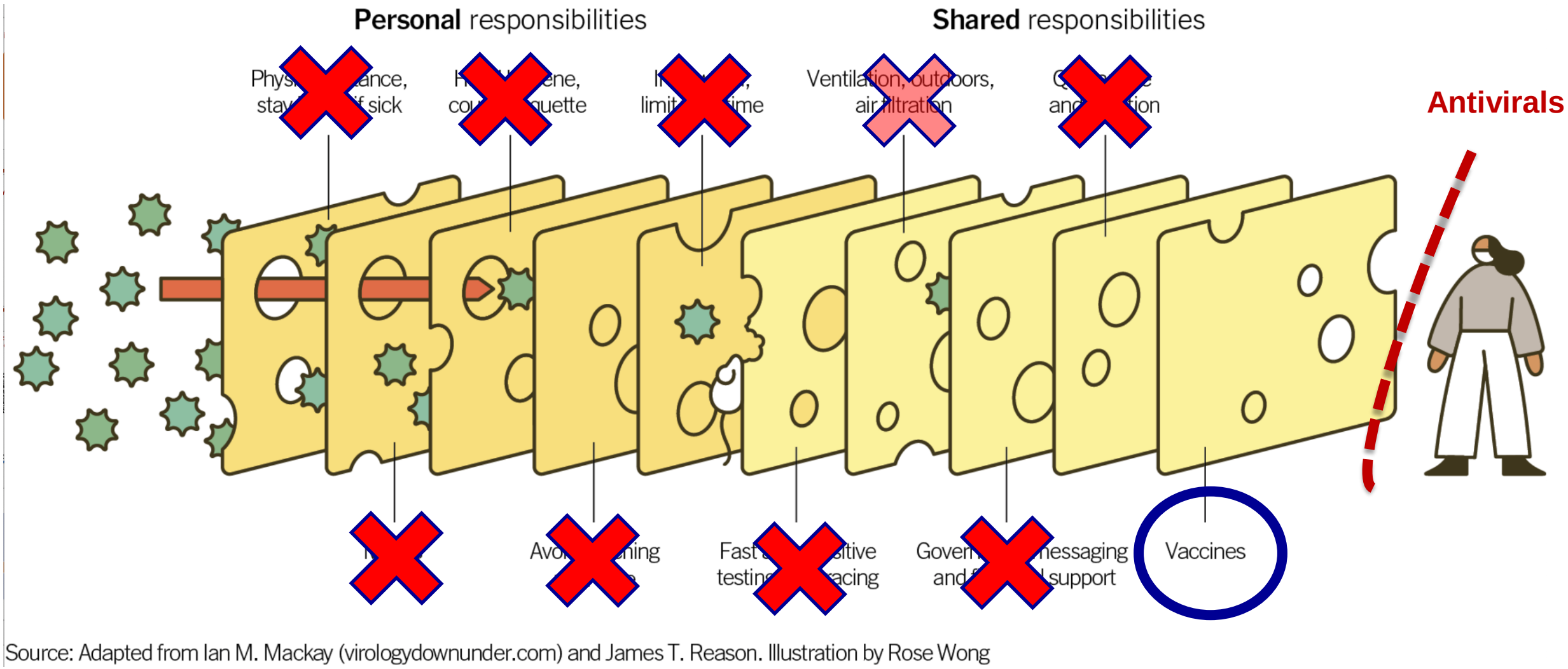
Second generation SARS-CoV-2 mAbs: Immunobridging

Roger Paredes

Hospital Germans Trias i Pujol

Swiss Cheese COVID-19 Prevention model



Source: Adapted from Ian M. Mackay (virologydownunder.com) and James T. Reason. Illustration by Rose Wong

The overall neutralising activity of vaccines is reduced in certain populations, such as those with immunocompromising conditions[1]

