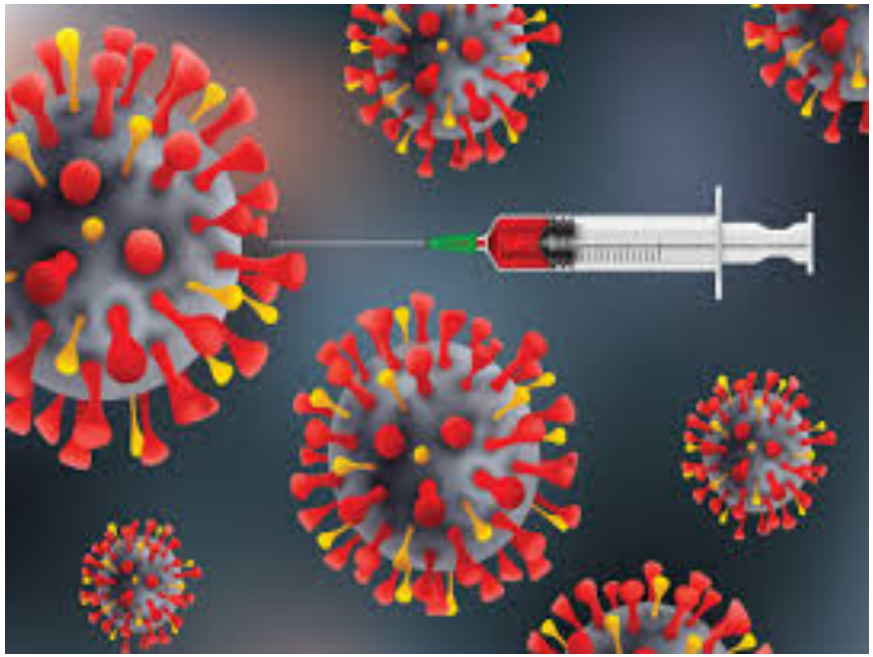
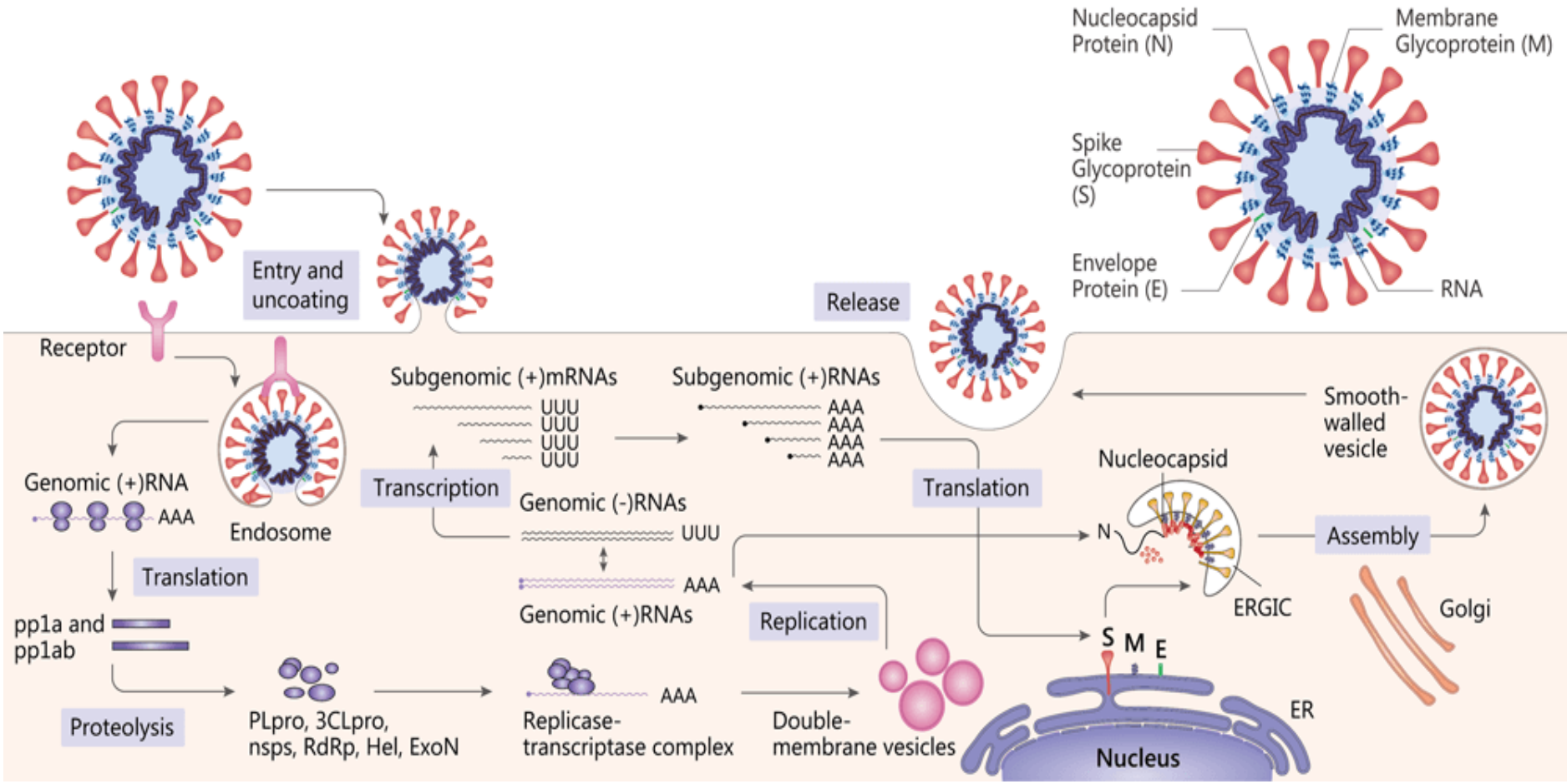
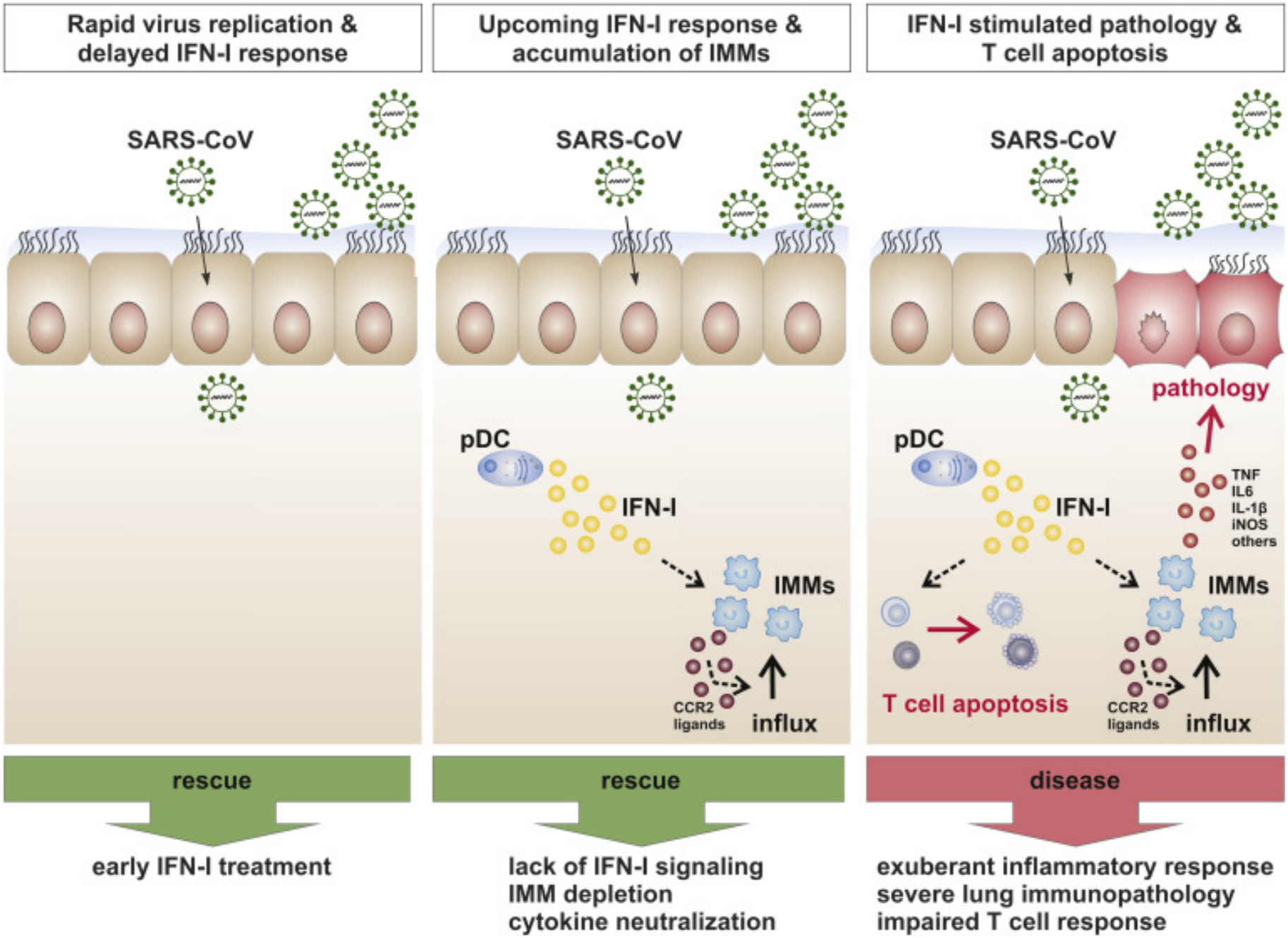
APAAACI Task Force
Module on COVID-19
Vaccine Adverse Reactions



