Bundesinstitut für Impfstoffe und biomedizinische Arzneimittel
Federal Institute for Vaccines and Biomedicines

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Our focus has been on health since 1896

Lessons learned from the SARS-CoV-2 pandemic - vaccines, neutralising antibodies, antigen tests -

Ralf Wagner, Elena Grabski, Heidi Meyer, Eberhardt Hildt et al.,
Isabelle Bekeredjian-Ding et al.,
Jan Müller-Berghaus,
Ger van Zandbergen, Steffen Groß, Bettina Klug et al.,
Dirk Mentzer, Brigitte Keller-Stanislawski et al.,
Klaus Cichutek

Klaus Cichutek *et al*.
Paul-Ehrlich-Institut

DGRA-Jahreskonferenz
27. Juni 2022
Bonn

Das Paul-Ehrlich-Institut ist ein Bundesinstitut im Geschäftsbereich des Bundesministeriums für Gesundheit.

The Paul-Ehrlich-Institut is an Agency of the German Federal Ministry of Health.

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Lessons learned from the SARS-CoV-2 pandemic - vaccines, neutralising antibodies, antigen tests -

- Vaccine platforms and efficacy (Hildt, Grabski, Meyer et al.)
- Booster vaccinations
- Vaccine pharmacovigilance

- CoV-2 neutralising antibodies
- Rapid antigen tests

- Summary

CHMP advice on lower boundary of the confidence interval for vaccine efficacy and on safety follow-up of vaccines (2021)

The pooled primary analysis should provide compelling evidence of VE, with a lower limit of the confidence interval surrounding the VE estimate that is well above zero (e.g. it would be highly desirable that the **lower bound is ≥20% or even ≥30%)** and the **point estimate of VE should be well above 50%.**

Evidence of COVID-19 vaccine safety will require a **safety database that includes a minimum of 3,000 participants** vaccinated with all of the required doses (the full regimen) . Considering that most adverse reactions occur within 4-6 weeks and rarely later, **safety data for at least 6 weeks after the final vaccine dose** would be expected at time of initial submission for authorisation. A longer follow-up period may be required before authorization on a case by case basis to address any potential risk.

Participants in clinical trials should continue to be **followed for at least 1 year and up to 2 years to assess the duration of protection and longer-term safety following authorisation** of the vaccine, and data should be provided to the regulators for assessment. Safety should also be supported by appropriate non-clinical studies, including robust studies assessing the risk of vaccine-associated enhanced respiratory disease.

CHMP advice on lower boundary of the confidence interval for vaccine efficacy and on safety follow-up of vaccines (2021)

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-> Vaccine efficacy turned out better than assumed.

-> Inclusion of 10,000 and more verum vaccinated participants in phase 2/3 trials allowed detection of rare adverse reactions and established a good safety data base.

Evidence of COVID-19 vaccine safety will require a **safety database that includes a minimum of 3,000 participants** vaccinated with all of the required doses (the full regimen) . Considering that most adverse reactions occur within 4-6 weeks and rarely later, **safety data for at least 6 weeks after the final vaccine dose** would be expected at time of initial submission for authorisation. A longer follow-up period may be required before authorization on a case by case basis to address any potential risk.

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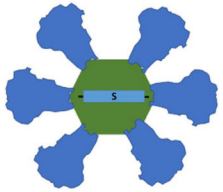
C

Inactivated vaccines are made of SARS-CoV-2 that is grown in cell culture and then chemically inactivated

whole virus inactivated vaccines

J

Inactivated vector vaccines carry copies of the spike on their surface but have been chemically inactivated



F

Recombinant RBD protein based vaccines

E

Recombinant spike protein based vaccines

protein subunit vaccines

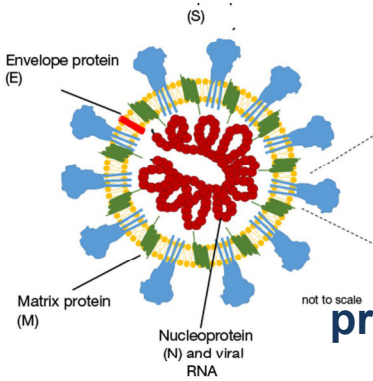
D

Live attenuated vaccines are made of genetically weakened versions of SARS-CoV-2 that is grown in cell culture

live attenuated virus vaccines

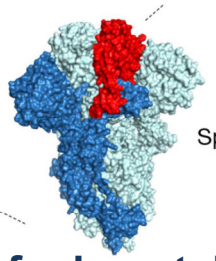
A

SARS-CoV-2



spike protein

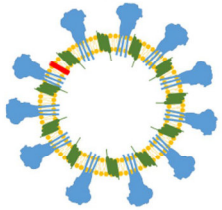
Receptor binding domain (RBD)



pre-fusion stabilized conformation

G

Virus-like particles (VLPs) carry no genome but display the spike on th surface



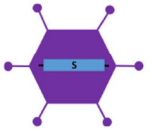
VLPs

vaccine platforms

protective antigen identification and design

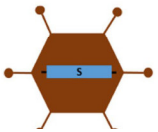
H

Replication competent vector vaccines can propagate to some extend in the vaccinee's cells and express the spike protein there.



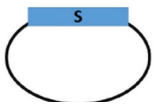
I

Non-replication competent vector vaccines cannot propagate in the vaccinee's cells but express the spike protein there



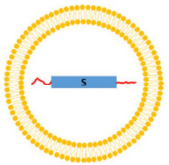
K

DNA vaccines consist of plasmid DNA coding for the spike gene under a mammalian promotor



L

RNA vaccines consist of RNA encoding for the spike protein and are typically packaged in lipid nanoparticles (LNPs)



genetic vaccines

Viral vaccine types

(1) Live attenuated vaccine (apathogenic vaccine virus)

(2) Inactivated vaccines
- whole virus inactivated vaccine
- vaccine based on purified virus components
  - split vaccine
  - subunit vaccine
- recombinant protein vaccine and virus-like particles (VLPs)

(3) Genetic vaccines
- RNA and DNA vaccine
- vector vaccine
  - replication-incompetent vector vaccine
  - conditionally replicating habrid virus

Drug substance DNA or RNA

Drug substances is protein

Viral vaccine types

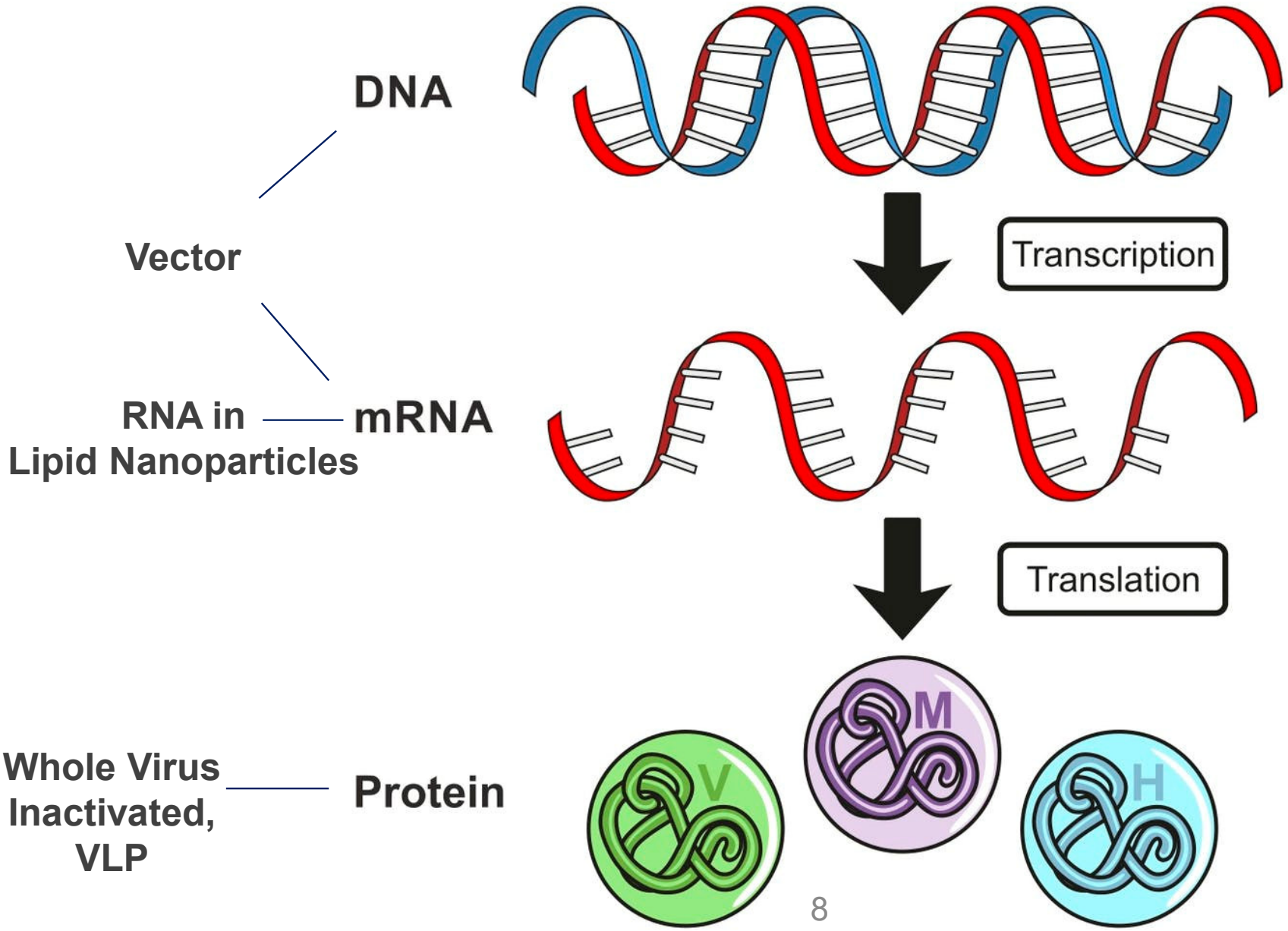
(1) Live attenuated vaccine (apathogenic vaccine virus)

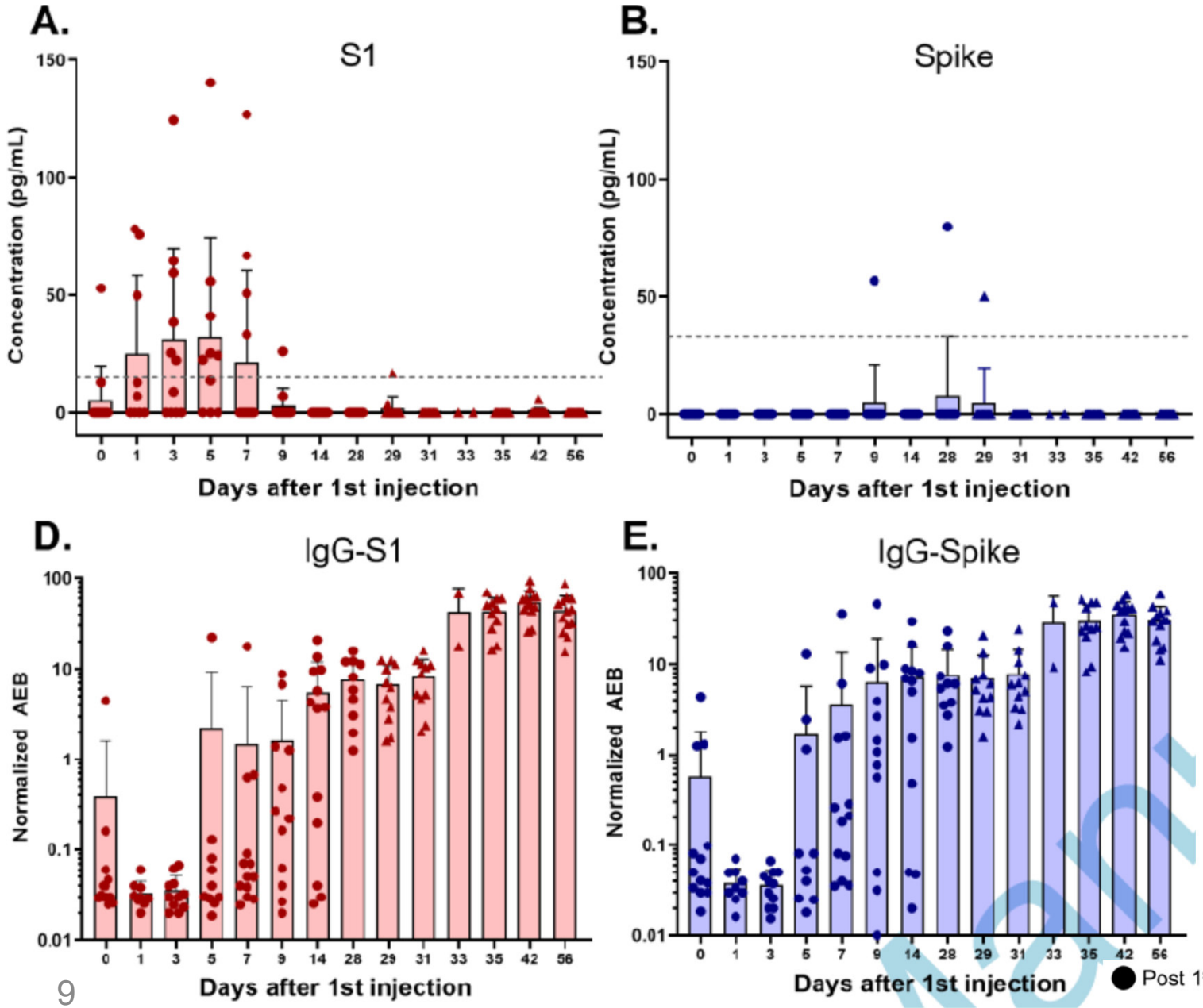
(2) Inactivated vaccines
- whole virus inactivated vaccine
- vaccine based on purified virus components
  - split vaccine
  - subunit vaccine
- recombinant protein vaccine and VLPs (Novaxovid)

