25 November: engage with the EMA!

4th public debate

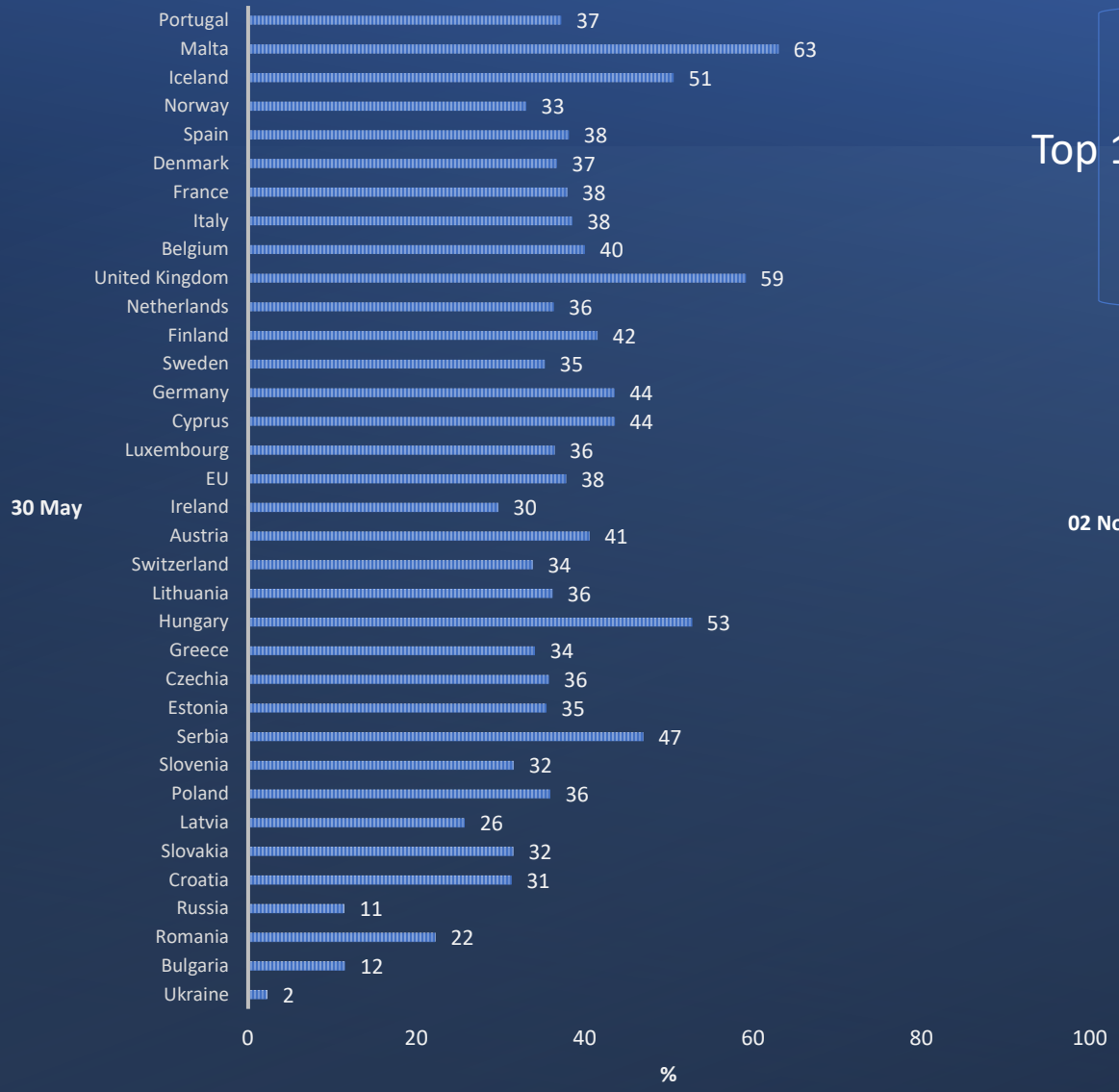
- Those interested in joining the virtual room during the public meeting should complete and **submit a registration form by 10 November 2021**:
  - Registration form
- The following topics will be covered:
  - COVID-19 therapeutics and vaccines in the EU, including vaccine effectiveness, and the use of booster and third doses in national vaccination campaigns
  - Update on vaccine safety information
  - COVID-19 epidemiological situation and vaccination coverage in the EU
  - Misinformation on COVID-19 vaccines
- https://www.ema.europa.eu/en/events/public-stakeholder-meeting-covid-19-vaccines-therapeutics-eu

Date: 25/11/2021
Location: Online, 13:00 - 15:15 Amsterdam time (CET)
Twitter: #EMAPublicMeeting4
Slido: #EMAPublicMeeting4

(1) Vaccination in Europe

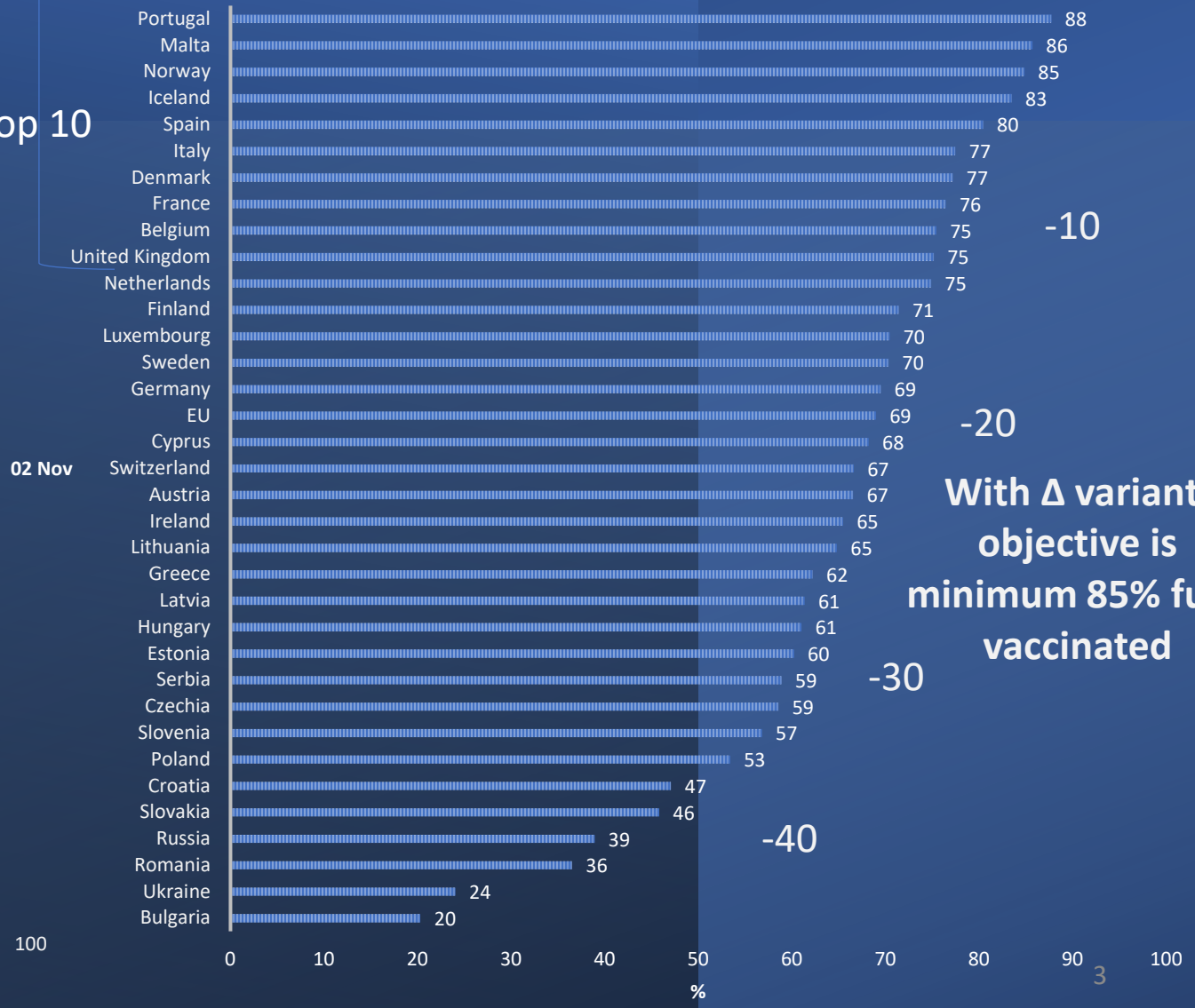
Short and mid-term estimates

Share of people who received at least one dose of a vaccine



Share of people who received at least one dose of a vaccine

Top 10



-10

-20

-30

-40

With Δ variant, objective is minimum 85% fully vaccinated

Country	% who said they wanted to be vaccinated 02/2021	% who received at least 1 dose 02/11/21	Difference
France	48,7	76,4%	27,7
Belgium	54,3	75,4%	21,1
Switzerland	46,9	66,6%	19,7
Latvia	44,8	61,3%	16,5
Lithuania	52,2	64,8%	12,6
Netherlands	63,2	74,9%	11,7
Austria	56,8	66,5%	9,7
Germany	61	69,5%	8,5
Cyprus	60,7	68,2%	7,5
Slovenia	50,2	56,8%	6,6
Portugal	82,6	87,7%	5,1
Hungary	56,1	61,0%	4,9
EU	64,4	69,0%	4,6
Estonia	57,2	60,2%	3,0
Luxembourg	67,4	70,4%	3,0
Croatia	45,1	47,1%	2,0
Malta	84	85,7%	1,7
Czechia	56,9	58,5%	1,6
Greece	61,6	62,2%	0,6
Spain	80,8	80,4%	-0,4
Italy	78,6	77,5%	-1,1
Poland	56,1	53,4%	-2,7
Russia	41,7	38,9%	-2,8
Norway	89,5	84,8%	-4,7
Denmark	86	77,2%	-8,8
Finland	80,3	71,4%	-8,9
Sweden	80,7	70,3%	-10,4
Slovakia	56,4	45,8%	-10,6
Bulgaria	32,5	20,3%	-12,2
United Kingdom	89	75,1%	-13,9
Ireland	86,5	65,4%	-21,1
Romania	59,4	36,5%	-22,9
Ukraine	61	24,0%	-37,0

