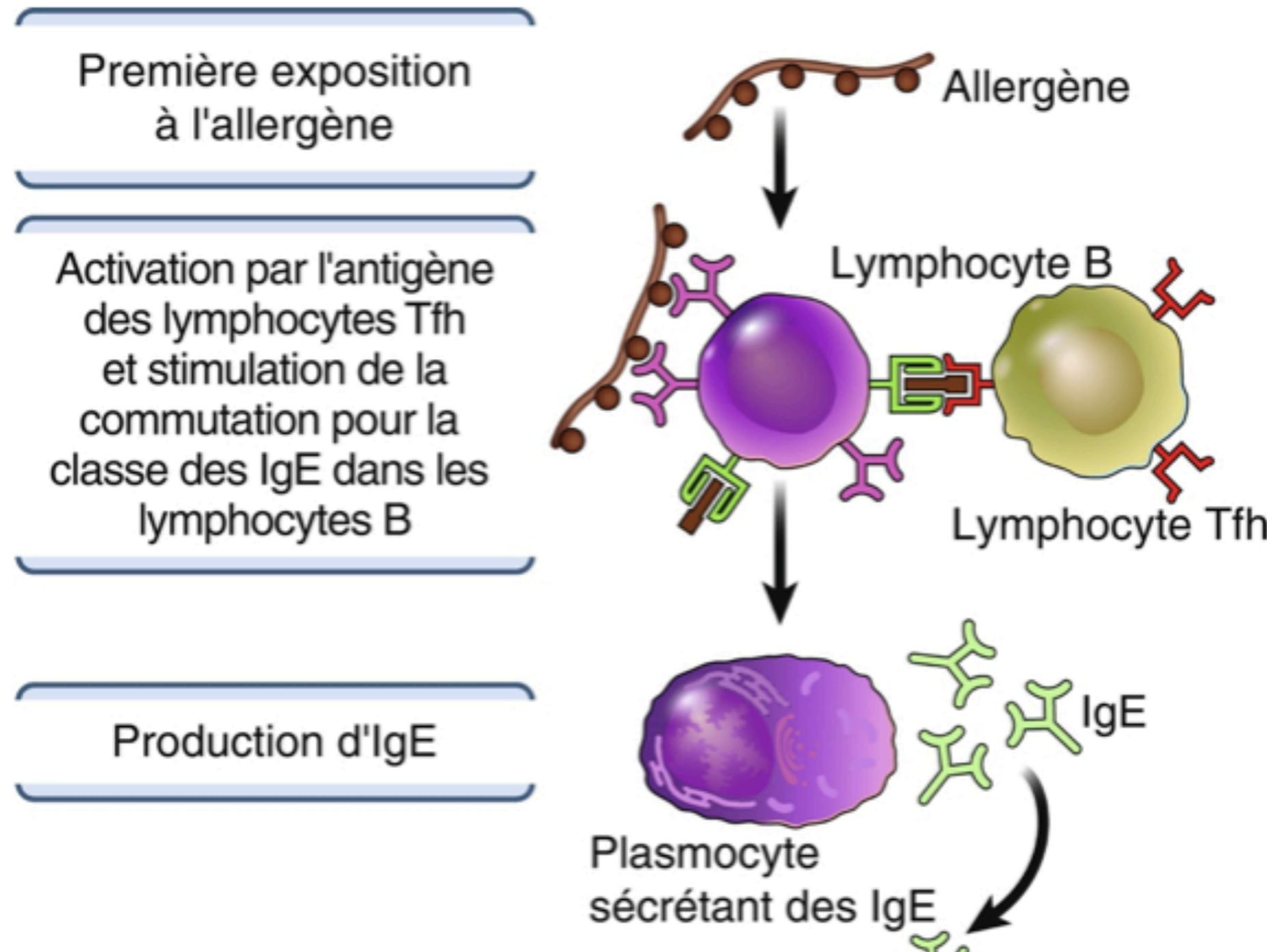
Vaccin et allergie : épidémiologie



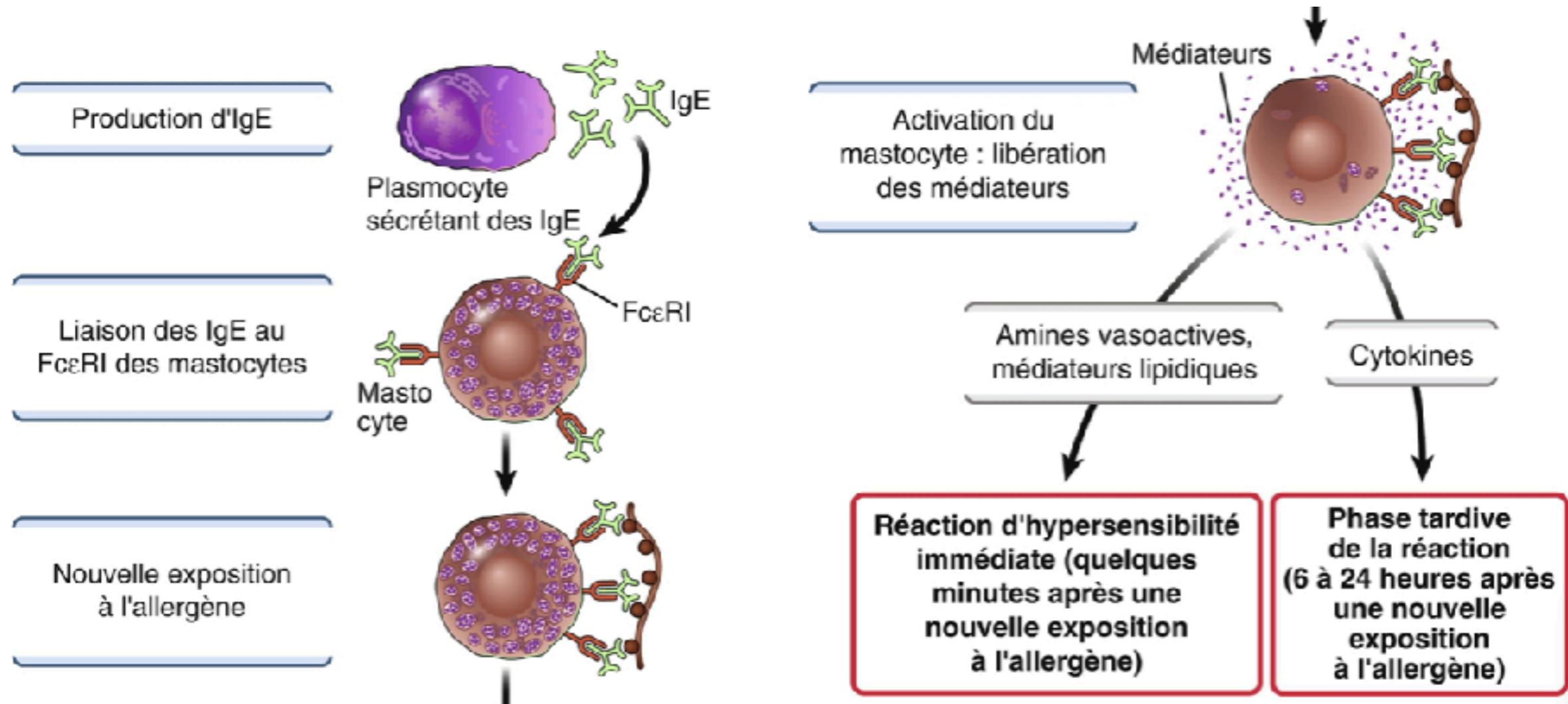
Vaccin et allergie : épidémiologie



Allergie: hypersensibilité IgE, type 1



Allergie: hypersensibilité IgE, type 1

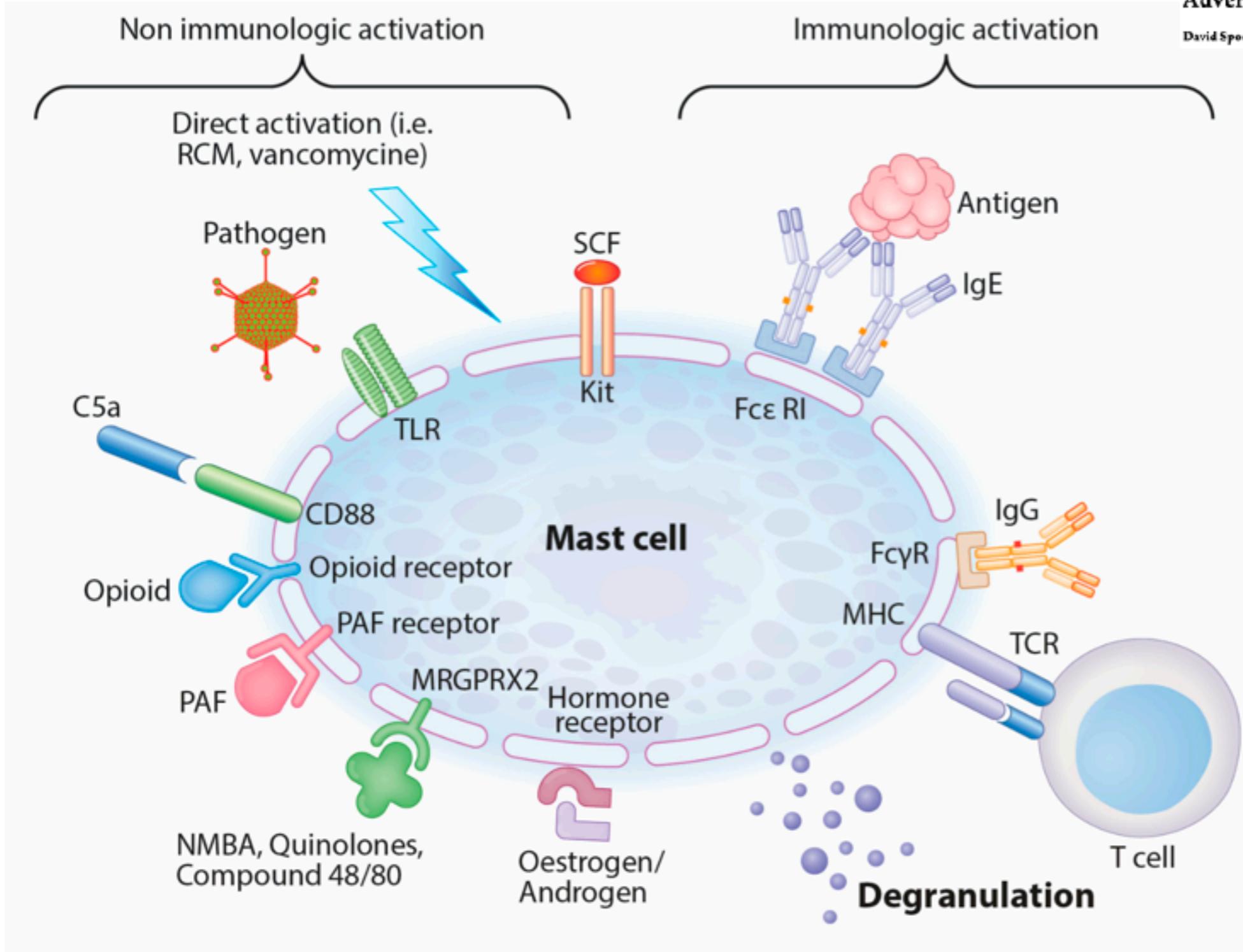


Allergie: hypersensibilité IgE, type 1

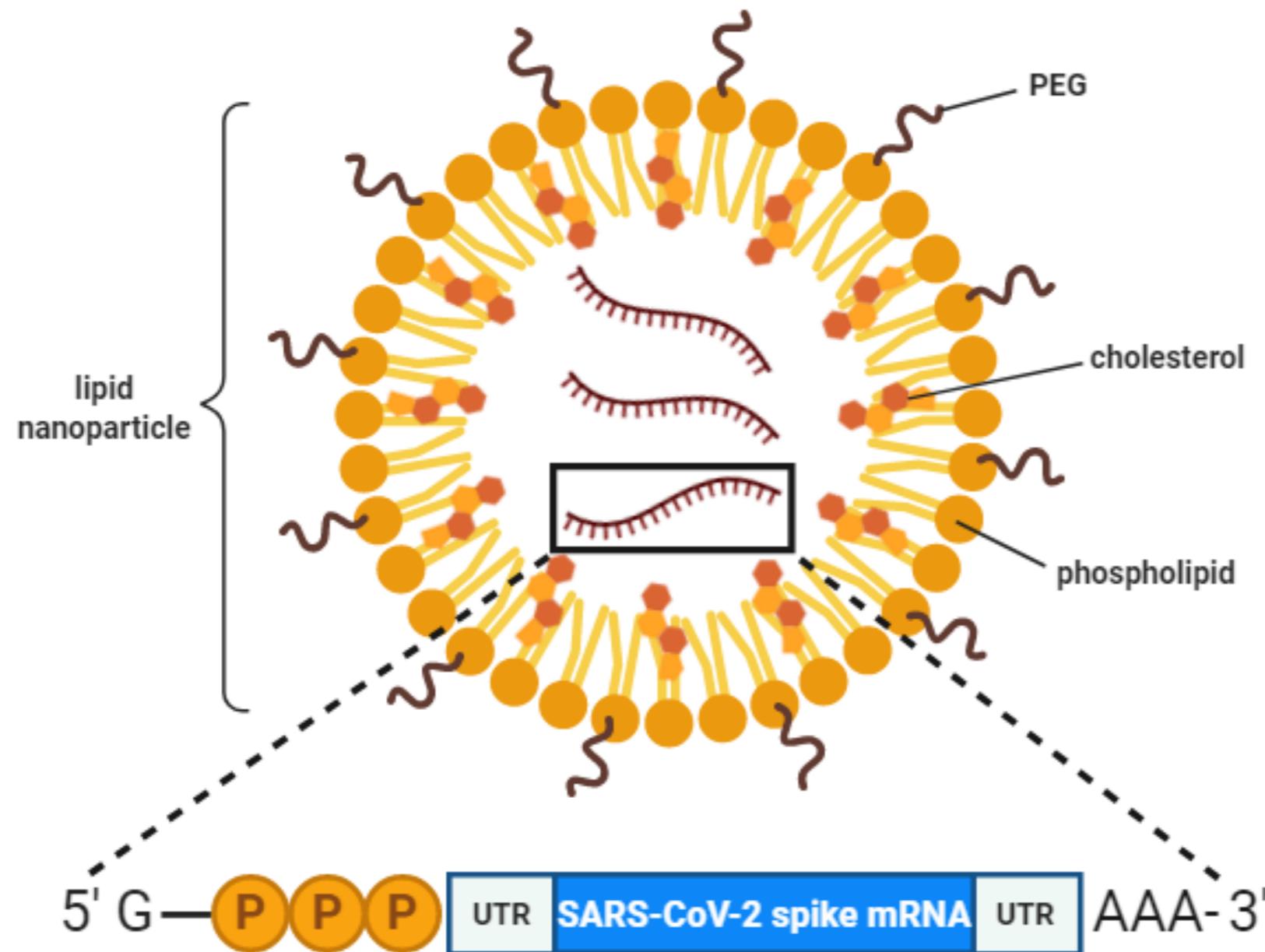
Review

Reclassifying Anaphylaxis to Neuromuscular Blocking Agents Based on the Presumed Patho-Mechanism: IgE-Mediated, Pharmacological Adverse Reaction or "Innate Hypersensitivity"?

David Spoerl ^{1,*}, Haig Nigolian ¹, Christoph Czarnetzki ² and Thomas Herr ¹