ASIA PACIFIC ASSOCIATION OF ALLERGY, ASTHMA AND CLINICAL IMMUNOLOGY
APAAACI

SARS-COV 2


Nucleocapsid Protein (N)
Membrane Glycoprotein (M)
Spike Glycoprotein (S)
Envelope Protein (E)
RNA
Entry and uncoating
Receptor
Endosome
Release
Genomic (+)RNA
AAA
Translation
pp1a and pp1ab
Proteolysis
PLpro, 3CLpro, nsps, RdRp, Hel, ExoN
Transcription
Subgenomic (+)mRNAs
UUU
Genomic (-)RNAs
Genomic (+)RNAs
Replication
Replicase-transcriptase complex
Double-membrane vesicles
Subgenomic (+)RNAs
Translation
Nucleocapsid
N
ERGIC
S M E
ER
Nucleus
Assembly
Smooth-walled vesicle
Golgi

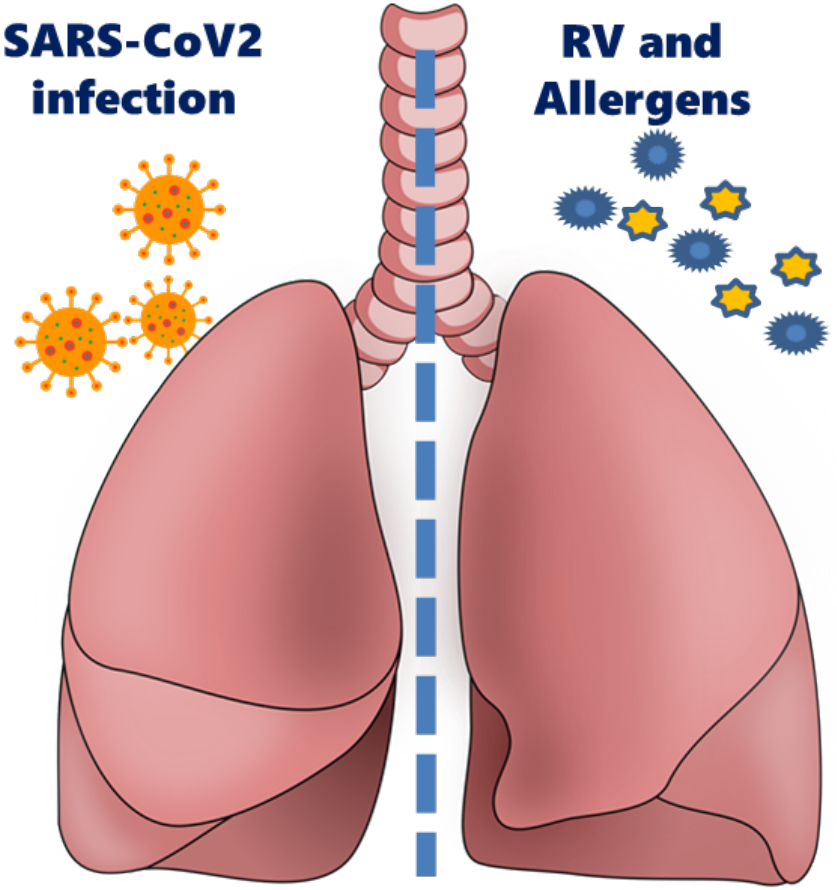

Rapid virus replication & delayed IFN-I response
Upcoming IFN-I response & accumulation of IMMs
IFN-I stimulated pathology & T cell apoptosis
SARS-CoV
SARS-CoV
SARS-CoV
pDC
IFN-I
IMMs
CCR2 ligands
influx
pDC
IFN-I
pathology
TNF
IL6
IL-1β
iNOS
others
IMMs
T cell apoptosis
CCR2 ligands
influx
rescue
rescue
disease
early IFN-I treatment
lack of IFN-I signaling
IMM depletion
cytokine neutralization
exuberant inflammatory response
severe lung immunopathology
impaired T cell response

COVID-19 and Asthma

Mucosal membranes
- ↑ ACE2 and TMPRSS2

Innate immunity
- ↑ IL-6 and TNFa
- ↓ Type I/III IFN
- ↑ Inflammatory macrophages

Adaptive immunity
- ↑ CD8+ cytotoxic T cells
- ↑ T lymphocyte exhaustion and Lymphocytopenia
- ↑ Cytokine Storms

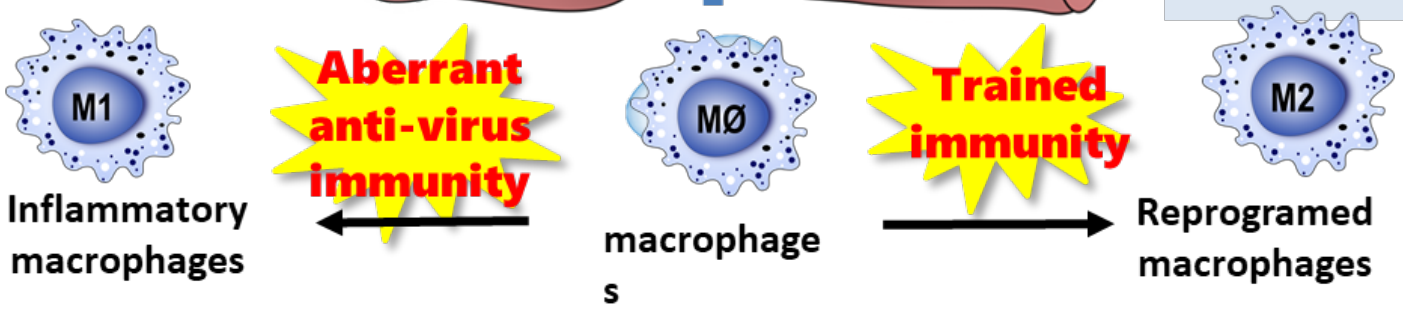


Mucosal membranes
- ↓ ACE2 and TMPRSS2

Innate immunity
- ↓ Type I/III IFN
- ↑ MBL and SP-D
- ↑ Reprogramed macrophages
- ↑ ILC2s and iNK cells

Adaptive immunity
- ↑ $CD4^+$ T helper cells

Anti-virus effect by Rx
- ICS +LABA
- Anti-IgE; Azithromycin



Wang JY, Pawankar R et al. Allergy 2020)

