EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Update on COVID-19 and Monkeypox vaccines and therapeutics

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An agency of the European Union

The new Emergency Task Force (ETF)

- ETF established with formal legal mandate as an **advisory and support body on medicines for public health emergencies and preparedness**
- Regulation sets out objectives and composition, but allowing flexibility & membership based on expertise
- **Strengthened** existing ETF responsibilities building on successful experience during past emergencies & COVID-19

Scientific advice and support to clinical trials

- assessed **directly** by ETF
- free of charge & fast-track for clinical trials and protocols
- **support study conduct**

Scientific reviews

- **systematic** assessment of evidence on medicines

ETF recommendations

- **on medicines not yet authorised**
- on scientific or **public health matters**

ETF composition for COVID-19

Co-Chairs: EMA chair, CHMP vicechair

Representatives from groups based on expertise:

Scientific Committees (CHMP, PRAC, PDCO, CMDh) **and EMA Representatives**

14

Working Parties' experts on vaccinology, biologics, infectious disease treatment, biostatistics, inspection, clinical trials, scientific advice assessment

19

Patients and Healthcare professionals identified by PCWP and HCPWP to bring the views of their respective communities

4

Clinical trial experts from various EU Member States (Clinical Trials Advisory Group (CTAG) and Clinical Trials Coordination Group (CTCG))

4

Additional experts and observers from academia, EU national or international regulators, EU bodies

Other tasks of the ETF

ETF

	KEY BENEFITS
• **Clinical trials sponsors** • **Competent authorities** for trial authorisation	Facilitate large multinational clinical trials
• Medicines Shortage Steering Group (**MSSG**) • **Expert panels** on medical devices	Cross-links during public health emergencies
• European Centre for Disease Control (**ECDC**) • International Coalition of Medicines Regulatory Authorities (**ICMRA**) • World Health Organisation (**WHO**) • US Food and Drug Administration (**FDA**), UK Medicines and Healthcare products Regulatory Agency (**MHRA**), Health Canada Regulatory Authority (**HC**), Swiss Medicines Agency (**Swissmedic**) • Networks for observational studies, Vaccine Monitoring platform	Improved preparedness, global harmonization and support, coordination for better RWE, publication joint recommendations

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)
- **Skycovion** (SK Chemicals GmbH)

Authorised for use in the EU

- **Comirnaty** (BioNTech and Pfizer)
- **COVID-19 Vaccine Valneva**
- **Nuvaxovid** (Novavax)
- **Spikevax** (Moderna)
- **Vaxzevria** (AstraZeneca)
- **Jcovden** (Janssen)

Adapted vaccines authorised for use as boosters in the EU

- **Comirnaty Original/Omicron BA.1** (BioNTech and Pfizer)
- **Comirnaty Original/Omicron BA.4-5** (BioNTech and Pfizer)
- **Spikevax bivalent Original/Omicron BA.1** (Moderna)

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

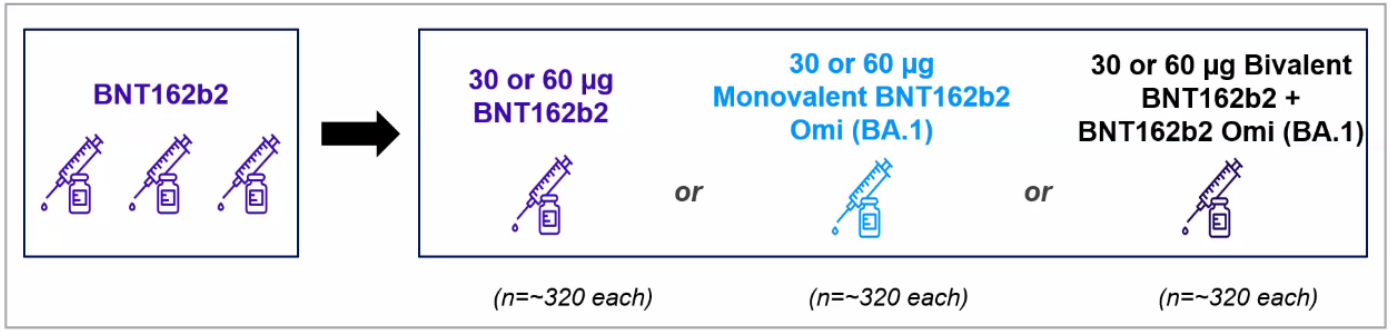
COVID-19 ADAPTED VACCINES FOR USE AS BOOSTER

Omicron-modified vaccines

Clinical Study to Evaluate Monovalent and Bivalent Omicron-Modified Vaccines in Vaccine-Experienced Participants

>55y Participants

C4591031 Substudy E Evaluates Safety & Immunogenicity in ~1920 participants >55 Years



Dose 4 administered a median of 6.3 months (4.7, 12.9) from Dose 3

Monovalent BNT162b2 Omi (BA.1) 60 µg (N~330), bivalent BNT162b2 + BNT162b2 Omi (BA.1) 30 µg (N~180) and 60 µg (N~480) also being evaluated in participants 18-55 years of age

Omicron-modified vaccines

Omicron BA.1 GMR Consistent with Simple Superiority Criterion for Omicron-modified Vaccines and Super Superiority for Monovalent

>55y Participants

Participants WITHOUT Evidence of Infection up to 1 Month After the Study Vaccination

Assay	Vaccine Groups	n	GMT (95% CI) 1M Post-Dose	Vaccine Group / BNT162b2 30 µg	
				GMR (95% CI)	Met Superiority (Y/N)*
SARS-CoV-2 neutralization assay – Omicron BA.1 - NT50 (titer)	BNT162b2 30 µg	163	455.8 (365.9, 567.6)		
	BNT162b2 OMI 30 µg	169	1014.5 (825.6, 1246.7)	2.23 (1.65, 3.00)	Y
	BNT162b2 OMI 60 µg	174	1435.2 (1208.1, 1704.8)	3.15 (2.38, 4.16)	Y
	Bivalent OMI 30 µg[1]	178	711.0 (588.3, 859.2)	1.56 (1.17, 2.08)	Y
	Bivalent OMI 60 µg[2]	175	900.1 (726.3, 1115.6)	1.97 (1.45, 2.68)	Y