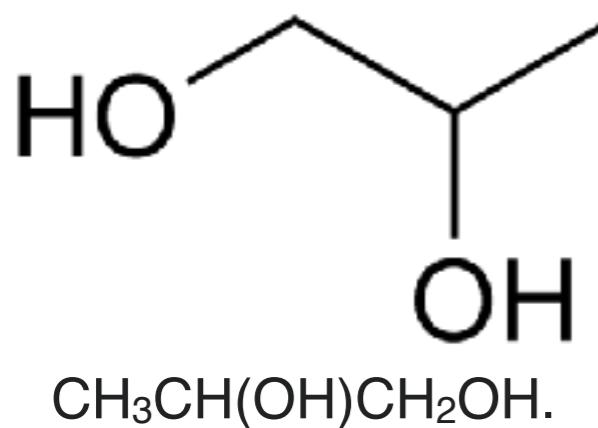
Allergie: hypersensibilité IgE, type 1



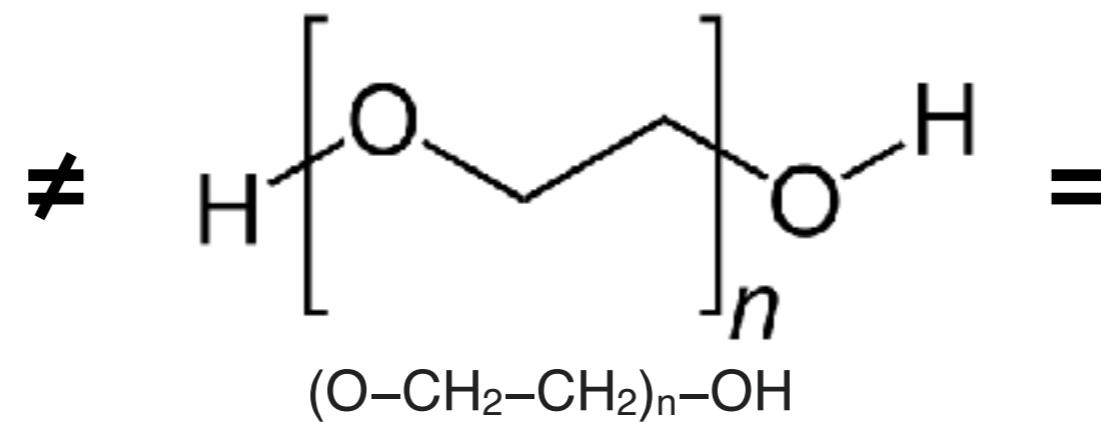
Allergie au PEG

De quoi on parle?

Propylene glycol



Polyethylene glycol



poly(oxyde d'éthylène)
poly(oxyéthylène)
PEG
Macrogol

PEG

- MW d'un monomère d'éthylene oxide est 44g/mol
- Taille des chaines PEG varie entre 200 to 35 000 g/mol
- Utilisé comme épaississant/gélifiant dans les cosmétiques (savon/crème/shampoing)
- Utilisé comme additif alimentaire
- Utilisé dans les gels hydroalcooliques
- Utilisé dans de nombreuses formulations parentérales
- Utilisé comme laxatif

Allergie au PEG

De quoi on parle?