In the next months: a winter surge in Europe

1. Variants. No population-based data to suggest Mu is driving surges yet. But this can completely change
2. Waning immunity. Steady evidence emerging from England, Scotland, Israel, a Mayo Clinic study in the US suggest there is waning immunity for infection for all of the vaccines
3. Data from Israel published in the *New England Journal of Medicine* this week starts to suggest that immunity for severe hospitalisation, severe cases, and for death may also start to wane and wanes faster for AstraZeneca than for Pfizer or Moderna

- IHME: Models will be adapted in the next few weeks. Third dose not in model yet

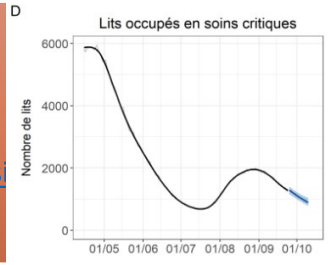
COVID-19 pandemic modelling Sources

Institute for Health Metrics and Evaluation, Uni. Washington, Seatle

https://covid19.healthdata.org

Institut Pasteur

https://modelisation-covid19.pasteur.fr/realtime-analysi



ECDC

Institut de Physique des 2 Infinis (IP2I), CNRS

https://doi.org/10.1038/s41598-020-72611-5

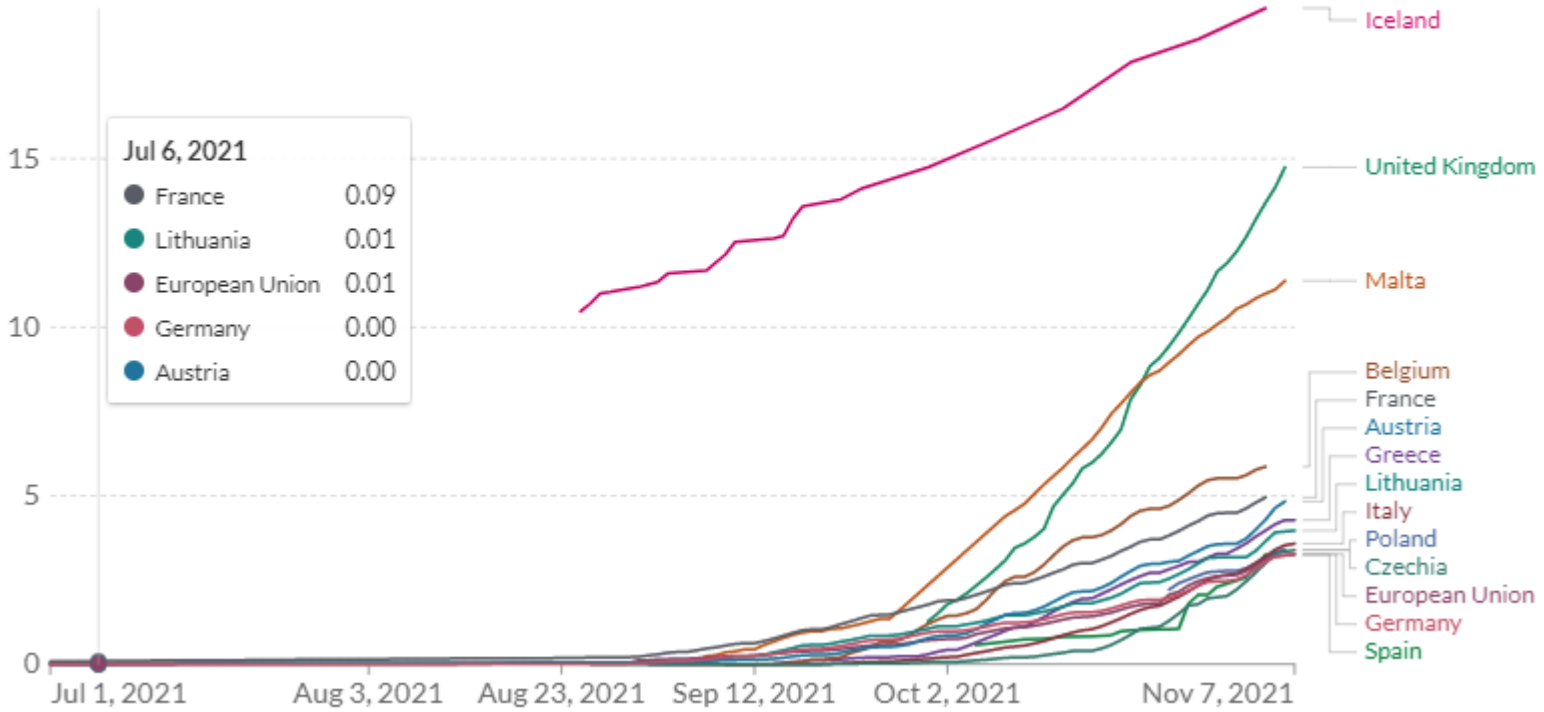
In the next months: a winter surge in Europe

COVID-19 vaccine booster doses administered per 100 people

Total number of vaccine booster doses administered, divided by the total population of the country. Booster doses are doses administered beyond those prescribed by the original vaccination protocol.

