EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Update of approved and candidate COVID-19 vaccines and therapeutics

Presented by Dr Marco Cavaleri on 1 June 2022
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Status of COVID-19 vaccines in the EU

Currently under rolling review

- **Sputnik V, Gam-COVID-Vac** (Gamaleya Institute)
- **COVID-19 Vaccine HIPRA (PHH-1V)** (HIPRA Human Health S.L.U.)
- **COVID-19 Vaccine (Vero Cell) Inactivated** (Sinovac)

Marketing authorisation application submitted

- **Vidprevtyn** (Sanofi Pasteur)
- **COVID-19 Vaccine Valneva**

Authorised for use in the European Union

- **Comirnaty** (BioNTech and Pfizer)
- **Nuvaxovid** (Novavax)
- **Spikevax** (Moderna)
- **Vaxzevria** (AstraZeneca)
- **Jcovden** (Janssen)

https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/treatments-vaccines/covid-19-treatments

6 April 2022
EMA/204784/2022

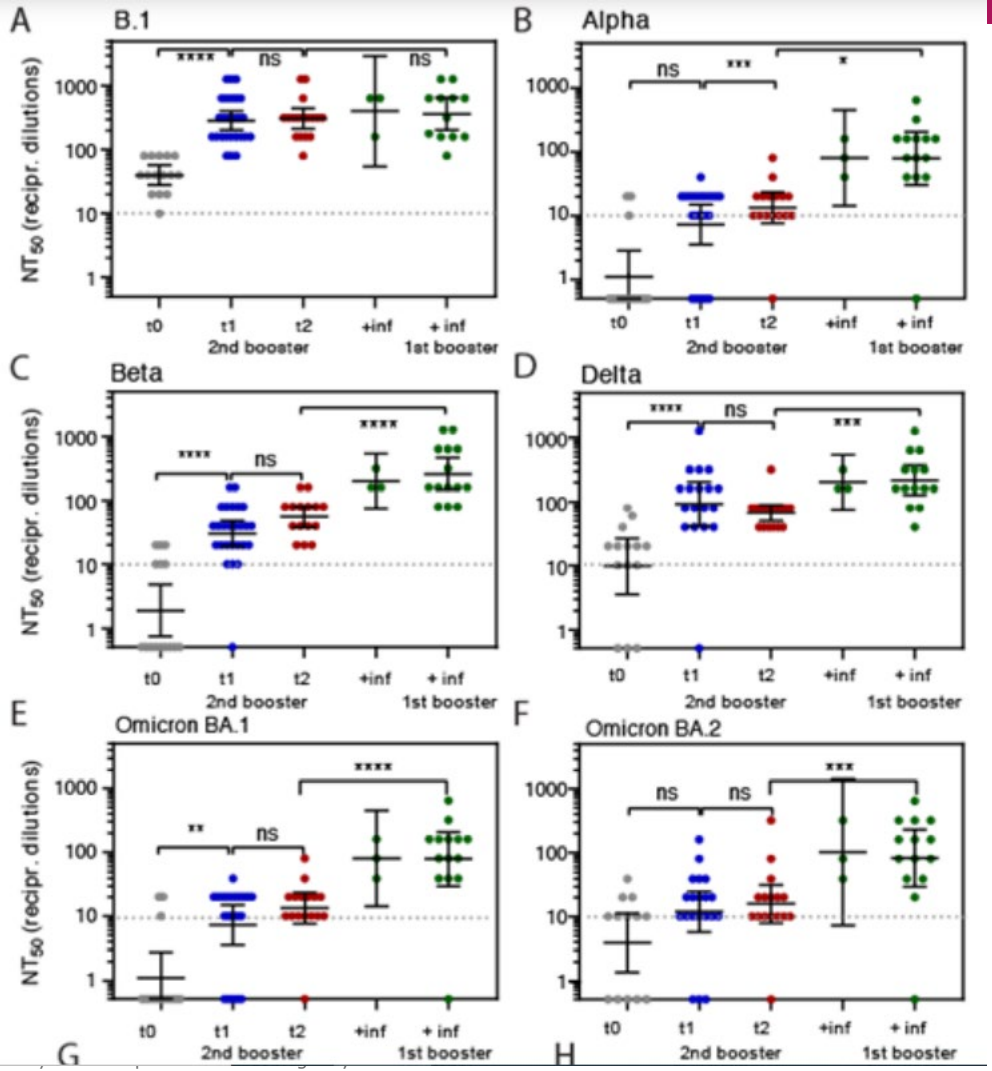
COVID-19: Joint statement from ECDC and EMA on the administration of a fourth dose of mRNA vaccines

Although data on the rate of waning protection among the very elderly (adults above 80 years of age) a second booster could be administered.

For immunocompetent individuals between 60 and 80 years of age, there are currently no clear epidemiological signals from the European region of substantial waning of vaccine protection against severe COVID-19. Therefore there is no indication of an imminent need for a second booster dose in this population. However, If signals of increase in severe disease emerge, a fourth dose may be considered for adults between the ages of 60 and 80 years . If made available, vaccines adapted to better match recently circulating variants would be in principle preferable for additional boosters.