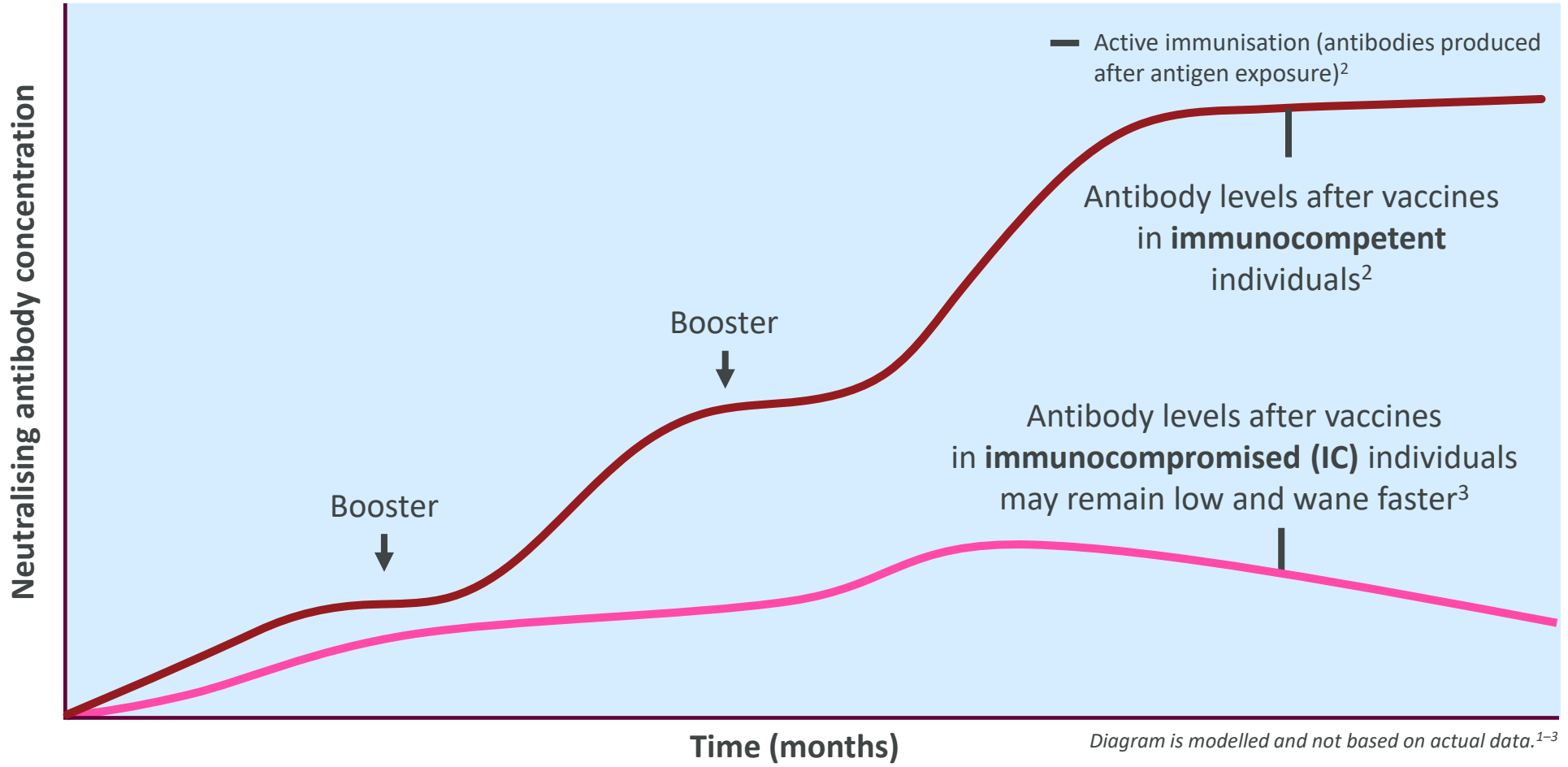