Our World in Data

LINEAR LOG Add country

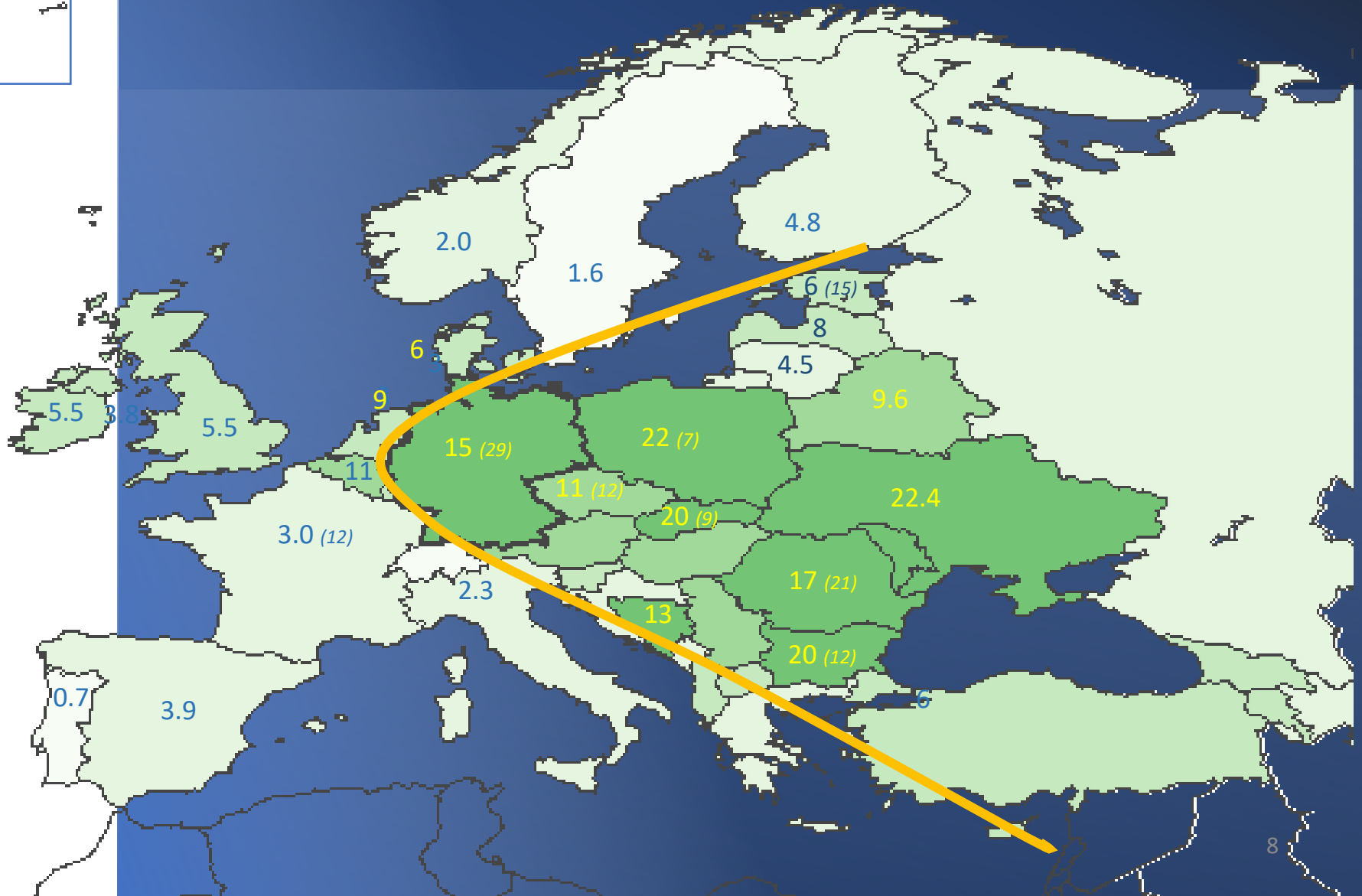


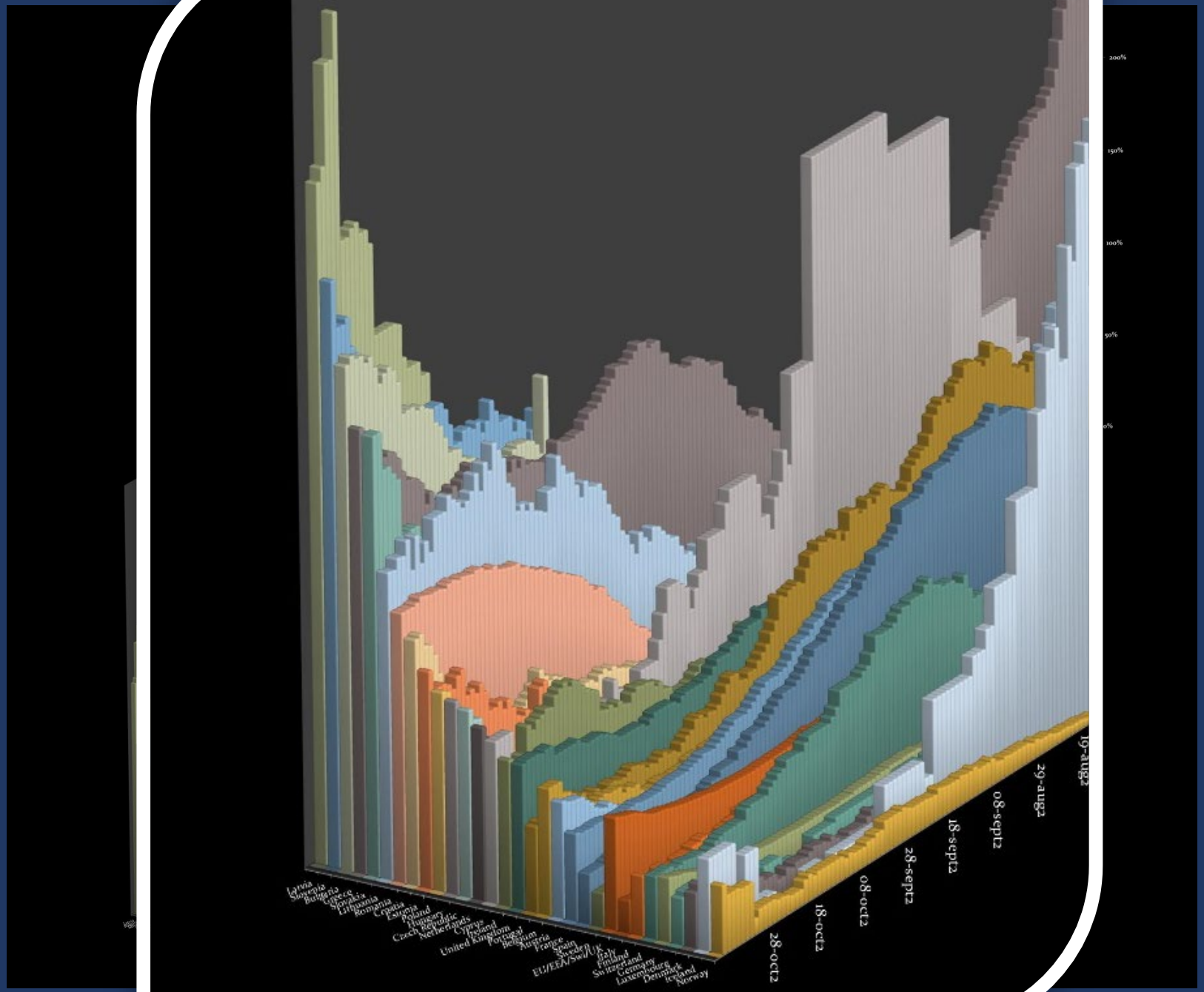
Source: Official data collated by Our World in Data – Last updated 8 November 2021, 11:00 (London time)

OurWorldInData.org/coronavirus • CC BY

Estimated number of ICU beds needed per 100,000 inhabitants
Source: Institute for Health Metrics and Evaluation (IHME)
Univ. Washington, Seattle

December 31, 2021

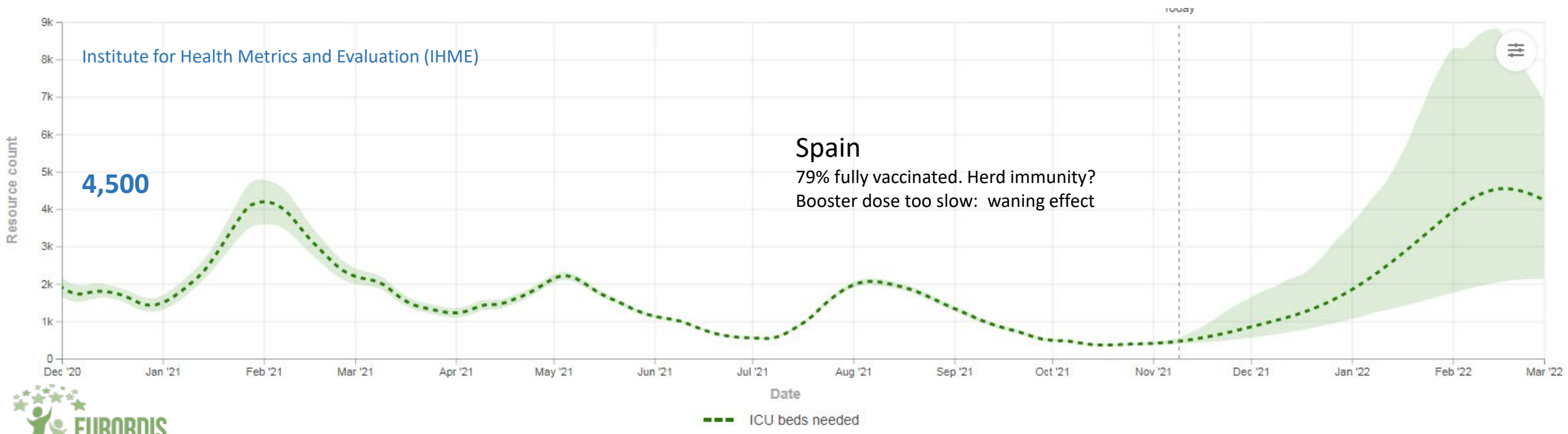




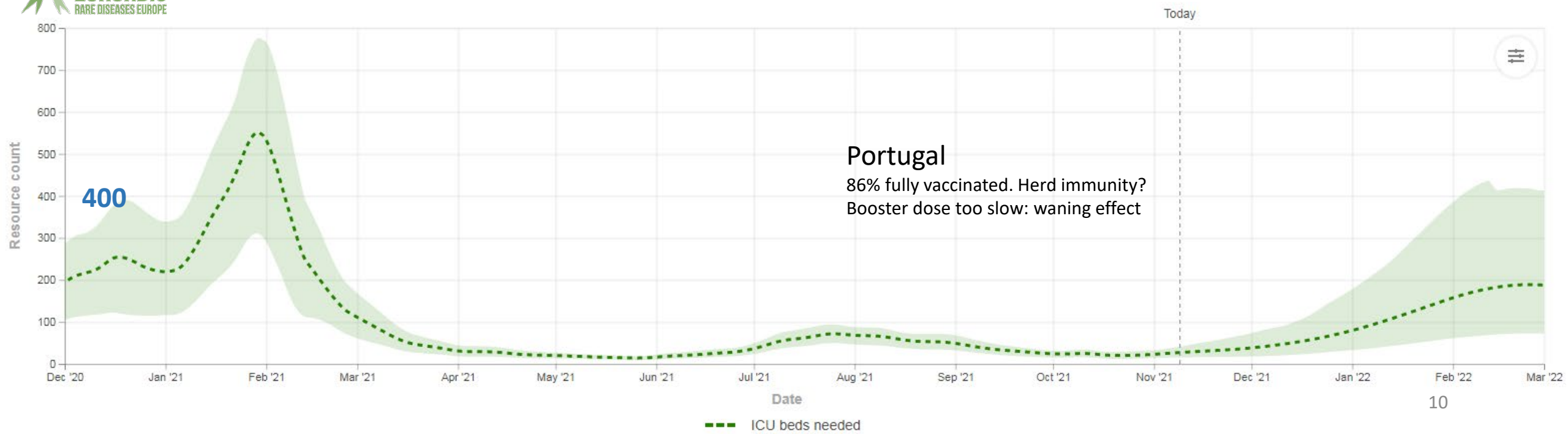
Initial variant

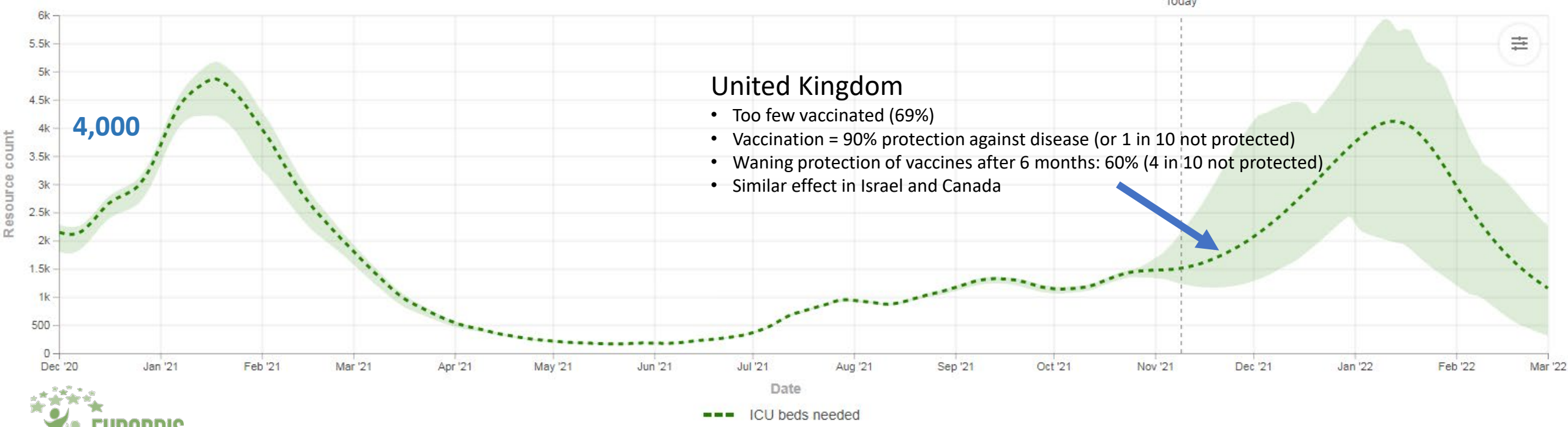
Delta variant

Institute for Health Metrics and Evaluation (IHME)



