EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Update on COVID-19 vaccines and therapeutics

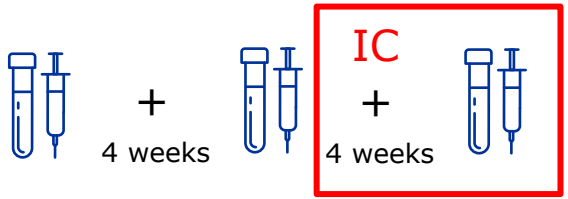
ENCEPP
30th November 2022

- Dr. Marco Cavaleri
- Head of Health Threats and Vaccines Strategy
- Chair of EMA Emergency Task Force

Vaccine	Platform*	Strain	Use	Population			
				≥6 months	≥5 years	≥12 years	≥18 years
Comirnaty (BioNTech)	mRNA	Original strain	Primary vaccination	✓ 6 months to 4 years	✓ 5-11 years	✓	✓
			Booster		✓ 5-11 years	✓	✓
		Original strain + Omicron BA.1 variant (adapted**)	Booster			✓	✓
		Original strain + Omicron BA.4-5 variants (adapted**)	Booster		✓ 5-11 years	✓	✓
Spikevax (Moderna)	mRNA	Original strain	Primary vaccination	✓ 6 months to 5 years	✓ 6-11 years	✓	✓
			Booster			✓	✓
		Original strain + Omicron BA.1 variant (adapted**)	Booster			✓	✓
		Original strain + Omicron BA.4-5 variants (adapted**)	Booster			✓	✓
Vaxzevria (AstraZeneca)	Adenoviral vector	Original strain	Primary vaccination				✓
			Booster				✓
Jcovden (Janssen)	Adenoviral vector	Original strain	Primary vaccination				✓
			Booster				✓
Nuvaxovid (Novavax)	Protein	Original strain	Primary vaccination			✓	✓
			Booster				✓
COVID-19 Vaccine Valneva (Valneva)	Inactivated	Original strain	Primary vaccination				✓ 18-50 years
VidPrevtyn Beta (Sanofi Pasteur)	Protein	Beta variant	Booster				✓

Efficacy in children for mRNA COVID-19 vaccines

Spikevax 25µg (6 months – 5 years of age)



- Phase 2/3 randomised, saline placebo-controlled, observer-blind study (N=5,500, Omicron circulating)

- 2-dose regimen with half dose as used in 6-11YOA (50ug) based on phase 1/2 data (3 doses in IC)

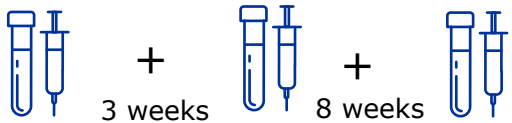
- **Immunobridging strategy common if no established correlate protection**: neutralising abs (primary endpoint) non-inferior to individuals 18-25 years of age where efficacy was demonstrated
- Good correlation seen between neutralising abs and vaccine efficacy for COVID-19, but no antibody threshold found

- Efficacy was evaluated as exploratory in seronegative subjects at baseline – preliminary data show low efficacy due to Omicron in line with adult data but estimates not reliable

- Duration of protection unknown
- Special populations not yet studied

Efficacy in children for mRNA COVID-19 vaccines

Comirnaty 3µg (6 months – 4 years of age)



- Phase 2/3 randomised, saline placebo-controlled, observer-blind study (N= 1300, most cases BA.2 and BA.2.12.1)

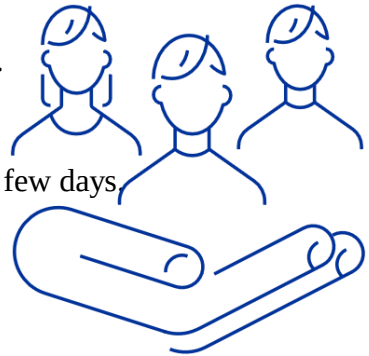
Table 8: Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 3 – Blinded Follow-Up Period – Participants Without Evidence of Infection Prior to 7 Days After Dose 3 – Phase 2/3 – 6 Months to 4 Years of Age – Evaluable Efficacy (3-Dose) Population

First COVID-19 occurrence from 7 days after Dose 3 in participants without evidence of prior SARS-CoV-2 infection*			
Subgroup	COVID-19 mRNA Vaccine 3 mcg/Dose N[a]=873 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=381 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI[e])
6 months through 4 years[c]	13 0.124 (794)	21 0.054 (351)	73.2 (43.8, 87.6)
2 through 4 years	9 0.081 (498)	13 0.033 (204)	71.8 (28.6, 89.4)
6 months through 23 months	4 0.042 (296)	8 0.020 (147)	75.8 (9.7, 94.7)

Abbreviations: NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein–binding; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; VE = vaccine efficacy.