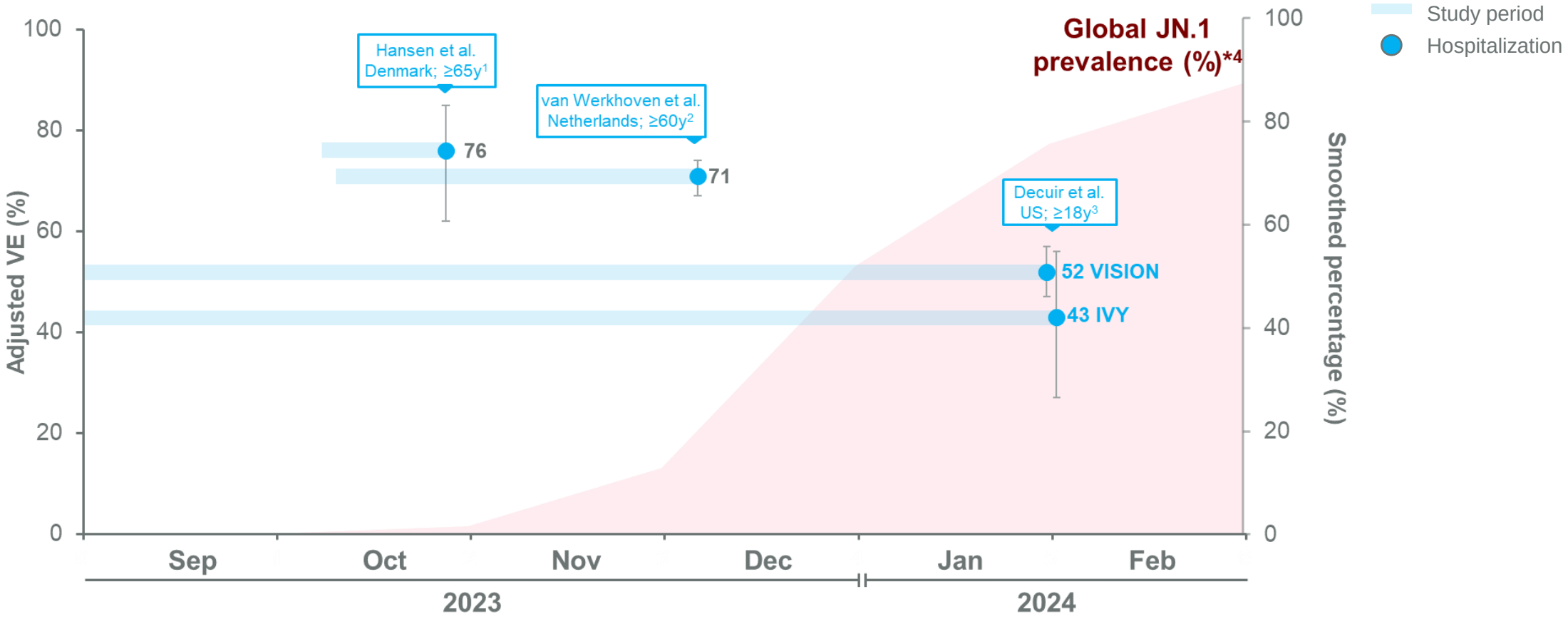