(3) Genetic vaccines
- RNA and DNA vaccine (Comirnaty, Spikevax)
- vector vaccine
  - replication-incompetent vector vaccine (Vaxzevria, Jcovden)
  - conditionally replicating hybrid virus

Drug substance DNA or RNA

Drug substances is protein


DNA
Vector
RNA in Lipid Nanoparticles
mRNA
Transcription
Translation
Whole Virus Inactivated, VLP
Protein
V
M
H



Biodistribution and Pharmakokinetics

- 1st dose Spikevax
- S1 subunit of the spike protein detectable in plasma for about a week
- Anti-spike protein antibodies formed about 2 weeks post vaccination

Ogata et al.
Clin Infect Dis. 2021 May 20 : ciab465.
Published online 2021 May 20.
doi: 10.1093/cid/ciab465

Anti-viral humoral immune response: neutralising antibodies inhibit cell entry of virus and thereby infection

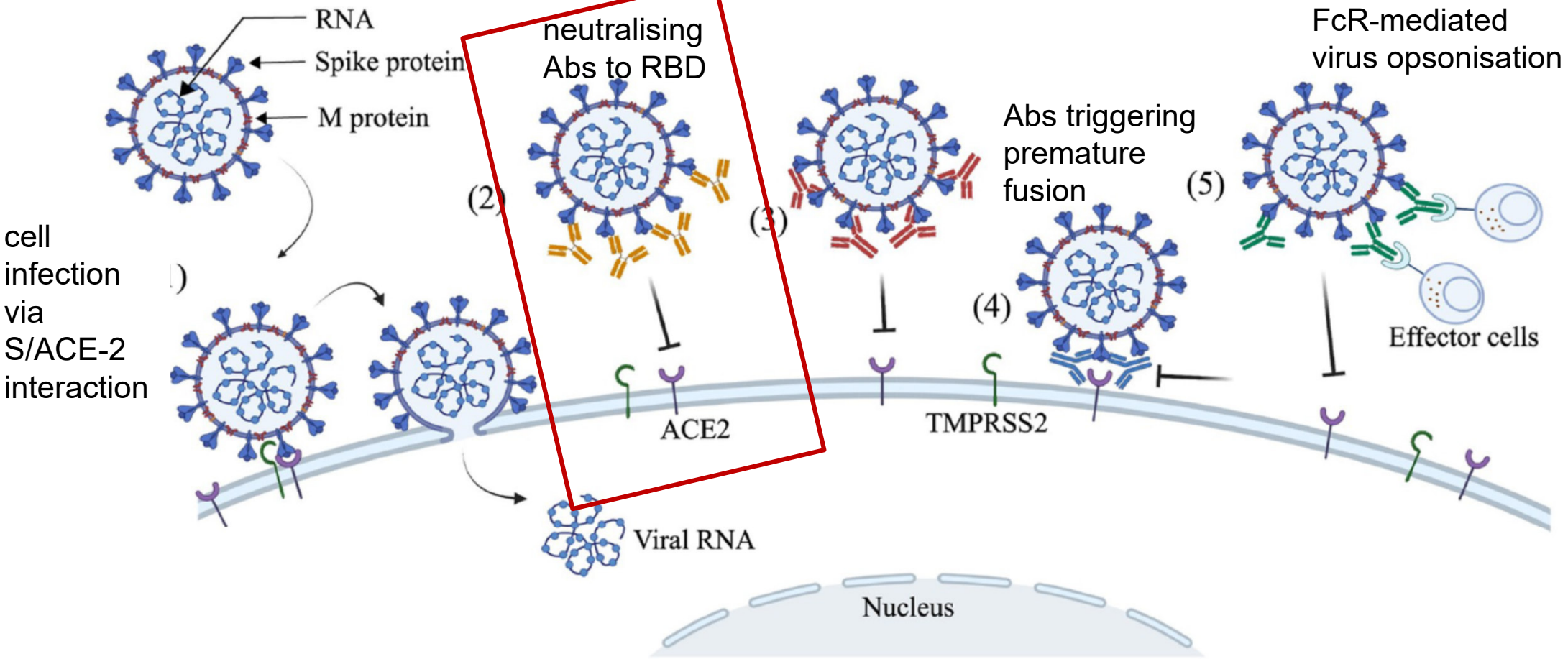


Fig 3. Antibody-mediated neutralization of envelope virus. SARS-CoV-2 virus entry into human cells is initiated by virus binding to the ACE2-cell surface receptors (point 1). The virus neutralization largely depends on the epitope targeted by antibodies. Some of the antibodies target the RBM

Fig 3. **Antibody-mediated neutralization of envelope virus.** SARS-CoV-2 virus entry into human cells is initiated by virus binding to the ACE2-cell surface receptors (point 1). The virus neutralization largely depends on the epitope targeted by antibodies. Some of the antibodies target the RBM (point 2) or NTD (point 3) or other regions of the spike protein, which can inhibit the virus spike protein and host ACE2–receptor interactions, and

Higher antibody titers in blood/serum of vaccinated persons correlate with better protection from CoV-2 infection

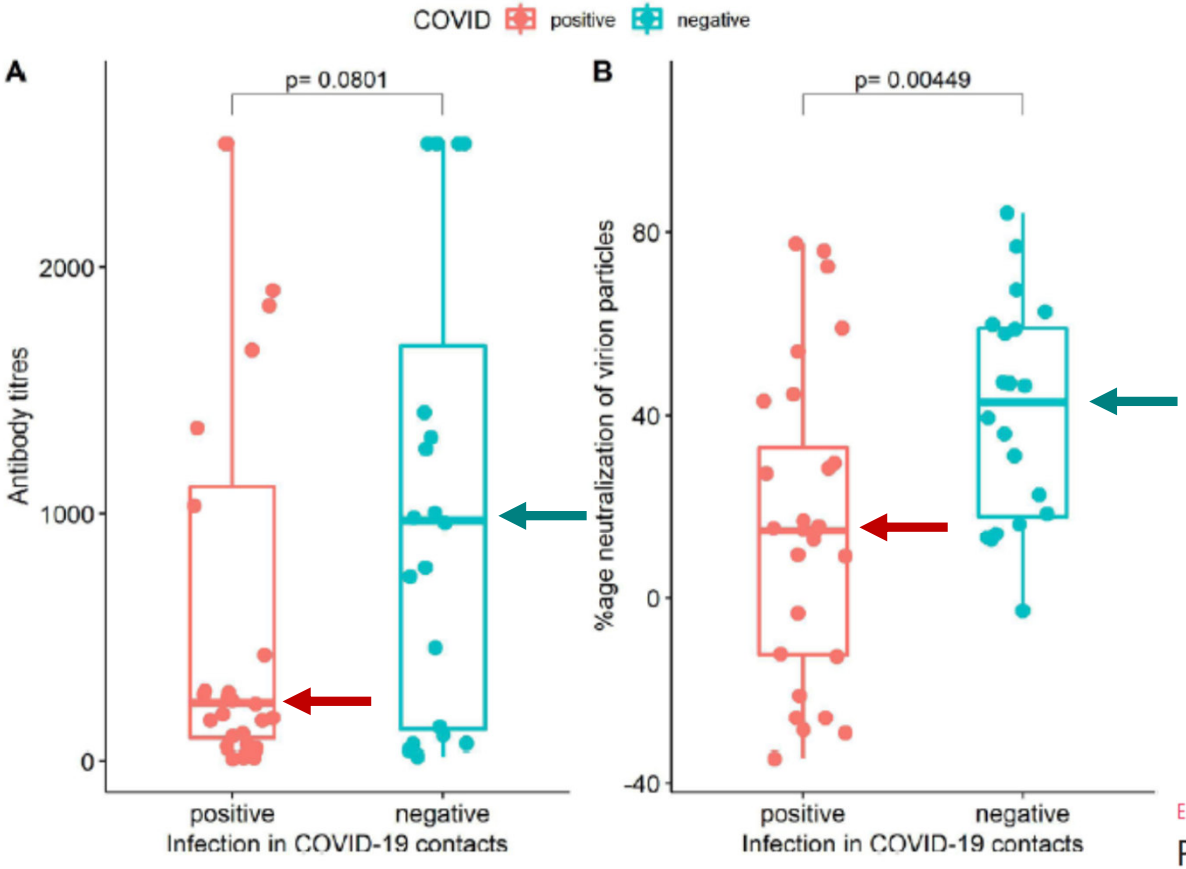


Figure 3 (A) Antibody titres in COVID-19 exposed who had breakthrough infections versus those who did not have. (B) Neutralisation assays in COVID-19 exposed who had breakthrough infections versus those who did not have.

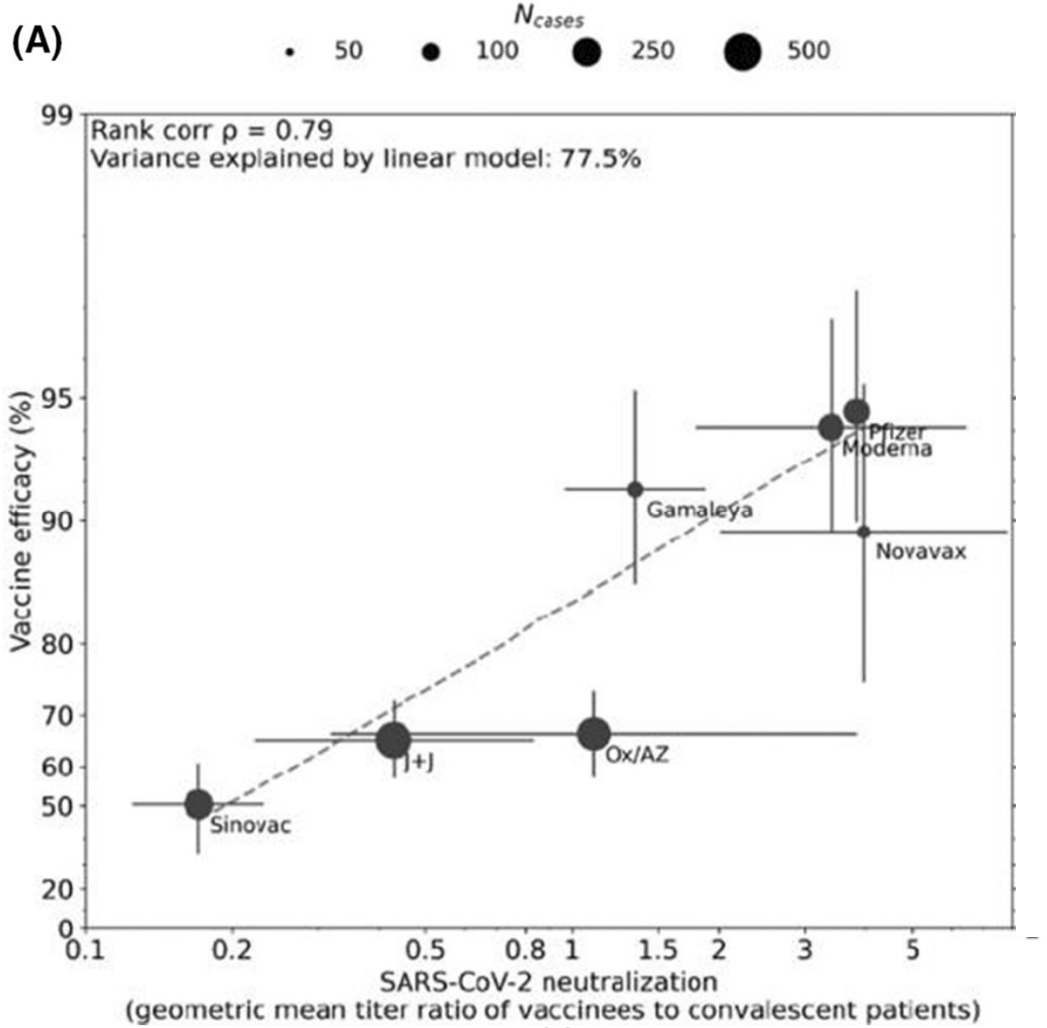
EPIDEMIOLOGICAL SCIENCE

Postvaccination antibody titres predict protection against COVID-19 in patients with autoimmune diseases: survival analysis in a prospective cohort