GMR Simple superiority criterion: the lower bound of 95% CI for GMR is >1.0; **Super superiority criterion**: the lower bound of 95% CI for GMR is >1.5

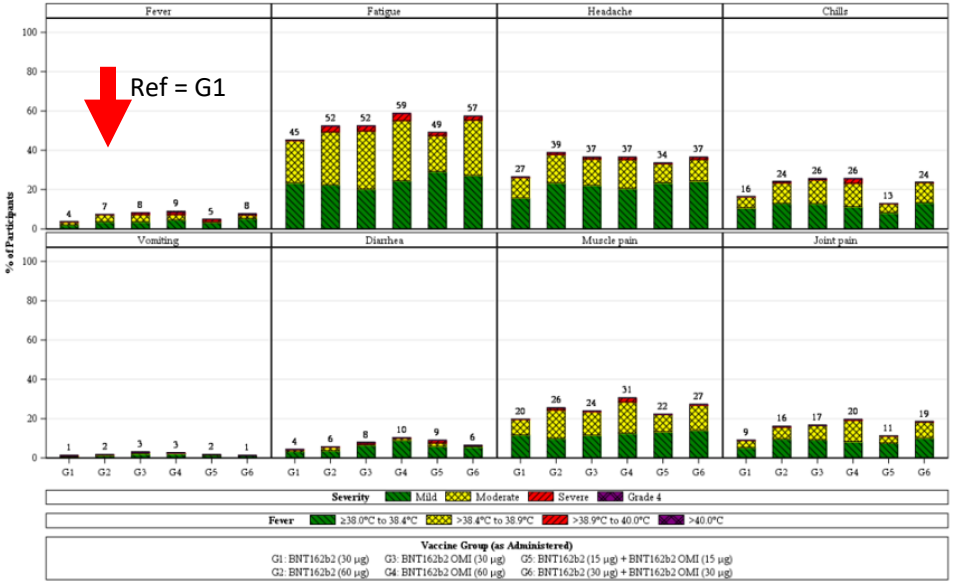
*Multiple hypotheses are to be evaluated in sequential order for alpha control. Declaration of OMI 30 mcg simple superiority pending outcome of additional hypotheses. CI – confidence interval
Omicron BA.1 NT50 measured using validated 384-well assay.

Comirnaty (Original/Omicron BA.1) - safety

- Safety database for Original/Omicron BA.1: approximately 620 subjects >55 years of age (Substudy E), 305 of whom received the 15/15 ug dose
- Approximately 1000 subjects above 18 years of age received Omicron BA.1 monovalent (Substudy D+E)
- Follow up time less than 2 months
- Local reactogenicity dose dependent and consistent with Comirnaty Original
- No new safety concerns
- Safety database not large enough to characterise frequency of rare events

Safety in >55 – systemic reactogenicity (Substudy E)

Figure 6. Participants Reporting Systemic Events, by Maximum Severity, Within 7 Days After the Study Vaccination – Expanded Cohort – Participants >55 Years of Age – Safety Population



Comirnaty (Original/Omicron BA.1)

One dose (0.3 mL) contains 15 micrograms of tozinameran and 15 micrograms of riltozinameran, a COVID-19 mRNA Vaccine (embedded in lipid nanoparticles).

4.1 Therapeutic indications

Comirnaty Original/Omicron BA.1 (15/15 micrograms)/dose dispersion for injection is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2, in individuals 12 years of age and older who have previously received at least a primary vaccination course against COVID-19 (see sections 4.2 and 5.1).

The use of this vaccine should be in accordance with official recommendations.

Posology

The dose of Comirnaty Original/Omicron BA.1 is 0.3 mL given intramuscularly.

There should be an interval of at least 3 months between administration of Comirnaty Original/Omicron BA.1 and the last prior dose of a COVID-19 vaccine.

Comirnaty Original/Omicron BA.1 is only indicated for individuals who have previously received at least a primary vaccination course against COVID-19.

COVID-19 ADAPTED VACCINES FOR USE AS BOOSTER

Spikevax bivalent (Original/Omicron BA.1) - safety

- 437 participants received 2nd booster dose of 1273.214 50 µg
- Median follow-up time 43 days/ cut off date 27 April 2022
- Overall incidence of solicited local ARs was comparable between 2 groups (79.4% vs. 79.5%)
- Higher local reactogenicity in the bivalent/omicron group (any pain 77.3% vs 76.6%; any erythema 6.9% vs 3.7%;); Grade 3 events similar (3.4%), no Grade 4 events
- Higher solicited systemic ARs in the bivalent/omicron group (70.3%) compared to (66.1%) in the Spikevax monovalent group; Grade 3 events 5.5% vs 4.6%; no grade 4 events

Spikevax demography

	4th Dose	
Characteristic	mRNA-1273 (N = 377)	mRNA-1273.214 (N = 437)
Age (years) – mean (range)	**57.5** (20, 96)	**57.3** (20, 88)
≥ 65 years	39.8%	39.8%
Female	50.7%	59.0%
Non-White Race	14.6%	12.8%
Hispanic / Latino Ethnicity	9.8%	10.5%
Interval between 2nd and 3rd Dose (months) – median (range)	**8.0** (5.6, 14.4)	**8.0** (4.7, 15.0)
Interval between 3rd and 4th Dose (months) – median (range)	**4.4** (3.0, 10.2)	**4.5** (2.9, 13.4)
Prior SARS-CoV-2 Infection	26.8%	22.0%

COVID-19 ADAPTED VACCINES FOR USE AS BOOSTER

Spikevax bivalent - immunogenicity against BA.5

Table 1 **Cross-neutralizing antibody responses (geometric mean neutralizing antibody titer ratio) to Omicron variant BA.4/5 28 days post second boost after 50 µg bivalent mRNA-1273.214 or 50 µg prototype mRNA-1273 Booster**