Diagram is modelled and not based on actual data.[1–3]

1. Parker EPK, et al. *Lancet Glob Health*. 2022;10(3):e326–e328; 2. Chopra H. Immunization. Available at: https://www.slideshare.net/harivanshchopra/immunization-137085346 (last accessed: September 2023); 3. Pearce FA, et al. *medRxiv*. 2023. doi:10.1101/2023.02.09.23285649.

RWE: Decreasing VE of XBB.1.5-adapted vaccines against hospitalization with increasing **JN.1**[1–4]

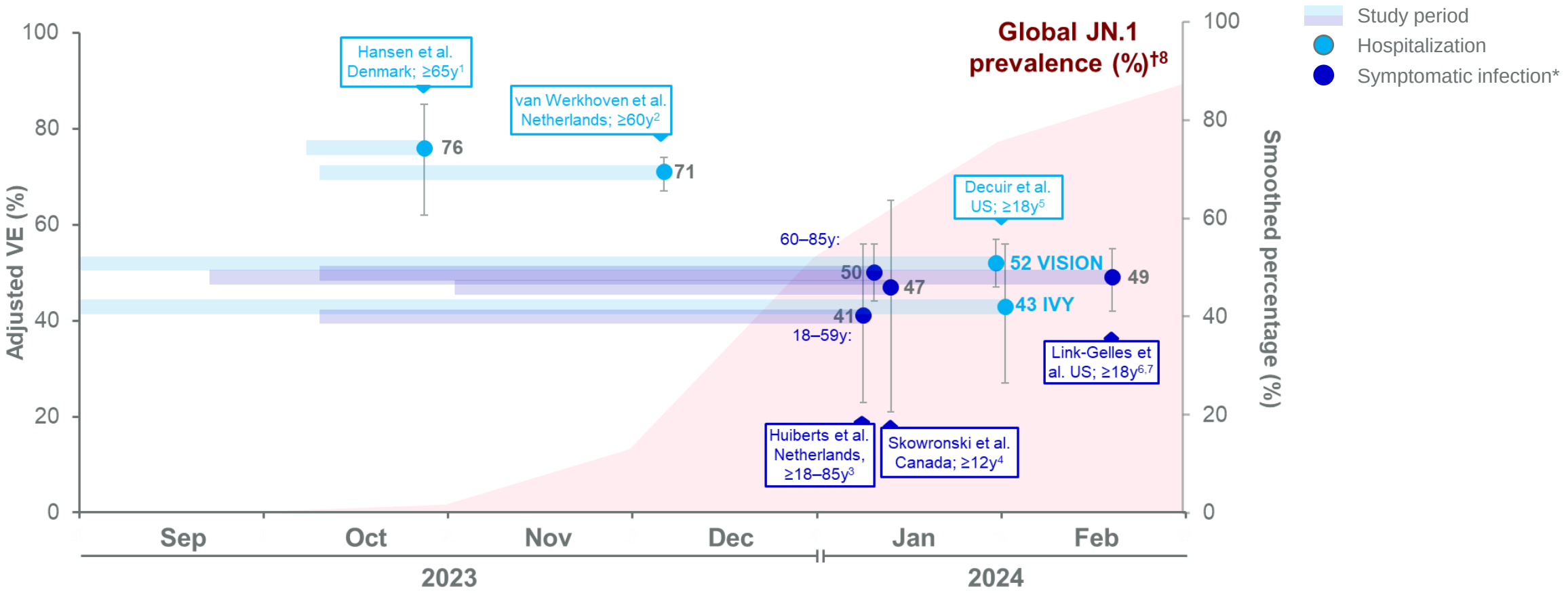


The results summarized on this slide are derived from studies with different designs and limitations, please refer to the preceding slides for design and limitation details.

*GISAID – hCoV19 variants.[4]

ED, emergency department; GISAID, Global Initiative on Sharing All Influenza Data; IVY, Investigating Respiratory Viruses in the Acutely Ill; RWE, real-world evidence; UC, urgent care; VE, vaccine effectiveness; VISION, Virtual SARS-CoV-2, Influenza and Other Respiratory Viruses Network. 1. Hansen CH et al. *Lancet Infect Dis* 2024;24:e73–e74; 2. van Werkhoven CH et al. *Euro Surveill* 2024;29:2300703; 3. DeCuir J et al. *MMWR Morb Mortal Wkly Rep* 2024;73:180–188; 4. GISAID. https://gisaid.org/hcov19-variants/ (accessed April 2024).

RWE: Decreasing VE of XBB.1.5-adapted vaccines against hospitalization and symptomatic infection with increasing **JN.1**[1–8]



The results summarized on this slide are derived from studies with different designs and limitations, please refer to the preceding slides for design and limitation details.