Allergie PEG et aux laxatifs

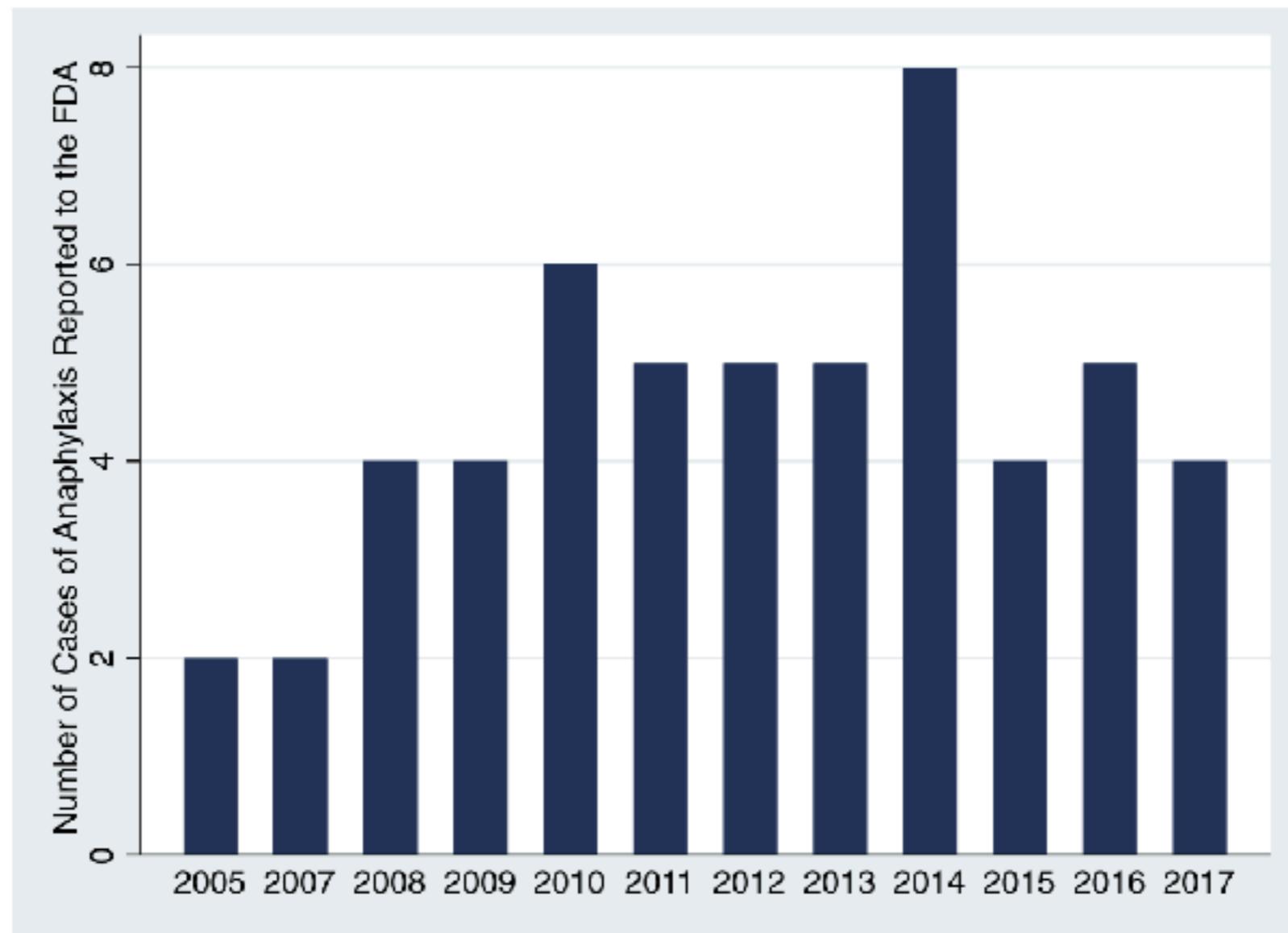
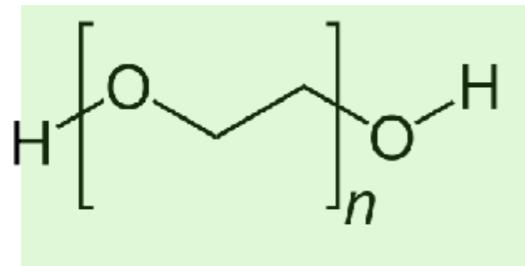


FIGURE 4. Cases of anaphylaxis reported to the FDA (FAERS) implicating PEG containing bowel preparations or laxatives, by year.
FAERS, FDA Adverse Event Reporting System; FDA, US Food and Drug Administration; PEG, polyethylene glycol.

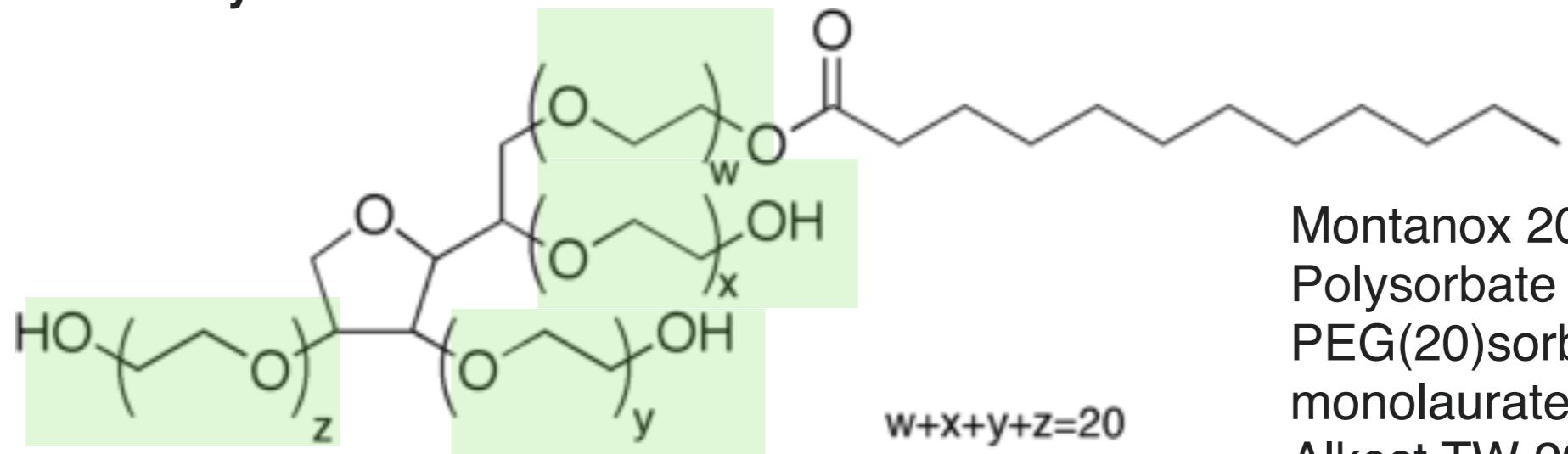
Allergie au PEG

De quoi on parle?