Vaccine	mRNA-1273.214 (Original + Omicron BA.1) 50 µg	mRNA-1273 (Original) 50 µg	mRNA-1273.214 (Original + Omicron BA.1) 50 µg	mRNA-1273 (Original) 50 µg	mRNA-1273.214 (Original + Omicron BA.1) 50 µg	mRNA-1273 (Original) 50 µg
Participant Population	All participants (n=428)	All participants (n=367)	No prior infection (n=334)	No prior infection (n=260)	Prior infection (n=94)	Prior infection (n=98)
Pre-booster GMT (95% CI)	172.72 (147.45, 202.31)	209.31 (179.48, 244.10)	115.59 (98.51, 135.64)	139.68 (119.51, 163.26)	719.54 (531.64, 973.86)	609.12 (448.08, 828.05)
Estimated GMTs at Day 29 (95% CI)[a]	**985.38** (914.77, 1061.43)	**588.36** (544.08, 636.24)	**776.45** (719.49, 837.92)	**458.28** (420.62, 499.32)	**2246.25** (1975.52, 2554.09)	**1406.89** (1227.88, 1612.01)
GMFR at Day 29 (95% CI)	5.44 (5.01, 5.92)	3.08 (2.84, 3.35)	6.30 (5.74, 6.91)	3.52 (3.21, 3.86)	3.25 (2.78, 3.80)	2.09 (1.80, 2.43)
GMR (95% CI) [a]	**1.68** (1.52, 1.84)		**1.69** (1.51, 1.90)		**1.60** (1.34, 1.91)	

[a] Based on ANCOVA modeling; the model includes adjustment for treatment group, pre-booster antibody titers, age groups, and SARS-CoV-2 status for all participants.

Risk of BA.5 Infection among Persons Exposed to Previous SARS-CoV-2 Variants (nejm.org)

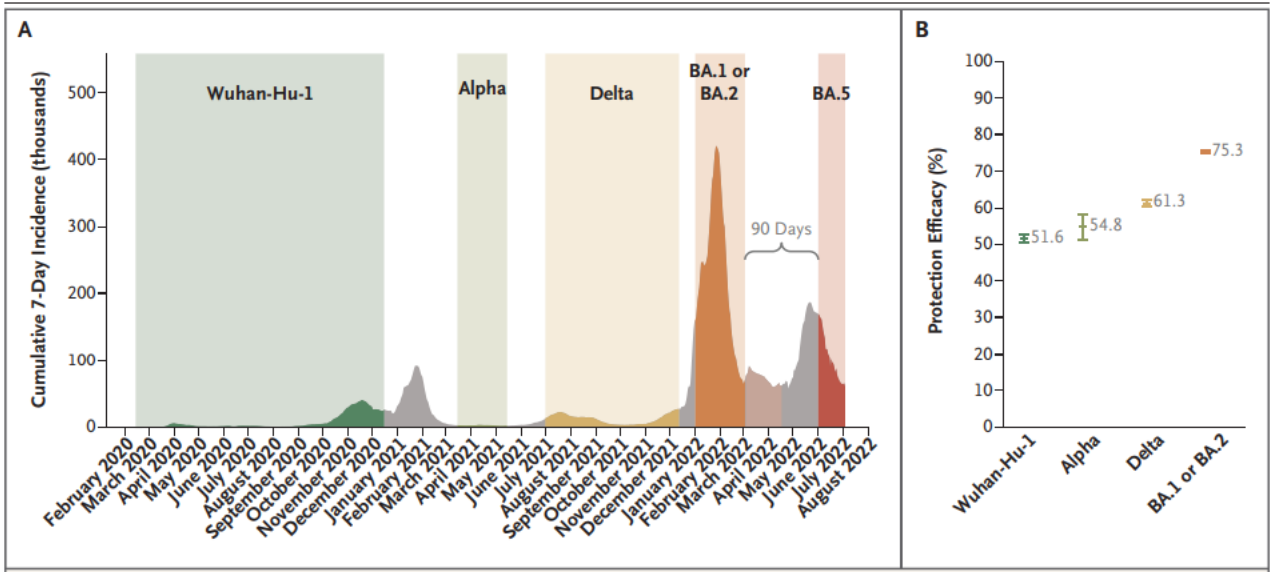


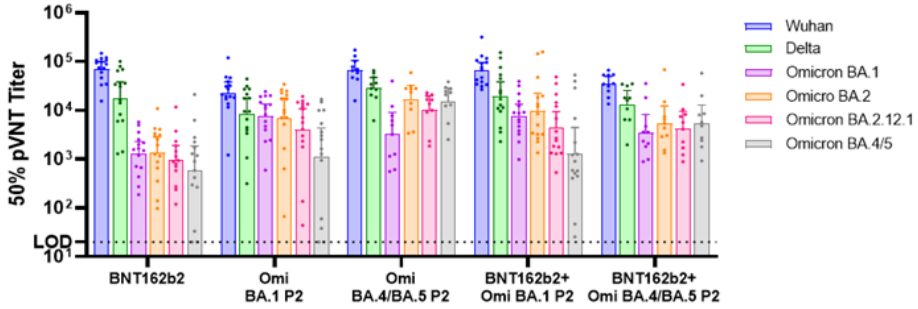
Figure 1. Protective Effect of Previous SARS-CoV-2 Infection on Infection with the Omicron BA.5 Subvariant.

As shown in Panel A, we identified the periods (in different colors) when one variant was represented in more than 90% of sample isolates (data from the national severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2] genetic diversity surveillance[4]). The periods in gray represent times when more than one variant was in circulation. Given the relatively slow transition between dominance by the omicron BA.1 subvariant and dominance by the omicron BA.2 subvariant, we pooled BA.1 and BA.2 in the analysis. We did not include anyone infected in the 90 days before dominance by the omicron BA.5 subvariant. Panel B shows protection efficacy against infection during the period of BA.5 dominance (from June 1, 2022) among persons with one infection in the periods of dominance of different variants, as represented in Panel A, as compared with persons without any documented infection until June 1. Persons with two infections before June 1 were not included in the study. I bars represent 95% confidence intervals.