EURORDIS
RARE DISEASES EUROPE



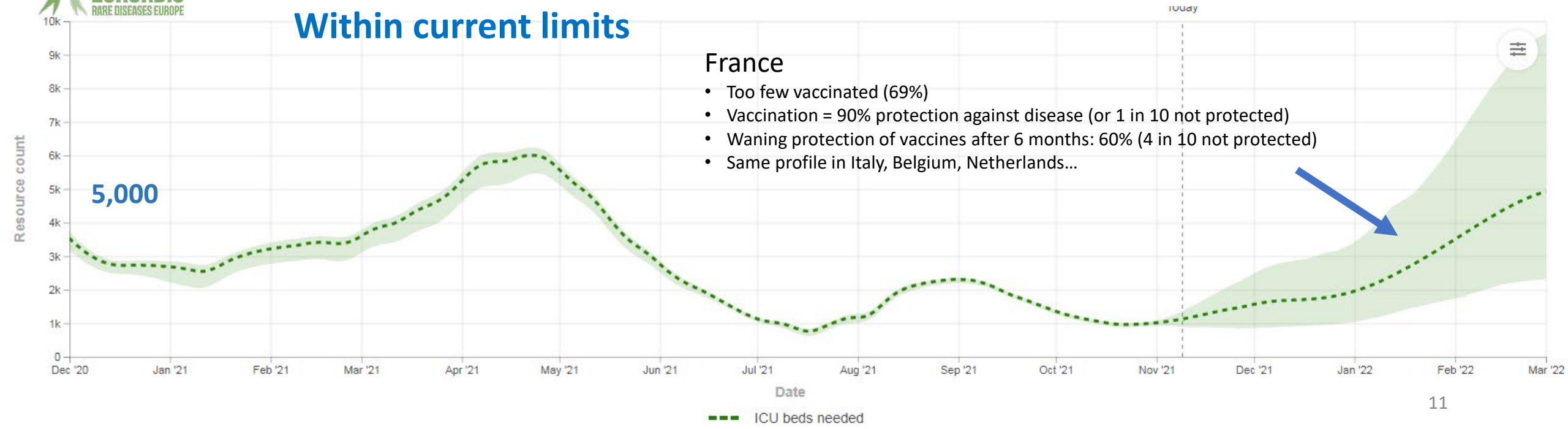


United Kingdom

- Too few vaccinated (69%)
- Vaccination = 90% protection against disease (or 1 in 10 not protected)
- Waning protection of vaccines after 6 months: 60% (4 in 10 not protected)
- Similar effect in Israel and Canada

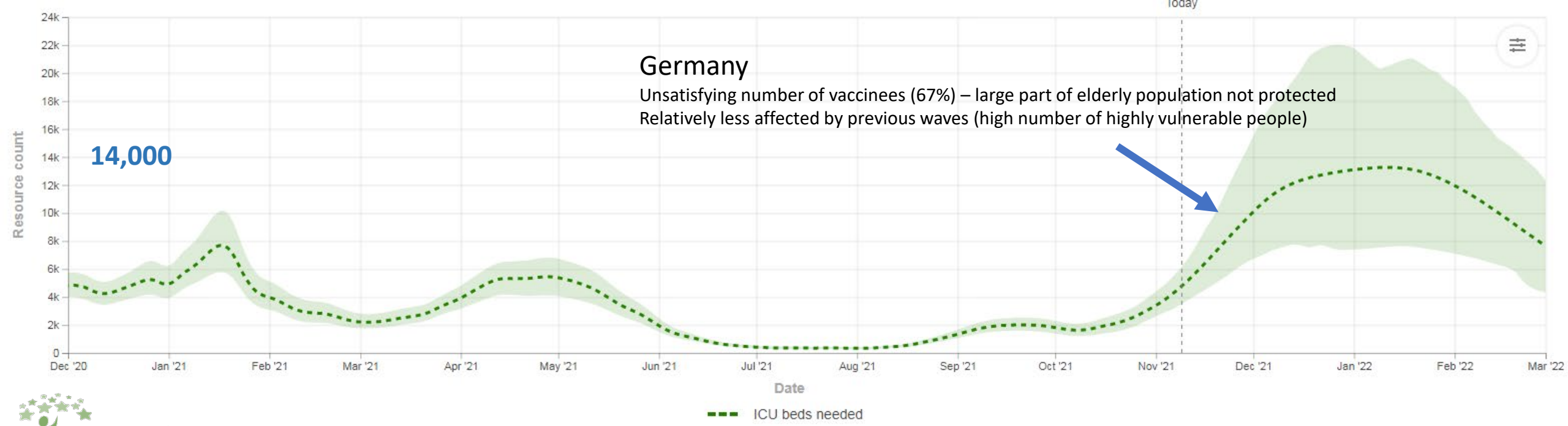
EURORDIS
RARE DISEASES EUROPE

Within current limits



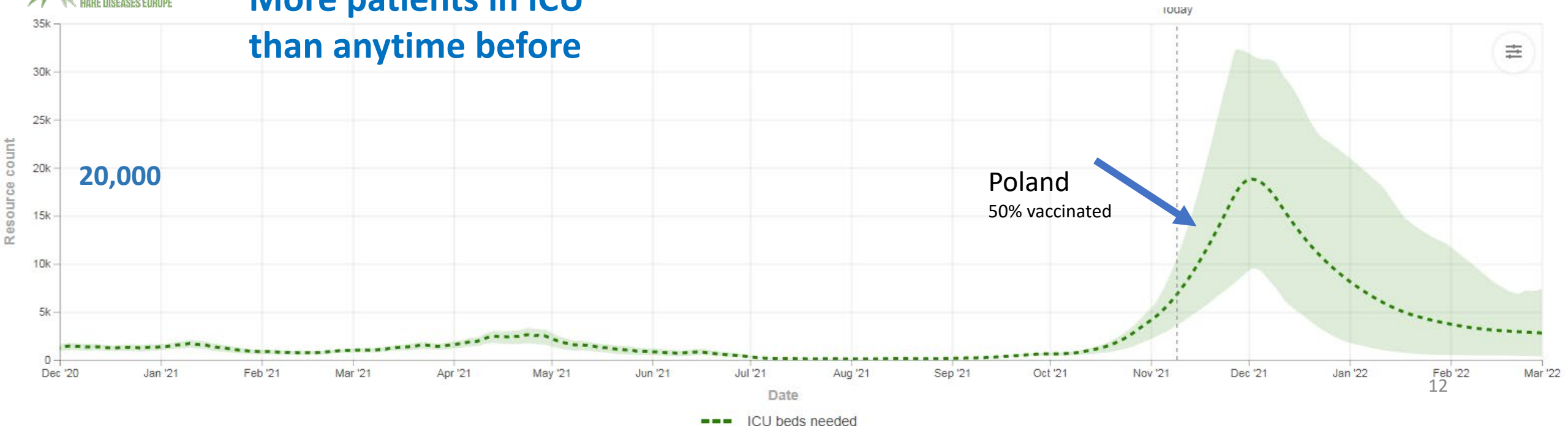
France

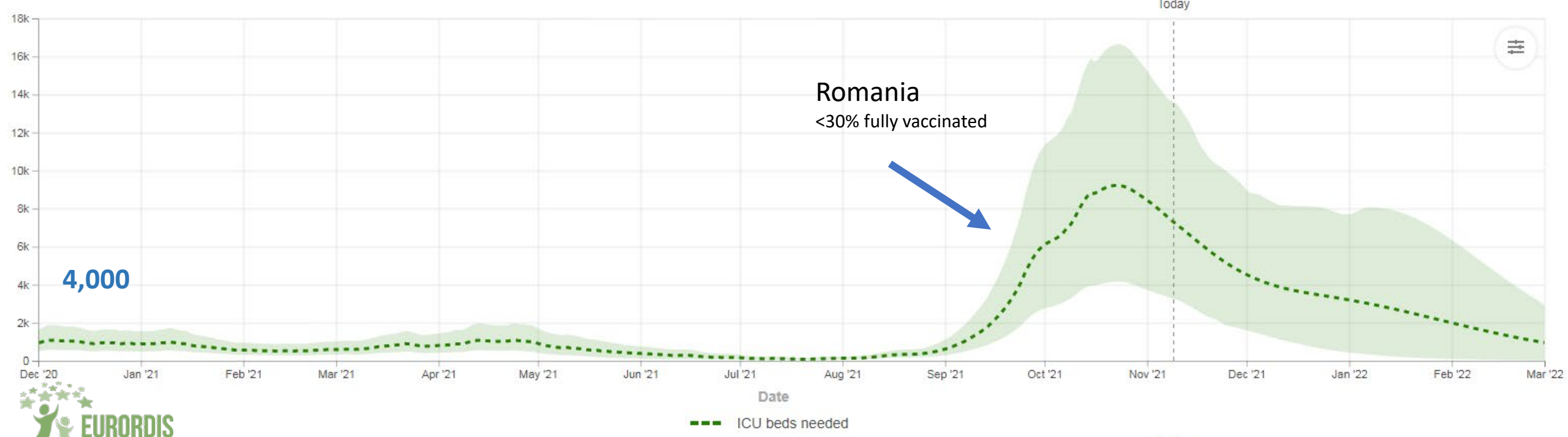
- Too few vaccinated (69%)
- Vaccination = 90% protection against disease (or 1 in 10 not protected)
- Waning protection of vaccines after 6 months: 60% (4 in 10 not protected)
- Same profile in Italy, Belgium, Netherlands…