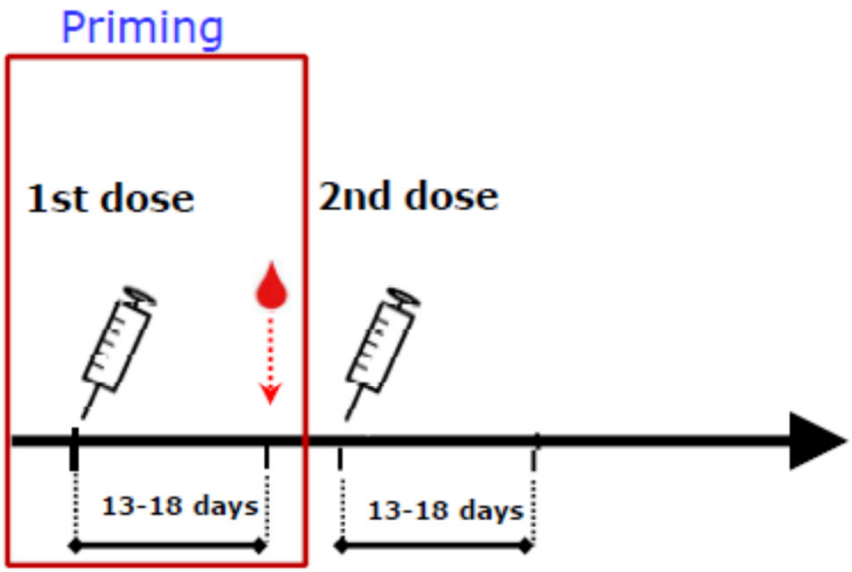
Sakir Ahmed [1], Pankti Mehta [2], Aby Paul,[3] S Anu,[3] Somy Cherian,[3] Veena Shenoy,[4] Kaveri K Nalianda,[3] Sanjana Joseph,[3] Anagha Poulose,[3] Padmanabha Shenoy [5]

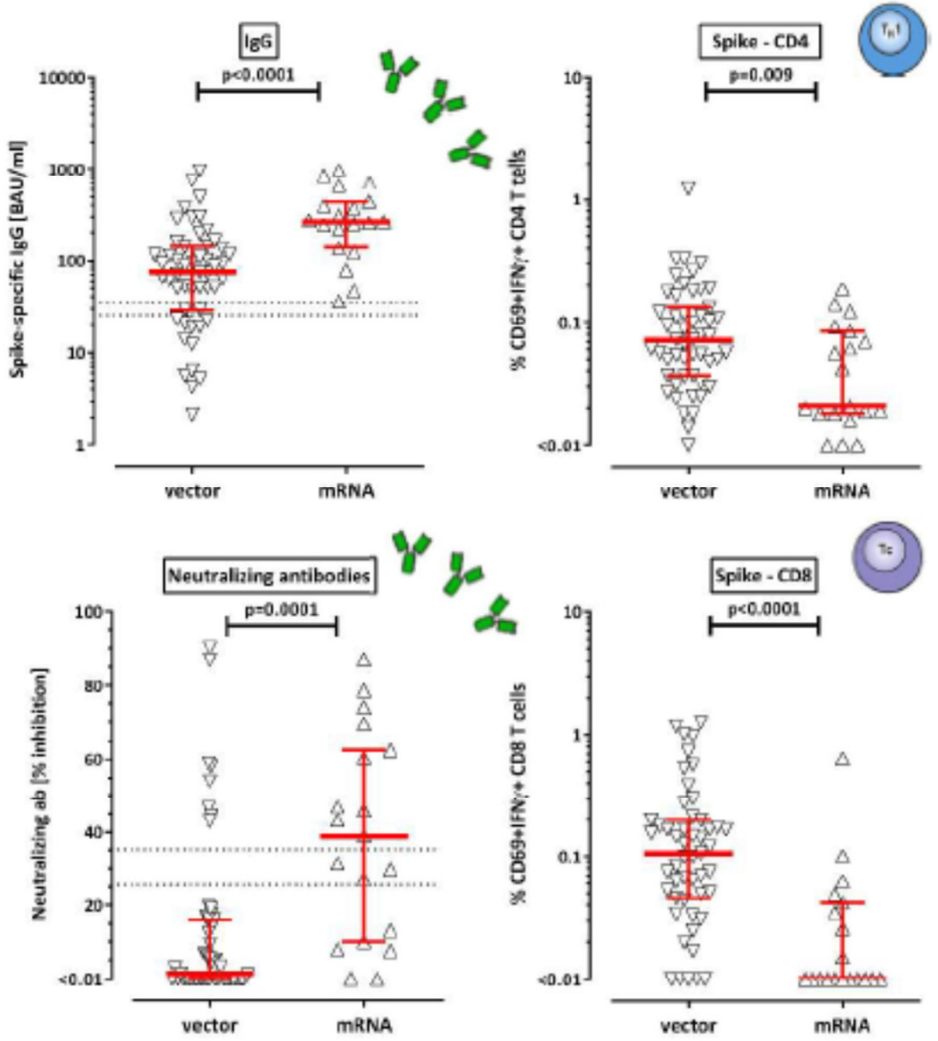
Ahmed S, *et al*. *Ann Rheum Dis* 2022;**0**:1–7. doi:10.1136/annrheumdis-2021-221922

Higher efficacy of COVID-19 vaccines correlates with higher titers of CoV-2 neutralising antibodies



Stronger anti-CoV-2 antibody responses to mRNA vaccines, stronger cellular immune responses to adenovector vaccines





70 immunocompetent persons after first vaccine dose

Schmidt *et al.* (2021) Am J Transplant

Heterologous COVID-19 vaccination schemes improve immune responses

mRNA → more antibodies

vector → more T cells

	antibodies		T cells	
	IgG	neutralizing	CD4	CD8
vector vector	+	+	+	+
vector mRNA	+++	+++	++	+++
mRNA mRNA	+++	+++	++	+
protein protein	++	+++	+	-

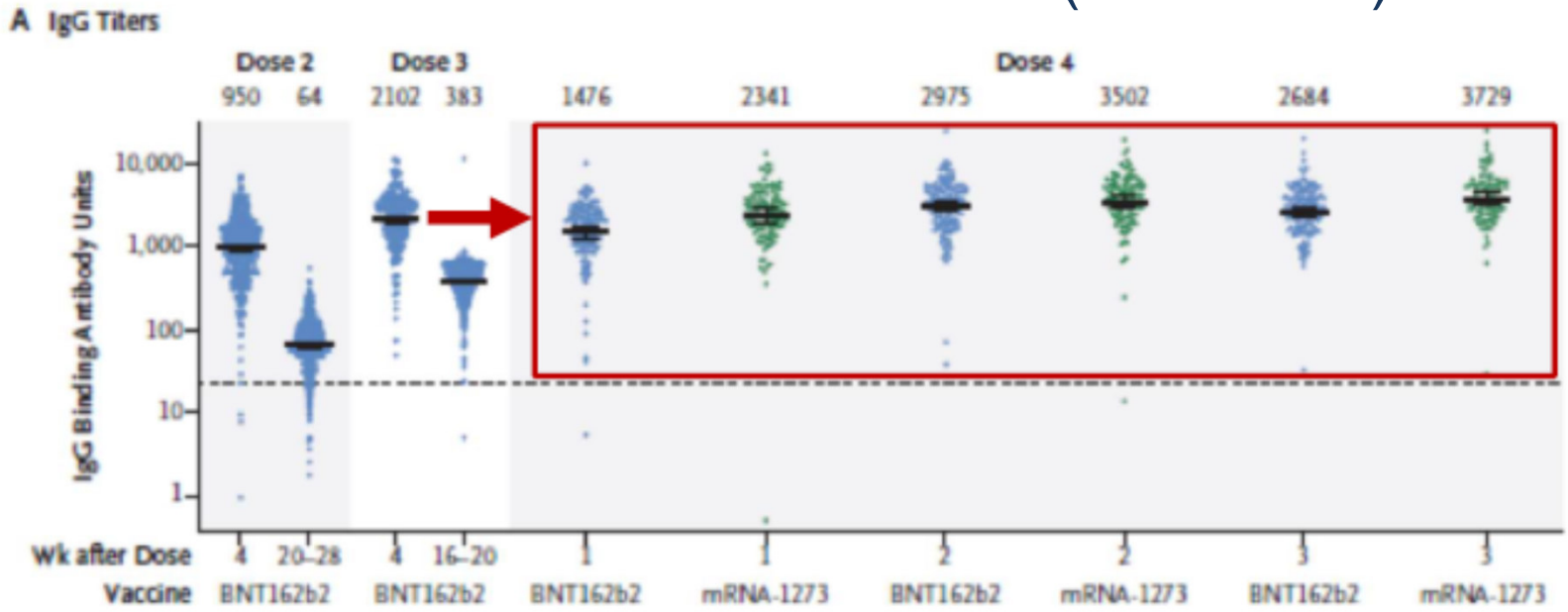
Lessons learned from the SARS-CoV-2 pandemic - vaccines, neutralising antibodies, antigen tests -

- Vaccine platforms and efficacy
- Booster vaccinations
- Vaccine pharmacovigilance

- CoV-2 neutralising antibodies
- Rapid antigen tests

- Summary

mRNA-induced humoral reponses wane within weeks or months,
4th RNA vaccine dose (2nd booster) increase anti-Omicron antibody titers
to the level after 3rd RNA dose (1st booster)

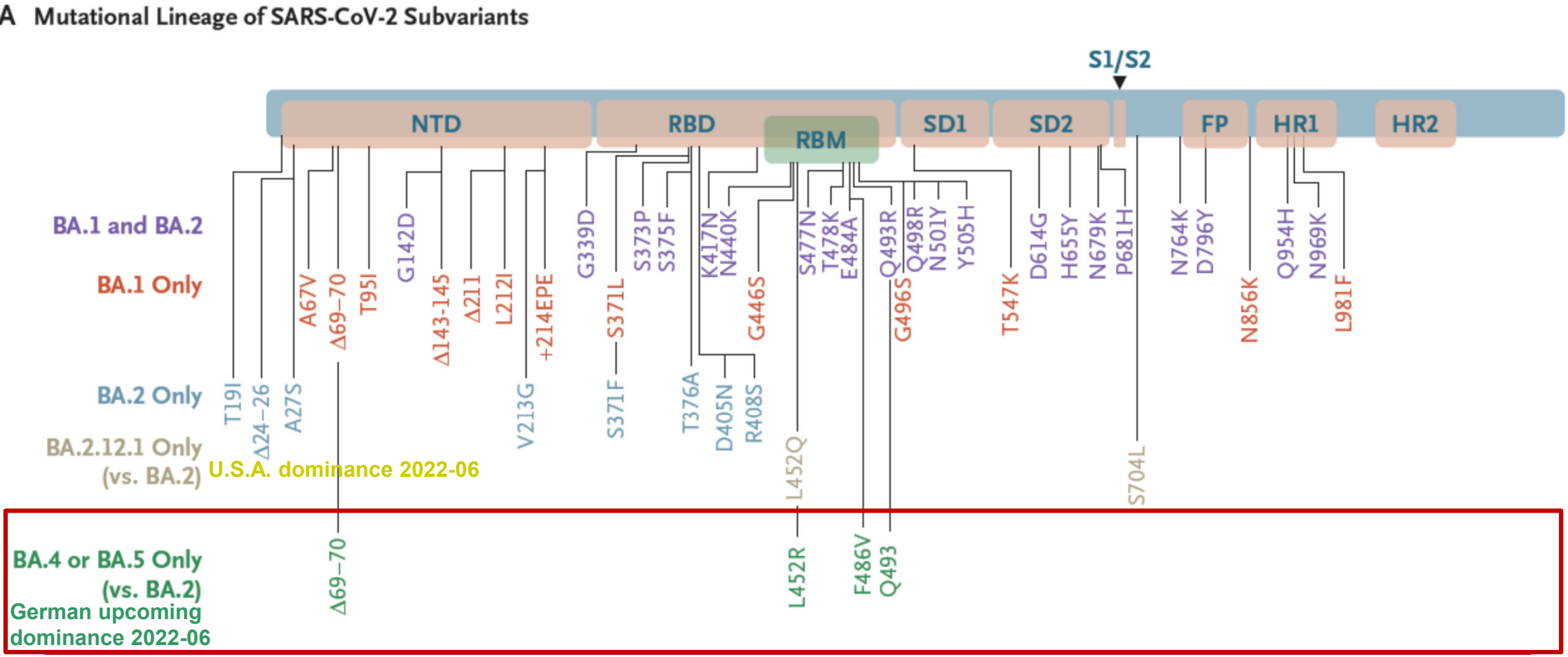


**-> Good level of protection against COVID-19,
reduced level of protection against infection.**

**-> Next generation COVID-19 booster vaccines shall induce
a broader immune response,
hopefully also against future escape variants.**