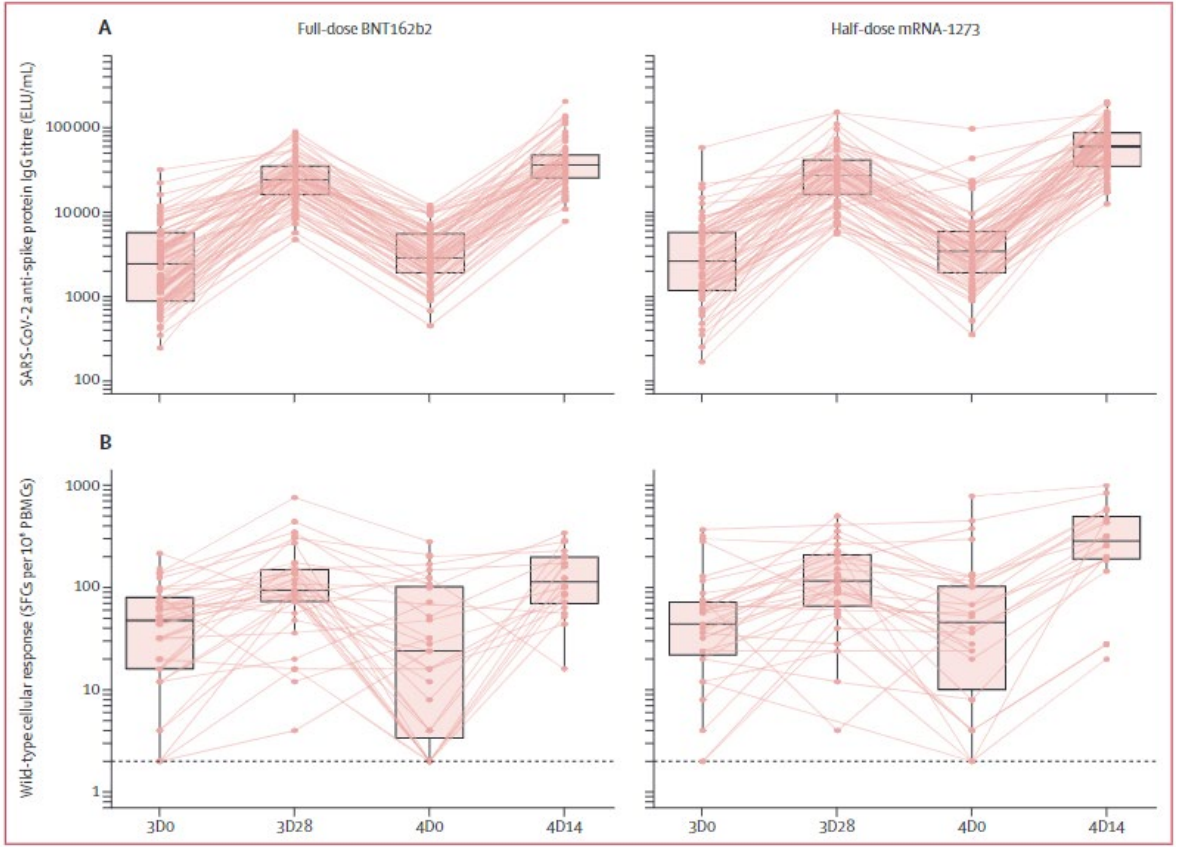
For immunocompetent individuals below 60 years of age, the administration of a second booster dose is not supported by the available data

Characterization of antibody response after second booster vaccination



[dd080770-8f63-4aa4-907d-915a6b83c812.pdf (researchsquare.com)]

Safety, immunogenicity, and reactogenicity of BNT162b2 and mRNA-1273 COVID-19 vaccines given as fourth-dose boosters following two doses of ChAdOx1 nCoV-19 or BNT162b2 and a third dose of BNT162b2 (COV-BOOST): a multicentre, blinded, phase 2, randomised trial | Elsevier Enhanced Reader



Antibody Response to a Fourth Dose of SARS-CoV-2 Vaccine in: Transplantation (lww.com)

Demographics and antibody responses of solid organ transplant recipients who received 4 doses of SARS-CoV-2 vaccine, stratified by pre-dose 4 anti-spike antibody response