Polyethylene glycol

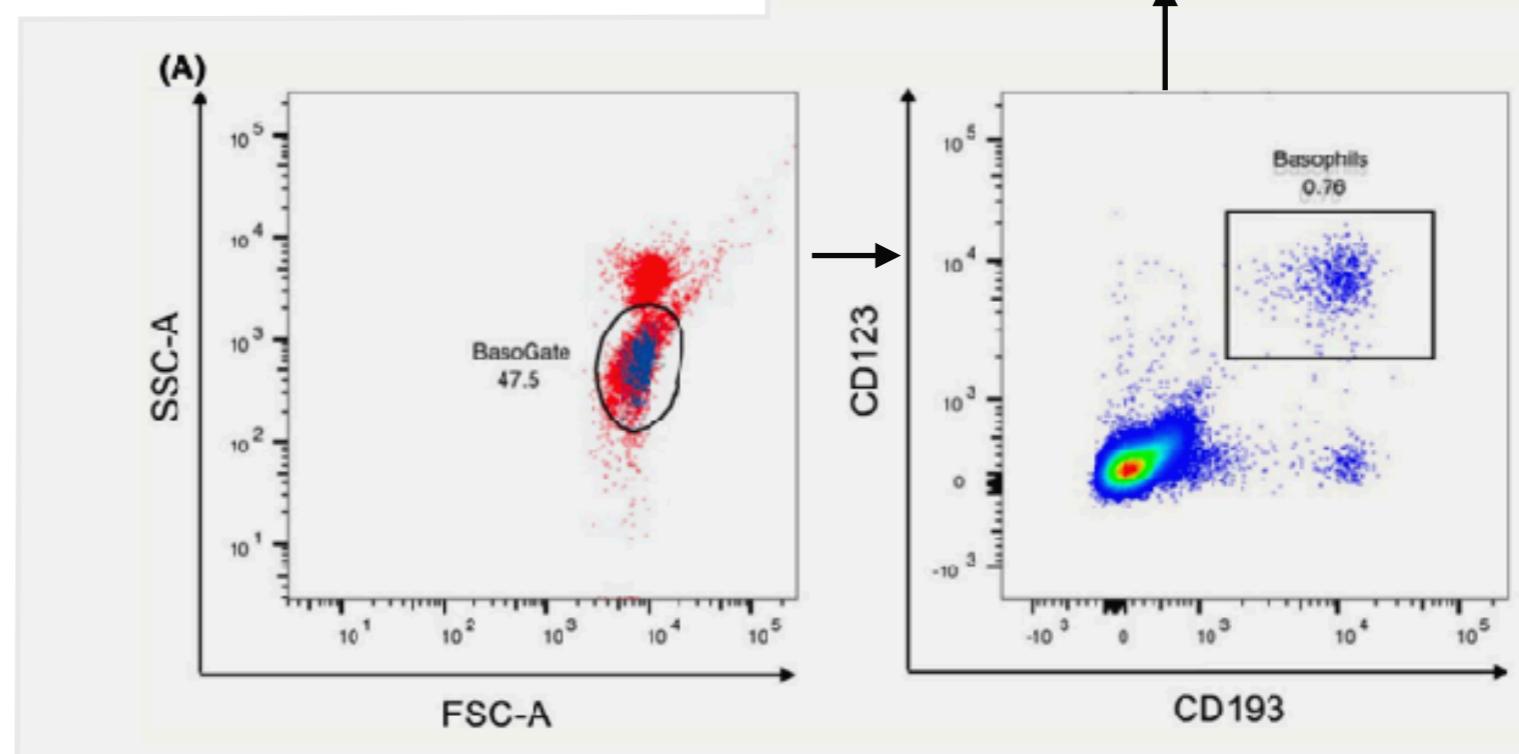
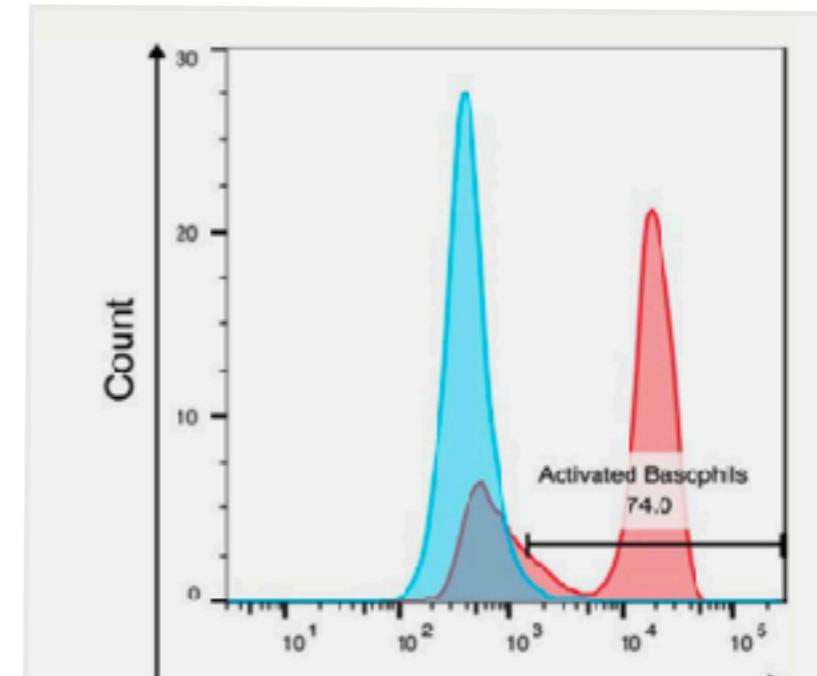
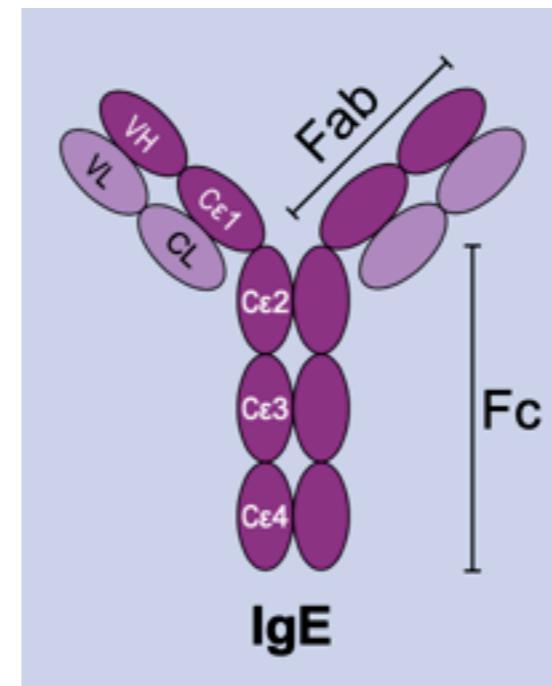
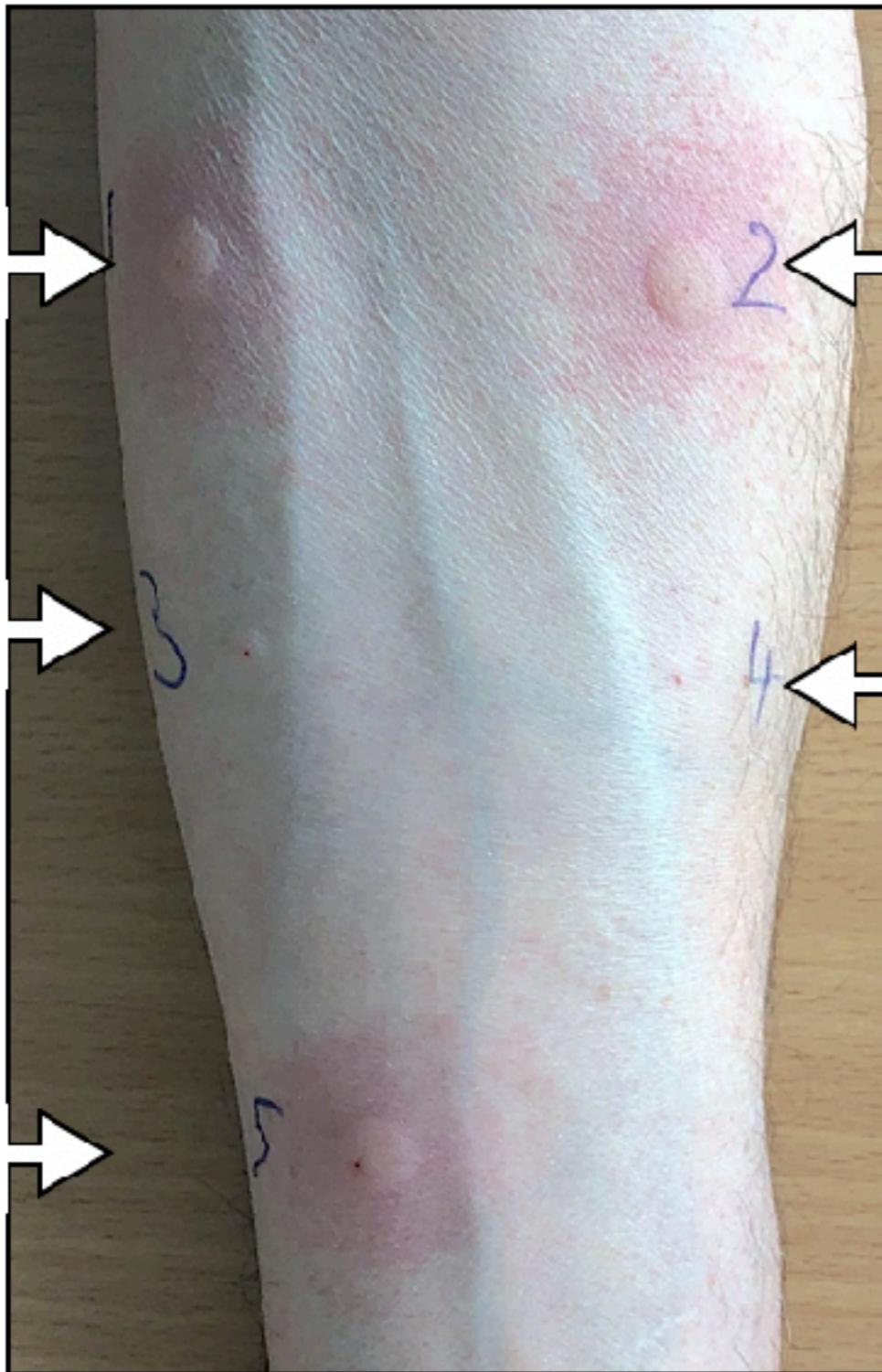