-Yochay *et al.* (2022) New Engl J Med

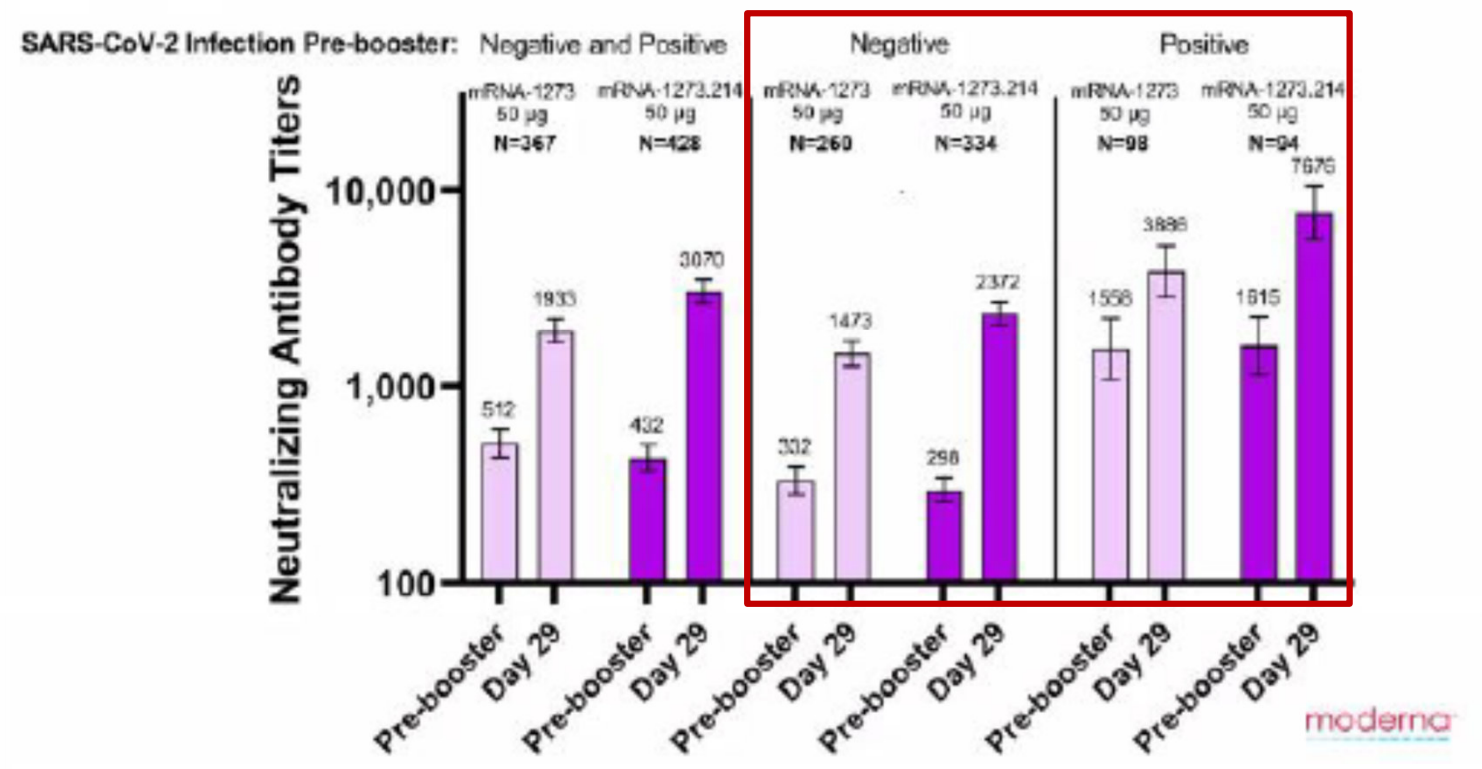
Omicron sublineages display escape mutations in the receptor-binding domain and N-terminal domain



RBM: receptor-binding motif

Omicron-adapted COVID-19 vaccines for autumn 2022
- bivalent Wuhan/Omicron candidate vaccines -

Figure 1 **Omicron Neutralizing Antibody Geometric Mean Titers post second boost after 50 µg bivalent mRNA-1273.214 or 50 µg prototype mRNA-1273 Booster**



-> Increase of neutralising antibody titers

-> Induction of antibodies against Omicron variant(s) (BA.1)

-> Goal: broadening of antibody response against BA.5 and future variants

Omikron-adapted COVID-19 vaccines for autumn 2022
- bivalent Wuhan/Omicron candidate vaccines -

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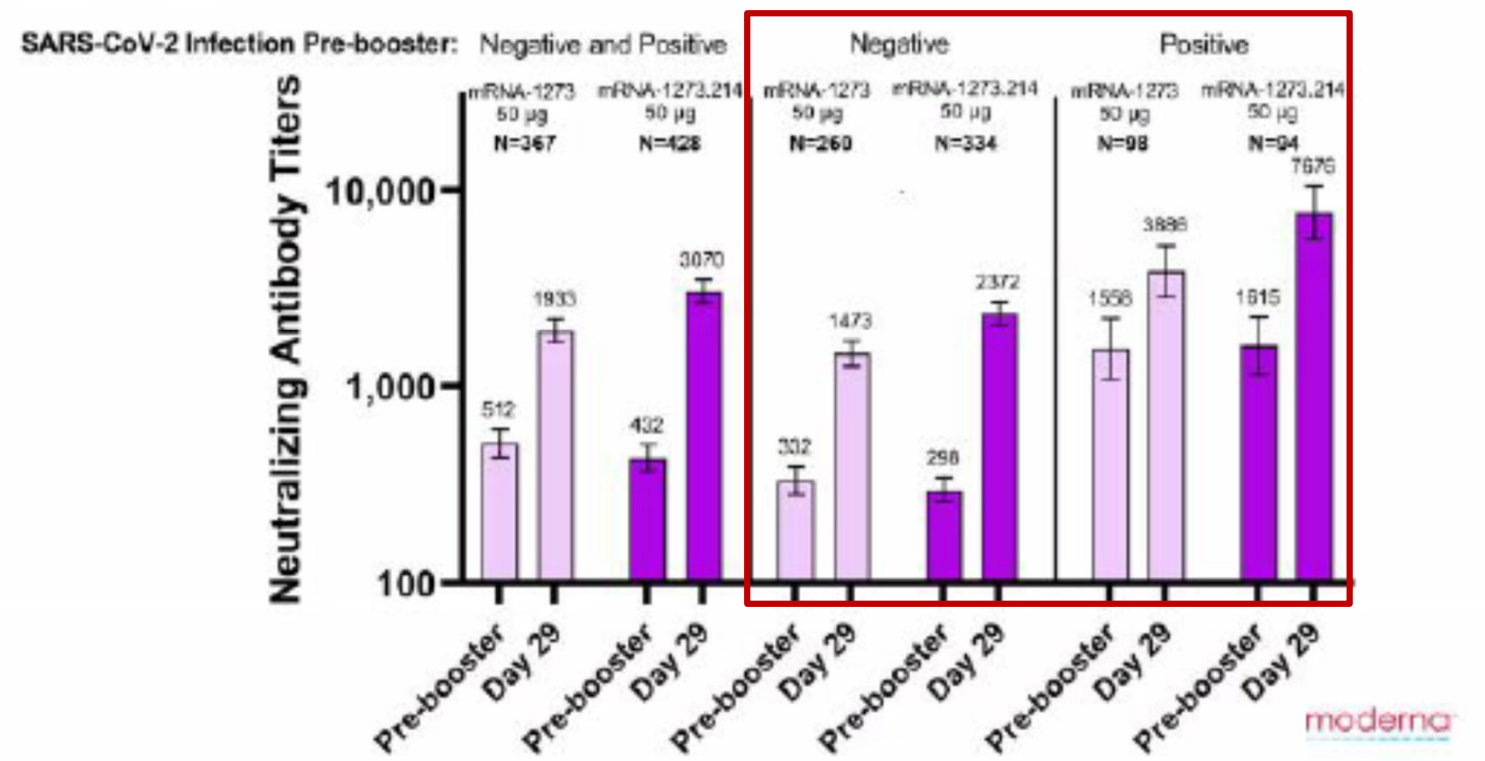


-> How do we keep up the development of variant-adapted COVID vaccines?

-> How do we adapt the regulation of such vaccines?

19

Lessons learned from the SARS-CoV-2 pandemic - vaccines, neutralising antibodies, antigen tests -

- Vaccine platforms and efficacy
- Booster vaccinations
- Vaccine pharmacovigilance (Keller-Stanislawski et al.)

- CoV-2 neutralising antibodies
- Rapid antigen tests

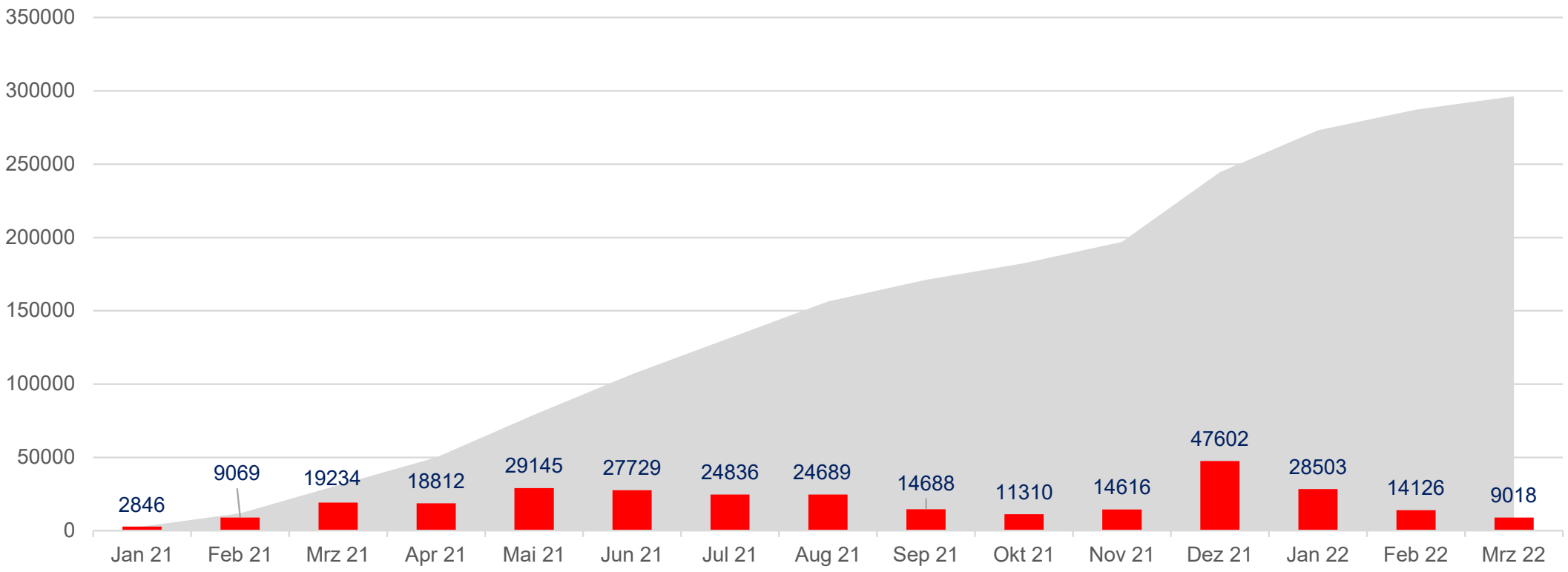
- Summary

COVID-19 vaccine doses administered in the EU/ EEA (24 April 2022; www.ema.europa.eu)

vaccine	MA holder	doses
Comirnaty	BioNTech	627.000.000
Spikevax	Moderna	135.000.000
Vaxzevria	AstraZeneca	69.000.000
Jcovden	Janssen-Cilag	19.400.000
Nuvaxovid	Novavax	178.000
		0.8 billion