Factor	Pre-dose 4 antibody levels[a]			P
	Negative	Low	High	
N	35	43	50	
Age, median (IQR)	63.5 (54.2–71.6) (n = 35)	62.3 (49.6–69.5) (n = 43)	58.4 (48.4–68.0) (n = 50)	0.54
Female, n (%)	20 (57)	24 (56)	26 (52)	0.90
Years since transplant, median (IQR)	4.6 (1.1–11.3)	4.9 (1.5–11.5)	7.2 (3.4–14.9)	0.11
Organ transplanted, n (%)				0.052
Kidney	27 (77)	23 (53)	25 (50)	
Liver	2 (6)	6 (14)	6 (12)	
Pancreas	0 (0)	0 (0)	2 (4)	
Lung	4 (11)	4 (9)	2 (4)	
Heart	1 (3)	4 (9)	11 (22)	
Multiorgan	1 (3)	6 (14)	4 (8)	
MMF, n (%)	30 (86)	31 (72)	37 (74)	0.33
Triple immunosuppression, n (%)	22 (63)	18 (42)	20 (40)	0.090
Initial vaccine series, n (%)				0.21
BNT162b2	22 (63)	28 (65)	24 (48)	
mRNA-1273	13 (37)	15 (35)	26 (52)	
Dose 3 vaccine type, n (%)				0.31
BNT162b2	16 (46)	15 (35)	17 (34)	
mRNA-1273	12 (34)	13 (30)	23 (46)	
Ad.26.CoV2.S	7 (20)	15 (35)	10 (20)	
Dose 4 vaccine type, n (%)				0.75
BNT162b2	15 (43)	14 (33)	17 (34)	
mRNA-1273	17 (49)	27 (63)	30 (60)	
Ad.26.CoV2.S	3 (9)	2 (5)	3 (6)	
Post-D4 antibody response category,[a] n (%)				<0.001
Negative	14 (40)	0 (0)	0 (0)	
Low	11 (31)	7 (16)	0 (0)	
High	10 (29)	36 (84)	50 (100)	
Pre-D4 anti-RBD titer, median (IQR)	<0.8 (<0.8 to <0.8) (n = 17)	103.3 (46.4–197.9) (n = 32)	1945.5 (1035.0 to >2500.0) (n = 34)	<0.001
Post-D4 anti-RBD titer, median (IQR)[b]	2.0 (<0.8 to 54.9) (n = 26)	2027.0 (475.0 to >2500.0) (n = 37)	>2500.0 (>2500.0 to >2500.0) (n = 35)	<0.001
Pre-D4 anti-S titer, median (IQR)	0.3 (0.1–0.6) (n = 18)	2.3 (2.0–2.9) (n = 11)	7.0 (5.4–8.8) (n = 16)	<0.001
Post-D4 anti-S titer, median (IQR)[b]	5.1 (2.0–8.2) (n = 9)	7.1 (5.1–8.9) (n = 6)	8.9 (8.6 to ≥8.94) (n = 15)	0.023

Limited cross-variant immunity after infection with the SARS-CoV-2 Omicron variant without vaccination (medrxiv.org)

Mice sera

Infection	Immunity against	Immunity boosts against
B.1	> 50%	WA1, B.1.1.7, B.1.617.2
	< 50%	B.1.351, B.1.1.529
B.1.617.2	> 50%	WA1, B.1.1.7, B.1.617.2, B.1.1.529
	< 50%	B.1.351
B.1.1.529	> 50%	B.1.1.529
	< 50%	WA1, B.1.1.7, B.1.617.2, B.1.351