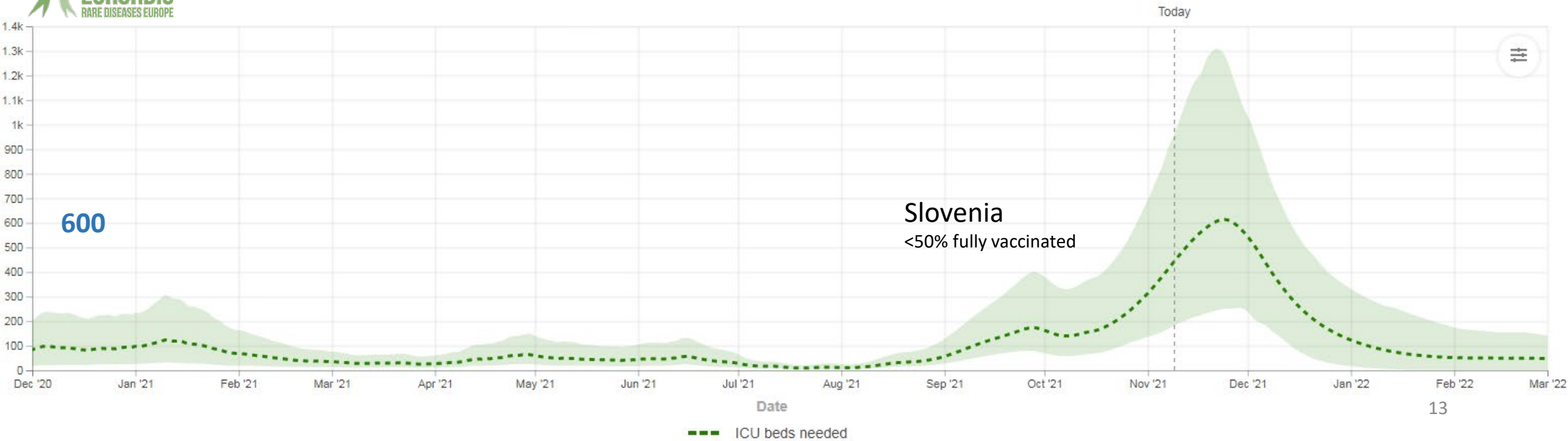


EURORDIS
RARE DISEASES EUROPE

More patients in ICU than anytime before



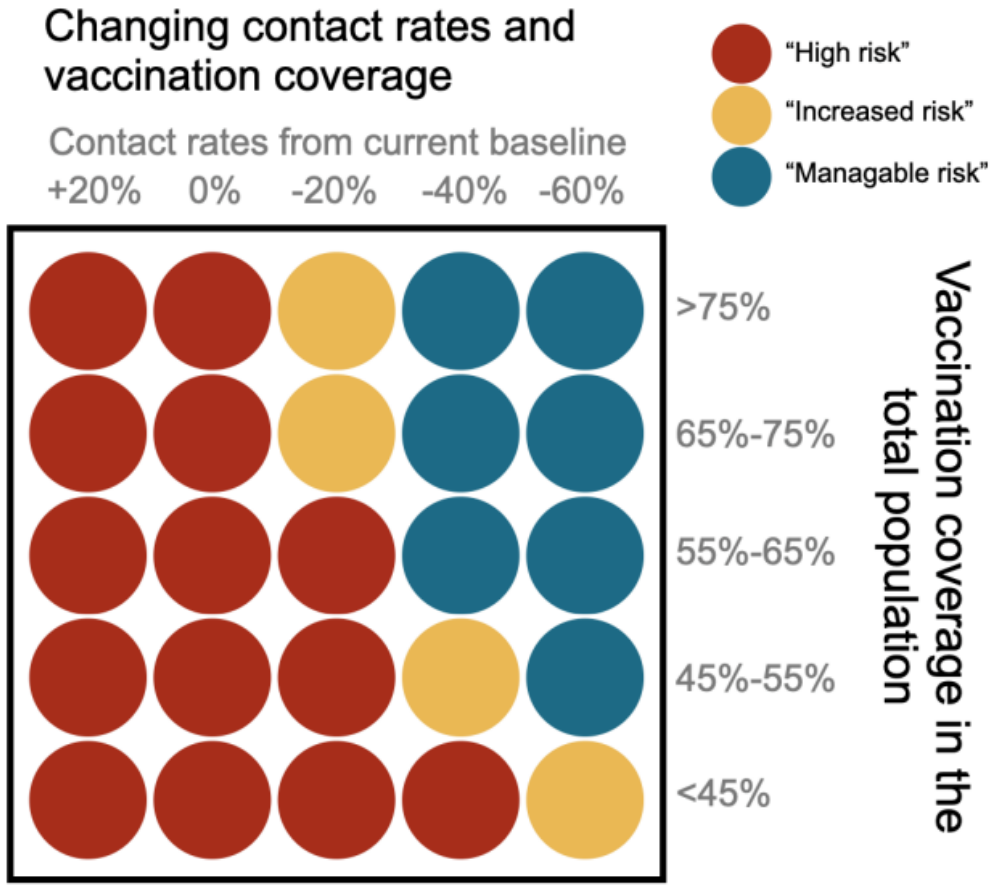

Today
18k
16k
14k
12k
10k
8k
6k
4k
2k
0
Romania
<30% fully vaccinated
4,000
Dec '20
Jan '21
Feb '21
Mar '21
Apr '21
May '21
Jun '21
Jul '21
Aug '21
Sep '21
Oct '21
Nov '21
Dec '21
Jan '22
Feb '22
Mar '22
Date
ICU beds needed


Today
1.4k
1.3k
1.2k
1.1k
1k
900
800
700
600
500
400
300
200
100
0
600
Slovenia
<50% fully vaccinated
Dec '20
Jan '21
Feb '21
Mar '21
Apr '21
May '21
Jun '21
Jul '21
Aug '21
Sep '21
Oct '21
Nov '21
Dec '21
Jan '22
Feb '22
Mar '22
Date
ICU beds needed

ECDC scenarii 30 September 2021

Figure 9. Projected burden of COVID-19 hospitalisations in relation to vaccination coverage between now and the end of November 2021.

Projected scenario outcomes across different COVID-19 vaccine coverages of the total population and contact rates relative to current baseline assuming waning of vaccine effectiveness against cases (mean of 57%, range 53%-61%)



https://www.ecdc.europa.eu/sites/default/files/documents/covid-19-rapid-risk-assessment-16th-update-september-2021.pdf

Different policies for third shot - EU

Recommendation of an additional vaccine dose as extension of primary series and/or a booster for waning immunity		No recommendation
13: Only for immuno-compromised, transplanted	10: Immuno-compromised, > 65 yo and other groups	1: No recommendation
Belgium, Estonia, Finland, Italy, Latvia*, Liechtenstein, Luxembourg, Malta, Netherlands, Norway*, Poland, Portugal, Spain	Austria*, Cyprus, Denmark, France**, Germany, Hungary*, Ireland, Lithuania, Slovenia, United Kingdom	Bulgaria
		7: Discussions
		Croatia, Czechia, Greece, Iceland, Romania, Slovakia, Sweden

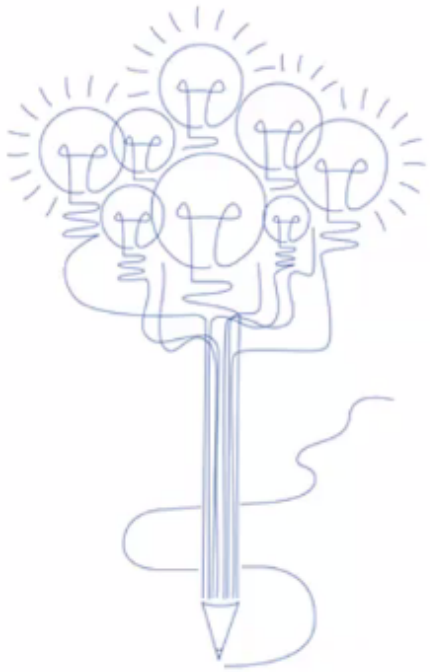
* Heterologous regimen possible, ** since April 2021

(2) Medicines for COVID-19

Progress as of 21-22 September 2021 / PCWP meeting

Marco Cavaleri, chair of EMA COVID-19 Pandemic Task Force

Summary of activities



219 therapeutics in discussion with EMA

66 vaccines identified for interaction

Rapid scientific advice proceeding for advanced vaccines and therapeutics (117 completed – 9 in the pipeline)

Booster and additional doses under assessment

Novavax, SP, Sinovac and Gamaleya under RR

EC expert group on variants and subgroup on therapeutics

Report from PCWP 21-22/09/2021

4 monoclonal antibodies products with neutralising activity received scientific opinion to support emergency use before approval and have started rolling review (Bamlanivimab / etesevimab, Casirivimab / imdevimab, Regdanvimab, Sotrovimab) and Dexamethasone

Currently under rolling review

- Evusheld (tixagevimab / cilgavimab)
- Molnupiravir
- Sotrovimab

Marketing authorisation application submitted

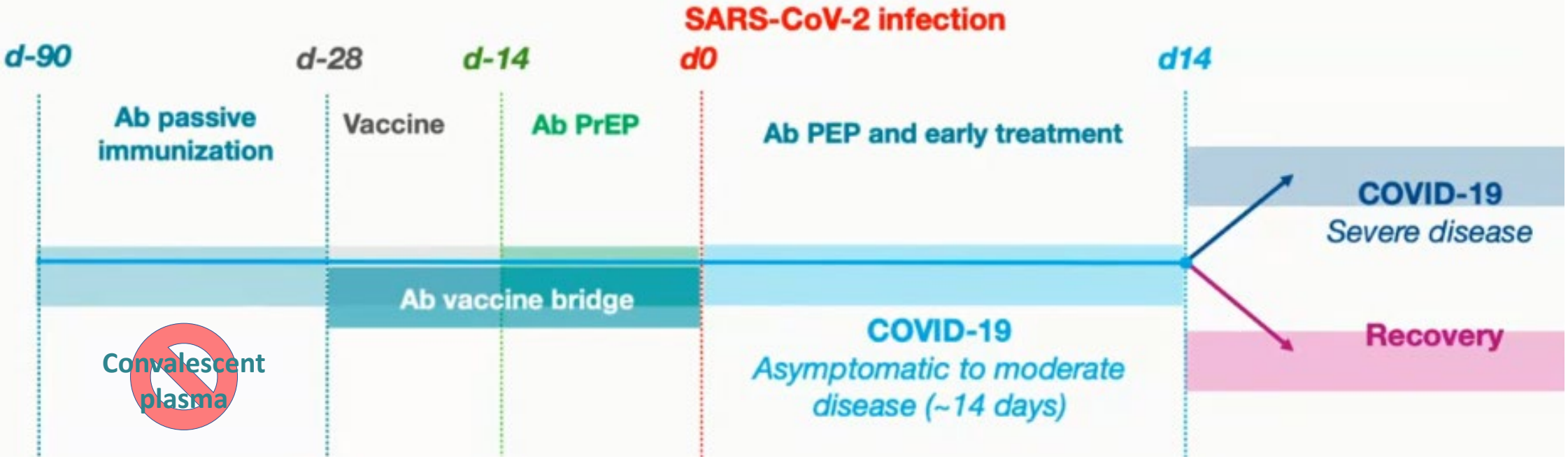
- Olumiant (baricitinib)*
- Kineret (anakinra)*
- Regkirona (regdanvimab)
- RoActemra (tocilizumab)*
- Ronapreve (casirivimab / imdevimab)

Authorised for use in the European Union

- Veklury (remdesivir)