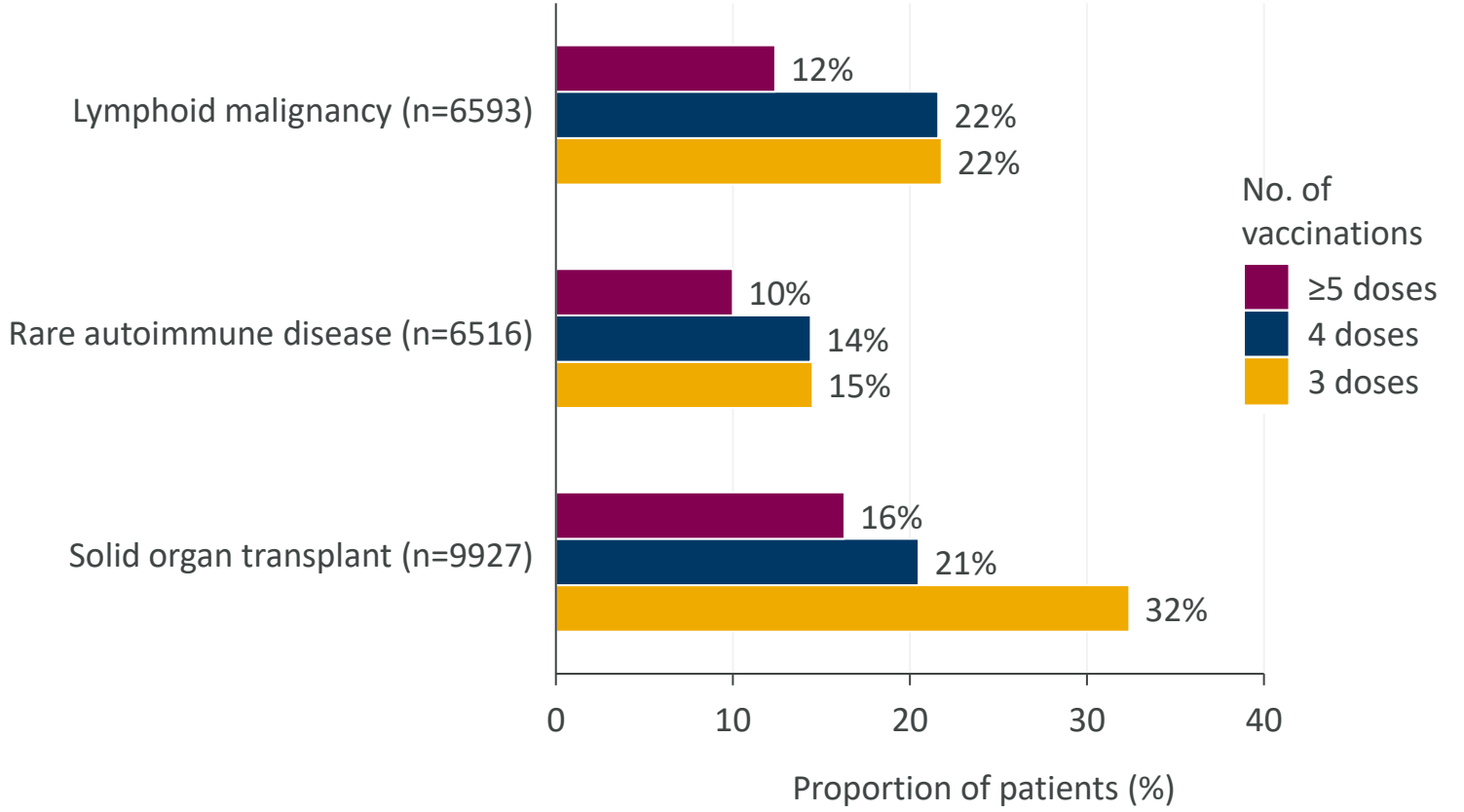
*Includes ED, UC, or outpatient visit; †GISAID – hCoV19 variants.[9]

ED, emergency department; GISAID, Global Initiative on Sharing All Influenza Data; IVY, Investigating Respiratory Viruses in the Acutely Ill; RWE, real-world evidence; UC, urgent care; VE, vaccine effectiveness; VISION, Virtual SARS-CoV-2, Influenza and Other respiratory viruses Network.

1. Hansen CH et al. *Lancet Infect Dis* 2024;24:e73–e74; 2. van Werkhoven CH et al. *Euro Surveill* 2024;29:2300703; 3. Huiberts AJ et al. *Euro Surveill* 2024;29:2400109; 4. Skowronski DM et al. *Euro Surveill* 2024;29:2400076; 5. DeCuir J et al. *MMWR Morb Mortal Wkly Rep* 2024;73:180–188; 6. Link-Gelles R. https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2024-02-28-29/04-COVID-Link-Gelles-508.pdf (accessed April 2024); 7. Link-Gelles R et al. *MMWR Morb Mortal Wkly Rep* 2024;73:77–83; 8. GISAID. https://gisaid.org/hcov19-variants/ (accessed April 2024).