- 3-dose regimen, since a two-dose regimen showed inferior immunogenicity in the 2-5 years old stratum, compared to young adults.
- **Immunobridging strategy**: GMTs and SCR of neutralising abs (primary endpoint) non-inferior to individuals 16-25 years of age where efficacy was demonstrated
- Efficacy analysis exploratory - similar with or without prior SARS-CoV-2 infection
- Preliminary data indicate comparable neutralization of delta and BA.1 vs. adults. Efficacy against BA.5 not studied.
- Duration of protection unknown
- Special populations not yet studied

Safety of mRNA COVID-19 vaccines (6m-4/5y)



- Most common side effects comparable to older age groups (fatigue, myalgia, nausea, injection site reactions etc).
- Irritability, sleepiness, loss of appetite, rash and tenderness at the injection site with Comirnaty (N= 4,550).
  Irritability, crying, loss of appetite and sleepiness with Spikevax (N=6,400). Mild or moderate, resolved within a few days.
- Risk of myocarditis/pericarditis compared to unexposed persons: very rare
  - Comirnaty: 0.3 extra cases in 12-29 y males / 10,000; 0.6 in 16-24y males / 10,000
  - Spikevax: 1.3 extra case in 12-29y males / 10,000; 1.9 extra cases in 16-24y males / 10,000
- Risk of heart complications higher with COVID-19 than after vaccination. Most patients fully recover
- **Emerging data** (including from the USA where **millions of children are vaccinated**) indicate that **COVID-19 vaccines are well tolerated in children**
  - ✓ Clinical trials showed that side effects of vaccines are usually mild or moderate and go away in a few days
  - ✓ Myocarditis much lower in 5-11 vs. 12-17-year-olds
  - ✓ No cases of myocarditis reported in 1.4 million children aged **6 months to 4 years** until October 2022 (CDC)

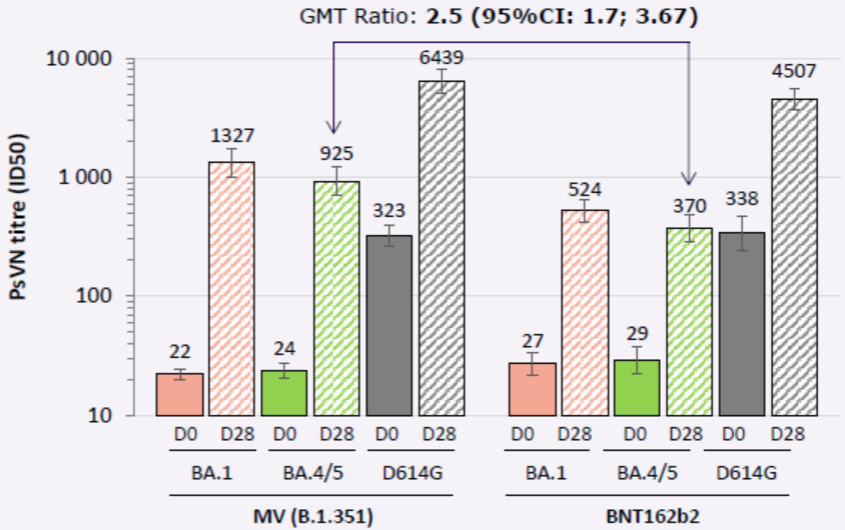
Vidprevtyn Beta
Re-analysis with validated Monogram PsVNA

Re-analysis against Omicron BA.4-5 conducted with validated Monogram PsVN assay as per request.

Results demonstrate higher titres against Omicron BA.4-5 with Vidprevtyn beta as compared to Pfizer/BioNTech. If pre-defined, analysis would meet superiority criteria.