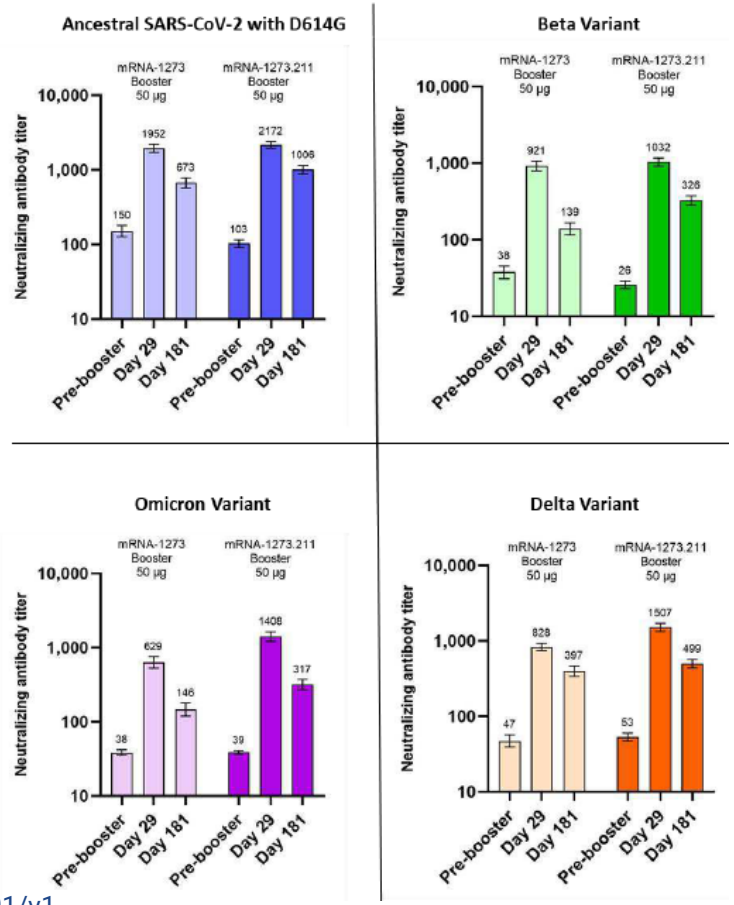
Human sera

Status	Immunity against	Immunity boosts against
Naïve	> 50%	
	< 50%	WA1, B.1.1.7, B.1.351, B.1.617.2, B.1.1.529
Convalescent	> 50%	WA1, B.1.617.2
	< 50%	B.1.1.7, B.1.351, B.1.1.529
Vaccinated + B.1.1.529	> 50%	WA1, B.1.1.7, B.1.351, B.1.617.2, B.1.1.529
	< 50%	

Safety, Immunogenicity and Antibody Persistence of a Bivalent Beta-Containing Booster Vaccine

Table 2: Neutralizing antibody estimated geometric mean titers after the 50-µg mRNA-1273.211 and the 50-µg mRNA-1273 booster doses.

	Day after booster dose	mRNA-1273.211 50 µg booster dose GMT* (95% CI)	mRNA-1273 50 µg booster dose GMT*(95% CI)	Geometric Mean Ratio
Ancestral SARS-CoV-2 with D614G	Day 29	2278.0 (2074.0, 2502.1)	1782.7 (1561.3, 2035.6)	1.28 (1.08, 1.51)
	Day 181	1040.0 (926.4, 1167.3)	617.2 (525.1, 725.5)	1.68 (1.38, 2.06)
Beta	Day 29	1095.3 (981.1, 1222.7)	825.6 (706.6, 964.7)	1.33 (1.09, 1.61)
	Day 181	343.5 (303.7, 388.5)	125.2 (105.4, 148.8)	2.74 (2.22, 3.40)
Omicron	Day 29	1389.8 (1212.1, 1593.4)	630.5 (520.0, 764.9)	2.20 (1.74, 2.79)
	Day 181	312.9 (269.5, 363.4)	145.6 (118.1, 179.5)	2.15 (1.66, 2.78)
Delta	Day 29	1481.2 (1335.8, 1642.3)	844.1 (730.2, 975.8)	1.75 (1.47, 2.10)
	Day 181	491.3 (437.8, 551.5)	408.0 (347.5, 479.1)	1.20 (0.99, 1.47)



DOI: https://doi.org/10.21203/rs.3.rs-1555201/v1

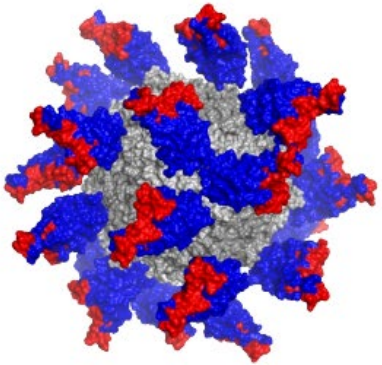
Pan-coronavirus vaccine pipeline takes form (nature.com)

TABLE 1 | SELECTED PAN-CORONAVIRUS VACCINES IN DEVELOPMENT

Vaccine	Sponsor	Properties	Status
Variant-proof COVID-19 vaccines			
SpFN	US Army	Ferritin nanoparticle with prefusion-stabilized spike antigens from the Wuhan strain of SARS-CoV-2	Clinical
RBD–scNP	Duke University	Sortase A-conjugated ferritin nanoparticle with RBD antigens from early WA-1 strain of SARS-CoV-2	Preclinical
GRT-R910	Gritstone bio	Self-amplifying mRNA delivering spike and T cell epitopes	Clinical
hAd5-S+N	Immunity Bio	Spike and nucleocapsid antigens delivered via human adenovirus serotype 5 vector	Clinical
MigVax-101	MigVax	Oral subunit vaccine with RBD and nucleocapsid domains, adjuvanted	Preclinical
Pan-sarbecovirus vaccines			
GBP511	SK bioscience	Mosaic nanoparticle containing RBDs from SARS-CoV-1, SARS-CoV-2 and 1–2 bat coronaviruses	Preclinical
Mosaic-8b	Caltech	Mosaic nanoparticle containing RBDs from SARS-CoV-2 and 7 animal coronaviruses	Preclinical
VBI-2901	VBI Vaccines	Virus-like particles expressing prefusion spike of SARS-CoV-2, SARS-CoV-1 and MERS-CoV	Preclinical
Pan-betacoronavirus vaccines			
DIOS-CoVax	DIOSynVax	Needle-free injection of undisclosed antigens	Clinical
Other			
mRNA-1287	Moderna	mRNA encoding antigens from four human-infecting coronaviruses that cause common colds	Preclinical