Epidemiology

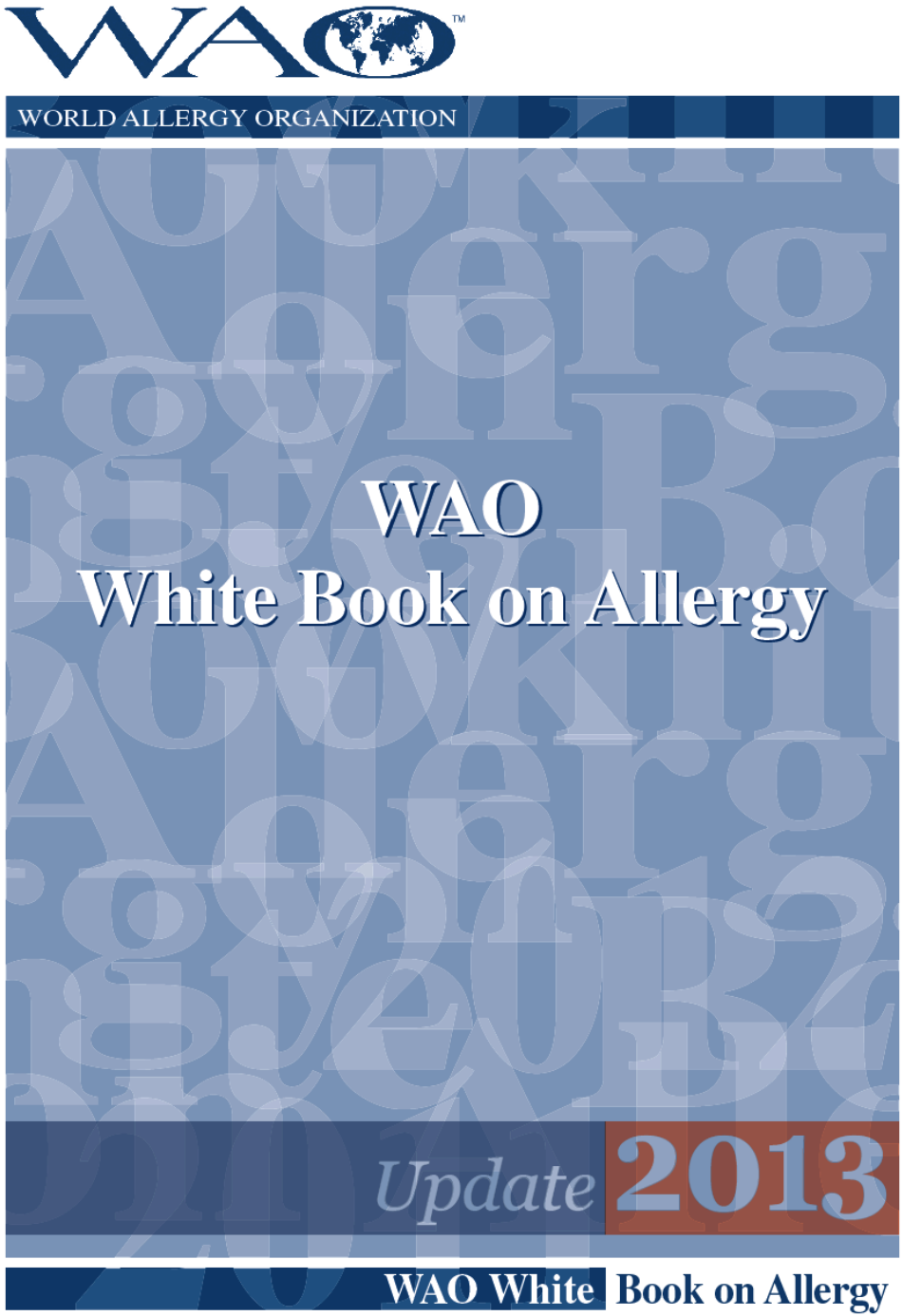
- Estimates of allergic reactions to vaccines including immediate hypersensitivity reactions, range from 1 in 50,000 to 1 in 1,000,000 doses
- Anaphylaxis: estimated 1 per 100,000 to 1 per 1,000,000 doses for most commonly administered vaccines
- Rates mostly from paediatric studies (childhood immunizations)
- True rate of allergic reactions is unknown because most reactions are not reported.

Classification (ICON 2016)

- Immediate non-allergic reactions
  - Local, injection site reactions (swelling, redness, and/or soreness) and constitutional symptoms, especially fever (common)

- Immediate allergic reactions
  - Limited: e.g. bronchoconstriction, rhinoconjunctivitis, gastrointestinal symptoms, generalized urticaria and/or angioedema; onset within minutes-4 hours
  - Anaphylaxis

Dreskin SC, et al World Allergy Organ J 2016 16;9(1):32.



Section 2.5. Anaphylaxis

Richard F. Lockey, Stephen F. Kemp, Philip L. Lieberman, Aziz Sheikh

Key Statements

- Epinephrine (adrenaline) at appropriate doses, injected intramuscularly into the mid- anterior lateral thigh, is the drug of choice to treat anaphylaxis.
- There is lack of consensus about the definition and diagnostic features of anaphylaxis and this definition contributes to the variability in its identification, treatment and the use of epinephrine.
- The variability and severity of anaphylaxis is somewhat dependent on the route by which the allergen or inciting agent is delivered, e.g., parenteral versus oral administration; the former is commonly associated with more severe reactions.
- There are a variety of other terms which describe anaphylaxis and which cause confusion, especially with its definition and treatment. These include: generalized systemic reaction; systemic allergic reaction; constitutional reaction; and serious hypersensitivity reaction.
- The illustrations in the *World Allergy Organization Guidelines for the Assessment and Management of Anaphylaxis*, published in 2011 and updated in 2012, are ideal for all physicians and other healthcare professionals.[1,2]
- Anaphylaxis includes both allergic and non-allergic etiologies.

References

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]

Cardona et al. World Allergy Organization Journal (2020) 13:100472
http://doi.org/10.1016/j.waojou.2020.100472

WORLD ALLERGY ORGANIZATION JOURNAL

POSITION PAPER

World allergy organization anaphylaxis guidance 2020

Victoria Cardona[a*], Ignacio J. Ansotegui[b], Motohiro Ebisawa[c], Yehia El-Gamal[d], Montserrat Fernandez Rivas[e], Stanley Fineman[f], Mario Geller[g], Alexei Gonzalez-Estrada[h], Paul A. Greenberger[i], Mario Sanchez Borges[j], Gianenrico Senna[K], Aziz Sheikh[l], Luciana Kase Tanno[m], Bernard Y. Thong[n], Paul J. Turner[o,1] and Margitta Worm[p,1]

Anaphylaxis (WAO 2020)

Anaphylaxis is highly likely when any one of the following 2 criteria are fulfilled:
1. Acute onset of an illness (minutes to several hours) with simultaneous involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula)
AND AT LEAST ONE OF THE FOLLOWING:
a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
b. Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
c. Severe gastrointestinal symptoms (eg, severe crampy abdominal pain, repetitive vomiting), especially after exposure to non-food allergens
2. Acute onset of hypotension[a] or bronchospasm[b] or laryngeal involvement[c] after exposure to a known or highly probable allergen[d] for that patient (minutes to several hours), even in the absence of typical skin involvement.

Table 2. Amended criteria for the diagnosis of anaphylaxis. *PEF, Peak expiratory flow; BP, blood pressure. a. Hypotension defined as a decrease in systolic BP greater than 30% from that person's baseline, OR i. Infants and children under 10 years: systolic BP less than (70 mmHg + [2 x age in years]) ii. Adults and children over 10 years: systolic BP less than <90 mmHg. b. Excluding lower respiratory symptoms triggered by common inhalant allergens or food allergens perceived to cause "inhalational" reactions in the absence of ingestion. c. Laryngeal symptoms include: stridor, vocal changes, odynophagia. d. An allergen is a substance (usually a protein) capable of triggering an immune response that can result in an allergic reaction. Most allergens act through an IgE-mediated pathway, but some non-allergen triggers can act independent of IgE (for example, via direct activation of mast cells). Adapted from ([26])*

Cardona V, Ansotegui IJ, Ebisawa M, El-Gamal Y, Fernandez Rivas M, Fineman S, Geller M, Gonzalez-Estrada A, Greenberger PA, Sanchez Borges M, Senna G, Sheikh A, Tanno LK, Thong BY, Turner PJ, Worm M. World Allergy Organ J 2020;13(10):100472.