COVID-19 ADAPTED VACCINES FOR USE AS BOOSTER

Comirnaty (Original/Omicron BA.4-5)

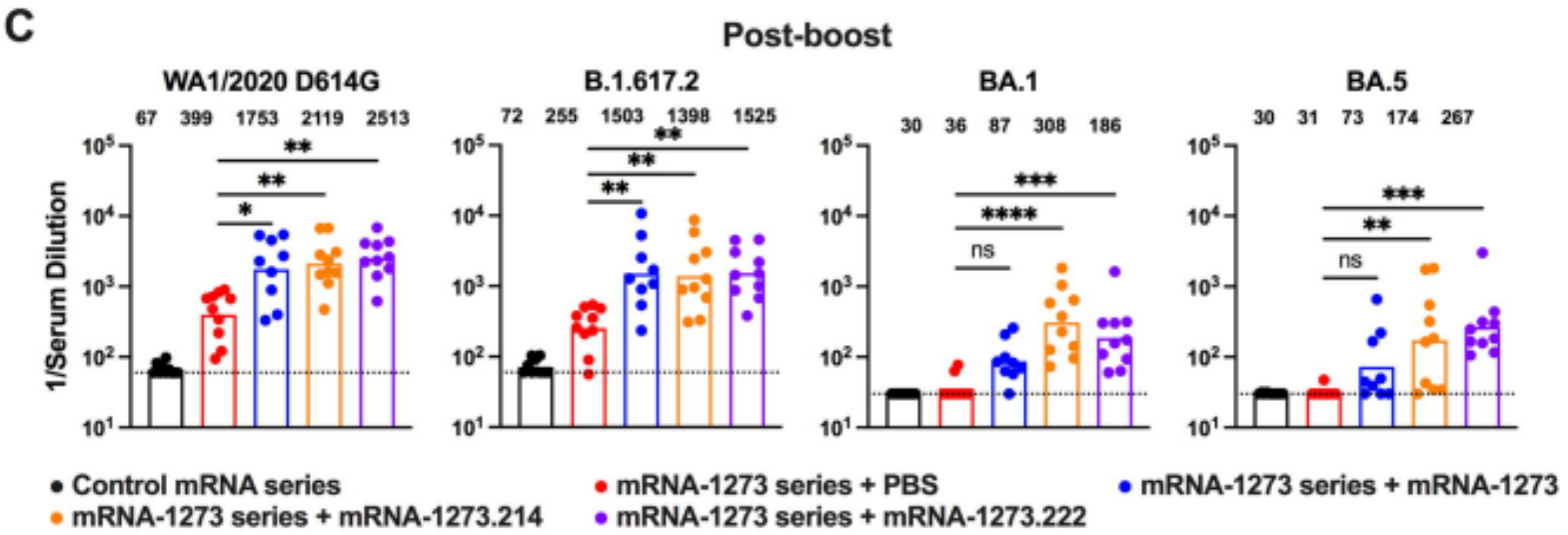
Comirnaty BA4 / BA5 vaccine (booster) in mice



Vaccine	Wuhan	Delta	Omicron			
			BA.1	BA.2	BA.2.12.1	BA.4/5
BNT162b2	70546	17911	1308	1378	973	603
Omi BA.1 P2	21998	8454	7575	7030	4049	1136
Omi BA.4/5 P2	65839	28865	3366	16677	10385	15522
BNT162b2 + Omi BA1 P2	65389	19206	7652	9855	4380	1294
BNT162b2 + Omi BA.4/5 P2	34457	13291	3537	5391	4294	5446

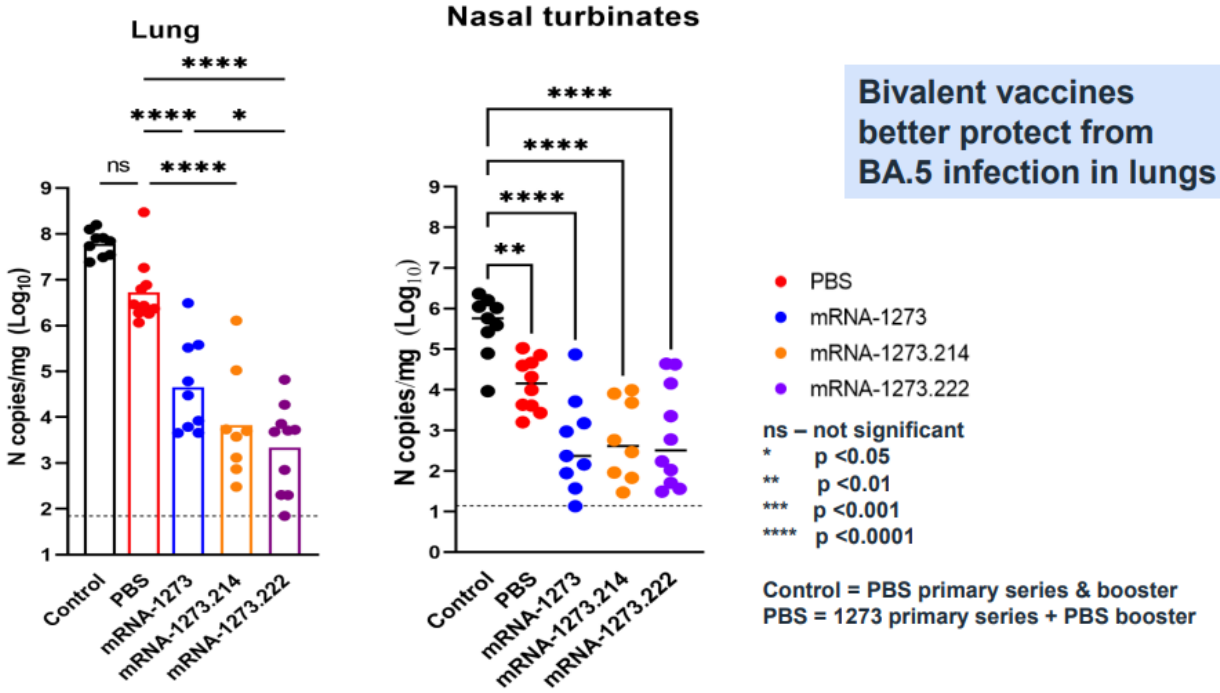
Increased Immunogenicity after Booster Dose of the BA.1 & BA.4/BA.5 Omicron Bivalent Vaccines (mRNA-1273.214 & mRNA-1273.222) in Mice