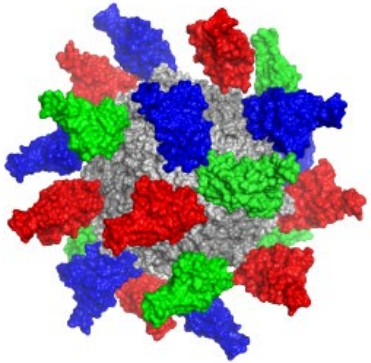
Mosaic conjugate nanoparticle immunogens

Monovalent RBD nanoparticle



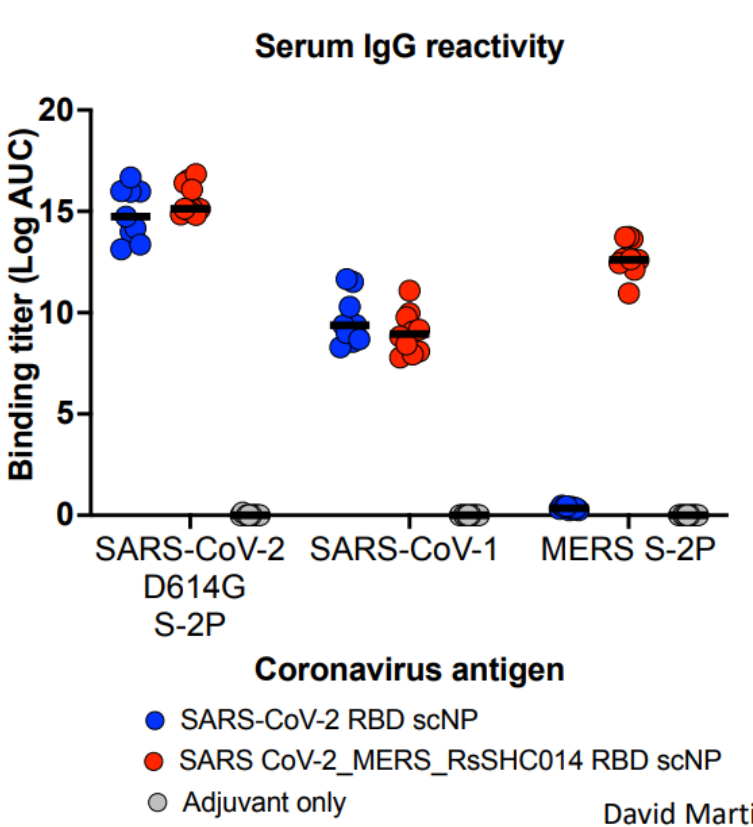
SARS-CoV-2 WT
RBD 24-mer

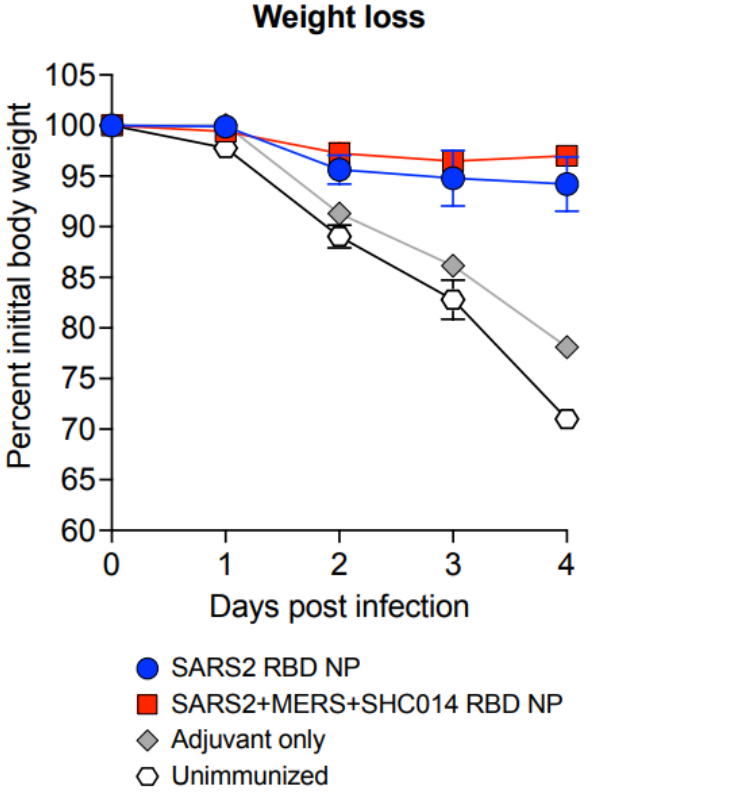
Trivalent Mosaic RBD nanoparticle



Groups 2b + 2c
MERS
SHC014
SARS-CoV-2
RBD 24-mer

Mosaic NP immunization generates Group 2B+2C reactive antibodies and protects against heterologous betacoronavirus infection