More than 1 in 10 people with IC conditions do not develop antibodies despite ≥5 vaccines[1]

Proportion of patients without detectable antibodies after vaccination*



This can contribute to an increased risk of SARS-CoV-2 infection, persistent viral shedding and severe COVID-19[2]

*UK database analysis of people with solid organ transplant (SOT), rare autoimmune disease and lymphoid malignancy conducted from 7th December 2021–26th June 2022. Participants had been vaccinated 3, 4 or ≥5 times (28.5%, 61.8% and 9.6%, respectively).
IC, immunocompromised.
1. Pearce FA, et al. *medRxiv*. 2023. doi:10.1101/2023.02.09.23285649; 2. Shoham S, et al. *eClinicalMedicine*. 2023;59:101965.

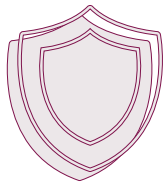
IC individuals may have have an impaired immune response to vaccination compared with the general population, in three key ways[1–4]

Quantity of antibodies[1,2] 1

IC individuals may produce low amounts of antibodies

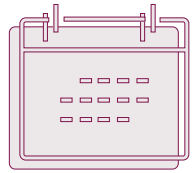
Quality of antibodies[1,3] 2

IC individuals may not develop neutralising antibodies against SARS-CoV-2 variants



Duration of protection[4] 3

Protection from COVID-19 vaccines may diminish within 3 months in IC individuals



IC, immunocompromised.

1. Chang A, et al. *J Clin Oncol*. 2022;40(26):3020–3031; 2. Alfonso-Dunn R, et al. *Front Immunol*. 2023;14:1194671; 3. Benning L, et al. *Am J Transplant*. 2022;22(7):1873–1883; 4. Britton A, et al. *MMWR Morb Mortal Wkly Rep*. 2022;71(42):1335–1342.

In some patients, reduced immune response to COVID-19 vaccination may be a result of immunosuppressive medication use

Several medications are associated with a reduced immune response to COVID-19 vaccination, including:[1–4]

- B-cell–depleting therapies
- Anti-TNF treatments
- Alkylating agents
- Tyrosine kinase inhibitors
- High-dose corticosteroids

These medications are used in various medical conditions, such as:[1–4]

- Autoimmune diseases
- Solid tumour and haematological cancers
- Solid organ transplant recipients

TNF, tumour necrosis factor.

1. Wack S, et al. *J Am Acad Dermatol.* 2021;85(5):1274–1284; 2. Ruggeri EM, et al. *ESMO Open*. 2022;7(1):100350; 3. Grupper A, Katchman H. *Curr Transplant Rep*. 2022;9(1):35–47; 4. Shields AM, et al. *Clin Exp Immunol*. 2022;207(1):3–10.

Other underlying disease factors may also contribute to an impaired immune response to COVID-19 vaccines

Individuals with end-stage kidney disease may have impaired immune responses to COVID-19 vaccines due to “inflammaging”

Several factors associated with kidney failure contribute to immune alterations

- Uremia
- Chronic kidney damage
- Oxidative stress
- EPO deficiency
- Vitamin D deficiency
- Immunosuppressives
- Intestinal permeability
- Dialysis membrane bio-incompatibility

Inflammaging

Premature immune system ageing

- Reduced lymphocyte proliferation, activation, maturation, migration
- Reduced antigen presentation by APCs

Inflammation

- pro-inflammatory cytokine expression

APC, antigen presenting cell; EPO, erythropoietin.

Babel N, et al. *Nat Rev Nephrol*. 2022;18(11):708–723.

INFORM: study overview

- **Aim:** to assess case-outcome rates, including hospitalisation, intensive care admission and case-mortality rates in patients in England who are immunocompromised and those who are not

Data sources[1,2]

NHS Digital*

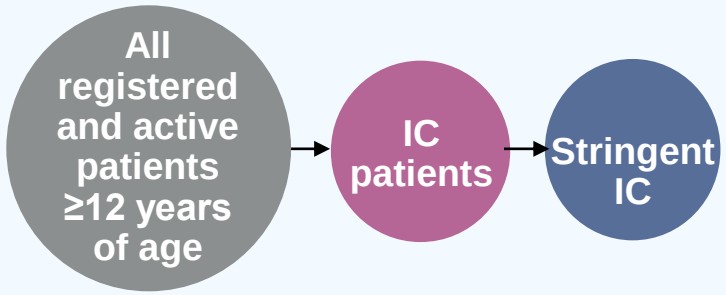
Linked data using a 25% sample of the total population of England