Anaphylaxis (WAO 2020)

Anaphylaxis is highly likely when any one of the following **two criteria is fulfilled**

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g. generalized hives, pruritus or flushing, swollen lips-tongue-uvula)

and at least one of the following

A. Airway/Breathing: Respiratory compromise.
(e.g. dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)

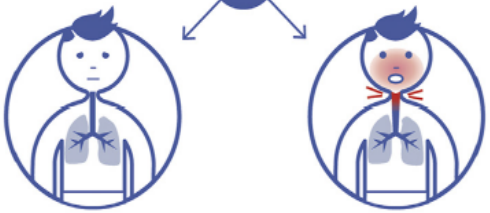
B. Circulation: Reduced BP or associated symptoms of end-organ dysfunction.
(e.g. hypotonia [collapse], syncope, incontinence)

C. Other: Severe gastrointestinal symptoms.
(e.g. severe crampy abdominal pain, repetitive vomiting), especially after exposure to non-food allergens)

2. Acute onset of **hypotension*** or **bronchospasm** or **laryngeal involvement#** after exposure to a known or highly probable allergen for that patient (minutes to several hours), **even in the absence of typical skin involvement.**

Infants and children: low systolic BP (age-specific) or greater then 30% decrease in systolic BP*

Adults: systolic BP of less than 90 mm Hg or greater than 30% drecrease from that person's baseline



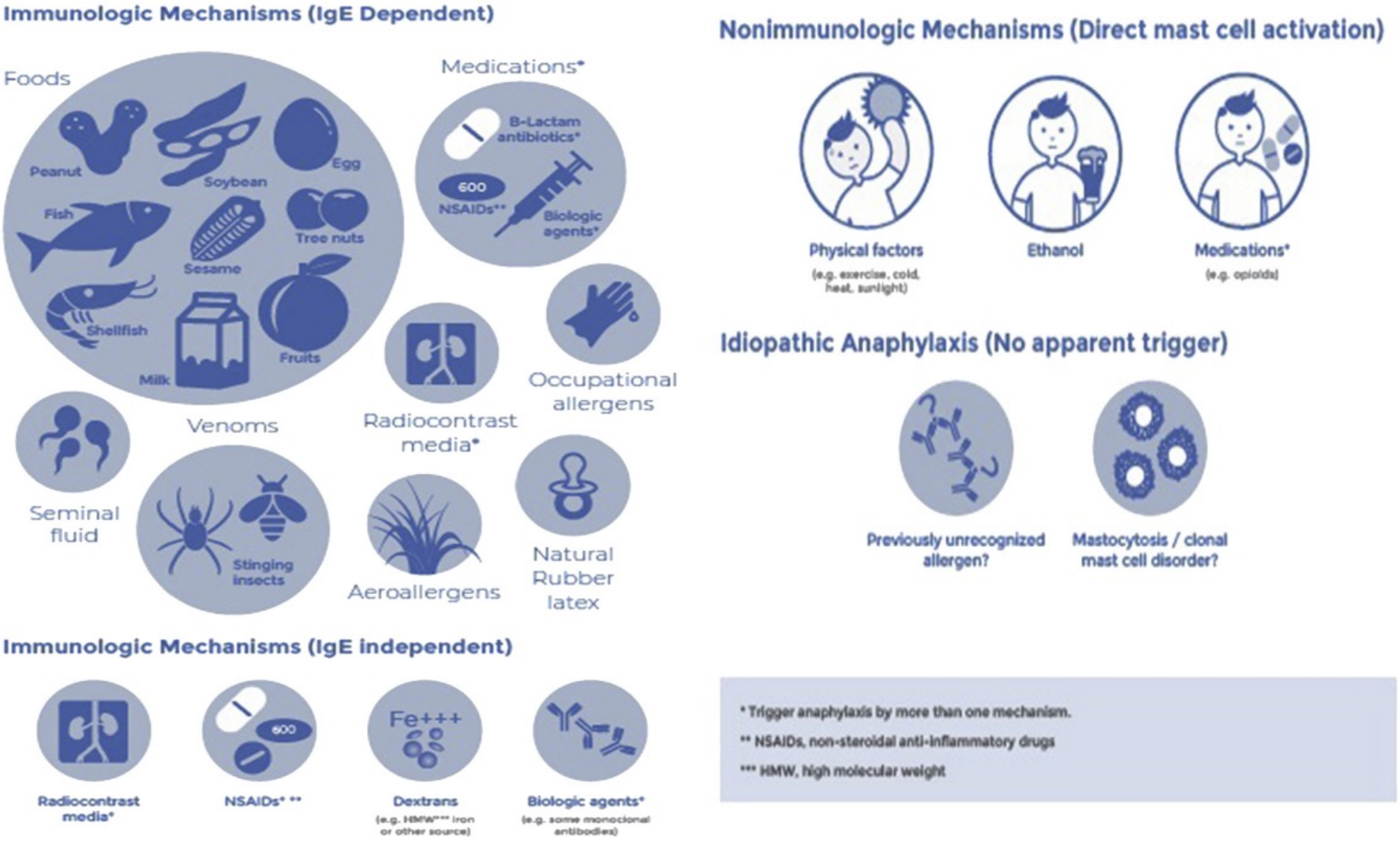
PEF, Peak expiratory flow; BP blood presure.

*Hypotension defined as a decrease in systolic BP greater than 3% from that person's baseline, OR
i. Infants and children under 10 years: systolic BP less than (70mmHg + [2 x age in years])
ii. Adults: systolic BP les than < 90 mmHg

Laryngeal symptoms include: stridor, vocal changes, odynophagia.

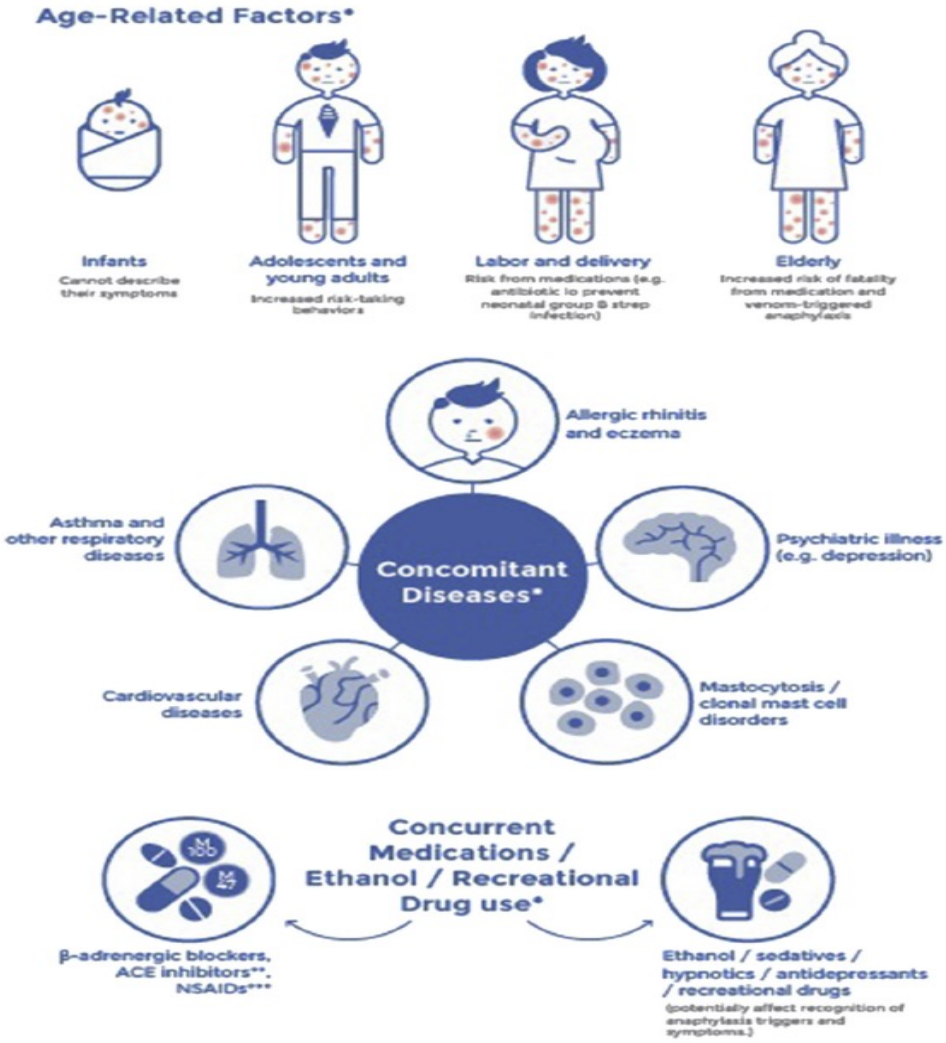
Cardona V, et al. World Allergy Organ J 2020;13(10):100472.