David Martinez, Alexandra Schaefer, Ralph Baric, Barton Haynes

RESEARCH

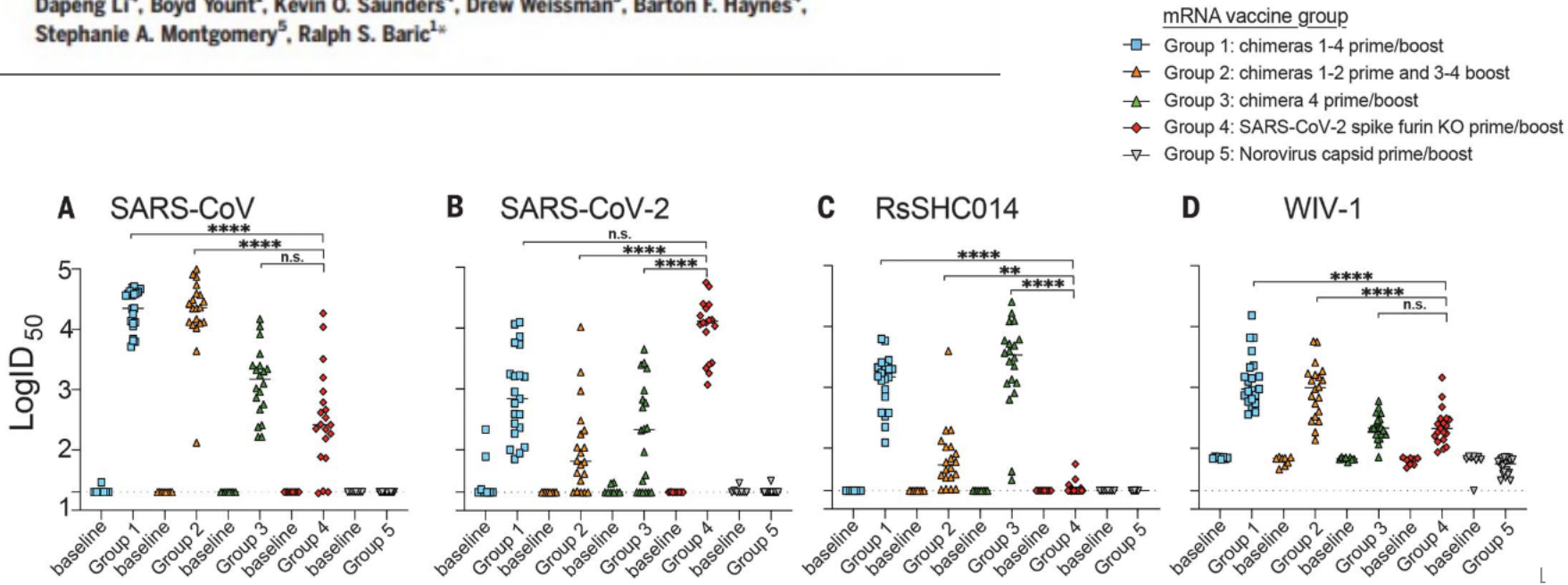
CORONAVIRUS

Chimeric spike mRNA vaccines protect against Sarbecovirus challenge in mice

David R. Martinez[1]*, Alexandra Schäfer[1], Sarah R. Leist[1], Gabriela De la Cruz[2], Ande West[1], Elena N. Atochina-Vasserman[3], Lisa C. Lindesmith[1], Norbert Pardi[3], Robert Parks[4], Maggie Barr[4], Dapeng Li[4], Boyd Yount[1], Kevin O. Saunders[4], Drew Weissman[3], Barton F. Haynes[4], Stephanie A. Montgomery[5], Ralph S. Baric[1]*

Chimeric spike mRNA-LNP immunogens

Chimera	RBD	NTD	S2
1	SARS-CoV	HKU3-1	SARS-CoV-2
2	SARS-CoV-2	SARS-CoV	SARS-CoV
3	SARS-CoV	SARS-CoV-2	SARS-CoV-2
4	RsSHC014	SARS-CoV-2	SARS-CoV-2



Status of COVID-19 therapeutics in the EU

Currently under rolling review

No treatments currently under rolling review

Marketing authorisation application submitted

- **Lagevrio** (molnupiravir)
- **Olumiant** (baricitinib)*

Authorised for use in the European Union

- **Evusheld** (tixagevimab / cilgavimab)
- **Kineret** (anakinra)*
- **Paxlovid** (PF-07321332 / ritonavir)
- **Regkirona** (regdanvimab)
- **RoActemra** (tocilizumab)*
- **Ronapreve** (casirivimab / imdevimab)
- **Veklury** (remdesivir)
- **Xevudy** (sotrovimab)

Advice to Member States on treatments that are not yet authorised specifically for patients with COVID-19:

- Lagevrio (molnupiravir)

Therapeutics are being approved which will complement, but not replace, vaccines in the fight against COVID-19

https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/treatments-vaccines/covid-19-treatments

BA.2.12.1, BA.4 and BA.5 escape antibodies elicited by Omicron infection

2022.04.30.489997v1.full.pdf (biorxiv.org)