Polysorbate



Montanox 20
Polysorbate 20
PEG(20)sorbitan monolaurate
Alkest TW 20
Tween 20

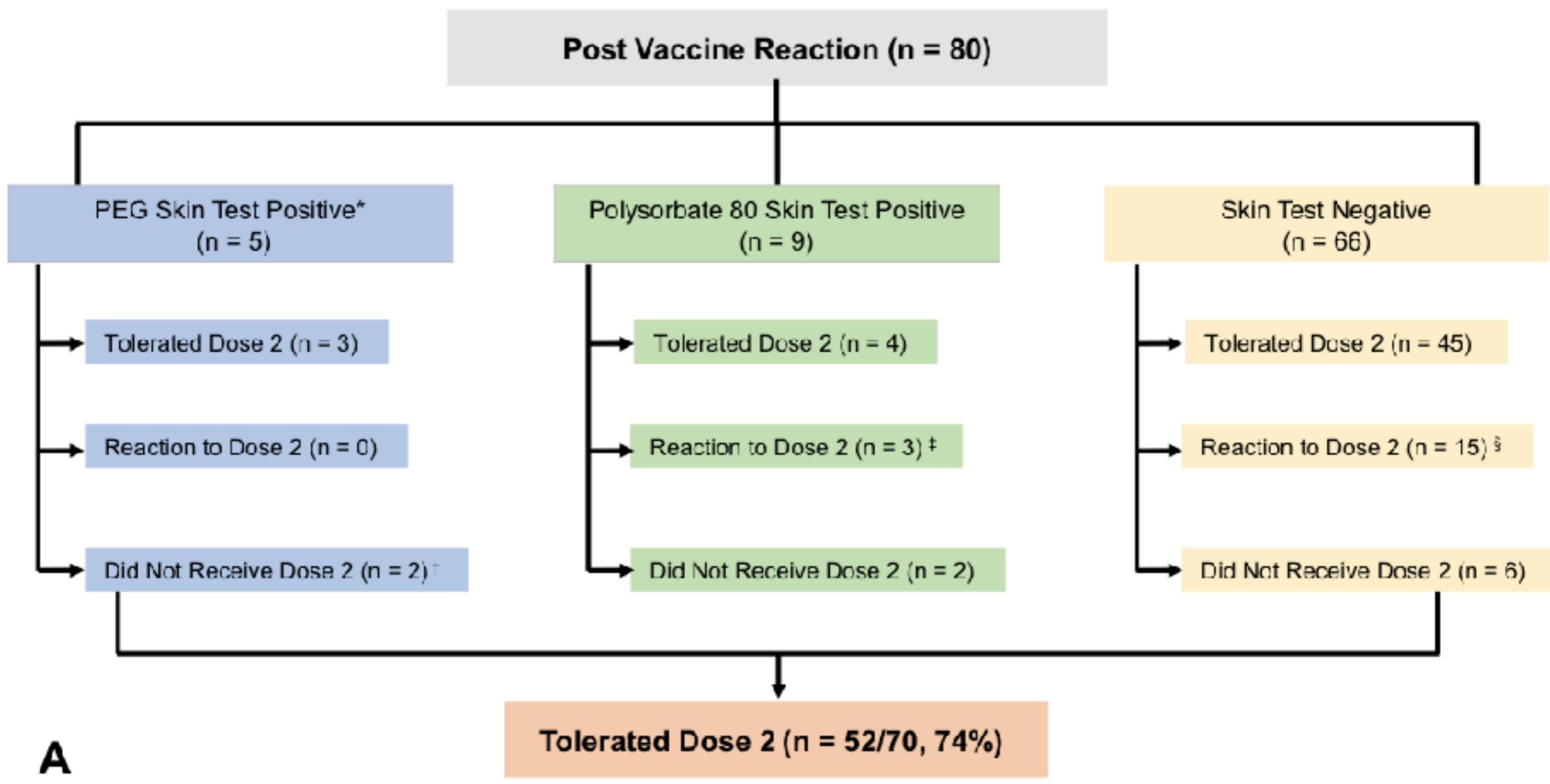
Allergologie: outils diagnostics

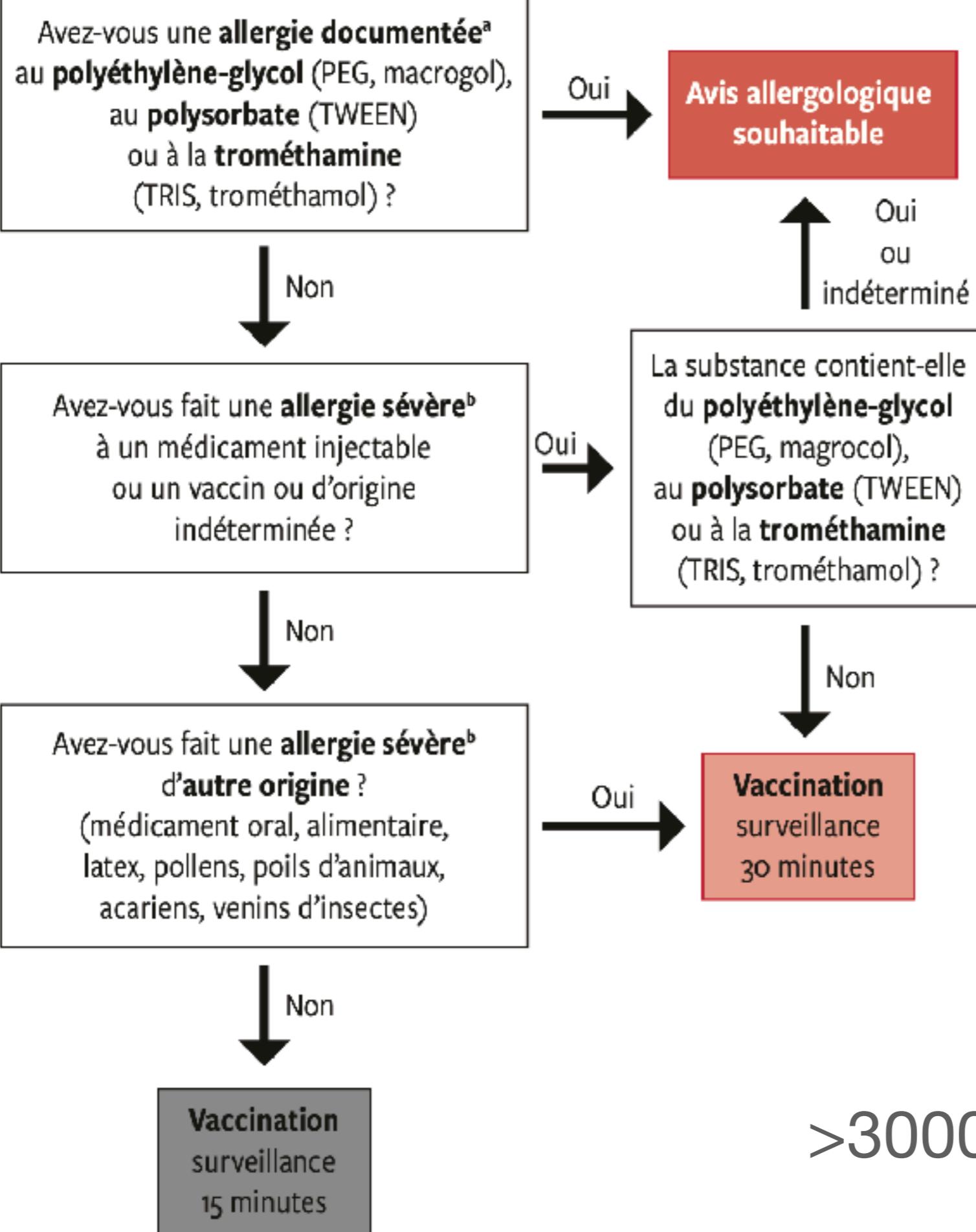


First-Dose mRNA COVID-19 Vaccine Allergic Reactions: Limited Role for Excipient Skin Testing



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}, Upika 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*