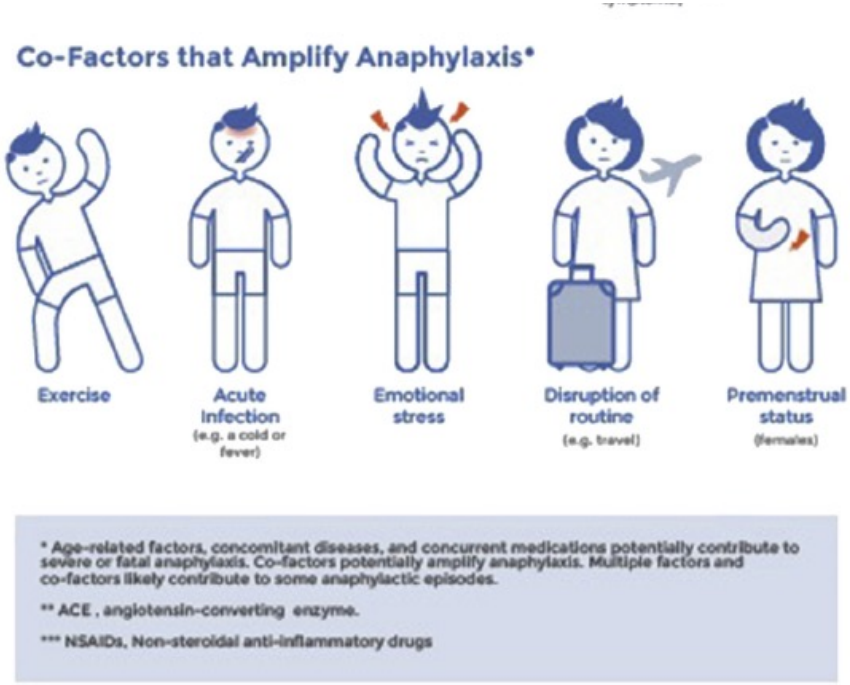
Anaphylaxis (WAO 2020)



Cardona V, et al. World Allergy Organ J 2020;13(10):100472.

Anaphylaxis (WAO 2020)



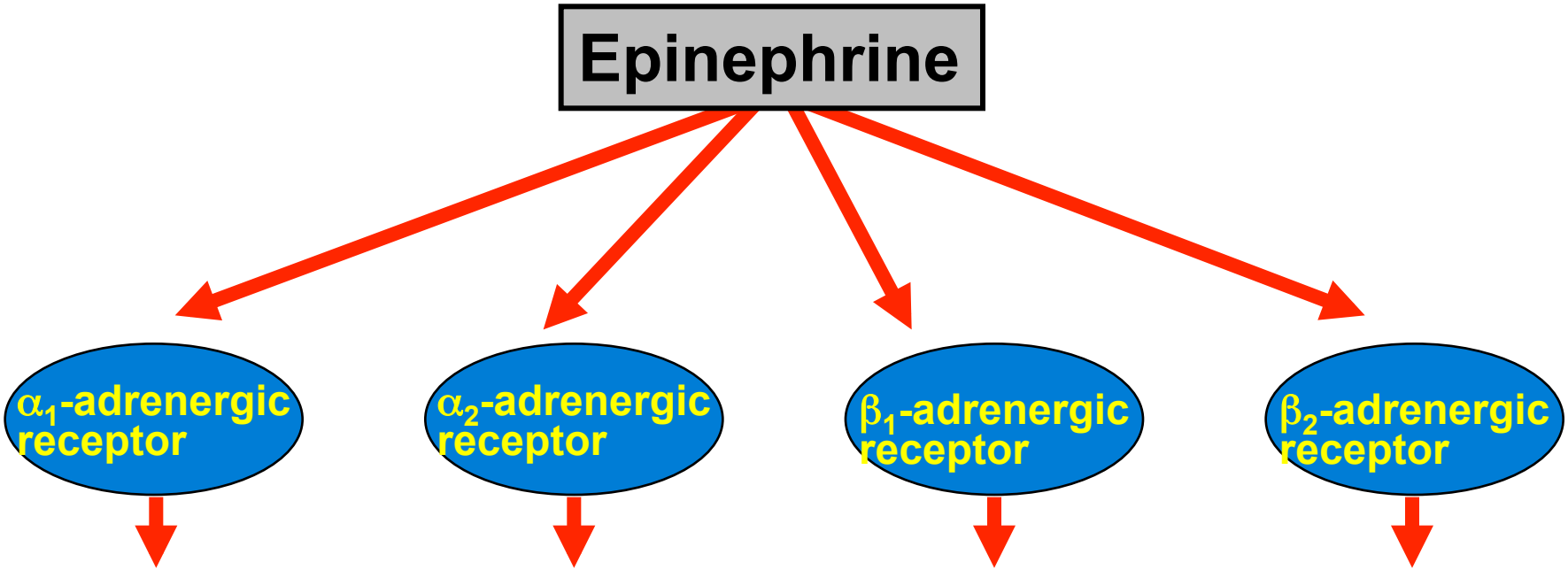


Cardona V, et al. World Allergy Organ J 2020;13(10):100472.

Tryptase and Histamine Dynamics

- **Tryptase levels provide a more precise measure of involvement of mast cells than clinical presentation[1]**
- **Total serum tryptase may remain elevated acutely for 6+ hours[2]**
  - **Peaks at 1 hour: obtain blood sample within 3 hours**
- **Normal serum tryptase value is <10 ng/mL; the higher the value, the higher the sensitivity[3]**
- **Positive predictive value of serum tryptase can be 92.6%[3]**
  - **Negative predictive value is only 52%**
- **Plasma histamine begins to rise within 5 minutes but remains elevated for 30 to 60 minutes[4]**
  - **Because of longer half-life, serum tryptase is preferred**

Action of Epinephrine



Respond Quickly!

- **Administer epinephrine quickly**
- **Activate EMS – 911**
- **Then, call emergency contacts**

Adrenaline auto-injector world wide availability

Area	Country	EpiPen/ Fastjekt	Anapen	Twinject
Europe	Austria	O	O	
	Germany	O	O	
	Hungary	O	O	
	Netherlands	O	O	
	Poland	O	O	
	Portugal	O	O	
	Sweden	O	O	
	Switzerland	O	O	
	Belgium	O		
	Czech Republic	O		
	Denmark	O		
	Finland	O		
	Italy	O		
	Luxemburg	O		
	Norway	O		
	Slovakia	O		
	Slovenia	O		
	Spain	O		
	UK	O		
	France		O	
	Greece		O	

Area	Country	EpiPen/ Fastjekt	Anapen	Twinject
North America	USA	O		O
	Canada	O		
South America	Argentina	O		
	Chile	O		
Africa and Middle East	Israel	O		
	South Africa	O		
Asia	Japan	O		
	Malaysia	O		
	Singapore	O		
	Thailand	O		
Oceania	Australia	O	O	
	New Zealand	O		

Vaccine Components

Components		Type
Active immunizing antigens and conjugating agents		Toxoids, live-attenuated viruses, killed viruses or portions of virus, viral proteins, carrier proteins and antigens
Culture media (protein/peptides)		Hen's egg, horse serum, murine and simian cells, kidney cells of dog, yeast
Additives	Antibiotics	Neomycin, chlortetracycline, gentamicin, streptomycin, erythromycin, kanamycin, polymyxin B, amphotericin B
	Preservatives	Thimerosal, 2-phenoxyethanol, phenol, benzethonium chloride
	Stabilizers	Gelatin, human serum albumin, amino acid mix, glutamate, glycine, monosodium glutamate, sucrose, lactose, sorbitol, ascorbic acid, phosphate, polysorbate 80/20, polygeline
	Adjuvants	Aluminum salts, MF-59, AS04 (deacylated monophosphoryl lipid A+ aluminum hydroxide)
	Inactivation residues	Formaldehyde, beta-propiolactone, formalin, gluteraldehyde
Contamination		Latex

Chung EH. Clin Exp Vaccine Res 2014;3(1):50-7

Vaccine Components

Excipients

- **Preservatives**, to prevent contamination e.g. thimerosal
- **Adjuvants**, to help stimulate a stronger immune response e.g. aluminum salts
- **Stabilizers**, to keep the vaccine potent during transportation and storage e.g. sugars or gelatin

Residual trace amounts of materials used during the manufacturing process and removed

- **Cell culture materials**, used to grow the vaccine antigens e.g. egg protein, various culture media
- **Inactivating ingredients**, used to kill viruses or inactivate toxins e.g. formaldehyde.
- **Antibiotics**, used to prevent contamination by bacteria e.g. neomycin.