- K18 hACE2 mice previously vaccinated with primary series of mRNA-1273 (n = 8-10 per group)
- Boosted with Original (mRNA-1273), BA.1 Omicron Bivalent (mRNA-1273.214), or BA.4/BA.5 Bivalent (mRNA-1273.222
- ~31 weeks between primary series & booster
- Low 0.25 µg dose used to allow for differences between dose regimens to be captured

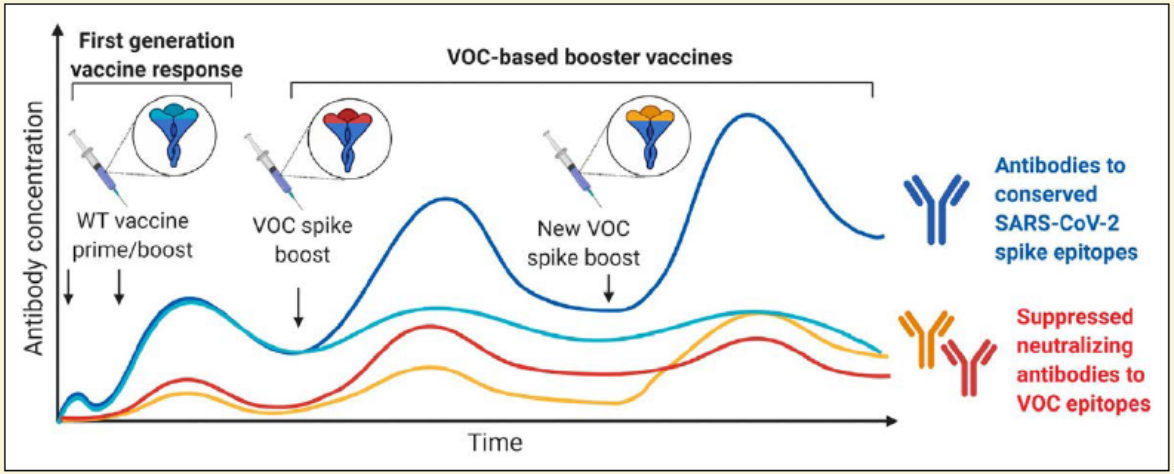


Increased Protection from BA.5 Challenge after Booster Dose of BA.4/BA.5 & BA.1 Omicron Vaccines (mRNA-1273.214 & mRNA-1273.222) in Mice

- Mice challenged with 10^4 PFU of BA.5 virus 4 weeks after booster dose

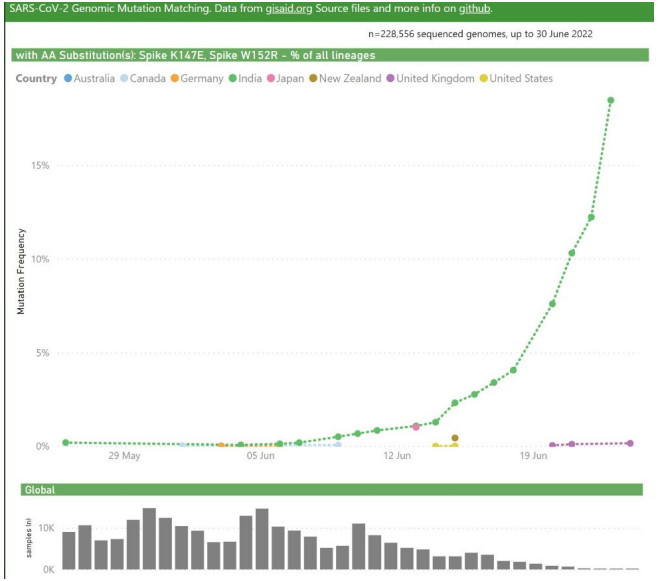


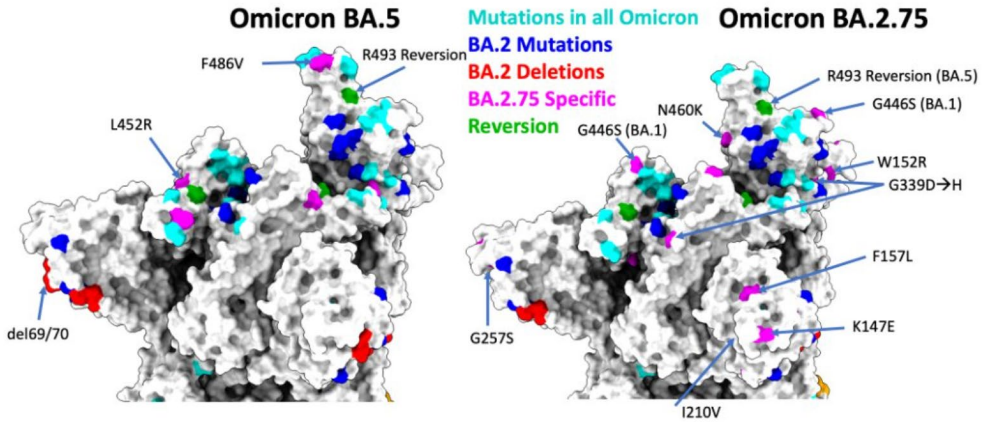
Repeated recall can dampen the emergence of new responses (antigenic imprinting or O.A.S.)