Vidprevtyn Beta induces higher cross-neutralizing BA.4/5 antibodies vs BNT162b2 prototype in fully validated PsVN assay

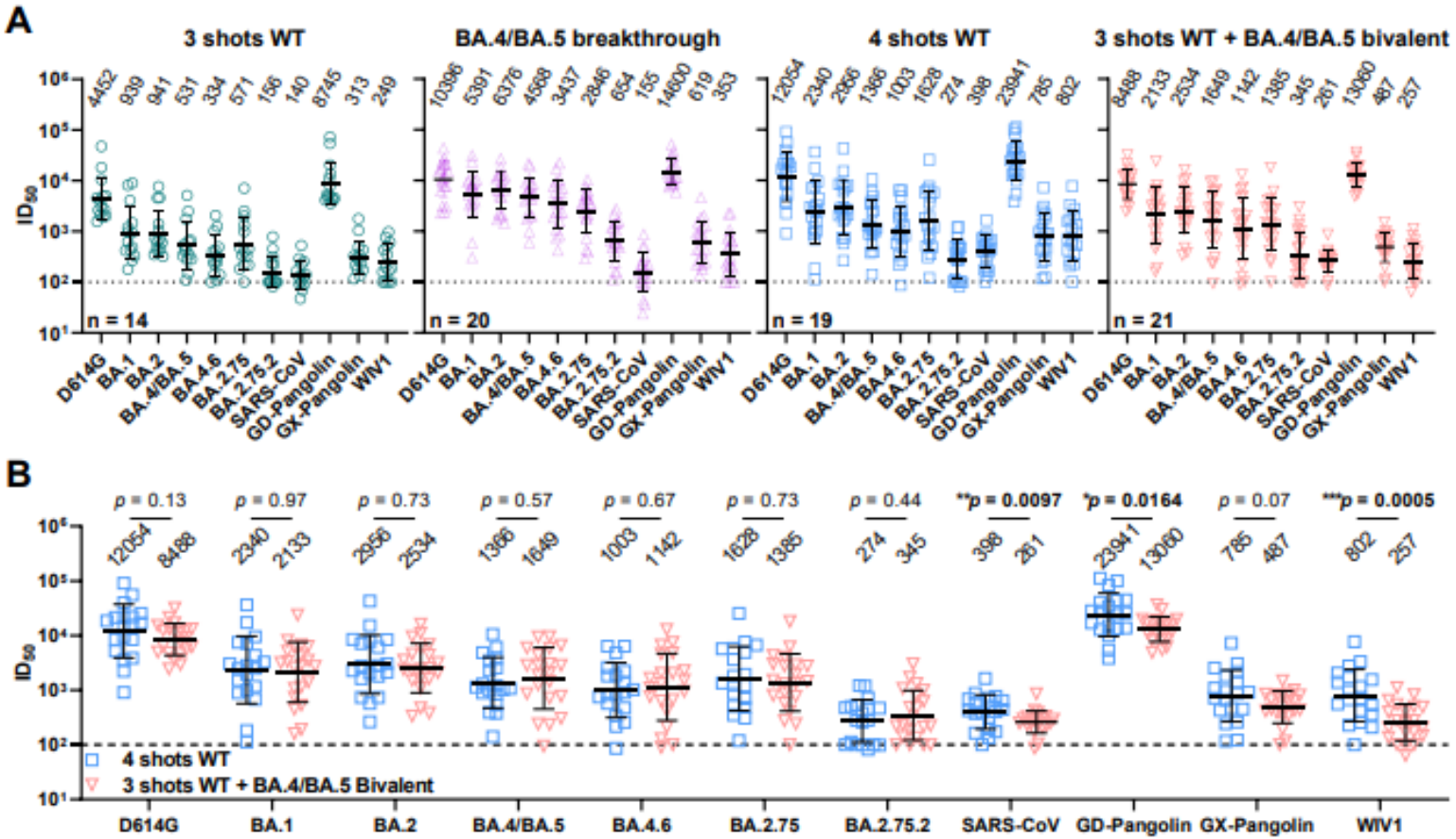
Results consistent with responses to Omicron BA.1 and D614G