IVS Institute for Vaccine Safety

Johns Hopkins Bloomberg School of Public Health

https://www.vaccinesafety.edu/components-Excipients.htm

Vaccine Immune Mediated Reactions

Immune mediated reaction	Frequent clinical manifestation
IgE mediated **Minutes to <4 hours**	Urticaria, angioedema, rhinoconjunctivitis, bronchospasm, anaphylaxis, gastrointestinal disorders (diarrhea, abdominal cramping, vomiting)
Immune complex (IgG)	Vasculitis, myocarditis
T-cell mediated **48-72 hours, rare**	Maculopapular exanthema, eczema, acute generalised exanthematous pustulosis (AGEP), erythema multiforme
Non-IgE mediated (pseudoallergic)	Urticaria, angioedema, anaphylactoid reactions, gastrointestinal disorders
Autoimmune/inflammatory	Thrombocytopenia, vasculitis, polyradiculoneuritis, macrophagic myofasciitis, rheumatoid arthritis, Reiter's syndrome, sarcoidosis (juvenile), bullous pemphigoid, lichen planus, Guillain-Barré syndrome, polymyalgia

Chung EH. Clin Exp Vaccine Res 2014;3(1):50-7

Vaccine Immune Mediated Reactions

- Self-reactive antibodies, created by molecular mimicry between the vaccine antigen and endogenous epitope
- Idiopathic thrombocytopenic purpura: 1 in 30,000 for measles, mumps, and rubella (MMR) vaccine
- Guillain-Barré syndrome (GBS) outbreak in 1976-1977
- Many people immunized with the swine influenza vaccine during the campaign period (approximately 0.04 per 100,000 vaccinations) developed GBS within 6 weeks following immunization
- Estimated rate of influenza vaccination-related GBS in Korea was reported to be 0-0.025 per 100,000 distributed doses which is considerably lower than 0.04 to less than one case per 100,000 vaccinations reported in previous studies
- Strong epidemiological data of an association between swine flu vaccination and GBS, the biological mechanisms remain unknown

Chung EH. Clin Exp Vaccine Res 2014;3(1):50-7

Gelatin

- Common cause of vaccine allergy
- Stabiliser
- When used in vaccines, gelatin is extensively cross-reactive and is of bovine or porcine origin

Vaccine	Gelatin content
Influenza (Fluzone; Sanofi Pasteur)	250 µg per 0.5 mL dose
Influenza (FluMist; MedImmune Vaccines)	2,000 µg per 0.2 mL dose
Measles, mumps, rubella (MMRII; Merck)	14,500 µg per 0.5 ml dose
Measles, mumps, rubella, varicella (ProQuad; Merck)	11,000 µg per 0.5 mL dose
Rabies (RabAvert; Novartis)	12,000 µg per 1.0 mL dose
Typhoid Vaccine Live Oral Ty21a (VIVOTIF; Berna)	Capsule
Varicella (VARIVAX, Merck)	12,500 µg per 0.5 mL dose
Yellow fever (YF-VAX; Sanofi Pasteur)	7,500 µg per 0.5 mL dose
Zoster (ZOSTAVAX; Merck)	15,580 µg per 0.65 mL dose

Chung EH. Clin Exp Vaccine Res 2014;3(1):50-7

Latex

- Latex, used to create a natural rubber latex and dry natural rubber, contains naturally occurring impurities
- Such impurities are often responsible for recipient allergic reactions
- Synthetic latex does not contain such impurities and therefore should be considered as an alternative when administering vaccinations
- Contact type allergy is more common than latex anaphylaxis
- Injection related latex allergies and anaphylaxis are thus very rare

Chung EH. Clin Exp Vaccine Res 2014;3(1):50-7

COVID-19 Vaccines

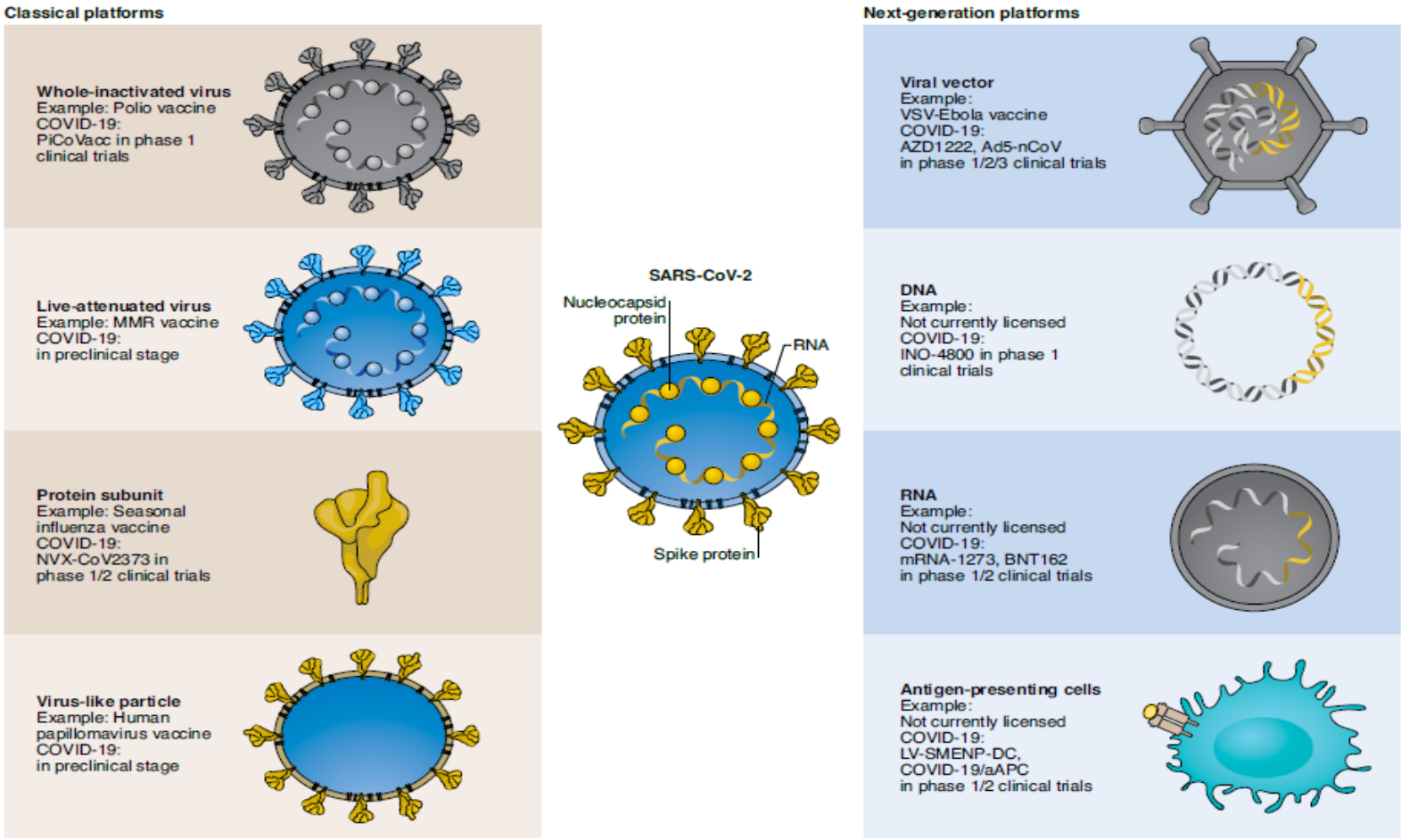


Fig. 1 | An overview of the different vaccine platforms in development against COVID-19. A schematic representation is shown of the classical vaccine platforms that are commonly used for human vaccines, and next-generation platforms, where very few have been licensed for use in humans. The stage of development for each of these vaccine platforms for COVID-19 vaccine development is shown; online vaccine trackers are available to follow these vaccines through the clinical development and licensing process[21].