Wheatley et al, *Trends Immunol*, 2021

Antibody evasion to omicron sublineages

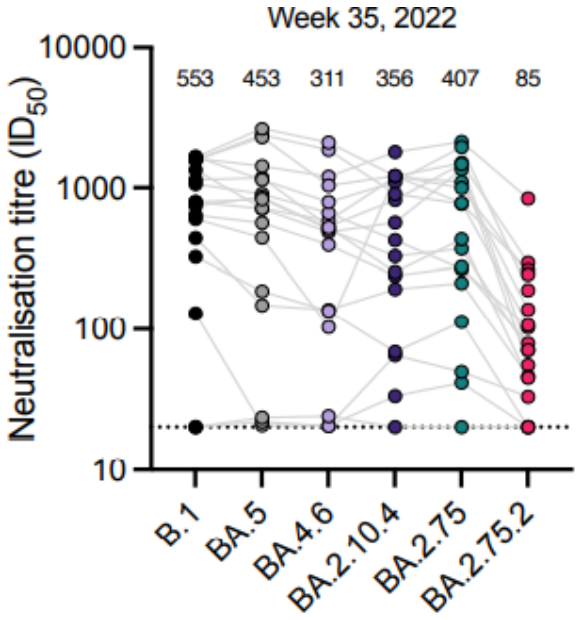




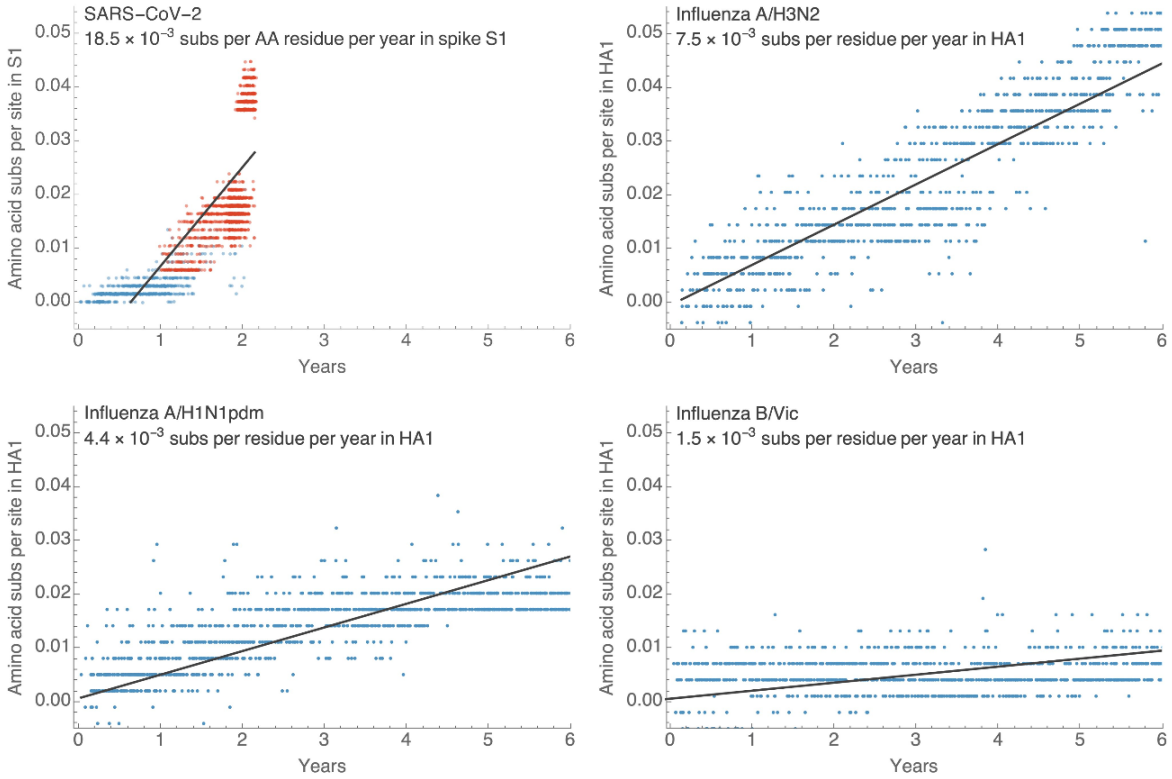
Antibody evasion to omicron sublineages

[Omicron sublineage BA.2.75.2 exhibits extensive escape from neutralising antibodies (biorxiv.org)]

IC50 (ng/ml)	B.1	BA.5	BA.4.6	BA.2.10.4	BA.2.75.2
S309 (sotrovimab)	119	559	925	560	442
Cilgavimab	12	71	>1000	168	>1000
Tixagevimab	4	>1000	>1000	>1000	>1000
Evusheld	6	120	>1000	816	>1000
LY-CoV1404 (bebtelovimab)	4	1	2	3	2
REGN10933 (casivirimab)	14	>1000	>1000	>1000	>1000
REGN10987 (imdevimab)	10	>1000	>1000	>1000	>1000
LY-CoV016 (etesevimab)	29	>1000	>1000	>1000	>1000
LY-CoV555 (bamlanivimab)	9	>1000	>1000	>1000	>1000
ADG-20	56	>1000	>1000	>1000	>1000
S2E12	4	>1000	>1000	>1000	>1000
S2K146	18	118	78	207	62
A23-58.1	6	>1000	>1000	>1000	>1000



Mutations rate SARS-COV2 and influenza strains



Status of monkeypox vaccines in the EU

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

19 August 2022
EMA/700120/2022
Emergency Task Force

Considerations on posology for the use of the vaccine Jynneos/ Imvanex (MVA-BN) against monkeypox

Conclusions

The results of the study in healthy adults demonstrated comparable humoral immunogenicity when MVA-BN was given as a standard SC dose or as 1/5th of a dose administered ID. The exact level of protection and duration of protection afforded by the vaccine regimens are unknown.