Opportunities for SARS-CoV-2 nAb intervention

Advancing SARS-CoV2 nAbs for treatment and prevention of COVID-19



- The prompt development of **highly efficacious vaccines** may decrease this need
- Value of nAbs for **PrEP** and as a **"vaccine bridge"** will depend on additional data on the onset of protective immunity post-vaccination
- **nAb efficacy in early infection** makes prompt diagnosis and linkage to care essential
- Available data indicate **lack of nAb efficacy in severe disease**
- Remaining potential for benefit in combination with emerging antiviral and host-directed therapies

12

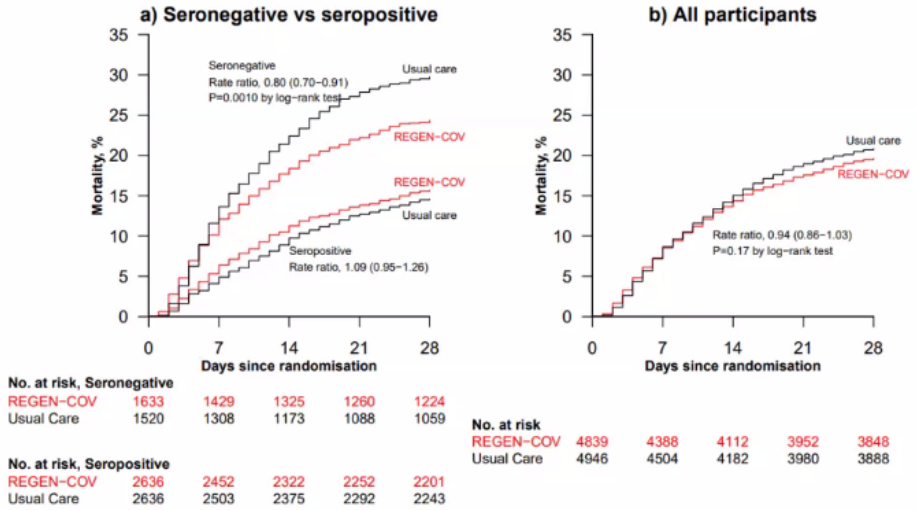
Combination of 2 monoclonal antibodies in patients admitted to hospital with COVID-19 (RECOVERY)

26 February 2021
CHMP opinion As a treatment at the hospital for confirmed cases

Japan: EUR 2,000
India: EUR 670
UK: EUR 1,166 to 2,332 (for 600 mg ?)

- In patients hospitalised with COVID-19, the monoclonal antibody combination of casirivimab and imdevimab (REGEN-COV) **reduced** 28-day mortality 50 among patients who were seronegative at baseline

Figure 2: Effect of allocation to REGEN–COV on 28–day mortality in: a) seronegative vs seropositive participants; and b) all participants



Source: https://www.medrxiv.org/content/10.1101/2021.06.15.21258542v1

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(1) REGN-COV2 (casirivimab/imdevimab, Ronapreve®) In not yet seroconverted people

France: early access programme HAS: 06/08/2021 (1 October: 1230/57,500)
UK: conditional authorisation 20/08/2021
Germany: NA
Netherlands: NA

(2) Sotrovimab (EMA advice 21/05/2021)

Xevudy®, GSK/ VIR BioTechNo

USA: USD 2,200 for 8 ml (500mg) - IV

- For confirmed COVID-19 in adults and adolescents (12+, 40kg+), not requiring O2, and at risk of severe COVID-19
- Efficacy trial in 1,340 volunteers, randomised 1:1
- Proportion of patients who have progression COVID-19 at day 29 after infusion (hospitalisation >24h or death)
  - Preliminary analysis: 41% patients reached day 29

	placebo	sotrovimab
Nb at interim analysis	292	291
Progression or death any cause	21 (7%)	3 (1%)
Adjusted Relative risk ratio Sotrovimab versus pbo	0.15	
97.24% Confidence interval	0.04-0.56	
P-value	0.002	

(3) A Long-lasting combination of neutralising antibodies from AstraZeneca

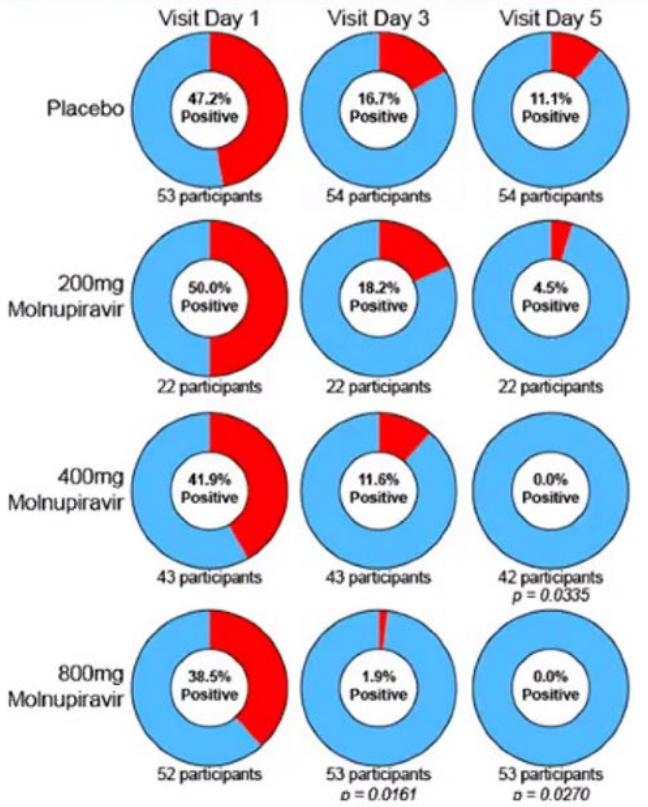
- AZD7442
  - tixagevimab (AZD8895) and cilgavimab (AZD1061)
- Single injection at 300 mg
  - effect can last for up to 12 months of protection from COVID-19
- PROVENT, pre-exposure prophylaxis trial
  - 87 sites in US, UK, Spain, France, Belgium
  - Infections at 6 months: a 77% risk reduction

mAb production challenges

- 30 000 kg Ab produced per year worldwide
  - = 3 B litres needed
- Spare production capacity: 33%
- Demand
  - 1 g / patient = 1 kg per thousand people
  - Enough to treat 17 million people
- If development for COVID-19 takes too long:
  - mAb no longer needed (vaccines)
  - Mutations and variants
- After COVID?
  - To switch production to other diseases
  - But demand will be much less
  - Over-capacity
- To disconnect capacity for COVID-19 and future uses? Or to take this opportunity to produce more Ab for other diseases and increase access?

Industry

- Viral mutagen
- Oral agent (twice a day x 5 days)
- Phase II trials completed
- Phase III trials on-going



https://www.medrxiv.org/content/10.1101/2021.06.17.21258639v1.full.pdf+html

(4) Molnupiravir (MSD): In vitro data

David Alain Wohl, MD, uni. North Carolina at Chapel Hill

- Invented 40 years ago (influenza, hepatitis C)
- Againt SARs-CoV-2:
  - Probably only useful if initiated early after diagnosis, in patients with moderate or severe forms, and with 1 risk-factor for a severe evolution
    - With the difficulties to diagnose new cases shortly after infection
  - Could reduce the risk of hospitalisation and/or death
    - 7,3 % hospitalisations in molnupiravir arm and no death, versus 14,3 % hospitalisations and 8 deaths (among 377 patients) in the placebo arm (MSD, October 2021)
- Safety concerns +++
  - Potentially highly cytotoxic, mutagenic and oncogenic
- France already purchased 50,000 courses

Molnupiravir = Lagevrio®

USD 700 for 5 days

- First orally administered experimental drug to be evaluated in clinical trials to specifically target COVID-19
  - Designed to block activity of the SARS-CoV-2 protease enzyme which is essential for replication of the virus
- The drug is to be used in combination with protease inhibitor ritonavir (risk of drug-drug interaction +++)
  - The co-administration of the drugs helps break down PF-07321332 so it is active in the body for longer
- Phase I completed
  - Australia already purchased 500,000 courses of PF-07321332

(5) PF-07321332 Pfizer

(3) Vaccines

Progress as of 21-22 September 2021 / PCWP meeting

Marco Cavaleri, chair of EMA COVID-19 Pandemic Task Force

Vaccine updates

Currently under rolling review

- NVX-CoV2373
- CVnCoV
- Sputnik V (Gam-COVID-Vac)
- COVID-19 Vaccine (Vero Cell) Inactivated
- Vidprevtyn

Marketing authorisation application submitted

No marketing authorisation applications currently under evaluation

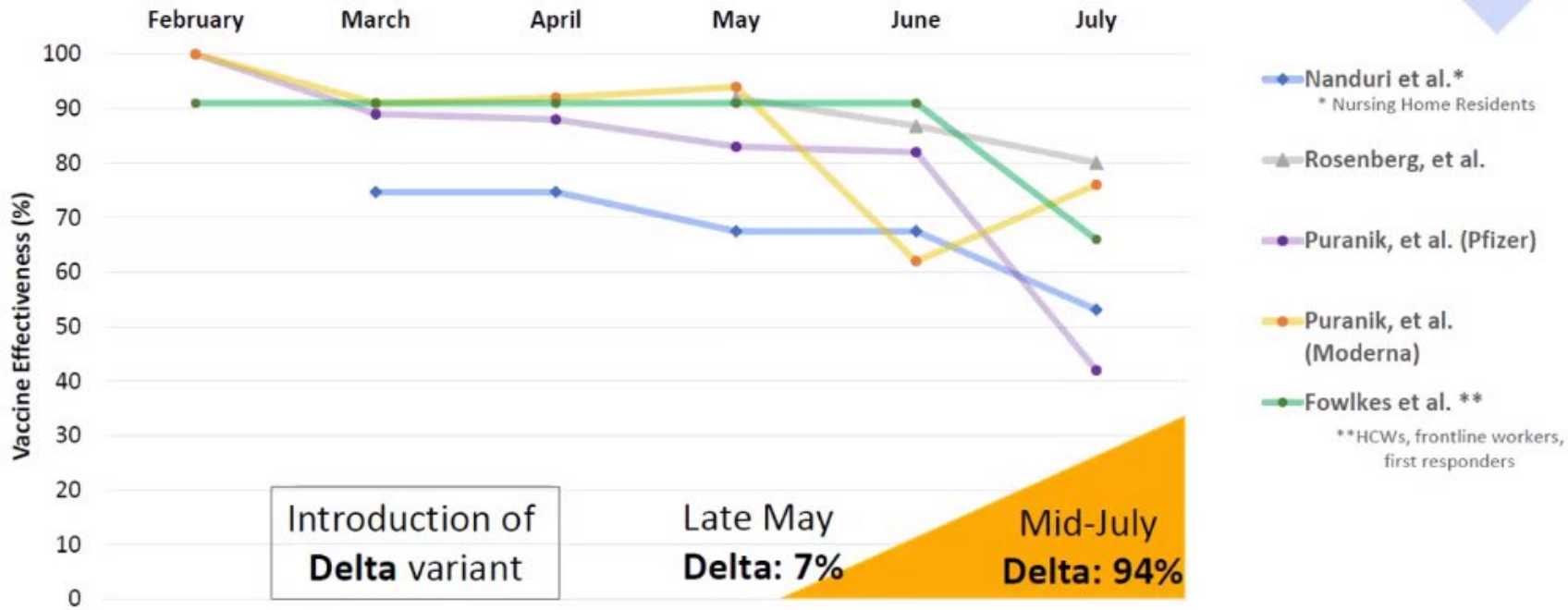
Authorised for use in the European Union