Spontanmeldungen Verdachtsfälle an das PEI (1.1.2021-31.03.2022)

Anzahl Meldungen Verdachtsfälle von Nebenwirkungen pro Monat und kumulativ (PEI)



Regulatory assessment of reported suspected adverse reactions

Report of a suspected adverse reaction

Assessment of individual cases taking prior diseases and additional clinical information into account

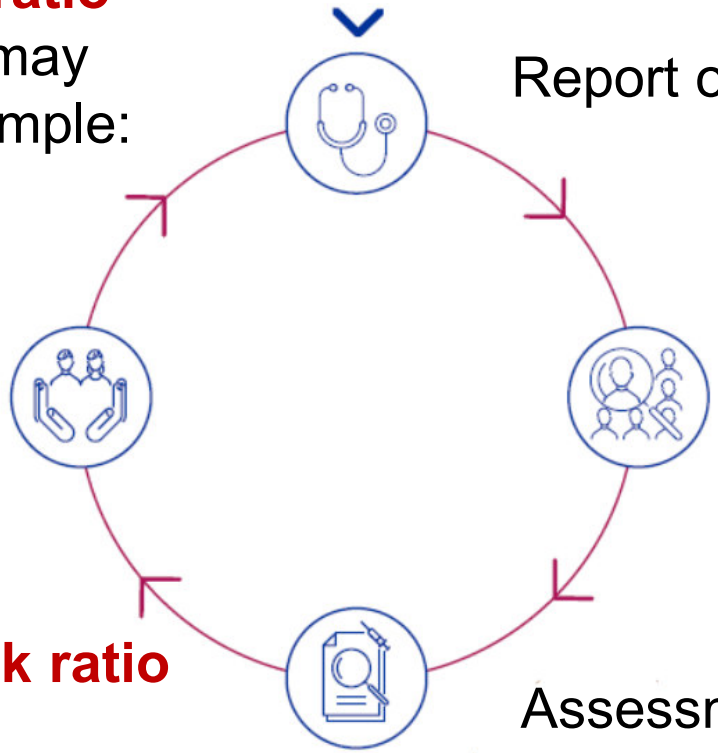
Assessment on the basis of statistical considerations, clinical study results and scientific publications

Regulatory assessment of reported suspected adverse reactions

Favourable benefit-risk ratio

New and increased risks may require measures, for example:

- modified indication(s)
- contra indications
- warning statements
- compulsory physical examinations or tests



Report of a suspected adverse reaction

Assessment of individual cases taking prior diseases and additional clinical information into account

Assessment on the basis of statistical considerations, clinical study results and scientific publications

Unfavourable benefit-risk ratio

Withdrawal of marketing authorisation of the vaccine product

Very rare serious adverse reactions to COVID-19 vaccines

- Ca. 1 Mrd. einillion Covid vaccine doses until 05-2022 in EU/EEA
- <10 reported suspected serious adverse reactions per 10.000 doses

- *Myocarditis/Pericarditis* post mRNA vaccinations
  - Erhöhtes Risiko bei jungen Männern <30 Jahre nach zweiter Dosis
  - Überwiegende Mehrheit (Peri-/Myokarditis-Patienten) spricht gut auf Behandlung an
  - Risiko sehr selten, aber etwas höher bei Spikevax im Vergleich zu Comirnaty

- *Anaphylaxis* post all COVID vaccines licensed in the EU
  - weniger als 1 Fall pro 100.000 Impfungen
  - vermutlich mehrheitlich nicht IgE-vermittelt, sondern über Komplement (CARPA complement activation-related pseudoallergy)

- *TTS* post adenovector vaccines, lethal outcome in single cases
- *GBS* post adenovector vaccines: 0.88 and 1.89 per 100.000 doses, respectively (Vaxzevria, Janssen)
- *ITP* (Immunthrombozytopenie), single reports post Janssen/Vaxzevria
- *Thrombosis* study results inconsistent – risk due to COVID-19 higher than post COVID vaccination

Figure 6

Parallels in Pathogenesis of VITT and autoimmune HIT

	VITT	aHIT
Anti-PF4 immunization (peri-vaccination)		
Antigen formation	PF4 binding to virus proteins and other anionic constituents in the vaccine => PF4/polyanion complexes	PF4 binding to heparin, bacterial polyanions, or DNA => PF4/polyanion complexes
Inflammatory co-signal	Vaccine EDTA-induced vascular leakage. Natural (preformed) antibodies bind to vaccinal viral and human proteins => immune complexes, inflammation, symptoms similar to serum sickness	Tissue trauma or infection Knee replacement surgery (tourniquet) (HIT pathogenesis: surgical > medical patients major > minor surgery)
=> IgG production ≥5 days later		
Immuno-thrombosis (≥5 days post-vaccination)	High-avidity anti-PF4 IgG autoantibodies induce platelet activation via FcγIIa receptors	High-avidity anti-PF4 IgG autoantibodies induce platelet activation via FcγIIa receptors (no heparin needed)
Thrombosis	Anti-PF4 IgG-induced granulocyte activation =>NETosis (with DNase deficiency) Polyanion-dependent and -independent anti-PF4 antibodies bind to PF4/DNA complexes in NETs => amplification	Anti-PF4 IgG-induced granulocyte activation =>NETosis (with DNase depletion) Polyanion-dependent and -independent anti-PF4 antibodies bind to PF4/DNA complexes in NETs => amplification

Proof of mechanism underlying TTS associated with COVID-19 adenovector vaccines

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Thrombotic Thrombocytopenia after ChAdOx1 nCov-19 Vaccination

Andreas Greinacher, M.D., Thomas Thiele, M.D., Theodore E. Warkentin, M.D., Karin Weisser, Ph.D., Paul A. Kyrle, M.D., and Sabine Eichinger, M.D.

ABSTRACT

BACKGROUND

Several cases of unusual thrombotic events and thrombocytopenia have developed after vaccination with the recombinant adenoviral vector encoding the spike protein antigen of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (ChAdOx1 nCov-19, AstraZeneca). More data were needed on the pathogenesis of this unusual clotting disorder.

METHODS

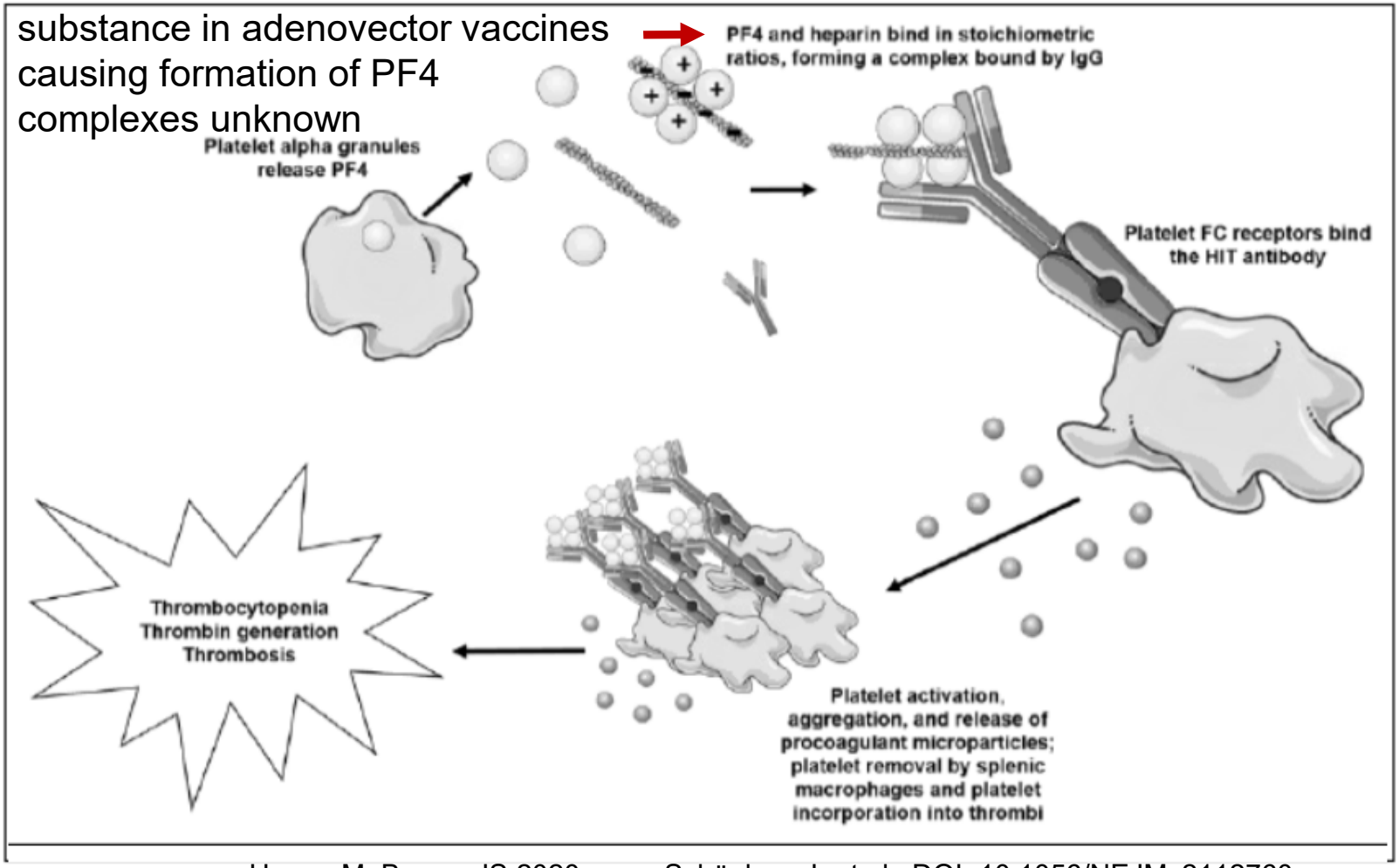
We assessed the clinical and laboratory features of 11 patients in Germany and Austria in whom thrombosis or thrombocytopenia had developed after vaccination with ChAdOx1 nCov-19. We used a standard enzyme-linked immunosorbent assay to detect platelet factor 4 (PF4)–heparin antibodies and a modified (PF4-enhanced) platelet-activation test to detect platelet-activating antibodies under various reaction conditions. Included in this testing were samples from patients who had blood samples referred for investigation of vaccine-associated thrombotic events, with 28 testing positive on a screening PF4–heparin immunoassay.

RESULTS

Of the 11 original patients, 9 were women, with a median age of 36 years (range, 22 to 49). Beginning 5 to 16 days after vaccination, the patients presented with one or more thrombotic events, with the exception of 1 patient, who presented with fatal intracranial hemorrhage. Of the patients with one or more thrombotic events, 9 had cerebral venous thrombosis, 3 had splanchnic-vein thrombosis, 3 had pulmonary embolism, and 4 had other thromboses; of these patients, 6 died. Five patients had disseminated intravascular coagulation. None of the patients had received heparin before symptom onset. All 28 patients who tested positive for antibodies against PF4–heparin tested positive on the platelet-activation assay in the presence of PF4 independent of heparin. Platelet activation was inhibited by high levels of heparin, Fc receptor–blocking monoclonal antibody, and immune globulin (10 mg per milliliter). Additional studies with PF4 or PF4–heparin affinity purified antibodies in 2 patients confirmed PF4-dependent platelet activation.

CONCLUSIONS

Vaccination with ChAdOx1 nCov-19 can result in the rare development of immune thrombotic thrombocytopenia mediated by platelet-activating antibodies against PF4, which clinically mimics autoimmune heparin-induced thrombocytopenia. (Funded by the German Research Foundation.)