No new safety signal was raised for ID administration of MVA-BN but the higher local reactogenicity following the ID administration of MVA-BN may raise concerns during the vaccination campaigns. In the ongoing emergency situation with continuous spread among individuals at high risk of infection and with significant shortage of vaccine, the safety profile of the vaccine following ID route can be considered acceptable. However, these data are limited, and more data may be generated in additional studies.

Imvanex - breakthrough infections after vaccination

[Breakthrough infections after post-exposure vaccination against Monkeypox (medrxiv.org)]

France May 27 – July 13, 2022. Describe the outcomes of high-risk contacts receiving third-generation smallpox vaccine and in particular tolerance of the vaccine and potential breakthrough infections within the 28 days after the first dose of vaccine.

Figure 1: Flow chart of early post-exposure vaccination against Monkeypox

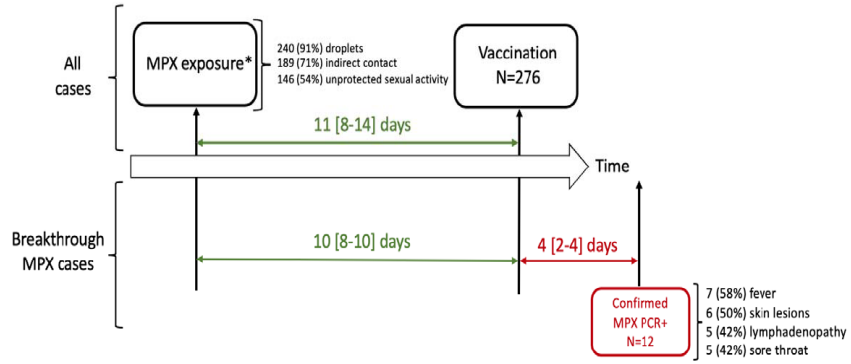
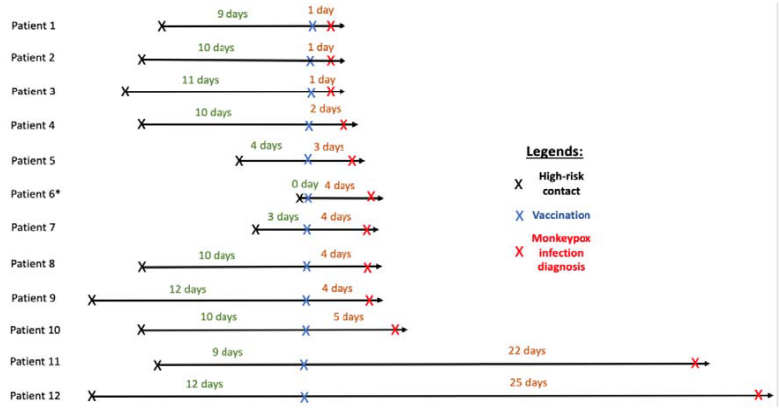


Figure 2: Delay between exposure, vaccination and confirmed Monkeypox infection in the 12 breakthrough infections



Legend: *Patient 6: Direct inoculation with a percutaneous needlestick

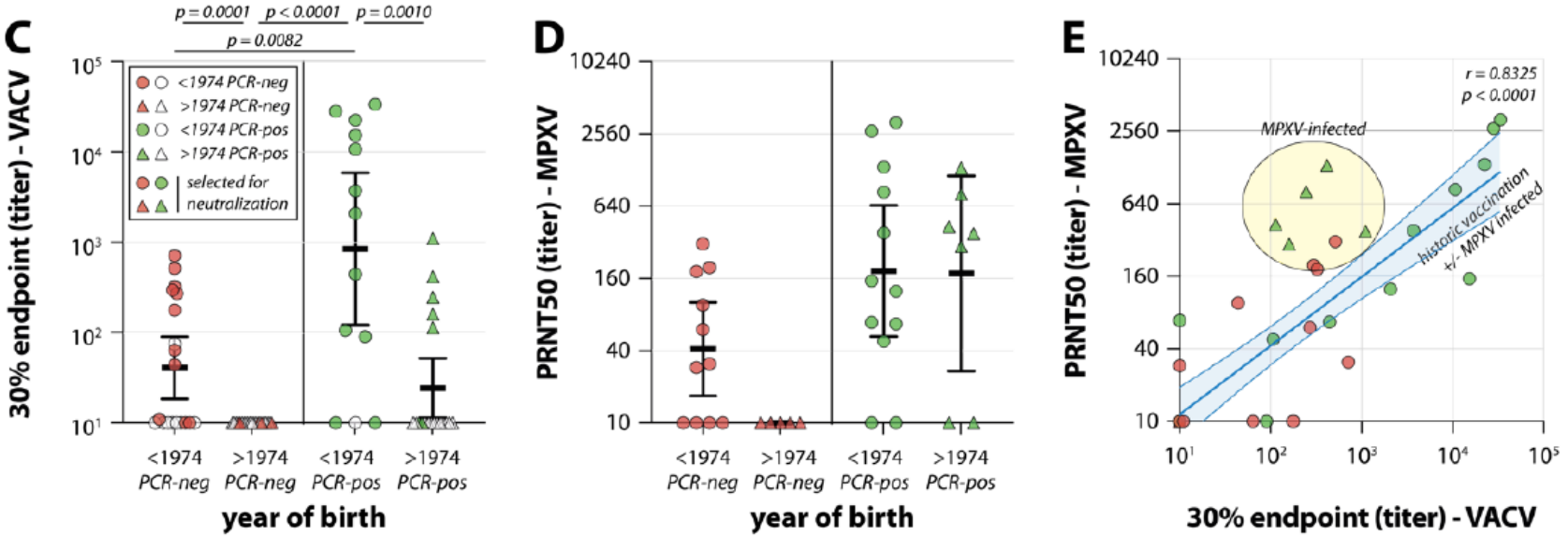
Imvanex - breakthrough infections after vaccination