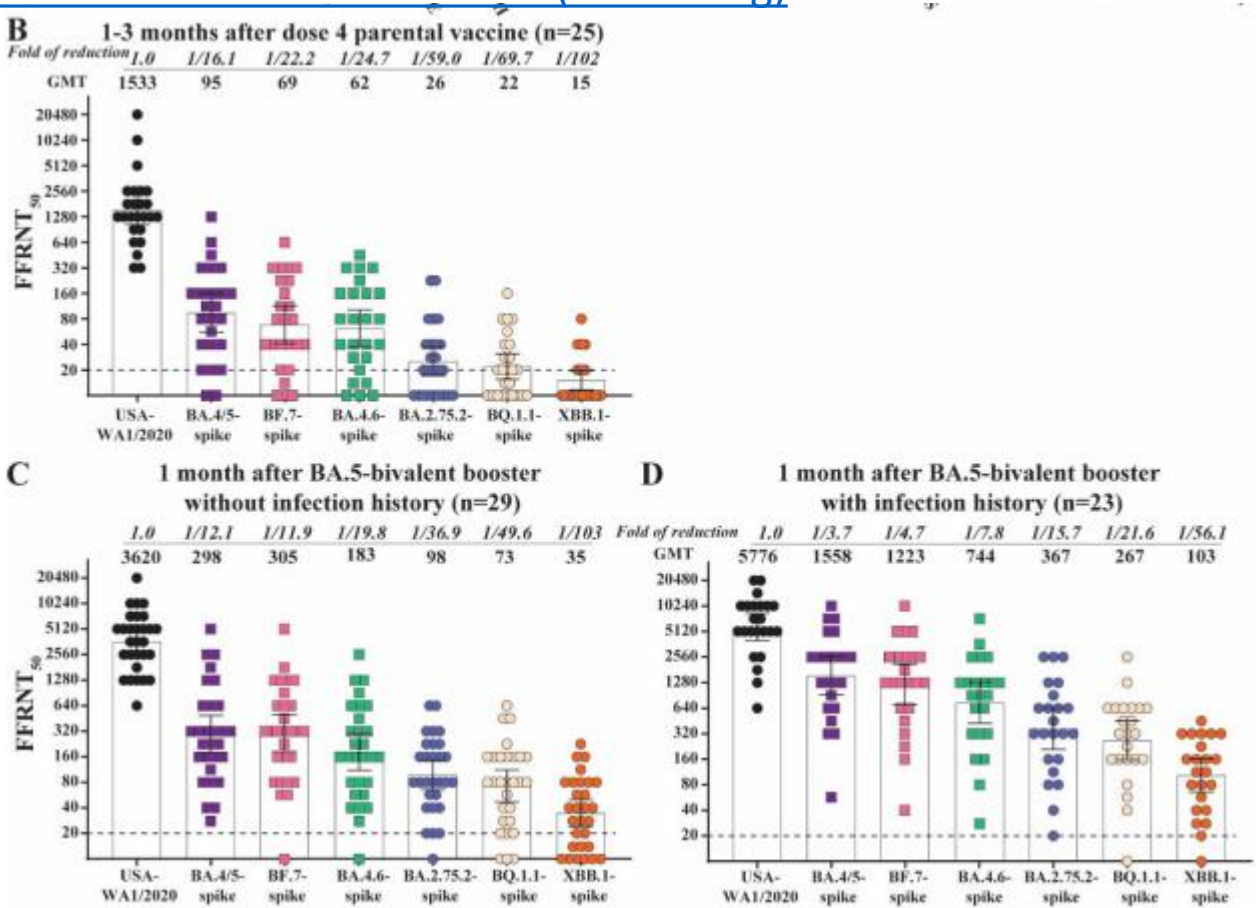
sanofi

VIDPREVTYN BETA - EMA/RAPPORTEURS/ETF CORE TEAM MEETING - 06 OCTOBER - CONFIDENTIAL

Antibody responses to Omicron BA.4/BA.5 bivalent mRNA vaccine booster shot | bioRxiv



Low neutralization of SARS-CoV-2 Omicron BA.2.75.2, BQ.1.1, and XBB.1 by 4 doses of parental mRNA vaccine or a BA.5-bivalent booster (biorxiv.org)



[Effectiveness of Bivalent mRNA Vaccines in Preventing Symptomatic SARS-CoV-2 Infection — Increasing Community Access to Testing Program, United States, September–November 2022 | MMWR (cdc.gov)]

Age group, yrs/mos since receipt of most recent monovalent dose	Relative VE (95% CI), by no. of monovalent doses received†			
	2 doses	3 doses	4 doses§	≥2 doses
18–49				
2–3	45 (31–56)	24 (14–33)	NA	30 (22–37)
4–5	47 (35–57)	41 (35–47)	NA	43 (38–48)
6–7	42 (30–52)	47 (42–52)	NA	46 (41–50)
≥8	53 (45–60)	58 (56–61)	NA	56 (53–58)
50–64				
2–3	—	15 (–4–31)	33 (24–41)	31 (24–38)
4–5	44 (18–62)	31 (18–42)	36 (29–43)	36 (30–41)
6–7	46 (22–62)	36 (25–45)	40 (32–47)	38 (32–43)
≥8	61 (49–70)	51 (45–55)	NA	48 (45–51)
≥65				
2–3	—	—	32 (23–40)	28 (19–35)
4–5	—	21 (1–36)	36 (29–42)	33 (27–39)
6–7	—	14 (–6–30)	40 (33–46)	36 (29–41)
≥8	45 (27–58)	42 (35–48)	NA	43 (39–46)