>3000 évaluations

2020

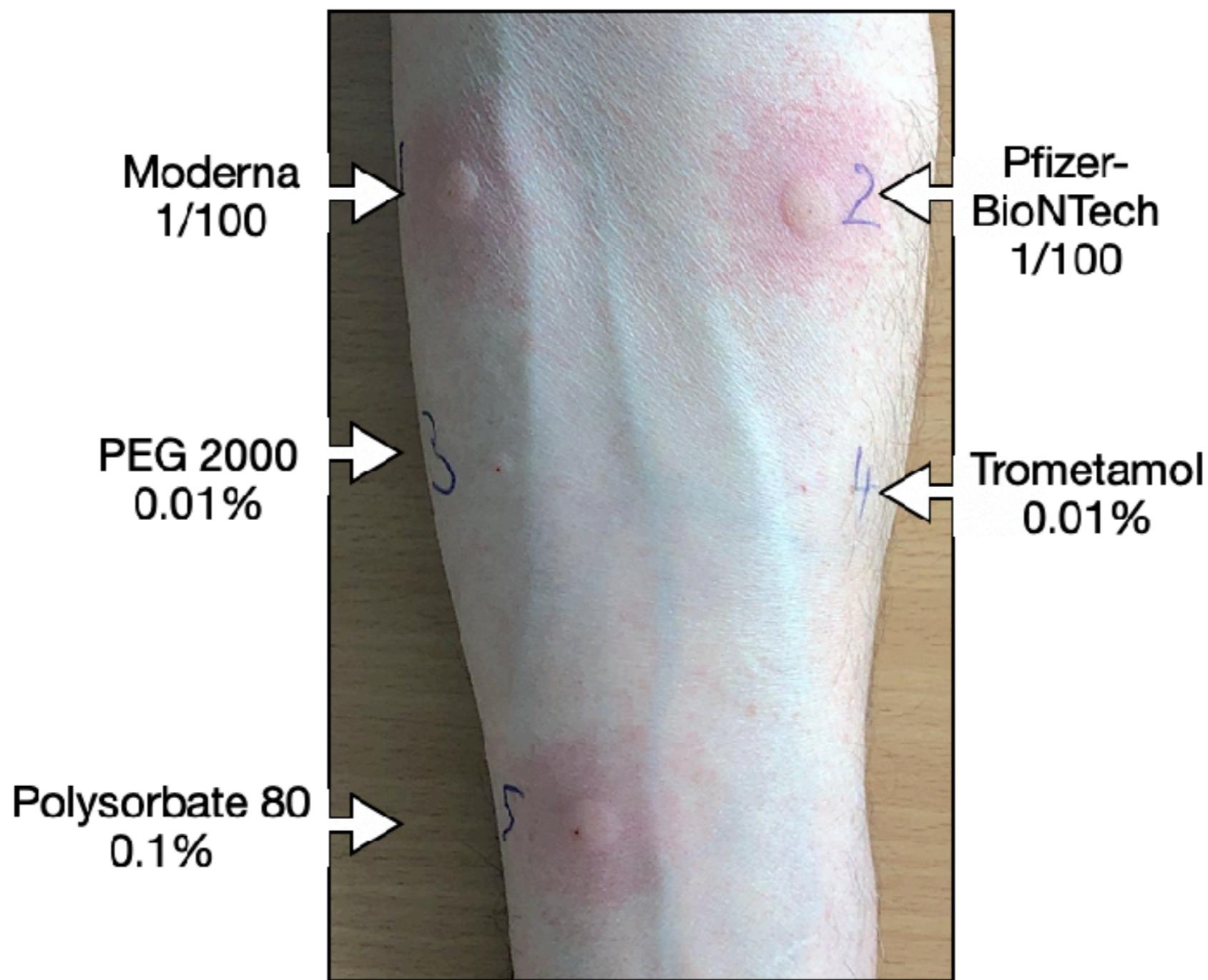
2021

+3 weeks

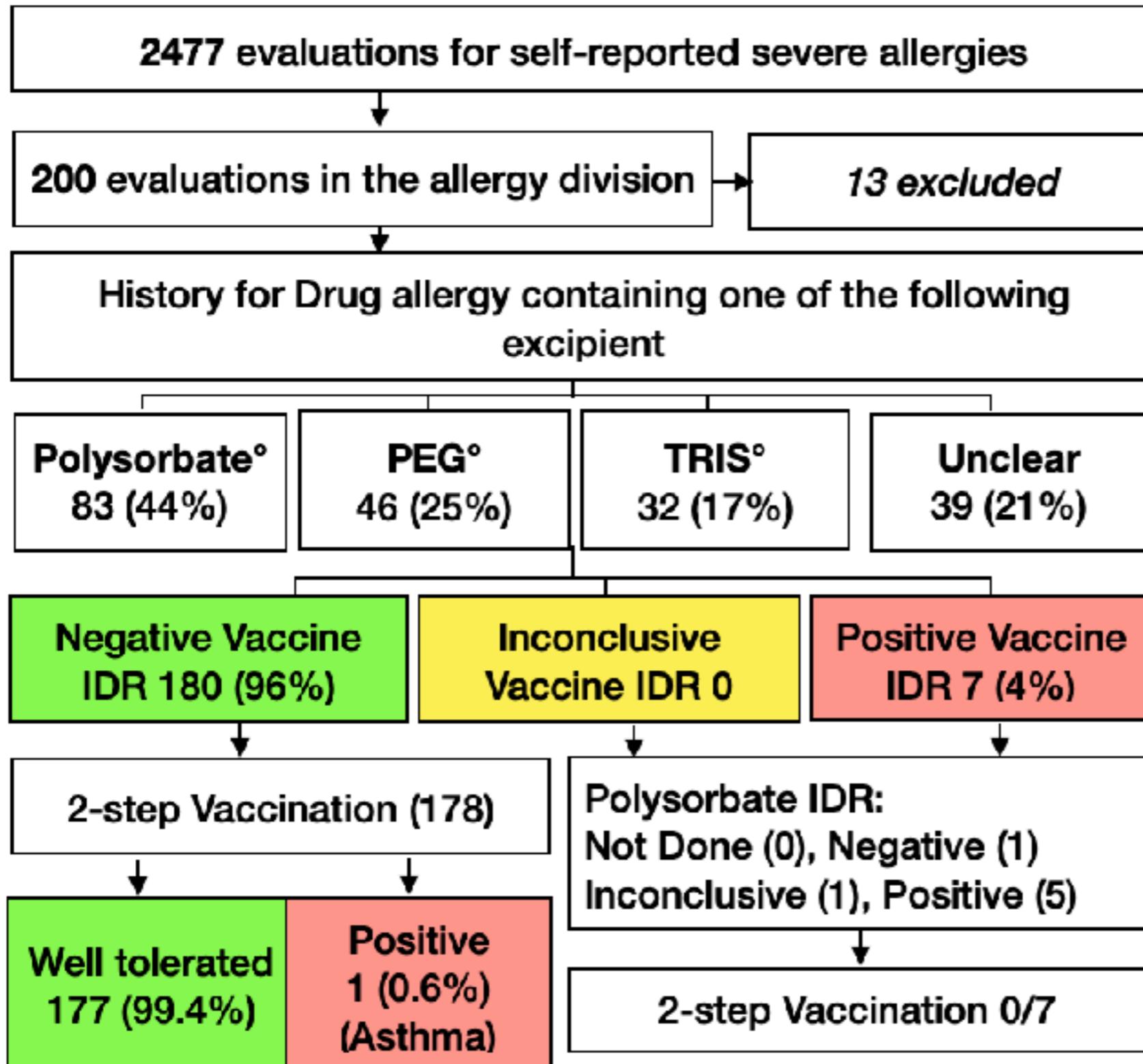
Anaphylaxis
to Plenvu

Skin tests

BAT



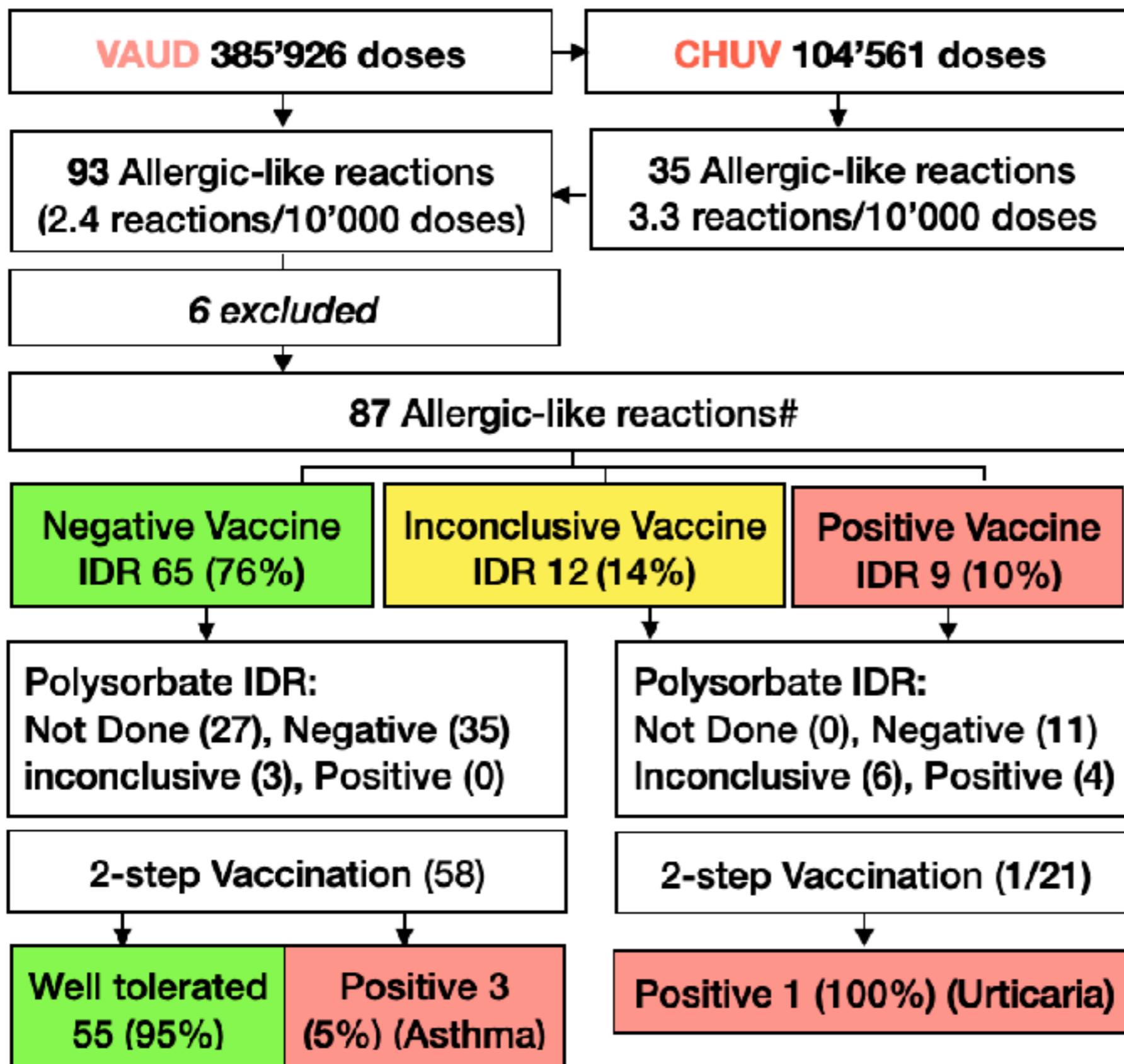
PRE-VACCINATION



°13 patients with history of allergy to >=2 different excipients

	Skin Tests Neg n= 180 (% or SD)	Skin Tests Pos n= 7 (% or SD)
Age (mean)	62.6 (+/-16.3)	62.7 (+/-11.7)
Female	140 (78%)	6 (85%)
Prior anaphylaxis	145/175 (83%)	6 (85%)
IDR with mRNA-1273	95/180 (53%)	7 (100%)
IDR with BNT162b2 mRNA	85 (47%)	7 (100%)
History of allergy with drugs containing:		
Polyethylene glycol	43 (24%)	3 (43%)
Polysorbate	81 (45%)	2 (29%)
Trométamol	30 (17%)	2 (29%)
Not defined	39 (22%)	0

POST-VACCINATION



1 patient excluded because of dermographism

Stehlin et al submitted

	Skin Tests Neg	Skin Tests Pos*	p value
Total of patients	65	21	
Age (mean +/-SD))	51.2(+/-15.1)	40.8 (+/-15.2)	<0.01
Female	57 (88%)	20 (95%)	ns
BNT-162b2 (%)	43 (66%)	3 (14%)	<0.01
Prior allergy sharing additives with vaccines	2 (3%)	1 (5%)	ns
Prior anaphylaxis	27 (41.5%)	7 (33%)	ns
Prior allergy (any)	60 (92%)	12 (57%)	<0.01
Normal Basal Tryptase	50/51 (98%)	19/19 (100%)	ns
Symptoms			ns
Cutaneous	53 (82%)	17(81%)	
Respiratory	22 (33%)	6 (29%)	
Digestive	7 (11%)	1 (5%)	
Cardiovascular	2 (3%)	1 (5%)	
Treatment			ns
AntiH1, Steroids only	50 (77%)	17 (81%)	
Autoresolutive	12 (19%)	4 (19%)	
Epinephrine	3 (5%)	0	
Timing			ns
Timing≤30 min	42 (65%)	11 (52%)	
Timing 30-60min	2 (3%)	0	
Timing>60min	21 (32%)	10 (48%)	
Anaphylaxis EAACI criteria	16 (25%)	2 (10%)	ns
Brighton Scale			ns
I	5 (8%)	2 (10%)	
II	9 (14%)	0	
III	1 (2%)	0	
No criteria	50 (77%)	19 (91%)	
Ring and Messmer Severity Scale			ns
I	40 (62%)	13 (62%)	
II	18 (28%)	8 (38%)	
III	7 (11%)	0	
IV	0	0	