- Confirmed human monkeypox cases in individuals previously vaccinated against smallpox: a case series. (Moschese, et al, Journal of Medical Virology pre-print)
- Six cases of patients, with a documented history of vaccination against smallpox, who were diagnosed with MPX in two Italian clinical centres between May and July 2022.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Gender	Male	Male	Male	Male	Male	Male
Risk factor	MSM	MSM on PrEP	MSM	MSM	MSM	MSM
Aquisition route	Sexual contact (unprotected)	Sexual contact (unprotected)	Sexual contact (unprotected)	Sexual contact (unprotected)	Sexual contact (unprotected)	Sexual contact (unprotected)
Age	50	44	41	50	64	51
Comorbidities	HIV (CD4 514/mmc; HIV-RNA undetectable), previous gonorrhoea	Previous HBV, previous gonorrhoea	n/a	HBV, HIV CD4 (511/mmc; HIV-RNA undetectable), syphilis, previous HCV	HBV	HIV (CD4 197/mmc; HIV RNA undetectable), SARS-CoV-2
Systemic symptoms	Fever	Fever	Fatigue, malaise, headache, diarrhoea, and fever	n/a	n/a	Fever
Localisation and number of skin lesions	Chin (1)	n/a	Genital and perianal area subsequently spread to arms, back and mouth	n/a	Penis (4)	Penis (1)
MPXV DNA	Oropharingeal swab, vesicle swab	Urethral swab	vesicle swab	Urethral swab	Oropharingeal swab, vesicle swab	Vesicle swab

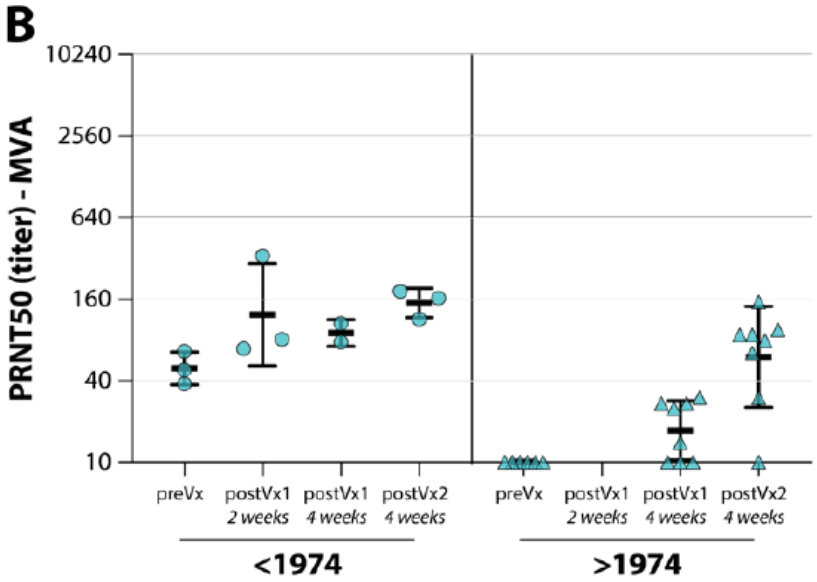
Imvanex - breakthrough infections after vaccination

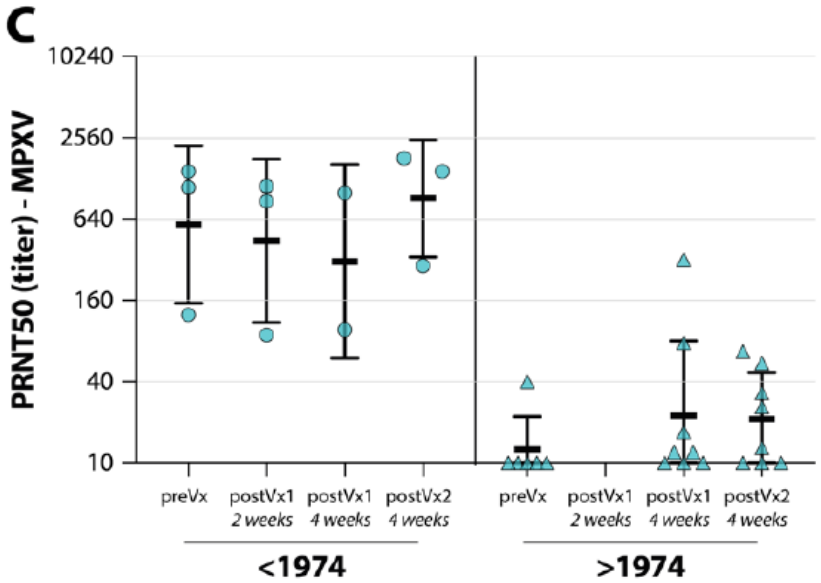
[Low levels of monkeypox virus neutralizing antibodies after MVA-BN vaccination in healthy individuals | medRxiv]



Imvanex - breakthrough infections after vaccination

[Low levels of monkeypox virus neutralizing antibodies after MVA-BN vaccination in healthy individuals | medRxiv]





Status of monkeypox vaccines in the EU

- There is no solid evidence regarding MVA-BN vaccine effectiveness against MPX
- We need more studies with different vaccination stretegies e.g. intradermal route, mix of SC dose followed by ID dose, 1 dose vs 2 doses, longer intervals between doses
- Data in specific populations such as immunosuppressed, paediatrics, pregnancy
- More vaccines may come and EMA ready to engage on rapid development and approval

Conclusions

- **Three adapted COVID mRNA vaccines approved** to better match current VOCs: two bivalent original/Omicron BA.1 and one bivalent original/Omicron BA.4-5
- EMA-ECDC recommended additional booster doses **in elderly above 6 years of age, immunocompromised subjects, individuals with underlying conditions and pregnant women. HCWs should also be vaccinated with adapted vaccines**
- **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 now slowing down and plateauing in many countries
- **Effectiveness data** with Imvanex are needed to understand the impact
- **RCTs with tecovirimat** to be started soon in the EU

Latest updates on EMA's corporate website:

COVID-19 pandemic

ema.europa.eu

@EMA_News

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