- Comirnaty
- Spikevax (previously COVID-19 Vaccine Moderna)
- Vaxzevria (previously COVID-19 Vaccine AstraZeneca)
- COVID-19 Vaccine Janssen

Framework for booster doses of COVID-19 vaccines – US CDC/ACIP

Booster doses of COVID-19 vaccines:
Vaccine effectiveness against **infection**

Public Health Problem



Rosenberg ES, Holtgrave DR, Dorabawila V, et al. New COVID-19 Cases and Hospitalizations Among Adults, by Vaccination Status — New York, May 3–July 25, 2021. MMWR Morb Mortal Wkly Rep. ePub: 18 August 2021.
Nanduri S. Effectiveness of Pfizer-BioNTech and Moderna Vaccines in Preventing SARS-CoV-2 Infection Among Nursing Home Residents Before and During Widespread Circulation of the SARS-CoV-2 B.1.617.2 (Delta) Variant — National Healthcare Safety Network, March 1–August 1, 2021. MMWR Morbidity and Mortality Weekly Report. 2021 2021;70.
Fowlkes A, Gaglani M, Groover K, et al. Effectiveness of COVID-19 Vaccines in Preventing SARS-CoV-2 Infection Among Frontline Workers Before and During B.1.617.2 (Delta) Variant Predominance — Eight U.S. Locations, December 2020–August 2021. MMWR Morb Mortal Wkly Rep. ePub: 24 August 2021.
Puranik A, Lenehan PJ, Silvert E, et al. Comparison of two highly-effective mRNA vaccines for COVID-19 during periods of Alpha and Delta variant prevalence. medRxiv 2021.08.06.21261707.

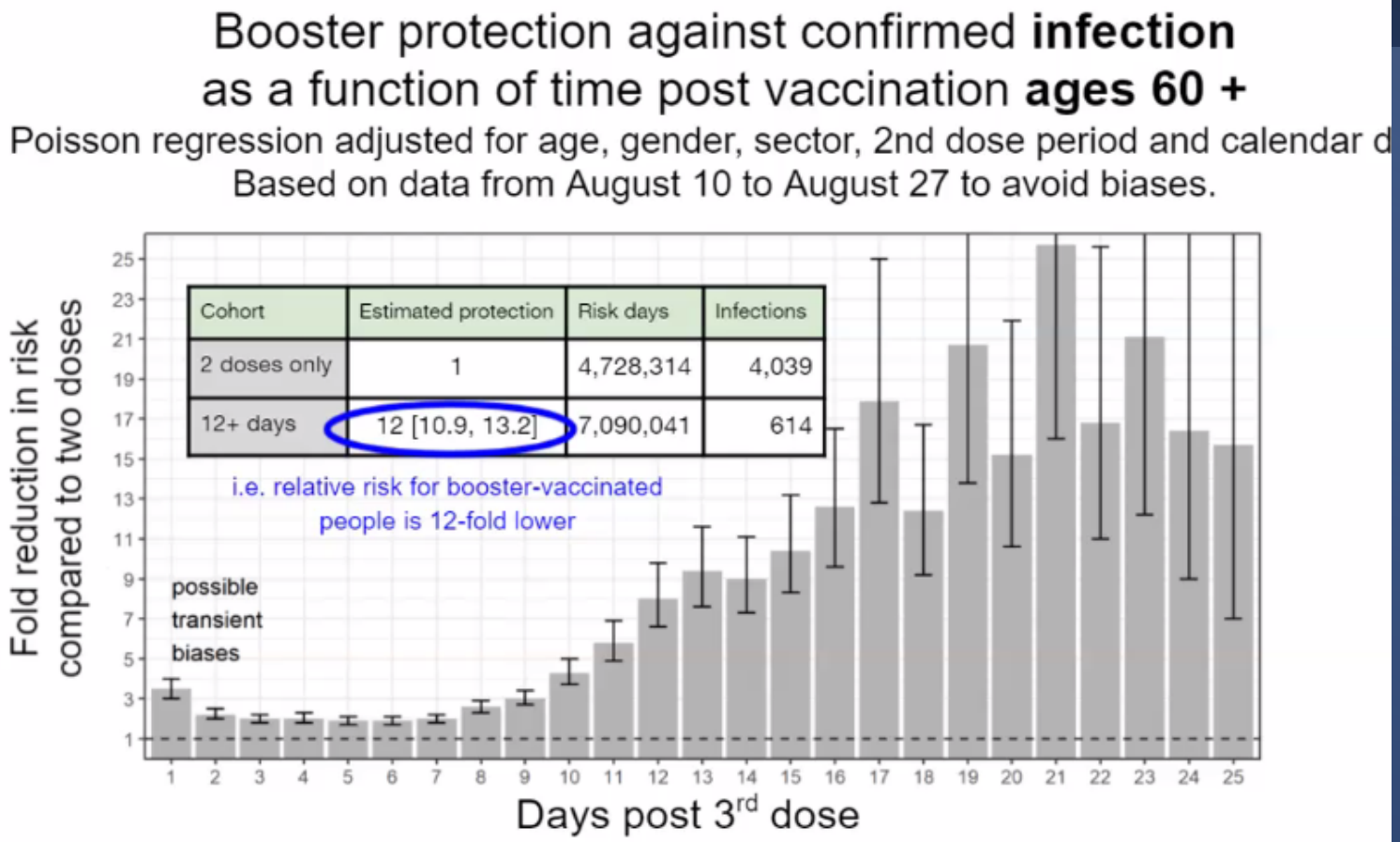
Source: https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-08-30/09-COVID-Oliver-508.pdf

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

EURORDIS RARE DISEASES EUROPE

BNT162b2 vaccine booster dose protection

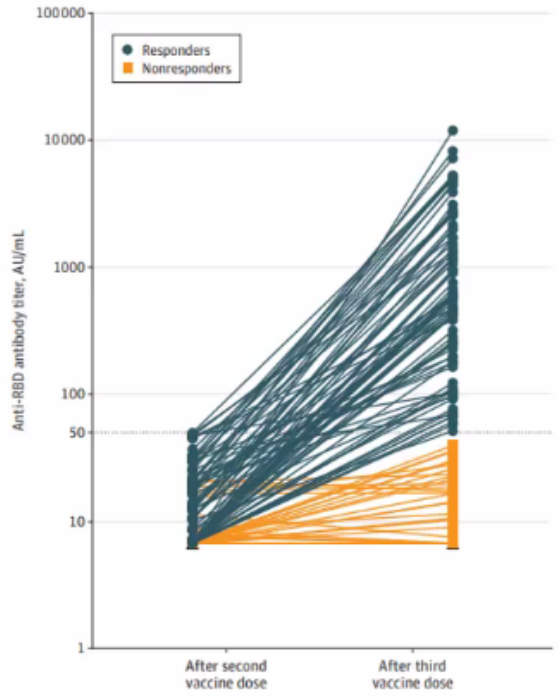
- Nationwide study from Israel
- In conjunction with safety reports, this study demonstrates the effectiveness of a third vaccine dose in both reducing transmission and severe disease and indicates the great potential of curtailing the Delta variant resurgence by administering booster shots



Source: https://www.medrxiv.org/content/10.1101/2021.08.27.21262679v1

Third Dose of mRNA vaccine in kidney transplant recipients

Figure. Anti-Receptor-Binding Domain (RBG) IgG Antibody Titers Measured 28 Days After the Third Dose of mRNA-1273 SARS-CoV-2 Vaccine in 159 Kidney Transplant Recipients



Horizontal dotted line indicates the cutoff for positivity (50 arbitrary units [AU]/mL). Blue lines indicate the antibody titers of kidney transplant recipients who seroconverted after the third dose (titers ≥50 AU/mL); orange lines, the evolution of antibody titers among nonresponders (titers <50 AU/mL). mRNA indicates messenger RNA.

- Study found that a third dose of mRNA vaccine induced a serologic response in 49% of kidney transplant recipients who did not respond after 2 doses
- Use of a third dose of vaccine **may** be considered in organ transplant recipients

Source: https://jamanetwork.com/journals/jama/fullarticle/2782538

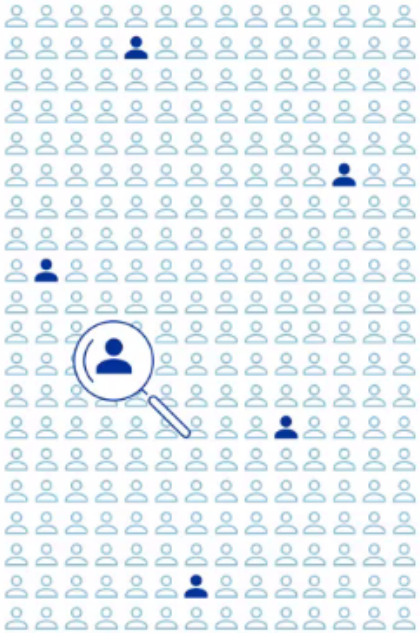
(4) Pharmacovigilance

Progress as of 21-22 September 2021 / PCWP meeting

Marco Cavaleri, chair of EMA COVID-19 Pandemic Task Force

How do we assess if side effects are caused by the vaccine?