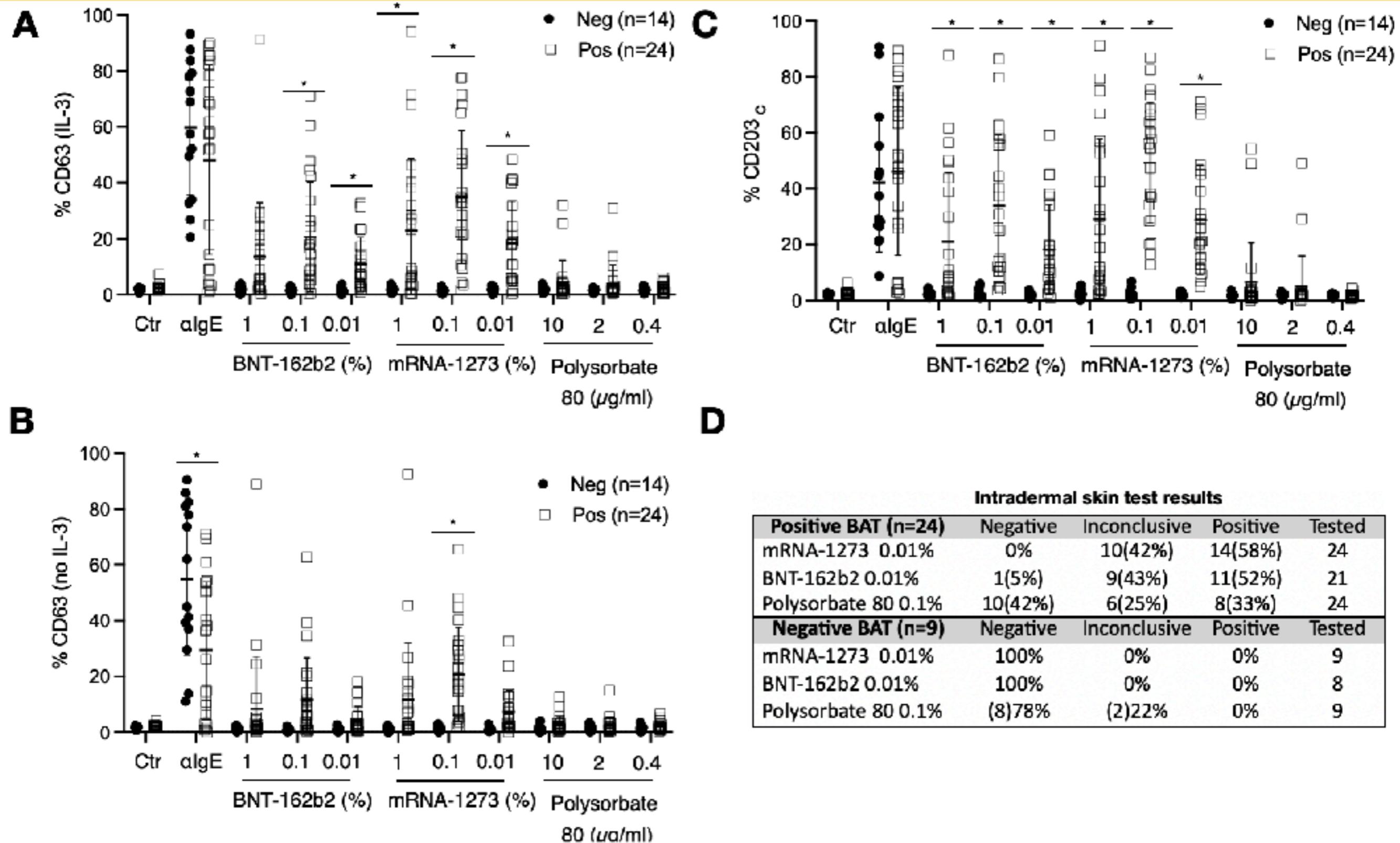
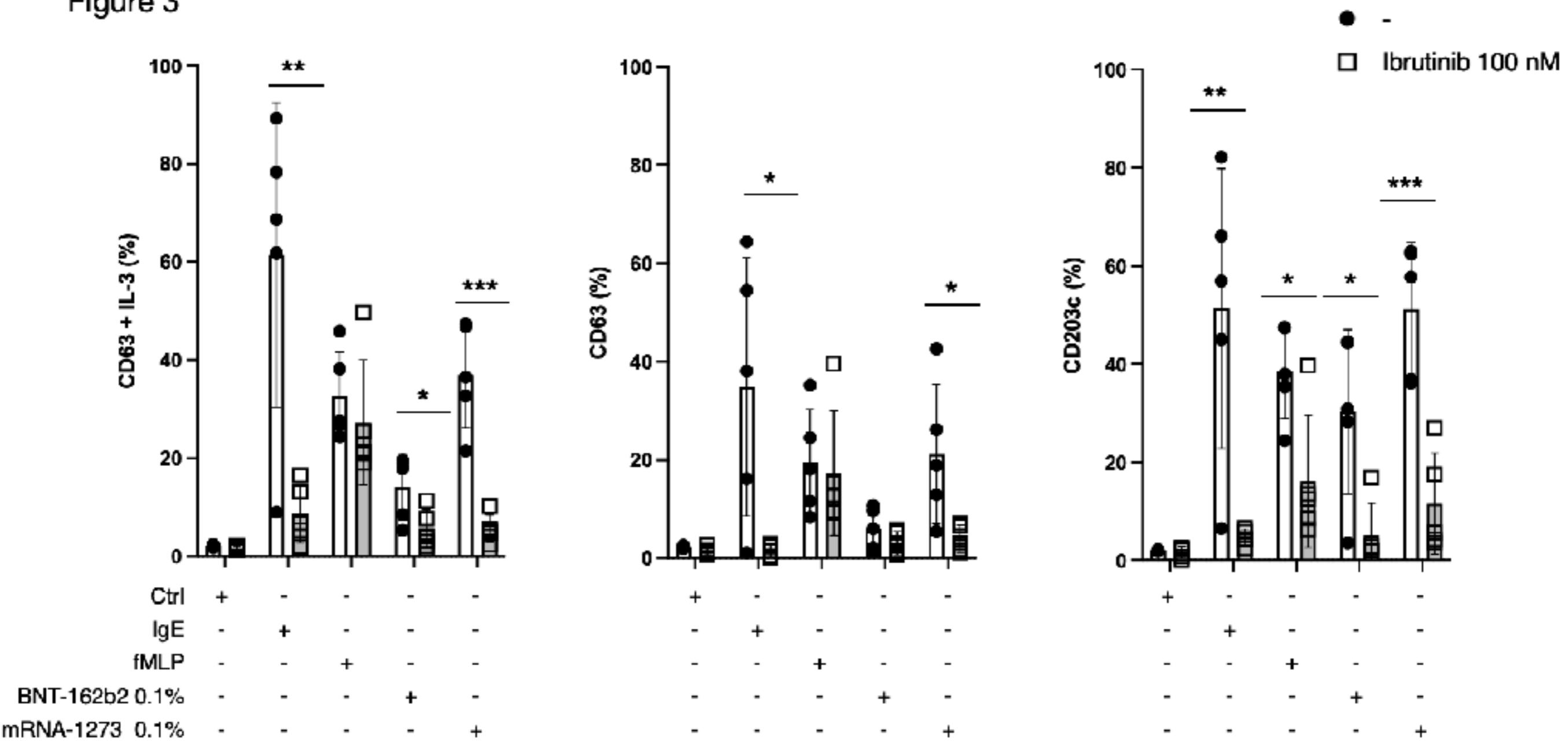


Figure 3



Allergie au PEG

IgG ou IgE

Anti-PEG IgE in anaphylaxis associated with polyethylene glycol

Zhao-Hua Zhou, PhD^a, Cosby A. Stone, Jr., MD, MPH^b,
Baruch Jakubovic, MD^c, Elizabeth J. Phillips, MD^b,
Gordon Sussman, MD^d, JuMe Park, MS^a,
Uyen Hoang, MS^a, Susan L. Kirshner, PhD^a,
Robert Levin, MD^e, and Steven Kozlowski, MD^a

Anticorps anti-PEG (IgG IgM and IgE) dans 1721 sera

- 5% to 9% positif pour anti-PEG IgG
- 3% to 6% positif pour anti-PEG IgM
- 0.1% positif pour anti-PEG IgE

Anticorps pré-existants: une explication pour les réactions anaphylactiques après la première exposition à un médicament

Allergie au PEG

IgG ou IgE

Anti-PEG IgE in anaphylaxis associated with polyethylene glycol

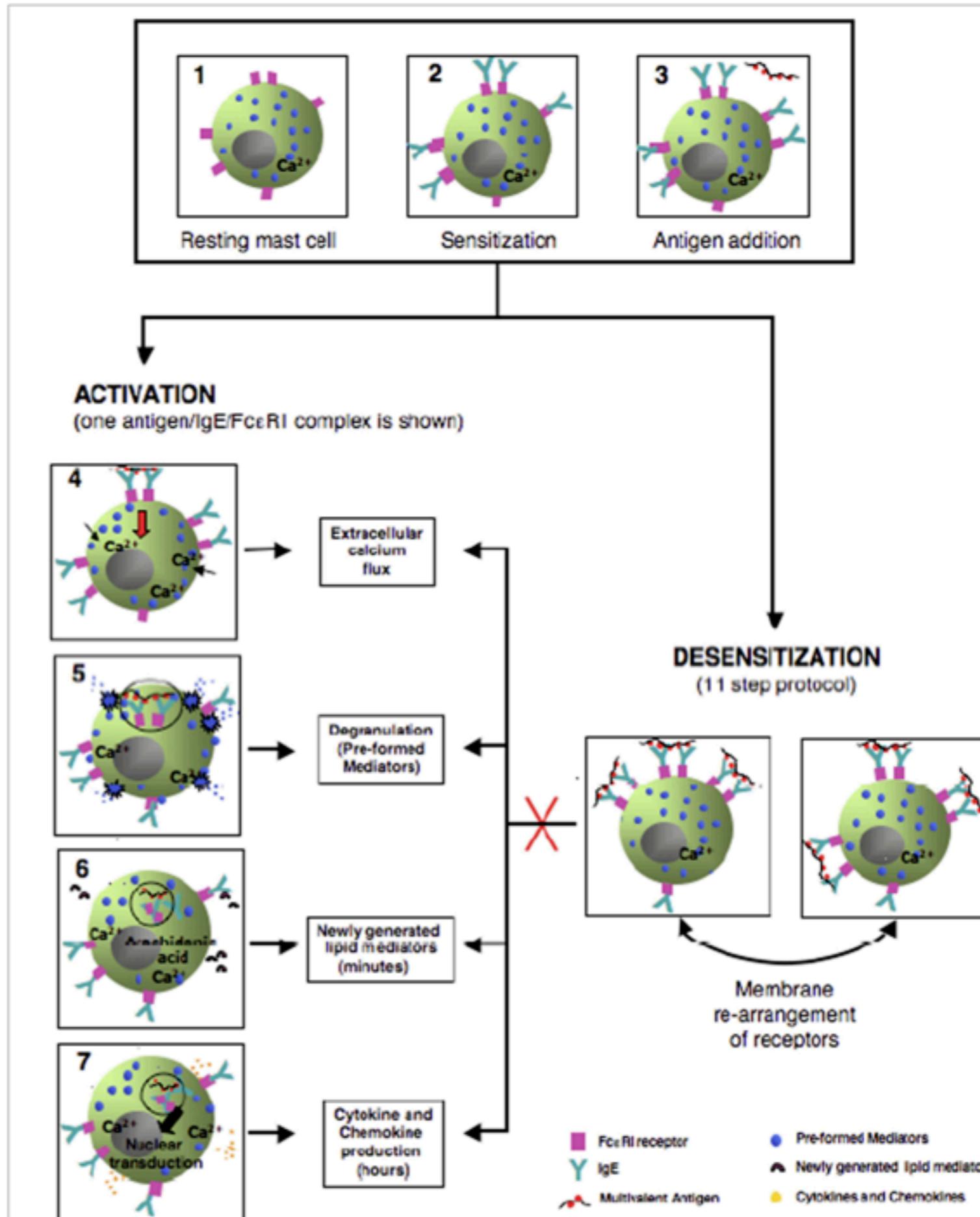
Zhao-Hua Zhou, PhD^a, Cosby A. Stone, Jr., MD, MPH^b, Baruch Jakubovic, MD^c, Elizabeth J. Phillips, MD^b, Gordon Sussman, MD^d, JuMe Park, MS^a, Uyen Hoang, MS^a, Susan L. Kirshner, PhD^a, Robert Levin, MD^e, and Steven Kozlowski, MD^a