COVID-19 treatments

Share

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)

Imprinted SARS-CoV-2 humoral immunity induces convergent Omicron RBD evolution (biorxiv.org)

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Pango lineages	REGN 10933	REGN 10987	REGN10933 +10987	COV2-2196	COV2-2130	COV2-2196+2130	BRII-196	BRII-198	BRII-196+198	S309	DXP-604	LY-CoV 1404	SA58	SA55	SA55+ SA58	Additional RBD mutations
BA.2	*	590	821	4312	6.3	8.2	8530	8990	8610	852	219	0.9	5.1	7.2	7.8	
BA.2.3.20	121	*	199	15	*	26	14	*	24	897	181	9.7	20	4.6	7.8	K444R+N450D+L452M +N460K+R493Q
BA.2.10.4	*	*	*	*	289	501	2109	7990	3984	706	6348	1.3	4.3	4.9	5.0	G446S+F486P+R493Q +S494P
BJ.1	*	*	*	3076	*	5985	7609	*	*	709	166	*	8163	3.7	8.6	D339H+R346T+L368I+ V445P+G446S+V483A +F490V
XBB	*	*	*	*	*	*	*	*	*	963	*	*	8805	5.3	9.8	D339H+R346T+L368I+ V445P+G446S+N460K +F486S+F490S+R493Q
BA.2.75	278	*	410	119	352	121	1730	6622	3861	672	5920	2.2	246	4.3	9.6	
BL.1	260	*	511	93	*	174	1251	*	3075	508	7193	2.8	7975	6.3	10	R346T
BR.1	319	*	679	117	*	170	1992	*	3160	564	6689	*	1616	5.9	9.7	L452R+K444M
BN.2.1	390	*	701	59	303	109	4101	*	8444	6979	8901	1.7	4960	5.7	9.4	K356T+F490S
BN.1	344	*	599	70	*	166	3683	*	7791	*	6012	3.3	8295	4.9	9.0	R346T+K356T+F490S
BA.2.75.2	*	*	*	*	*	*	*	*	*	852	*	3.0	6922	5.9	9.7	R346T+F486S
BM.1.1	*	*	*	*	*	*	*	*	*	879	*	2.3	8823	5.2	8.9	R346T+F486S
BM.1.1.1	*	*	*	*	*	*	*	*	*	956	*	1.9	8082	4.8	10.5	R346T+F486S+F490S
BR.2	*	*	*	*	*	*	*	*	*	921	*	2.6	7263	4.7	10.5	R346T+L452R+F486I
CA.1	*	*	*	*	*	*	*	*	*	897	*	3.2	6927	6.0	11.5	R346T+L452R+F486S
BA.4/5	*	520	709	*	23	40	7124	*	*	1055	6264	0.8	3.9	5.0	4.5	
BA.4.6.1	*	2338	5402	*	*	*	4763	*	7809	4456	4634	1.2	50	4.8	9.9	R346T
BA.5.6.2	*	*	*	*	*	*	4636	*	7883	1408	5892	1662	58	5.1	8.9	K444T
BQ.1	*	*	*	*	*	*	*	*	*	1709	*	1905	44	6.6	9.2	K444T+N460K
BU.1	*	*	*	*	*	*	*	*	*	1082	*	26	56	5.3	10.5	K444M+N460K
BQ.1.1	*	*	*	*	*	*	*	*	*	5581	*	*	900	5.9	10.3	R346T+K444T+N460K

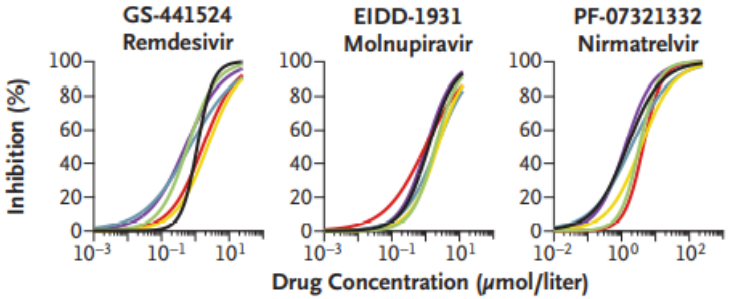
Pseudovirus IC50 (ng/mL) | <100 | 100~1,000 | >1,000