Hogan M, Berger JS 2020 Schönborn L et al., DOI: 10.1056/NEJMc2112760

COVID-19 vaccine safety and regulation made fully transparent

Bundesinstitut für Impfstoffe und biomedizinische Arzneimittel
Federal Institute for Vaccines and Biomedicines

Paul-Ehrlich-Institut

Langen, den 04.05.2022

SICHERHEITSBERICHT

Das Paul-Ehrlich-Institut fasst im aktuellen Sicherheitsbericht die Meldungen über Verdachtsfälle von Nebenwirkungen und Impfkomplikationen zusammen, die es seit Beginn der Impfkampagne in Deutschland am 27.12.2020 bis zum 31.03.2022 erhalten hat.

Inhalt

Bundesinstitut für Arzneimittel und Medizinprodukte

Paul-Ehrlich-Institut

BULLETIN ZUR ARZNEIMITTELSICHERHEIT

Informationen aus BfArM und PEI

INHALT Ausgabe 1 | März 2022

Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM)
Das BfArM überprüft die Wirksamkeit, Sicherheit und Qualität von Arzneimitteln. Auch nach der Zulassung wertet das BfArM neue Hinweise auf Gesundheitsrisiken systematisch aus und koordiniert Maßnahmen zur Risikominimierung. Neben der kontinuierlichen Verbesserung der Arzneimittelsicherheit durch Zulassung, Pharmakovigilanz und Forschung sind die Genehmigung klinischer Prüfungen, die Risikobewertung von Medizinprodukten und die Überwachung des Betäubungsmittelverkehrs weitere Aufgaben des BfArM.

Paul-Ehrlich-Institut (PEI)
Das Bundesinstitut für Impfstoffe und biomedizinische Arzneimittel überprüft die Qualität, Wirksamkeit und Unbedenklichkeit von Human- und Veterinärimpfstoffen, Allergenen, Blutprodukten und Gewebezubereitungen, Antikörpern, Sera, Zell-/Gentherapeutika und Tissue-Engineering-Produkten für den Menschen. Zu den Aufgaben gehören die Genehmigung klinischer Prüfungen, Zulassung, staatliche Chargenprüfung und Sicherheitsbewertung biomedizinischer Arzneimittel und von Hochrisiko-In-vitro-Diagnostika.

ZIEL
Das vierteljährlich erscheinende Bulletin zur Arzneimittelsicherheit informiert aus beiden Bundesoberbehörden zu aktuellen Aspekten der Risikobewertung von Arzneimitteln. Ziel ist es, die Kommunikation möglicher Risiken von Arzneimitteln zu verbessern und die Bedeutung der Überwachung vor und nach der Zulassung (Pharmakovigilanz) in den Blickpunkt zu rücken.

MELDUNG VON VERDACHTSFÄLLEN
Das Meldesystem von Verdachtsfällen von Nebenwirkungen ist ein wichtiges Früherkennungssystem im Bereich der Arzneimittelsicherheit nach der Zulassung. Beide Behörden rufen alle Angehörigen von Heilberufen nachdrücklich dazu auf, Verdachtsfälle auf Arzneimittelnebenwirkungen bzw. Impfkomplikationen nach der Zulassung zu melden. Insbesondere bei Meldungen im Zusammenhang mit der Anwendung biologischer Arzneimittel (arzneilich wirksame Bestandteile, die aus Ausgangsmaterial biologischen Ursprungs gewonnen werden) sollte die Chargennummer mit angegeben werden, um die Rückverfolgbarkeit zu erleichtern. Für die Meldung von Impfreaktionen nach § 11 Abs. 4 des Infektionsschutzgesetzes (IfSG) sowie von unerwünschten Wirkungen im Zusammenhang mit der Anwendung von Blutprodukten und gentechnisch hergestellten Plasmaproteinen nach § 16 Abs. 2 des Transfusionsgesetzes (TFG) ist die Angabe der Chargennummer gesetzlich vorgeschrieben.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

12 May 2022

COVID-19 vaccines safety update

Comirnaty (BioNTech Manufacturing GmbH)
Jcovden (previously COVID-19 Vaccine Janssen) (Janssen-Cilag International NV)
Nuvaxovid (Novavax CZ, a.s.)
Spikevax (Moderna Biotech Spain, S.L.)
Vaxzevria (AstraZeneca AB)

The safety of authorised COVID-19 vaccines is continuously monitored and updated information is regularly provided to the public.

Safety updates outline the outcomes from assessments of emerging worldwide safety data carried out mainly by EMA's Pharmacovigilance Risk Assessment Committee (PRAC) (section 1). They also outline how safety is monitored and contain high-level information on suspected adverse reaction reports, which PRAC takes into account in its assessments (section 2).

This safety update follows the update of 13 April 2022 and reflects the main assessment outcomes of the PRAC meeting held 02 to 05 May 2022.

EMA confirms that the benefits of all currently authorised COVID-19 vaccines continue to outweigh their side effects, given the risk of COVID-19 illness and related complications, including hospitalisation and death.

Lessons learned from the SARS-CoV-2 pandemic
- vaccines, neutralising antibodies, antigen tests -

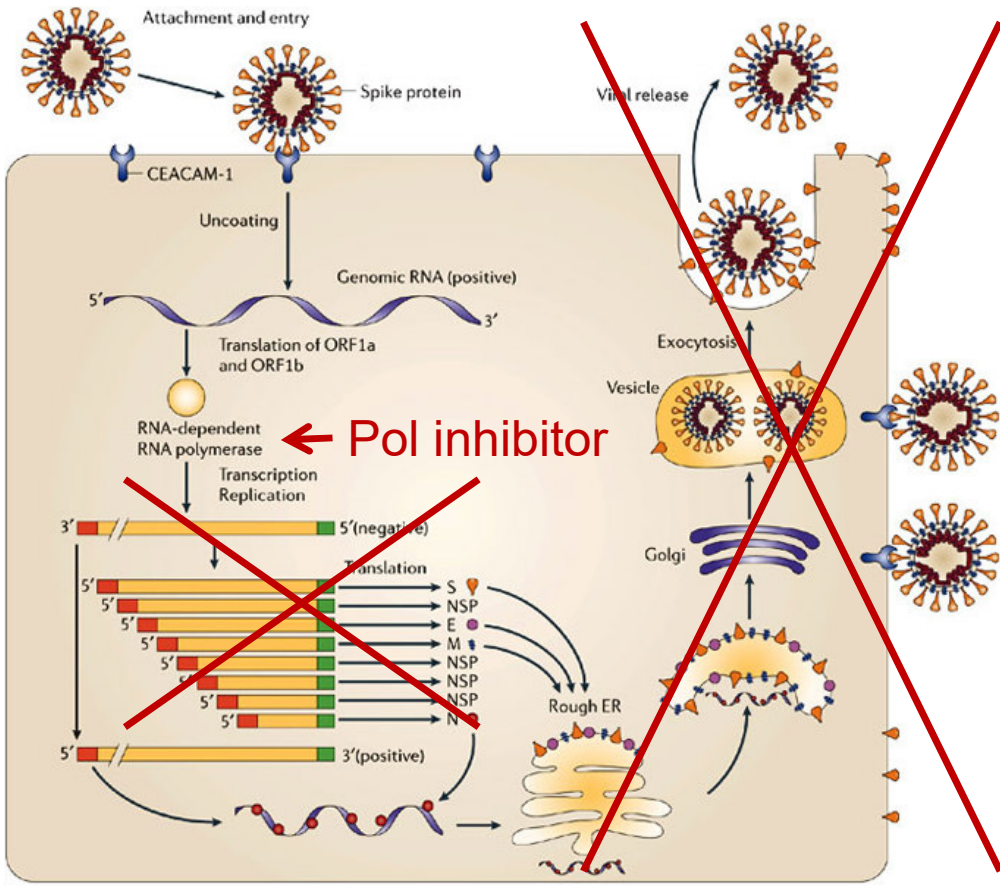
- Vaccine platforms and efficacy
- Booster vaccinations
- Vaccine pharmacovigilance

- CoV-2 neutralising antibodies (van Zandbergen, Groß, Klug et al.)
- Rapid antigen tests

- Summary

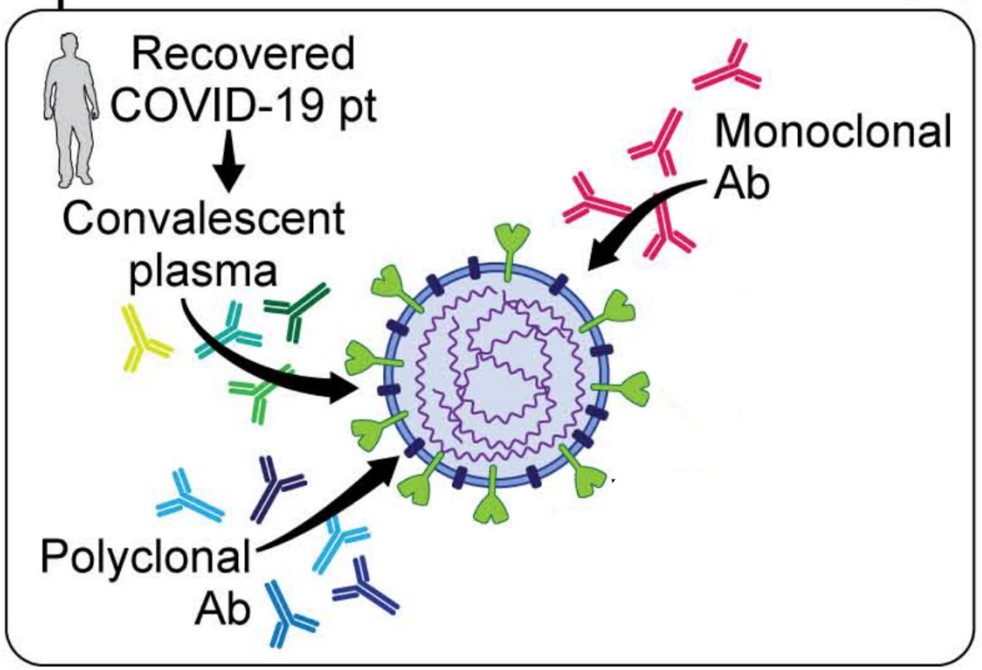
Medicines for Covid-19 therapy

- Viral replication inhibitors (molnupiravir, paxlovid)
  - Reduce multiplication of viral genomes and new virus particle formation within each infected cell
- Neutralising antibody-containing medicines reducing spread of virus within the body
  - Neutralising monolconal antibodies and antibody cocktails
  - Specific immunoglobulin preparations
  - Convalescent plasma (directional administration)
- Immunomodulation
  - Monoclonal antibodies reducing cytokine storm targeting e.g. the IL-6 receptor



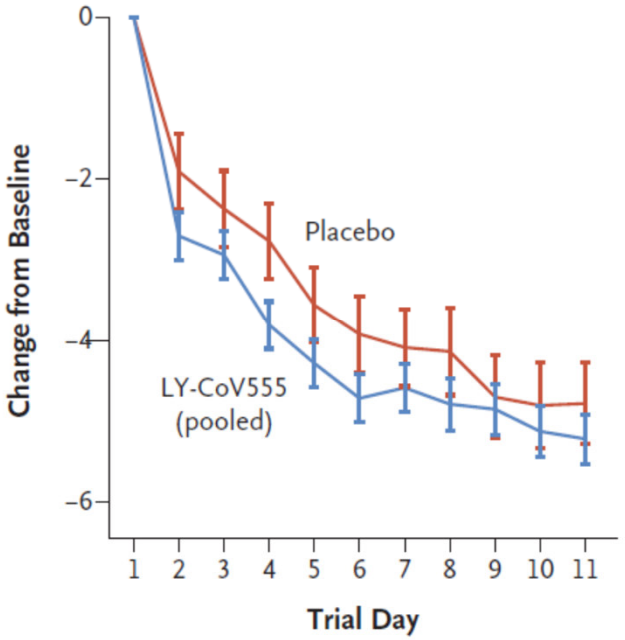
Biomedicines for Covid-19 therapy

- Viral replication inhibitors (small molecules)
  - Reduce the multiplication of viral genomes and new virus particle formation within each infected cell
- Neutralising antibody-containing medicines reducing spread of virus within the body
  - Neutralising monoclonal antibodies and antibody cocktails
  - ~~Specific immunoglobulin preparations~~
  - ~~Convalescent plasma (directional administration)~~
- Immunomodulation
  - Dexamethasone
  - Monoclonal antibodies reducing cytokine storm targeting e.g. the IL-6 receptor



Neutralising monoclonal antibodies for Covid-19 therapy (Feb. 2021)