van Riel D, de Wit E. Nat Mater 2020;19(8):810-812

COVID-19 Vaccines

Whole-inactivated virus

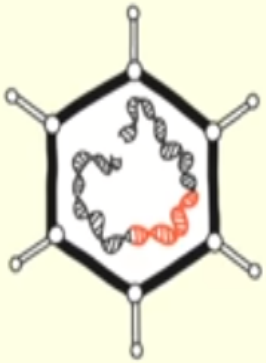
Sinovac

Wuhan Institute of Biological Products/Sinopharm

Beijing Institute of Biological Products/Sinopharm

Protein subunit

Novavax



Adenovirus vector

The University of Oxford/AstraZeneca

CanSinoBIO/Beijing Institute of Biotechnology

Gamaleya Research Institute

Johnson & Johnson/Janssen Pharmaceuticals

mRNA

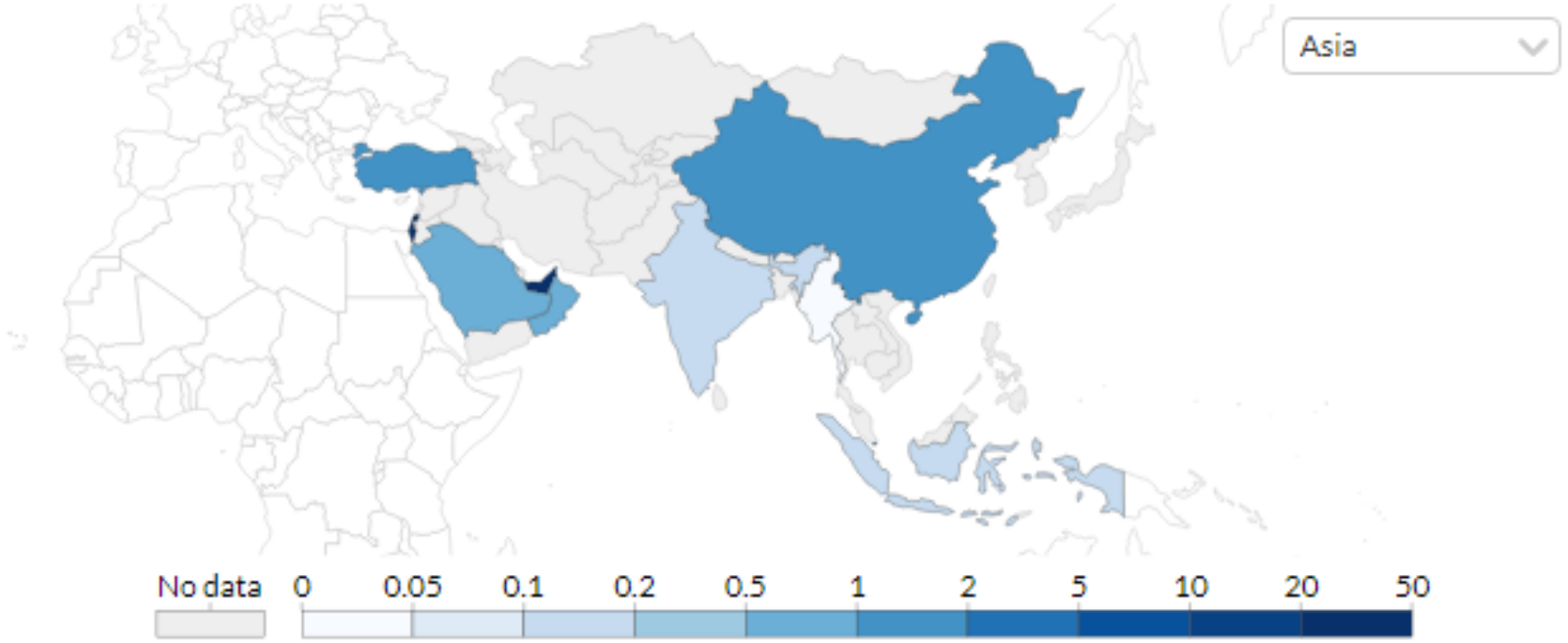
Moderna/NIH

Pfizer/BioNTech

COVID-19 vaccine doses administered per 100 people, Jan 27, 2021

Our World in Data

Total number of vaccination doses administered per 100 people in the total population. This is counted as a single dose, and may not equal the total number of people vaccinated, depending on the specific dose regime (e.g. people receive multiple doses).



Source: Official data collated by Our World in Data – Last updated 28 January, 14:00 (London time)
OurWorldInData.org/coronavirus • CC BY

Dec 15, 2020 — Jan 27, 2021

https://ourworldindata.org/

COVID-19 Vaccine Anaphylaxis

1. Allergic reactions including anaphylaxis as defined by the Brighton Collaboration Working Group was used as part of the Vaccine Adverse Event Reporting System (VAERS) where based on spontaneous reporting, 21 cases of anaphylaxis after 1,893,360 first doses of Pfizer-BioNTech (11.1 cases per million doses) were reported, with 71% of cases occurring within 15 minutes of vaccination.

2. During December 21, 2020-January 10, 2021, monitoring by the VAERS detected 10 cases of anaphylaxis after administration of a reported 4,041,396 first doses of Moderna COVID-19 vaccine (2.5 cases per million doses administered. In 9 cases, onset occurred within 15 minutes of vaccination. No anaphylaxis-related deaths were reported.

[1] MMWR Morb Mortal Wkly Rep. ePub: 6 January 2021
[2] MMWR Morb Mortal Wkly Rep. ePub: 22 January 2021

Polyethylene-glycol (PEG)

- PEG is a hydrophilic polymer frequently used as an excipient in everyday products including medicines, cosmetics, or foods
- Increased number of allergic reactions to PEG (IgE and non-IgE-mediated)
- Cross-reactivity Polysorbat 80 due to the shared chemical moiety: $-(CH_2\text{-}CH_2O)_n$
- Skin prick testing and intradermal testing with different dilutions of PEG, basophil activation test, oral provocation testing are recommended in suspected individuals
- No commercial specific IgE assays
- ** Oxford/Astra-Zeneca COVID-19 vaccine does not contain PEG

Cabanillas B, et al. Allergy 2020 Dec 15. doi: 10.1111/all.14711
Wenande E, et al. Clin Exp Allergy 2016;46(7):907-22
Stone CA Jr, et al. J Allergy Clin Immunol Pract 2019;7(5):1533-1540

Current Recommendations

	US CDC	UK	APAAACI
Severe allergic reaction to currently available mRNA COVID-19 vaccine			
Severe allergic reaction after 1st dose mRNA COVID-19 vaccine			
Non-severe immediate allergic reaction to currently available mRNA COVID-19 vaccine e.g. hives, swelling, wheezing			
Non-severe immediate allergic reaction after 1st dose mRNA COVID-19 vaccine			
Previous allergic reaction to polyethylene glycol (PEG) or polysorbate			

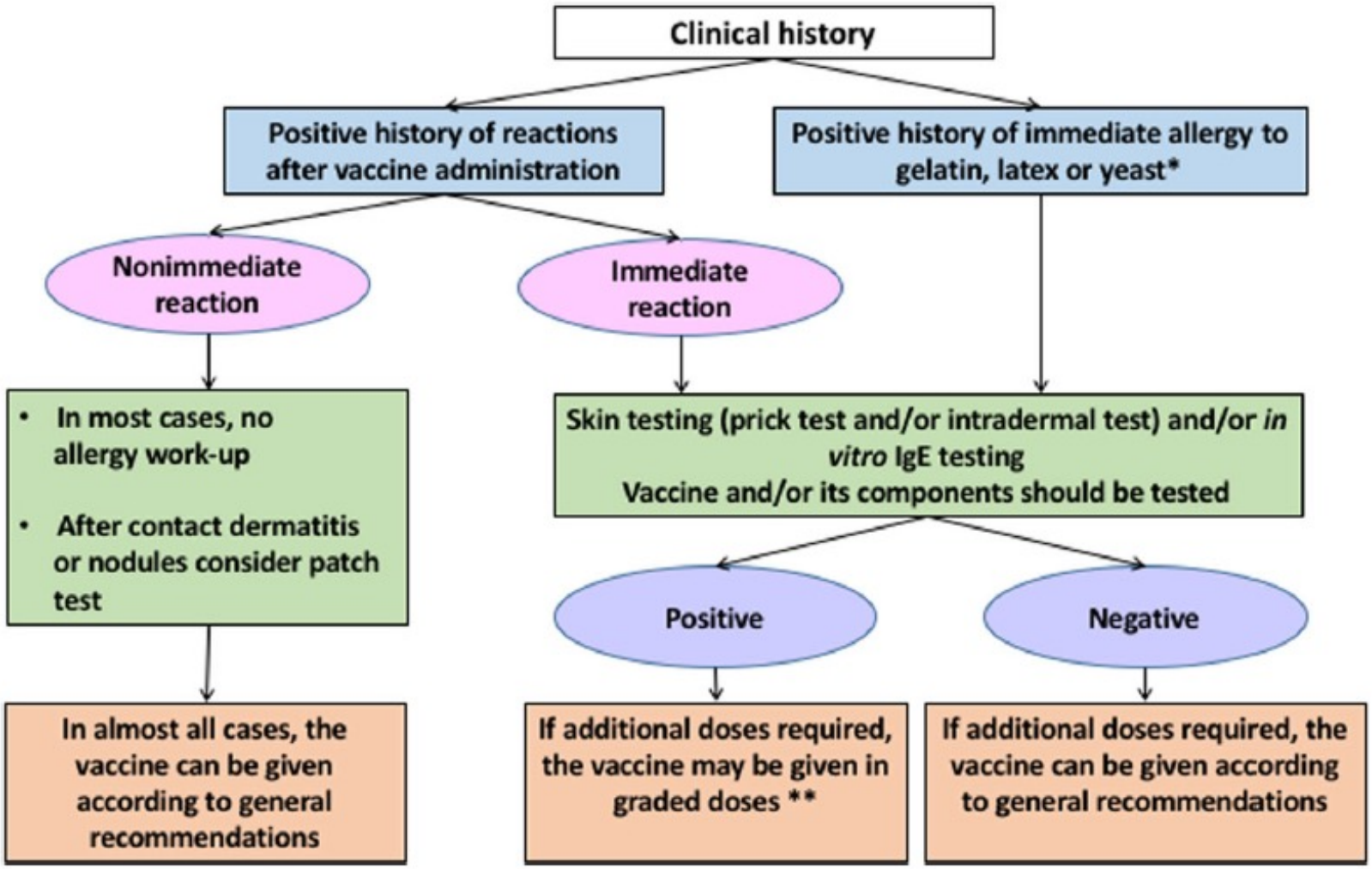
US CDC as of 31 Dec 2020
UK MHRA & BSACI Expert Vaccine Allergy Group as of 30 Dec 2020