Impact of virus variants on activity of antivirals vs Mabs SARS-COV2

B Neutralization Efficacy of Monoclonal Antibodies

	REGN10987 Imdevimab	REGN10933 Casirivimab	COV2-2196 Tixagevimab	COV2-2130 Cilgavimab	S309 Sotrovimab Precursor	LYCoV1404 Bebtelovimab	REGN10987 plus REGN10933	COV2-2196 plus COV2-2130
	$FRNT_{50}$ (ng/ml)							
Ancestral strain: SARS-CoV-2/UT-NC002-1T/Human/2020/Tokyo	1.87	4.01	3.17	5.36	16.71	3.31	4.89	5.35
Delta: hCoV-19/USA/WI-UW-5250/2021	4.31	7.15	4.63	8.93	255.55	1.72	3.26	10.57
Omicron BA.2: hCoV-19/Japan/UT-NCD1288-2N/2022	653.29	>50,000	2020.05	27.12	>50,000	6.9	390.97	38.93
Omicron BA.5: hCoV-19/Japan/TY41-702/2022	174.78	>50,000	>50,000	70.34	>50,000	3.03	394.6	92.62
Omicron BA.4.6: hCoV-19/USA/WI-UW-12757/2022	322.57	>50,000	>50,000	>50,000	>50,000	3.8	258.83	>10,000
Omicron BA.4.6: hCoV-19/USA/WI-UW-12767/2022	307.11	>50,000	>50,000	>50,000	>50,000	2.26	426.89	>10,000

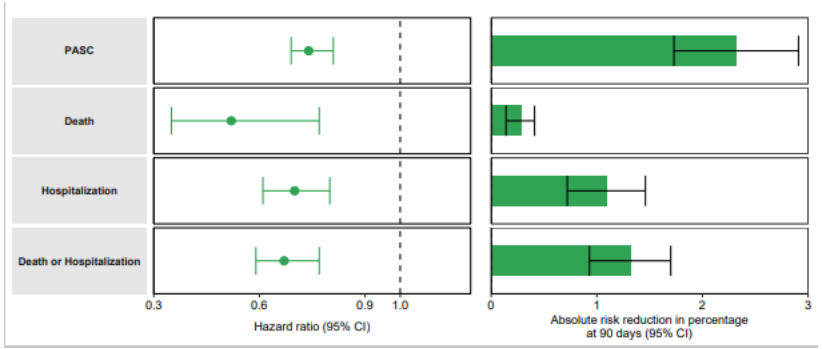
C Inhibitory Activity of Antiviral Drugs