IC50 (ng/mL)	LY-CoV016	LY-CoV555	LY-CoV1404	REGN 10933	REGN 10987	COV2-2196	COV2-2130	BRII-196	BRII-198	S309	DXP-604	ADG-2	S2K146	SA58 (BD55-5840)	SA55 (BD55-5514)	LY-CoV016+ LY-CoV555	REGN10933+ REGN10987	COV2-2196+ COV2-2130	BRII-196+ BRII-198	SA55+SA58
D614G	32	15	0.7	5.6	5.7	1.6	2.5	53	1239	74	11	11	17	0.9	11	20	5.0	2.1	81	2.1
BA.1	*	*	0.6	*	*	5419	3007	7118	1171	361	285	979	11	4.4	1.7	*	*	491	1890	3.2
BA.1.1	*	*	1.8	8912	*	4764	*	6324	*	314	198	991	17	4.5	3.0	*	*	8090	*	3.3
BA.2	*	*	0.9	*	590	4312	6.3	8530	8990	918	219	*	20	12	7.2	*	821	8.2	8610	7.8
BA.3	*	*	1.1	*	*	5609	11	7833	1687	972	259	6226	16	8.1	7.1	*	*	19	2190	6.4
BA.2.13	*	*	1.0	9221	417	3591	6.6	6902	*	700	148	*	16	4.9	5.9	*	699	7.1	*	4.8
BA.2.12.1	*	*	0.8	*	499	5521	11	7620	*	989	201	*	13	5.0	5.2	*	714	18	*	5.0
BA.4/BA.5	*	*	0.9	*	520	*	23	7124	*	792	6264	*	221	3.9	5.0	*	709	40	*	4.5
SARS-CoV-1	*	*	*	*	*	*	*	*	*	31	*	1.7	108	5.6	4.4	*	*	*	*	4.6
Pangolin-GD	1125	6.8	8.6	157	84	17	*	13	*	*	7.4	5.0	14	296	5.7	10	98	27	33	7.7
RaTG13	*	*	*	*	*	*	*	16	*	*	1.1	*	3.9	*	38	*	*	*	29	49

PAEDIATRIC HEPATITIS CASES - AETIOLOGY

- A post-infectious SARS-CoV-2 syndrome (including an Omicron restricted effect).
- A drug, toxin or environmental exposure.
- A novel pathogen either acting alone or as a coinfection.
- A new variant of SARS-CoV-2
- Role of Adenovirus

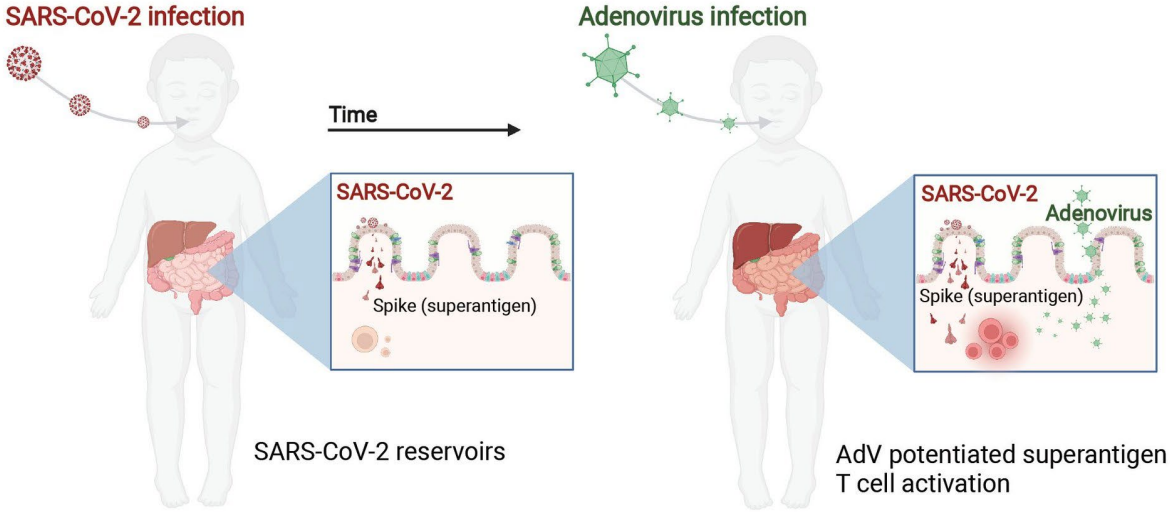


Figure 1. Hypothesis of AdV potentiated SARS-CoV-2 superantigen-mediated pathology in severe, acute hepatitis. Following infection with SARS-CoV-2 virus, viral reservoirs have been reported and could over time lead to repeated super-antigen mediated immune cell activation as shown in Multisystem inflammatory syndrome, MIS-C. If such viral reservoirs are present and a child is subsequently infected with AdV, this superantigen-mediated effect could be much more pronounced and potentially give rise to immunopatthology such as the recently reported acute, severe hepatitis which is why evidence of such immunopathology should be investigated in these cases.