Current Recommendations

	US CDC	UK	APAAACI
Immediate allergic reaction to other types of vaccines or injectable			
Anaphylaxis to other vaccines, drugs or food			
Allergies not related to vaccines or injectables e.g. food, pets, environmental, latex			
History of drug allergy/ hypersensitivity			
Family history of severe allergic reactions			

US CDC as of 31 Dec 2020
UK MHRA & BSACI Expert Vaccine Allergy Group as of 30 Dec 2020

Clinical Approach



Dreskin SC, et al World Allergy Organ J 2016 16;9(1):32.

Premedication for those with a h/o allergies

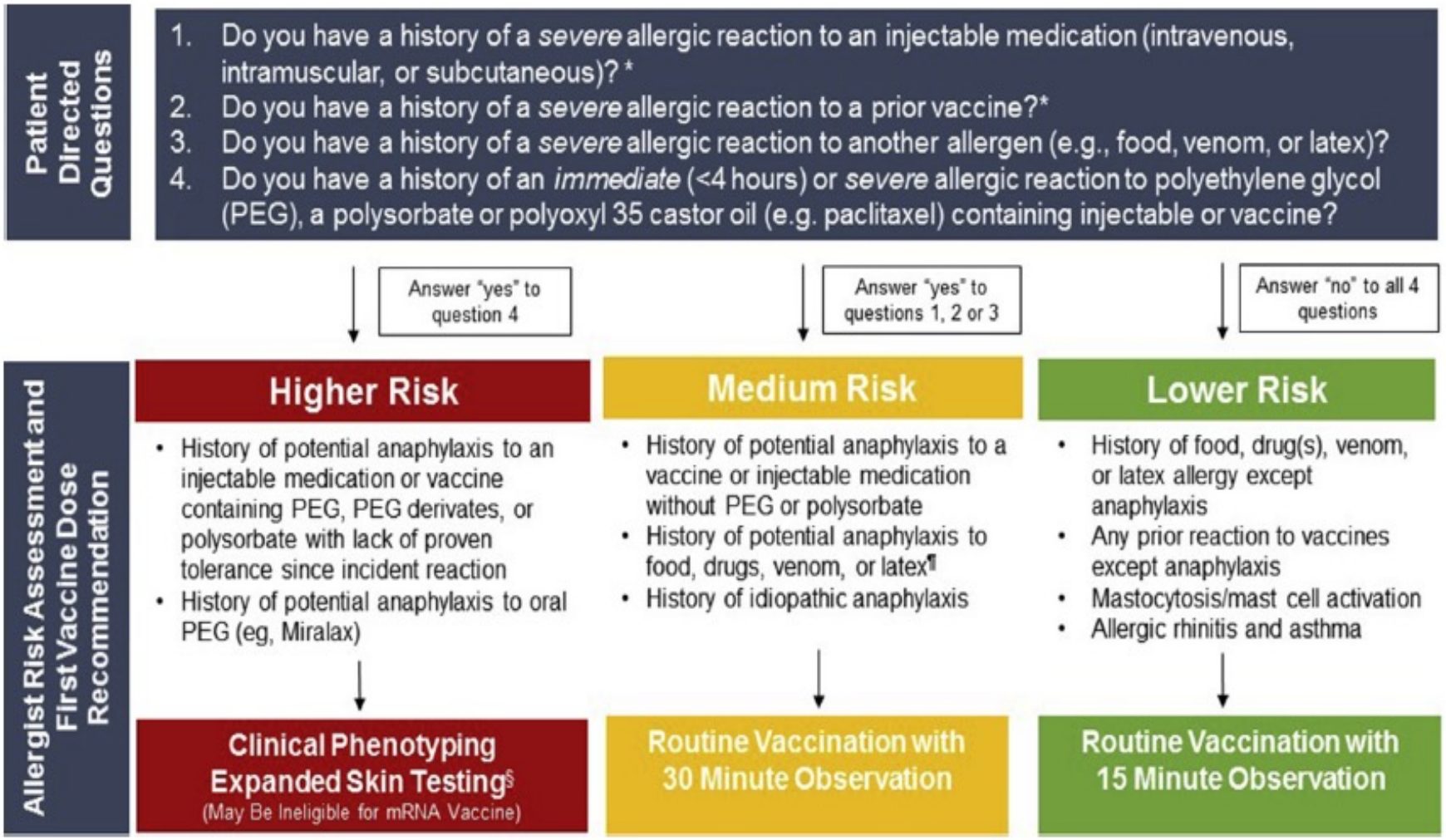
30 min prior vaccination

- Hi antihistamine
- H2 antihistamine
- Montelukast

For emergency in case of anaphylaxis

- Epipen on hand

Diagnostic Tests



Banerji A, et al. J Allergy Clin Immunol Pract 2020 Dec 31:S2213-2198(20)31411-2

Healthcare Settings Vaccination Sites Anaphylaxis Kit

- Chlorpheniramine 4 mg x 10 tablets
- Diphenhydramine 50 mg/ml injection x 2 vials
- Salbutamol 0.5% respiratory solution x 10 ml x 2 units
- Prednisolone 20 mg tab x 10 tablets
- Epinephrine 1mg/ml injection x 5 vials
- Hydrocortisone sodium succinate 100 mg injection x 2 units.

Diagnostic Tests

Banerji A, et al. J Allergy Clin Immunol Pract 2020 Dec 31:S2213-2198(20)31411-2

Skin Tests

		PEG3350		Control*	Polysorbate 20	Polysorbate 80¶		
		Miralax	**Methyl-prednisolone Acetate** (Depo-Medrol) §	**Methyl-prednisolone Sodium Succinate** (Solu-medrol)‡	**Hepatitis A vaccine or Twinrix**	**Triamcinolone Acetonide** (also contains carboxymethyl-cellulose)	**Refresh - sterile eye drops**	**Prevnar 13**
SPT	Step 1 Epicutaneous	1:100 (1.7mg/mL)	40 mg/ml	40 mg/ml	1:1	40 mg/ml	1:1	1:10
SPT	Step 2 Epicutaneous	1:10 (17 mg/mL)						
SPT	Step 3 Epicutaneous	1:1** (170 mg/mL)						
IDT	Step 4 Intradermal		0.4 mg/ml	0.4 mg/ml	1:100	0.4 mg/ml	1:10	1:100
IDT	Step 5 Intradermal		4 mg/ml	4 mg/ml	1:10	4 mg/ml		
IDT	Step 5 Intradermal					40 mg/ml		

Banerji A, et al. J Allergy Clin Immunol Pract 2020 Dec 31:S2213-2198(20)31411-2

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