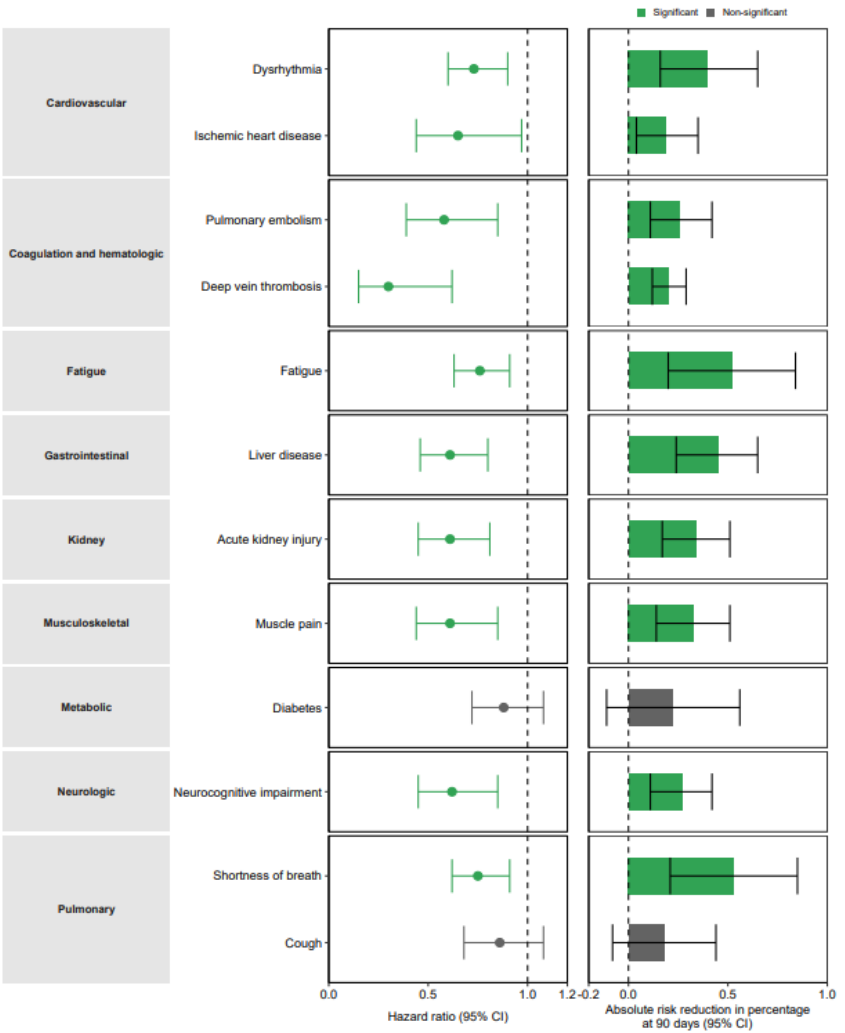


D Viral Susceptibility to Drug

	GS-441524 Remdesivir	EIDD-1931 Molnupiravir	PF-07321332 Nirmatrelvir
	IC_{50} (μmol/liter)		
Ancestral strain: SARS-CoV-2/UT-NC002-1T/Human/2020/Tokyo	1.23	1.46	1.08
Delta: hCoV-19/USA/WI-UW-5250/2021	0.61	1.85	3.29
Omicron BA.2: hCoV-19/Japan/UT-NCD1288-2N/2022	2.68	6.60	3.69
Omicron BA.5: hCoV-19/Japan/TY41-702/2022	0.78	8.36	2.01
Omicron BA.4.6: hCoV-19/USA/WI-UW-12757/2022	1.95	8.38	4.43
Omicron BA.4.6: hCoV-19/USA/WI-UW-12767/2022	0.54	2.62	1.29

Nirmatrelvir and the Risk of Post-Acute Sequelae of COVID-19



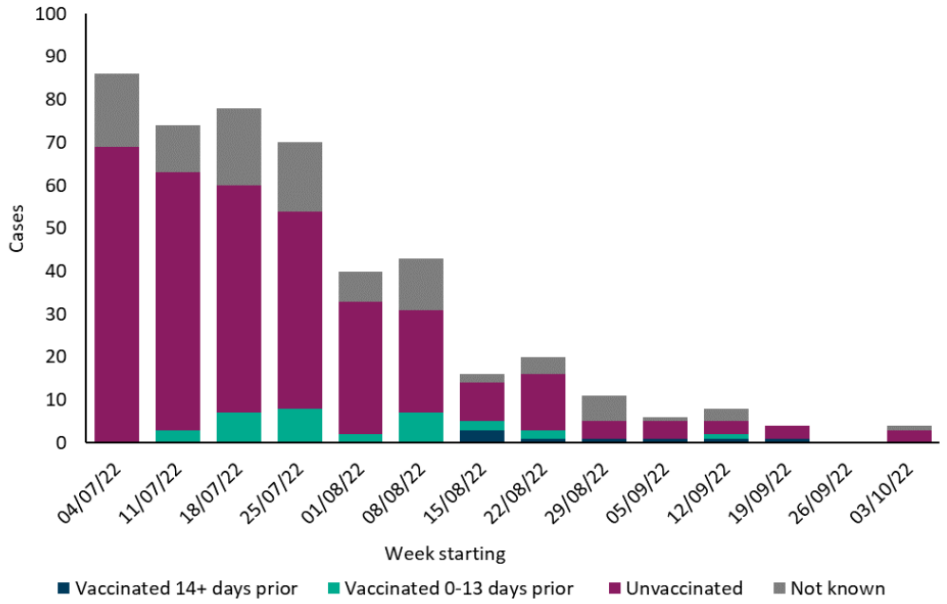


[97708236 (medrxiv.org)]

BREAKTHROUGH INFECTIONS – VACCINATED VS UNVACCINATED - CURRENT MPOX PHEIC

- Effectiveness of one dose of MVA-BN smallpox vaccine against monkeypox in England using the case-coverage method. Bertran, et al (UKHSA) preprint.
- Assessed the VE of a single MVA-BN dose in high-risk gay, bisexual and other MSM (excluded female and heterosexual). Case-coverage method: vaccination rates among cases is compared to population coverage. 363 confirmed cases. The central estimate of VE after ≥ 14 days of a single dose of smallpox vaccine was 78% (95% CI: 54%-89%) (range 71%-85% in sensitivity analyses), with no evidence of protection in the first 13 days after vaccination.