- **Established analysis techniques** are in place to assess whether a side effect is likely to be caused by the vaccine
- Since **millions of people** will be getting the vaccine in a short time, many of them will develop illnesses for other reasons in close proximity to vaccination
  - focus on **A**dverse **E**vents of **S**pecial **I**nterest
  - Compare **O**bserved cases (EudraVigilance) **vs** **E**xpected cases in the general population
  - Use of coverage data (ECDC) stratified by age and gender
- Should the review of cases be suggestive of a causal association and **OE** analysis shows an imbalance –> PRAC/Rapporteur is informed

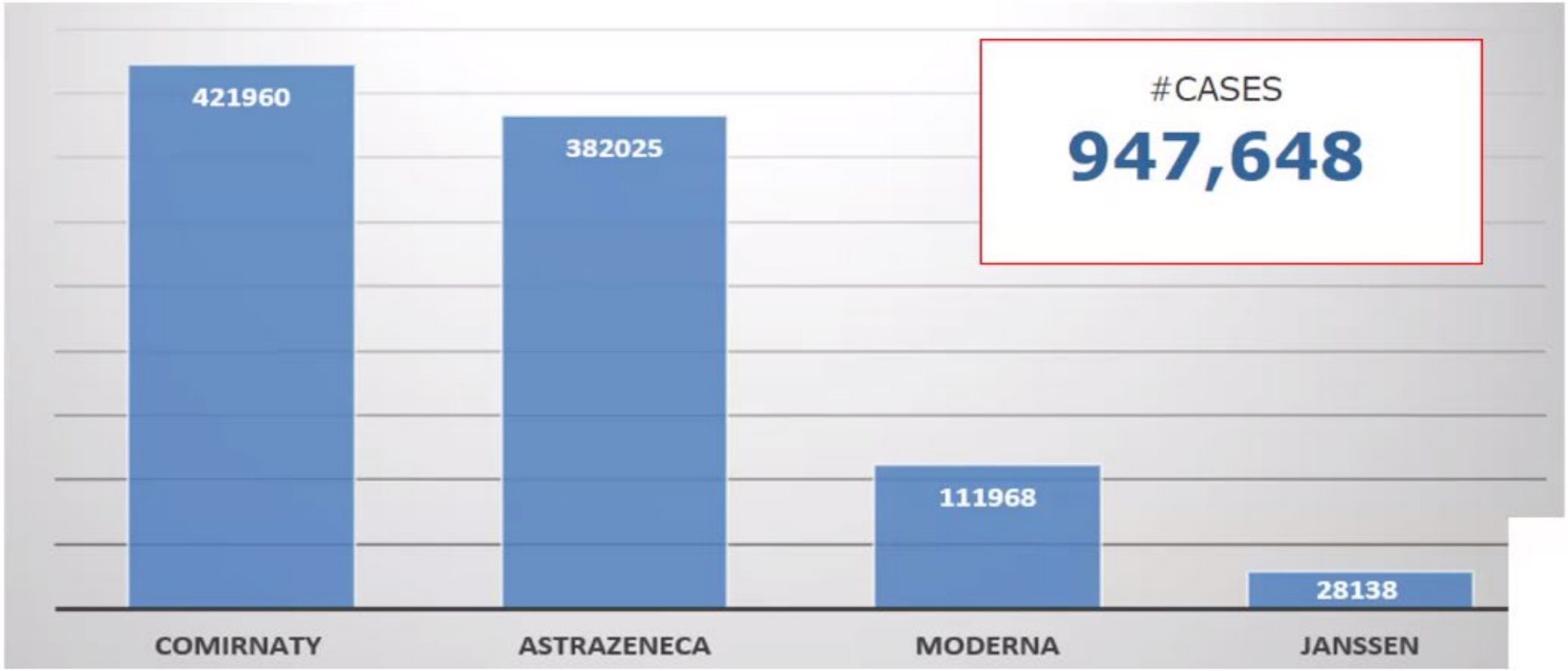


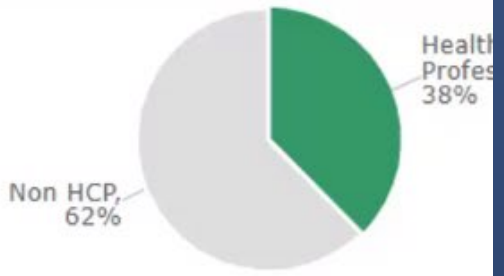
Specific focus has been put in place in our current signal detection methods using new strategies to help shaping existing approaches

Potential risk identification	Preliminary orientation	Risk assessment and management	Communication
• Member states' monitoring • EMA/EudraVigilance regular monitoring **NEW** Supplemented by increased frequency (every 2 days) of adverse events of special interest **NEW** International partners engagement (hot line, regular teleconferences with ICMRA and WHO) **NEW** Companies' monthly safety summary reports (MSSRs) **NEW** EMA funded studies for prospective monitoring	**NEW** EMA Task Force (ETF) on COVID-19 bi-weekly meetings **NEW** Contribution to the Pharmacovigilance Risk Assessment Committee (PRAC) activities on emerging pharmacovigilance issues related to COVID-19	• PRAC recommendations **NEW** Additional data: Commissioning of independent studies following PRAC request (framework in place) **NEW** Core risk management plan	• PRAC Highlights • Public health communications **NEW** Monthly/ ad-hoc safety updates **NEW:** ad-hoc/twice a month press briefings

Spontaneous adverse event report to EudraVigilance

More reports received with 4 vaccines than all other centrally authorised products in 1 year





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Safety of mRNA vaccines

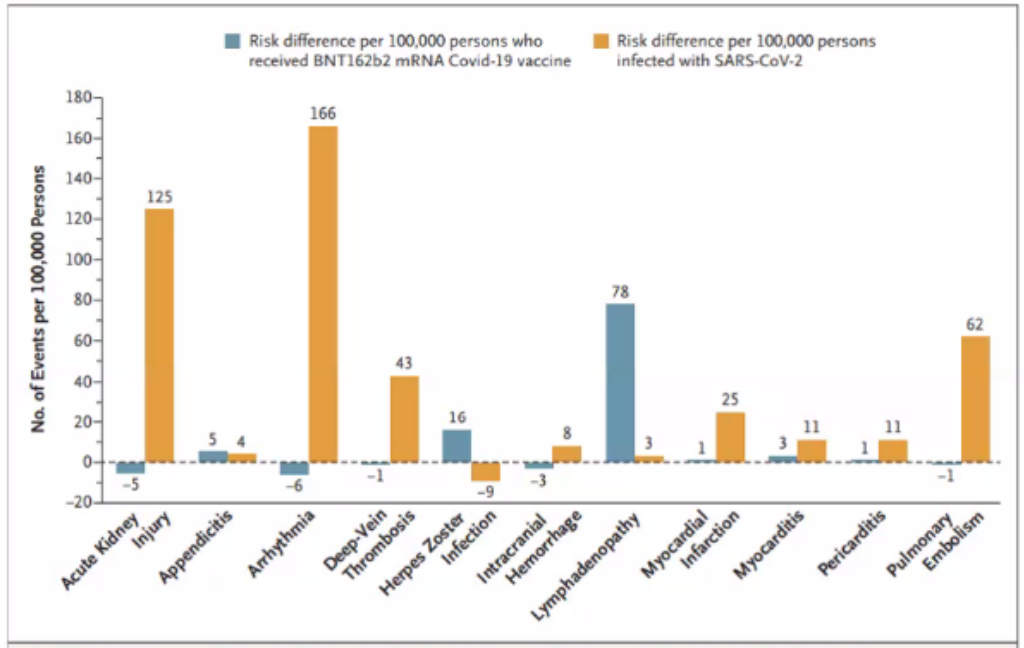

Figure 4. Absolute Excess Risk of Various Adverse Events after Vaccination or SARS-CoV-2 Infection.

Point estimates of the risk differences for selected adverse events are shown. Estimates were derived 42 days after vaccination or SARS-CoV-2 infection with the use of the Kaplan–Meier estimator. Risk differences are shown per 100,000 persons and rounded to the nearest integer. Negative differences (decreased risk) are represented as negative values on the y axis, and positive differences (increased risk) are represented as positive values on the y axis. The abbreviation mRNA denotes messenger RNA.

Source: https://www.nejm.org/doi/full/10.1056/NEJMoa2110475

- Study in a nationwide mass vaccination setting
- Results indicate SARS-CoV-2 **infection is itself a very strong risk factor for myocarditis**, and it also substantially increases the risk of multiple other serious adverse events
- Findings help to shed light on the short- and medium-term risks of the vaccine and place them in clinical context
- **Further studies needed** to estimate the potential of long-term adverse events

Risk management in practice

EUROPEAN MEDICINES AGENCY

Advice to healthcare professionals and vaccinated people

Anaphylaxis
- Talk to your doctor about past allergies to vaccines
- 15 min observation time
- Equipment
- Go to a doctor immediately if swelling, rash, nausea, stomach pain, breathing difficulties or fainting occurs

Comirnaty | Spikevax

Myo/pericarditis
- Go to a doctor immediately if breathlessness, strong heartbeat or chest pain occurs

Vaxzevria | Janssen

Capillary leak syndrome
- Don't' vaccinate if CLS history
- Go to a doctor immediately if arms and legs swelling, sudden weigh gain or feeling faint occurs
- Intensive care

Vaxzevria | Janssen

TTS

Go to a doctor immediately if breathlessness, chest pain, leg swelling/pain, persistent abdominal pain, severe or persistent headaches, blurred vision, confusion, seizures or skin bruising occurs
- Investigate thrombocytopenia within three weeks after vaccination for thrombosis/investigate for thrombocytopenia
- Special care

Vaxzevria | Janssen

Guillain-Barré syndrome
- Go to a doctor immediately if weakness/paralysis in arms and legs, which can progress to chest and face, occurs

General
- Talk to your doctor about existing severe illness, existing weakened immune system, bleeding problems or vaccination anxiety before vaccination

Please see full product information

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Thank you for your attention

François Houÿez
Director of Treatment Information and Access
francois.houyez@eurordis.org