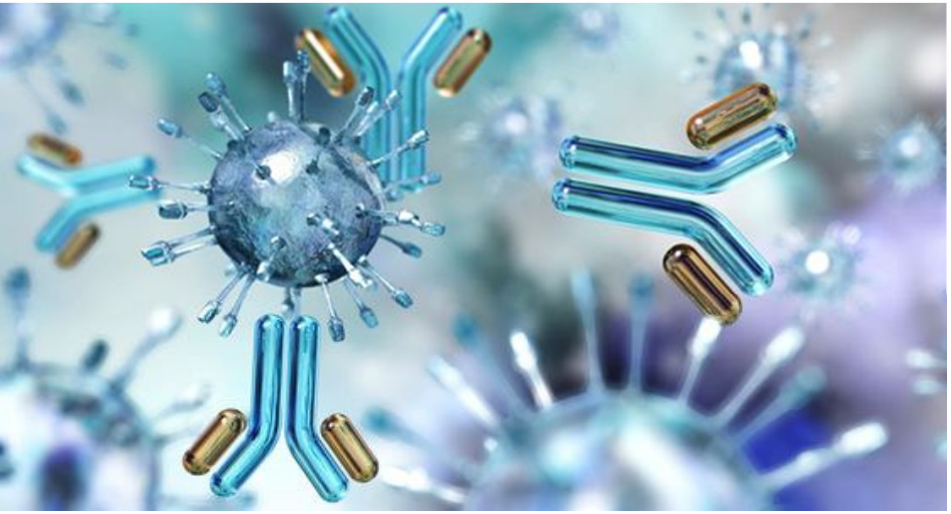
In this interim analysis of a phase 2 trial, one of three doses of neutralizing antibody LY-CoV555 appeared to accelerate the natural decline in viral load over time, whereas the other doses had not by day 11. (Funded by Eli Lilly; BLAZE-1 ClinicalTrials.gov number, NCT04427501.)



	Delta Value (95% CI)
Day 2	−0.79 (−1.35 to −0.24)
Day 3	−0.57 (−1.12 to −0.01)
Day 4	−1.04 (−1.60 to −0.49)
Day 5	−0.73 (−1.28 to −0.17)
Day 6	−0.79 (−1.35 to −0.23)
Day 7	−0.50 (−1.06 to 0.07)
Day 8	−0.65 (−1.28 to −0.02)
Day 9	−0.15 (−0.75 to 0.45)
Day 10	−0.32 (−0.94 to 0.29)
Day 11	−0.44 (−1.02 to 0.15)

Figure 3. Symptom Scores from Day 2 to Day 11.

Shown is the difference in the change from baseline (delta value) in symptom scores between the LY-CoV555 group and the placebo group from day 2 to day 11. The symptom scores ranged from 0 to 24 and included eight domains, each of which was graded on a scale of 0 (no symptoms) to 3 (severe symptoms). The I bars represent 95% confidence intervals. Details about the symptom-scoring methods are provided in the Supplementary Appendix.



SARS-CoV-2-neutralizing mAbs

	Wiltype	Delta	BA.1	BA.2	BA.5
Ronapreve/Regn-CoV2 (Casirivimab/Imdevimab) Roche/Regeneron Since 12.11.2021 EU/1/21/1601/001; in Germany available via MedBVSV Artikel 5(3) **(treatment / prophylaxis)**	✓	✓			
 **Regkirona** (Regdanvimab) Celltrion Since 12.11.2021 EU/1/21/1597/001; not launched yet **(treatment)**	✓	✓			
 **Xevudy** (Sotrovimab) GSK Since 17.12.2021 EU/1/21/1562/001; launched in Germany since 01/2022 **(treatment)**	✓	✓	✓	✓	
 **Evusheld** (Tixagevimab/Cilgavimab) AstraZeneca Since 18.02.2022 EMEA/H/C/005788; in Germany available via MedBVSV Artikel 5(3) **(prophylaxis/*treatment ongoing line ext.*)**	✓	✓	✓	✓	✓

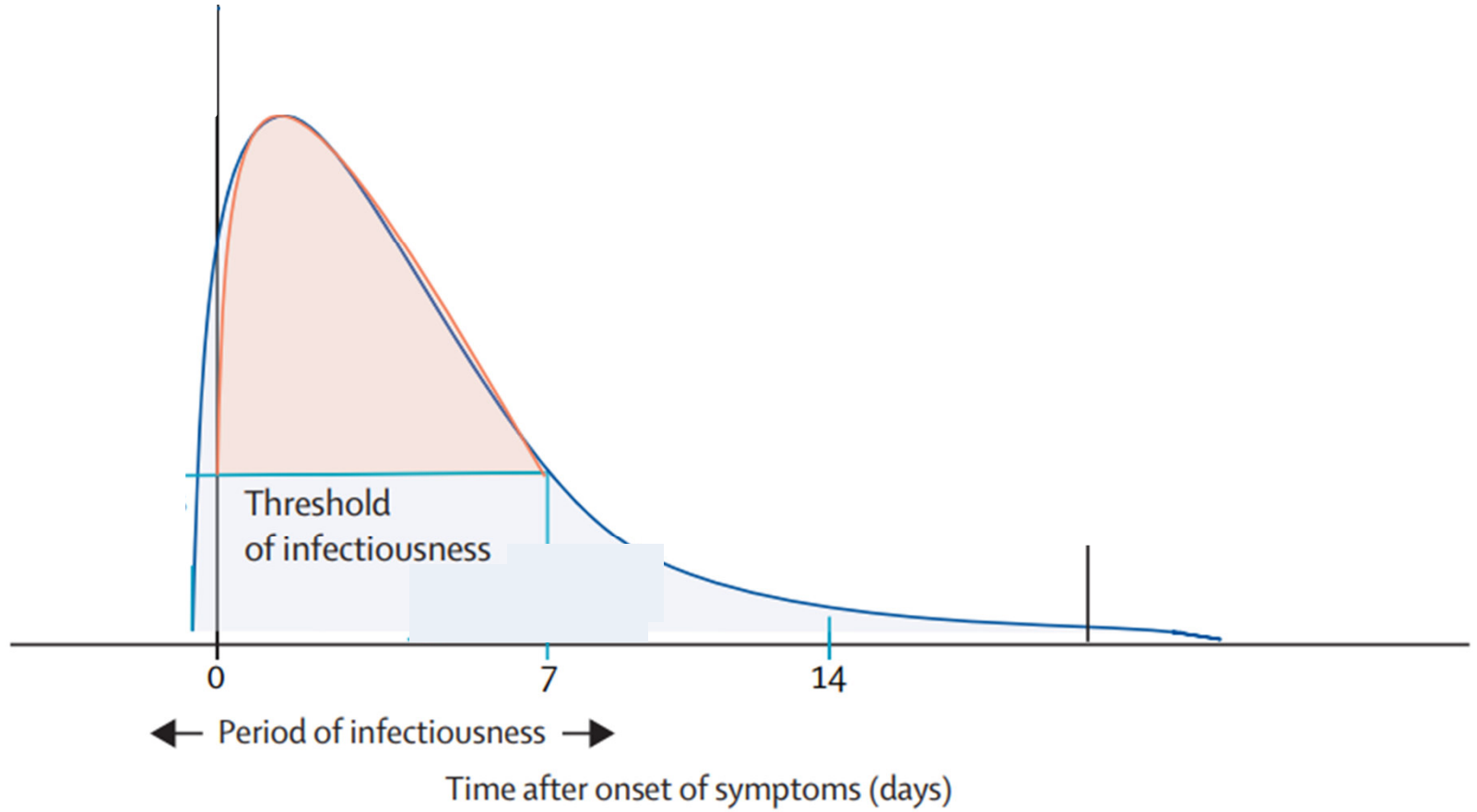
Lessons learned from the SARS-CoV-2 pandemic - vaccines, neutralising antibodies, antigen tests -

- Vaccine platforms and efficacy
- Booster vaccinations
- Vaccine pharmacovigilance

- CoV-2 neutralising antibodies
- Rapid antigen tests (Nübling, Scheiblauer)

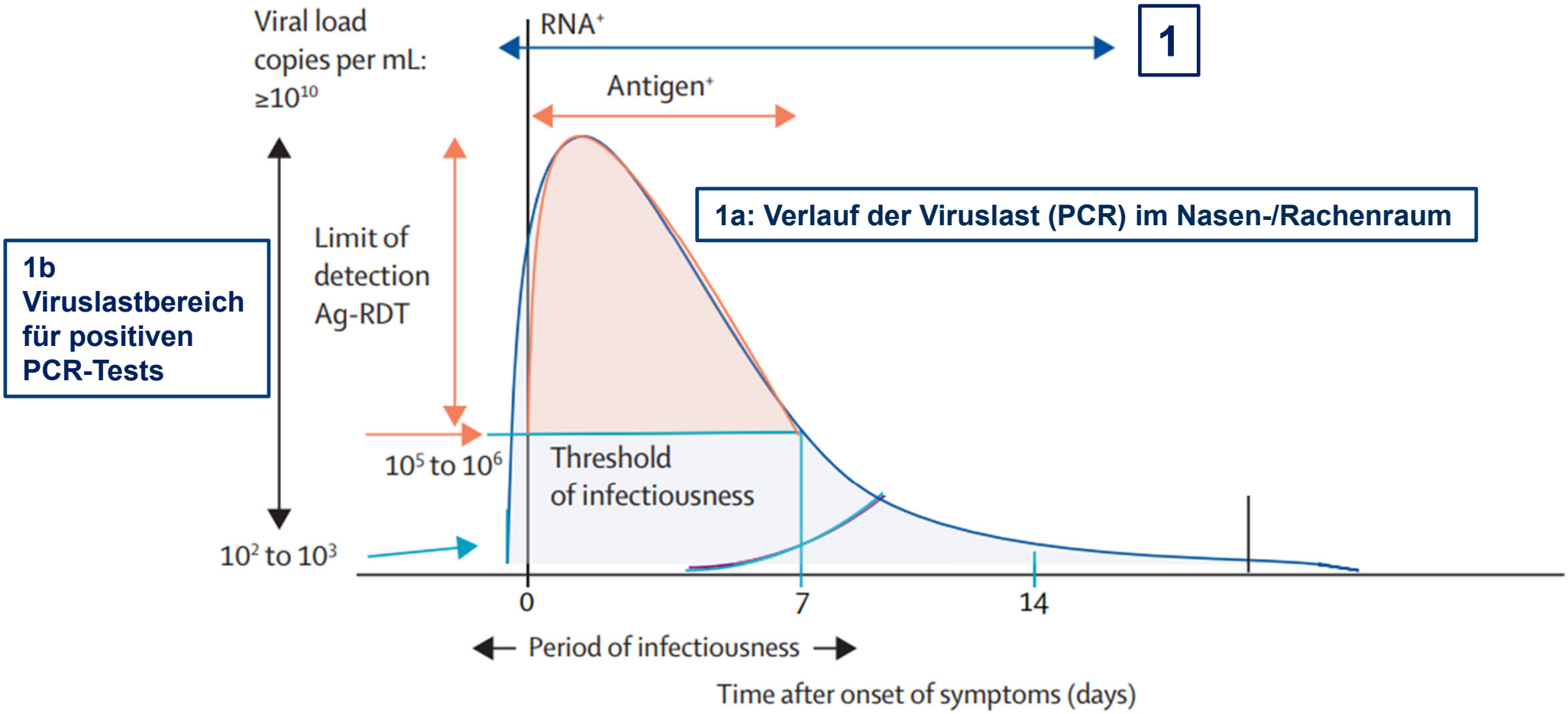
- Summary

Course of SARS-CoV-2 load in nasopharynx - PCR and rapid antigen test results both positive for high virus loads-