TABLE I. Anti-PEG IgE and anti-PEG IgG in sera from cases and controls of PEG-associated anaphylaxis

Lab ID	Clinic	Anti-PEG IgE			Anti-PEG IgG		
		Positivity (Max MFI)	Titration	Inhibition	Positivity (Max MFI)	Titration	Inhibition
PEG1	Case	+++ (4,855)	>512	100%	++ (154,969)	>16,384	100%
PEG2	Case	+ (1,076)	>32	100%	++ (109,079)	>8,192	100%
PEG3	Control	+/- (295)	>4	ND	+ (39,826)	>2,048	100%
PEG4	Control	- (-86)		ND	- (130)	1	ND
PEG5	Control	- (0)		ND	- (4,603)	>1	ND
PEG6	Case	++ (493)	>90	100%	+++ (40,419)	>10,000	100%
PEG7	Case	++ (291)	>100	100%	+++ (78,647)	>10,000	100%
PEG8	Case	++ (1,800)	>90	100%	+ (29,494)	>2,500	100%
PEG9	Case	+ (4,058)	>30	100%	++ (160,690)	>6,000	100%

MFI, Median fluorescence intensity; ND, not done.

Note: Number of "+" was assigned on the basis of titer; for IgE, a titer >30 is +, >90 is ++, and >512 is +++; for IgG, a titer >2,000 is +, >6,000 is ++, and >10,000 is +++. Max MFI is the maximum difference in target and control beads. Titer is the dilution where target-control bead MFI becomes flat.



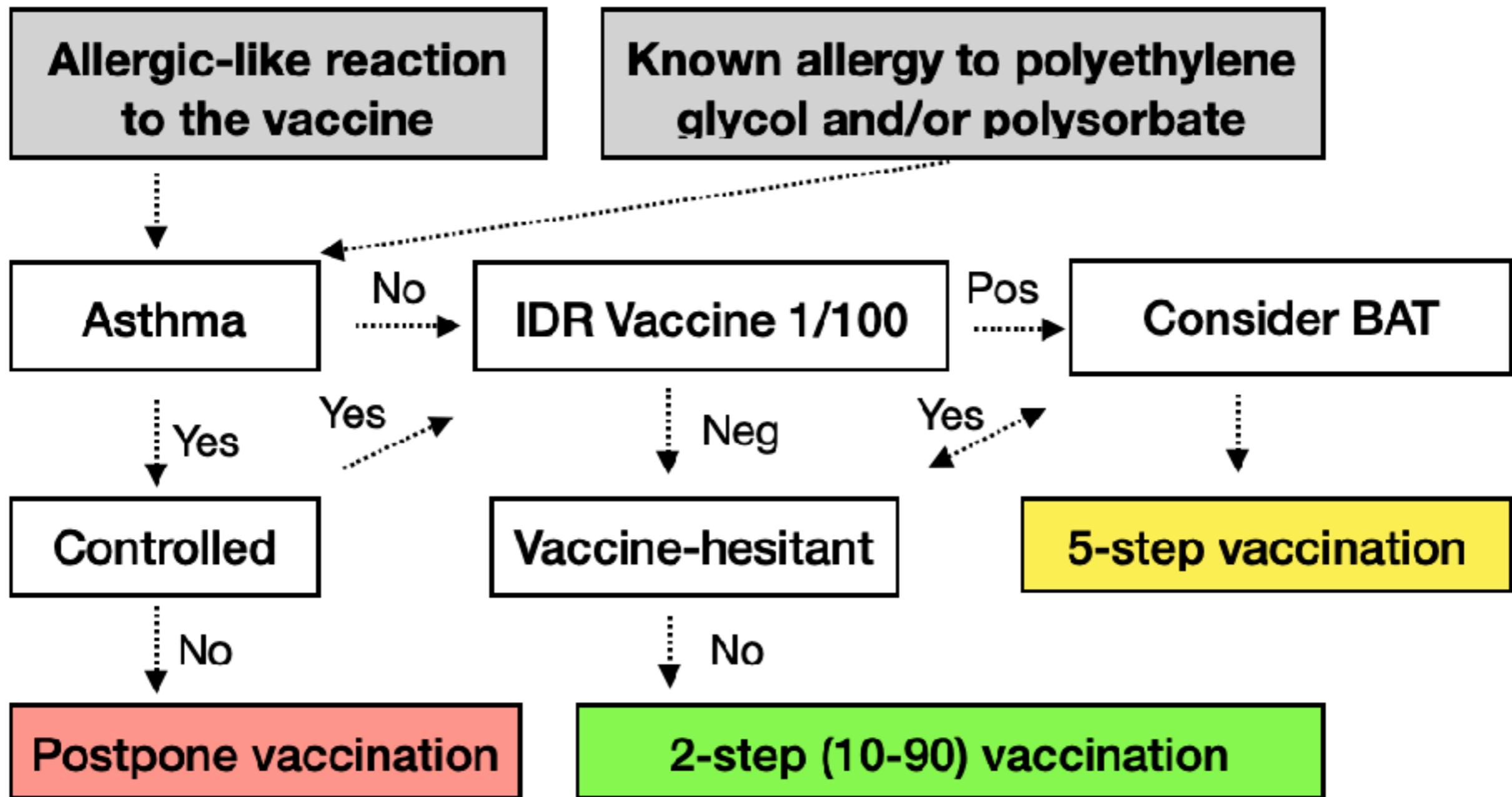
Pediatrics induction protocol

Premedication	5-step induction protocol		Percentage
Anti-histamine 12 hours before	<u>mRNA-1273</u> 1 μ g (0.5ml)	<u>BNT-162b2</u> 0.3 μ g (0.5ml)	1%
2 hours before	10 μ g (0.2ml) 20 μ g (0.4ml) 30 μ g (0.6ml) 40 μ g (0.8ml)	or 3 μ g (0.15ml) 6 μ g (0.3ml) 9 μ g (0.45ml) 12 μ g (0.6ml)	10% 20% 30% 40%
Total	101μg	30.3μg	101%
30minutes intervals			

Age	Sex	Cohort	Timing of the reaction	Anaphylaxis EAACI criteria	BNT-162b2 mRNA IDR	mRNA-1273 IDR	Polysorbate IDR	BA C
75	F	post	>60min	No	inconclusive	inconclusive	negative	
22	F	post	>60min	No	positive	positive	positive	
41	F	post	≤30 min	No	positive	positive	positive	
37	F	post	>60min	No	ND	inconclusive	positive	
46	F	post	>60min	No	Inconclusive	Inconclusive	negative	
53	F	post	≤30 min	No	ND	positive	inconclusive	
36	F	post	≤30 min	No	inconclusive	positive	negative	
52	F	post	>60min	No	inconclusive	inconclusive	negative	
52	F	post	≤30 min	Yes	positive	positive	negative	
39	F	post	≤30 min	No	ND	positive	positive	
66	F	pre	-	-	positive	positive	inconclusive	
45	F	pre	-	-	negative	negative	negative	
66	F	pre	-	-	positive	positive	negative	
68	F	pre	-	-	positive	positive	positive	

AT BNT-162b2 CD63/IL-3 (%)	BAT BNT-162b2 CD63 (%)	BAT BNT-162b2 CD203c (%)	BAT mRNA-1273 CD63/IL-3 (%)	BAT mRNA-1273 CD63 (%)	BAT mRNA-1273 CD203c (%)
4	3,4	3,6	5,8	8	38,1
47,7	21,3	57,9	17,8	44,6	68,8
ND	ND	ND	ND	ND	ND
0,4	0,8	15,1	0,1	2	28,3
60,5	39,3	79,7	48,3	23,4	54,2
14,3	6,3	25,1	10,7	7,8	20,1
60,5	39,3	79,7	48,3	23,4	54,2
11,5	9,1	10,4	41,2	40,2	37
33,6	34,6	55,5	24,4	29,4	47,3
26,4	14,3	40,2	18	27,7	60
16,6	2,8	37,2	19,1	8	54,7
ND	ND	ND	ND	ND	ND
5,3	1,2	3,6	5,1	5,5	36,8
0,5	0,4	4,4	1,3	2,2	12,8

73	Vaccine used	IT Completed	Reaction during IT
	mRNA-1273	Yes	-
	mRNA-1273	Yes	Local urticaria
	mRNA-1273	Yes	-
	mRNA-1273	Yes	-
	mRNA-1273	Yes	-
	BNT-162b2 mRNA	Yes	-
	BNT-162b2 mRNA	Yes	mild asthmatic exacerbation
	BNT-162b2 mRNA	Yes	mild asthmatic exacerbation
	BNT-162b2 mRNA	Yes	-



Conclusions

- Patients with negative skin tests for the anti-SARS-CoV2 vaccines BNT162b2 from Pfizer-BioNTech or mRNA-1273 from Moderna can be safely vaccinated using a two-step vaccination protocol (10%-90%).
- A high correlation between positive skin tests and positive BATs for mRNA vaccines.
- A high rate of positive skin tests for polysorbate-80 in vaccine sensitized patients suggesting a cross-reactivity that is mediated by Polyethylene glycol (PEG). Yet, skin tests with PEG-2000 (at the concentration we used in this study) were not useful for the evaluation of vaccine hypersensitivity.
- A selective inhibition of CD63/CD203c upregulation with ibrutinib suggesting an IgE-dependent mechanism for mRNA vaccine sensitization.
- Several cases of acute asthmatic exacerbation despite negative skin tests.
- Vaccine-sensitized individuals may receive the vaccine with a five-step vaccination protocol.
- The severity of the allergic reaction does not predict vaccine sensitization. In fact, we found a high rate of vaccine-sensitized patients who were vaccinated with the mRNA-1273 from Moderna. To our opinion, the mechanisms and potential clinical consequences should be urgently studied.

Remerciements

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