Eurosurveillance | Severe acute hepatitis and acute liver failure of unknown origin in children: a questionnaire-based study within 34 paediatric liver centres in 22 European countries and Israel, April 2022; Acute hepatitis of unknown aetiology technical briefing 2 (publishing.service.gov.uk); Severe acute hepatitis in children: investigate SARS-CoV-2 superantigens | Elsevier Enhanced Reader

MONKEYPOX

- Incubation 4—14 days (up to 21 days)
- Usually mild, self-limiting (rash ~2wks)
  - Pruritis, rarely painful
- Rarely:
  - Bacterial superinfection
  - Conjunctivitis/keratitis
  - Pneumonitis
  - Encephalitis
- Highest risk:
  - Pregnant women
  - Neonates/infants/young children
  - HIV / immunocompromised

Antiviral treatment approved in EU

Tecovirimat (Tecovirimat SIGA – 200 mg hard capsules)

- Only antiviral authorized in EU for the treatment of monkeypox. Approved in January 2022 under **exceptional circumstances**.
- The evidence for the anticipated antiviral effect in humans comes from **the in-vitro and in-vivo nonclinical studies**. Clinical studies offers PK-PD analyses to support the clinical dose regimen and the safety assessment.
- Tecovirimat targets the membrane protein **VP37** of vaccinia virus required for the production of extracellular forms of virus. EC50 is similar for all orthopoxviruses.
- **Indication and posology**:
    - treatment of smallpox, monkeypox, cowpox and vaccinia virus in adults and children >13 Kgs.
    - dose varies by body weight: 200-600 mg BID for 14 days.
- **Good safety profile** (most common AE: headache, nausea). DDI: repaglinide, midazolam. No data in pregnancy.
- **Low resistance barrier**, amino acid substitutions in the VP37 protein can confer reductions in antiviral activity.

Other antivirals with activity against orthopoxviruses

Brincidofovir (TEMBEXA – 100 mg tablets/10 mg/ml oral suspension)

- Approved by **FDA** in June 2021 under the agency's **Animal Rule**. Efficacy findings derives from animal studies. Safety findings comes from clinical trials for non-smallpox indications (CMV infection in patients who received hematopoietic stem cell transplants).
- Brincidofovir is an orthopoxvirus nucleotide analog DNA polymerase inhibitor.
- **Indication**: treatment of human **smallpox disease** caused by variola virus in adult and pediatric patients, including neonates. **Adult posology**: 200 mg once weekly for 2 doses (on Days 1 and 8)
- **Safety:** most common AEs are diarrhea, nausea, vomiting. Elevation in hepatic transaminases. Increased risk for mortality when used for longer duration (24 weeks). May cause embryo-fetal toxicity.

Cidofovir (solution for infusion)

- Authorised at EU level for the treatment of **CMV retinitis in patients with AIDS** and normal renal function.
- Proven activity against poxviruses in **in vitro** and **animal studies**.
- Important **nephrotoxicity**.

Vaccines for prevention of smallpox authorised in the EU

- **Imvanex:** third generation, replication-deficient Modified Vaccinia Ankara for active immunisation against smallpox in adults

- **Posology**: 2 doses of 0.5ml at not less than 28 days interval if not previously vaccinated against smallpox; data inadequate to indicate a booster in previously vaccinated

- **Acceptable safety profile**: 5,261 Vaccinia-naïve sbj (most common ARD injection site reactions and systemic reactions typical for vaccines lid/moderate resolved in 7 days w/o treatment)
- Data available in HIV patients and patients with atopic dermatitis (slightly more reactogenicity, possible flare up of skin conditions)

- **Efficacy/Immunogenicity:**
  - **Animal Model** protection against severe disease after lethal challenge with monkeypox virus in NHPs and comparable immune responses to traditional smallpox vaccines (significant prevention of morbidity and mortality compared to non-vaccinated animals)
  - **Human trials (**HIV and AD patients) immune responses (seroconversion between 82% and 100% 14 days after 2nd dose in naïve); booster effect shown 2 years after Imvanex or long time after previous licensed smallpox vaccine
  - One study demonstrated non-inferior responses compared to licensed ACAM20000 (2nd generation live attenuated smallpox vaccine)

Conclusions

- Currently EMA-ECDC recommended additional booster doses **in elderly above 80 years of age and in immunocompromised subjects**
- **mRNA vaccines update of composition** to better match current VOCs under investigation for possible approval in time for vaccination campaigns later this year
- **Other vaccines in the pipeline** may come to rapid approval to enlarge our portfolio of options
- **Additional safe and effective therapeutics** will help in the fight against COVID-19**,**
- **Monkeypox outbreak** in Europe is unprecedented but it is for now not considered a public health emergency or a major threat such as COVID-19
- The disease is generally **mild and self-limiting** with low transmission rate
- **EMA approved one vaccine and one antiviral** that represent the best tools to prevent and treat the disease

Latest updates on EMA's corporate website:

COVID-19 pandemic

ema.europa.eu

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European Medicines Agency