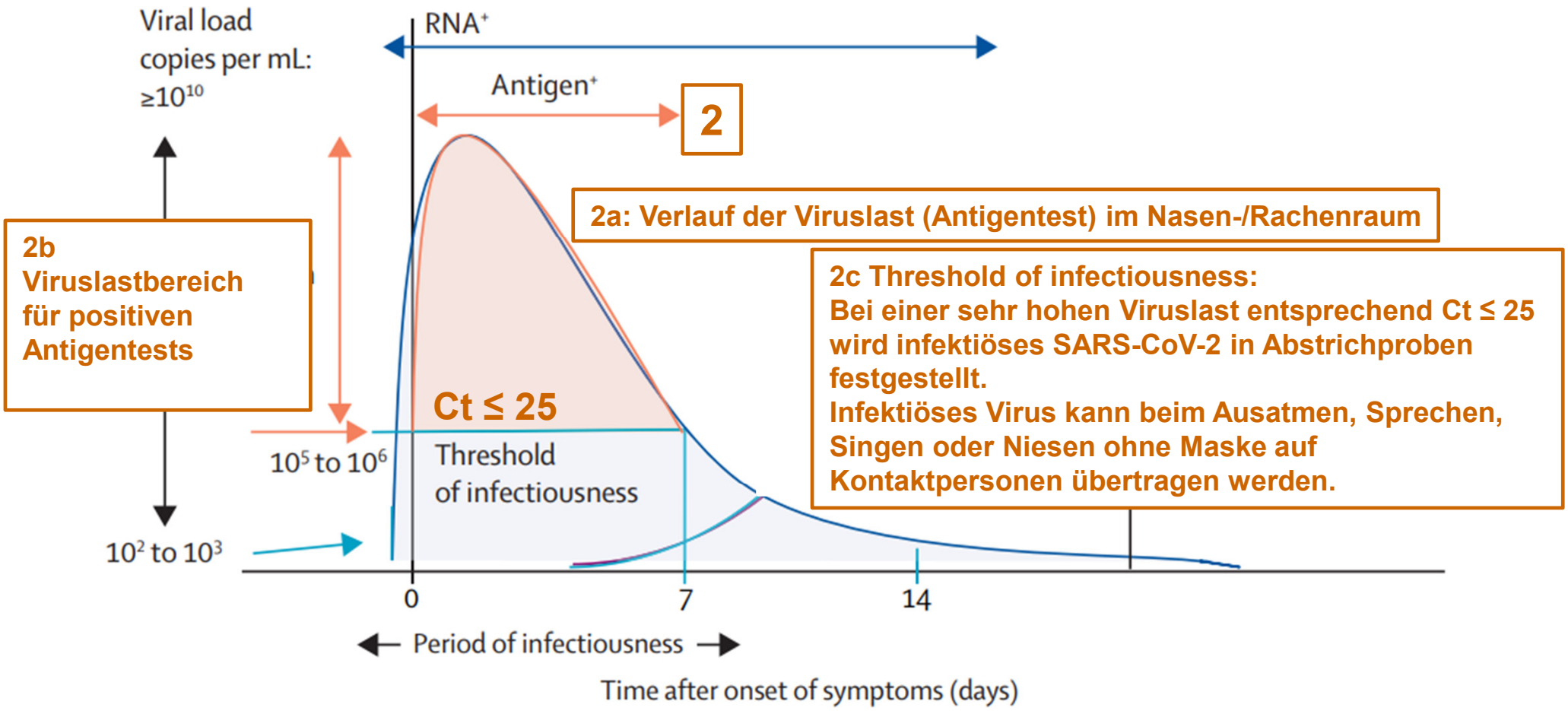
Quelle*:* Peeling et al (2022). The Lancet 399, 757-768

PCR tests positive for a wide range of virus loads
- reliable detection of CoV-2 infection at all stages of disease/infection -



Quelle*:* Peeling et al (2022). The Lancet 399, 757-768

Rapid antigen tests postive for high virus loads
- detection of persons posing a risk for transmission (very high virus loads) -

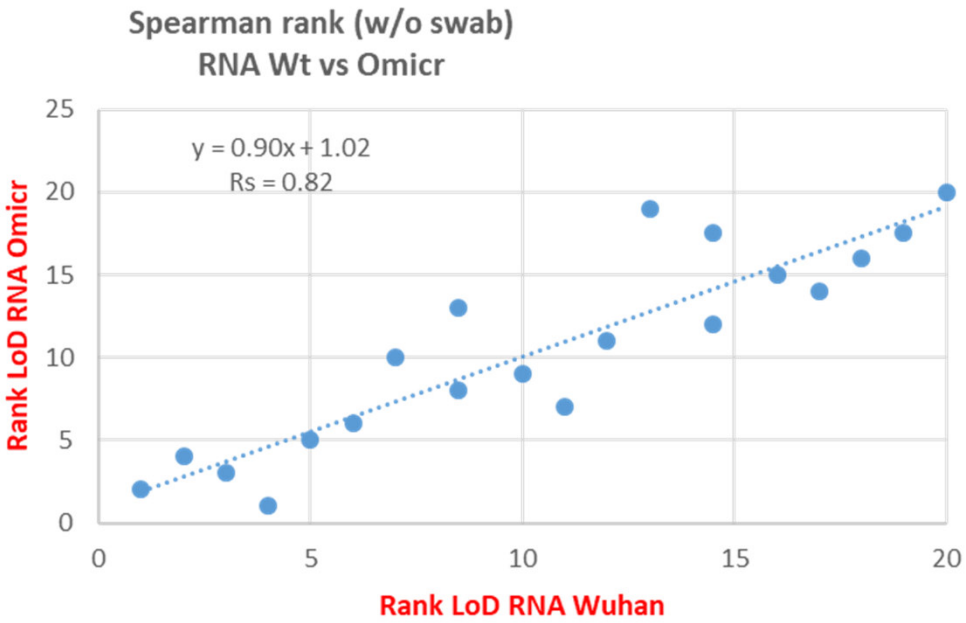


Niedriger Ct-Wert = hohe Viruslast

Quelle: Peeling et al (2022). The Lancet 399, 757-768

Antigen test sensitivity: Wuhan vs Omicron (PEI mit IM Bundeswehr)

PEI-Liste Rank			1	7
Wuhan				
	2,80E+08			
		Viral RNA copies per sample (25 µl)		
1	8	8,8E+08	387	18
2	32	2,2E+08	279	8
3	128	5,5E+07	189	4
4	512	1,4E+07	52	5
5	2.048	3,4E+06	8	0
6	8.192	8,5E+05	0	0
LoD RNA			2,E+06	1,E
Omicron				
	1,50E+08			
		Viral RNA copies per sample (25 µl)		
1	8	4,7E+08	352	19
2	32	1,2E+08	277	12
3	128	2,9E+07	182	3
4	512	7,3E+06	24	3
5	2.048	1,8E+06	4	2
6	8.192	4,6E+05	0	0
LoD RNA			1,E+06	7,E



- Sensitivity ranking of CoV-2 antigen tests :
  - similar for Wuhan vs Omicron (PEI mit IM Bundeswehr)
- CoV-2 antigen tests not affected by the four Omicron mutations in the N protein (test target)
  - Labeled “ja” in list of antigen tests which can be reimbursed

Kooperationen / Danksagung

- Robert-Koch-Institut (RKI) Berlin: Prof. Andreas Nitsche, Dr. Andreas Puyskens, Dr. Janine Michel
- Institut für Mikrobiologie der Bundeswehr (IMB), München: Dr. Katrin Zwirglmaier, Prof. Roman Wölfel
- Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM) Berlin, Abt. 93 aktive Medizinprodukte und In-vitro-Diagnostika: Dr. Ekkehard Stößlein, Dr. Laura van Diepen, Dr. Kathrin Dörr
- Paul-Ehrlich-Institut, Langen: Dr. Angela Filomena, Dr. Katharina Esser-Nobis, Dr. Carla Steffanowski, Dr. Micha Nübling
- Den Mitarbeitenden des IVD-Prüflabors am PEI für ihre hervorragende Arbeit und ihr hohes Engagement

Lessons learned from the SARS-CoV-2 pandemic - vaccines, neutralising antibodies, antigen tests -

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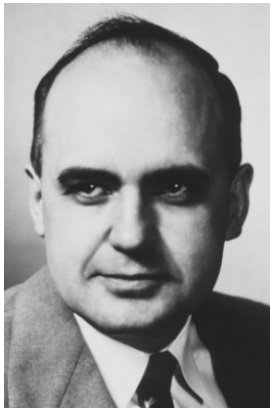
- Vaccine pharmacovigilance

- CoV-2 neutralising antibodies
- Rapid antigen tests

- Summary

Heroes of vaccine research and development



Maurice Hilleman
1919-2005

Live attenuated virus vaccines

- mumps
- measles
- rubella
- hepatitis A and B
- chickenpox…

Katalin Kariko

Pioneer in RNA technology

- 1999 in vivo transfer of RNA in mice mediates encoded protein expression (urokinase rec.)
- 2005 RNA methylation reduces acute innate immune response

Ugur Sahin

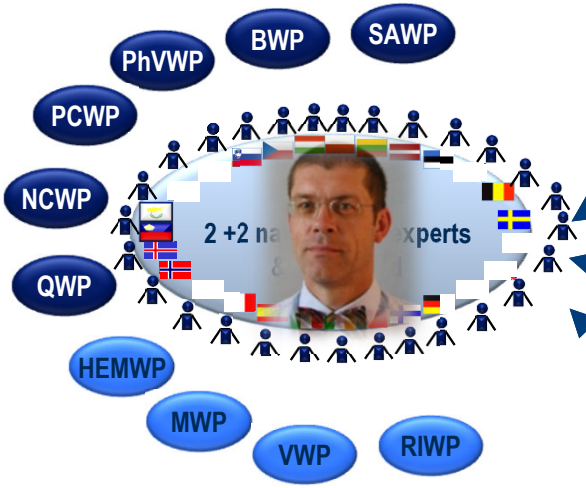
Cancer immunotherapy pioneer

- 1997 human tumour antigen serology/immunotherapy
- 2010 actively personalized cancer immunotherapy
- 2020 COVID-19 mRNA vaccine

Regulatory support for vaccine and biomedicine developments and pandemic preparedness

PRAC
Div. Pharmacovigilance, PEI

CHMP and WPs



Div. Virology, PEI (human viral vaccines)

Div. Immunology, PEI (antibodies)

GMDP
IWP

BWP

CTCG

Center for Pandemic Vaccines and Therapeutics
ZEPAI, PEI

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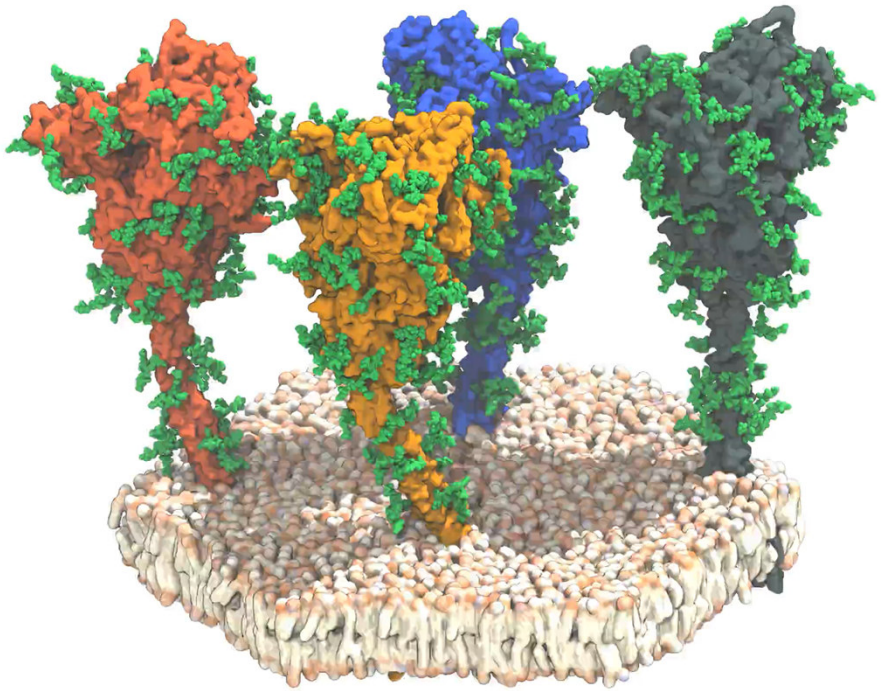

10.1126/science.abd5223 (2020).

In situ structural analysis of SARS-CoV-2 spike reveals flexibility mediated by three hinges

Beata Turoňová[1,2*], Mateusz Sikora[3*], Christoph Schürmann[4*], Wim J. H. Hagen[1], Sonja Welsch[5], Florian E. C. Blanc[5], Sören von Bülow[3], Michael Gecht[5], Katrin Bagola[6], Cindy Hörner[4,7], Ger van Zandbergen[6,8,9], Jonathan Landry[10], Nayara Trevisan Doimo de Azevedo[10], Shyamal Mosalaganti[1,2], Andre Schwarz[1], Roberto Covino[3,11], Michael D. Mühlebach[4,7], Gerhard Hummer[3,12†], Jacomine Krijnse Locker[13†], Martin Beck[1,2†]

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