Figure 2. Number of monkeypox cases by week and vaccination status from 4 July 2022 (week 27) to 9 October 2022 (week 40)



VACCINE– EFFORTS IN DATA COLLECTION

- Several initiatives in different MSs that could be extended for an EU or global initiative, have been presented and discussed at ETF for scientific advice.
- Collaboration with VACCELERATE - EU network for vaccines clinical trials.
- The newly established **Vaccine Monitoring Platform (VMP)**, a joint collaboration between EMA and ECDC, is serving as forum for discussing the technical aspects and looking into funding options.
- Safety and effectiveness of MVA-BN vaccination against MPXV infection in at-risk individuals in Germany (SEMVAc study): multicenter, prospective, non-interventional, observational, pre-exposure prophylaxis cohort study. Primary endpoint: VE of MVA-BN against symptomatic PCR-confirmed MPX, defined as reduction in risk of infection/disease in vaccinated versus unvaccinated individuals. N=15,000 individuals (5000 vaccinated).

TECOVIRIMAT – EFFORTS IN DATA COLLECTION

- Several initiatives in different MSs that could be extended for an EU or global initiative, have been presented and discussed at ETF for scientific advice.

- MOSAIC study. Changed design to Low-interventional clinical trial sponsored by Oxford University, ANRS (FR) and HUG (CH) extended to EU MSs after discussion with ETF including CTCG members. A cohort study collecting harmonised data in patients treated or not treated with tecovirimat. Focus on the longer term will be on patients with more severe disease.

- Contribution to RCT study design developed by WHO CORE protocol

TECOVIRIMAT – EFFORTS IN DATA COLLECTION

- For mild-moderate MPX, there is agreement that a randomised clinical trial is ethical and needed to ascertain the clinical impact of the use of antivirals

- European Randomized Clinical Trial on Monkeypox Infection (EPOXI). Conducted by the EU funded network European Clinical Research Alliance on Infectious Diseases Ecraid home | Ecraid that aims to advance clinical research in the field by establishing a network in Europe.
- This is a platform trial to find the best treatment for monkeypox disease.
- The initial intervention will be an international randomized placebo-controlled double-blind clinical trial to evaluate tecovirimat 600mg bid for 14 days. UMC Utrecht is the study sponsor, and NL is the proposed reference MS when applying through CTIS. The initial sample will be 1000 adults, that suffer from mild, moderate or severe monkeypox disease and have a positive PCR for monkeypox virus.
- Primary endpoint is days from randomization until resolution of lesions.

Timeline of EMA-funded COVID-19* studies

2020 **2021** **2022** **2023**

ACCESS
Pre-pandemic background rates AESIs

CONSIGN
Medicines in pregnancy

E-CORE
(international cohorts)

Natural history of **coagulopathy** and use of anti-thrombotic agents in COVID-19 patients and SARS-COV-2 vaccinees

Early-Covid-Vaccine (safety) **Monitor (ECVM)**

Two-year **Covid-Vaccine** (safety) **Monitor (CVM)**

Association between thrombosis with thrombocytopenia syndrome (**TTS**) or **thromboembolic (TE)** events, and COVID-19 vaccines

Benefit Risk contextualisation of COVID-19 vaccines in the EU

Impact of EU label changes and regulatory communication on adenovirus vector vaccines in context of TTS: risk awareness and adherence

Comparative effectiveness of heterologous and homologous primary- and booster SARS-CoV-2 vaccination in the Nordic countries

Effectiveness of heterologous and booster Covid-19 vaccination in 5 EU countries

Safety in children (myocarditis and TE events, IMDs)

MPX (SEMVAc study DE)

Coverage, safety & effectiveness of COVID-19 **maternal** immunisation (TBD)

Safety
Benefit/risk
Effectiveness
Impact

*one MPX study

How can ENCePP support public health crisis management?

- Evidence from pharmacoepidemiological studies on COVID-19 vaccines has contributed to EMA decision-making → e.g., rolling appraisals of emerging independent evidence by EMA's pandemic task force (ETF)

- EMA extended mandate (ECDC/EMA vaccine monitoring platform): effectiveness studies, benefit/risk contextualisation → importance of methods and selection of suitable data sources

- Research questions important for regulatory decision-making may be discussed with / addressed by the ENCePP community → leverage expertise