Data:

1 Jan 2022–31 Dec 2022[1]
1 Jan 2023–30 Jun 2023[2]

N=12,024,035[2]

Study populations[1,2]



Outcomes[1,2]

Main outcomes
(COVID-19–related)

Hospitalisation†
Length of stay

ICU admission
Days in ICU

Deaths
Death in ONS mortality data with COVID-19 as the cause, or in-hospital death during a COVID-19 hospitalisation

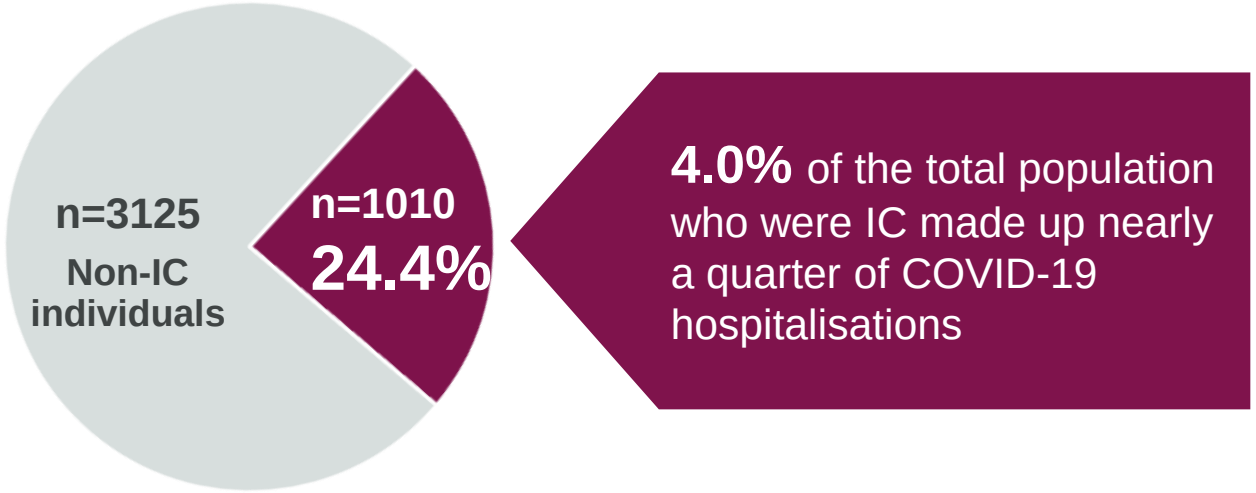
*Datasets used included: General Practice Extraction Service Data for Pandemic Planning and Research (GDPPR), COVID-19 Second Generation Surveillance System (SGSS) from Pillar 1 and Pillar 2, COVID-19 vaccination status data, Hospital Episode Statistics (HES), NHS Business Service Authority (BSA) dispensing data, Office of National Statistics (ONS) data, and Personal Demographics Service (PDS) data[1]; †COVID-19-related hospitalisation, defined as ≥1 in-patient overnight stay with COVID-19 recorded as the primary diagnosis (discharge and rehospitalisation within 7 days were considered to be the same event)[1].

INFORM is an AstraZeneca-sponsored study. IC, immunocompromised; ICU, intensive care unit; NHS, National Health Service; ONS, Office for National Statistics.

1. Evans RA, et al. *Lancet Reg Health Eur.* 2023;35:100747; 2. Dube S, et al. Abstract 2688. Poster presentation at the 34th ECCMID Congress; 27–30 April 2024; Barcelona, Spain

Despite accounting for 4.0% of the English population, IC individuals accounted for nearly a quarter of COVID-19–related hospitalisations in 2023

4135 COVID-19-related hospitalisations in the overall study population (1 January–30 June 2023)



IC individuals had a higher risk of hospitalisation and death than the general population, even among those who had received ≥4 vaccine doses

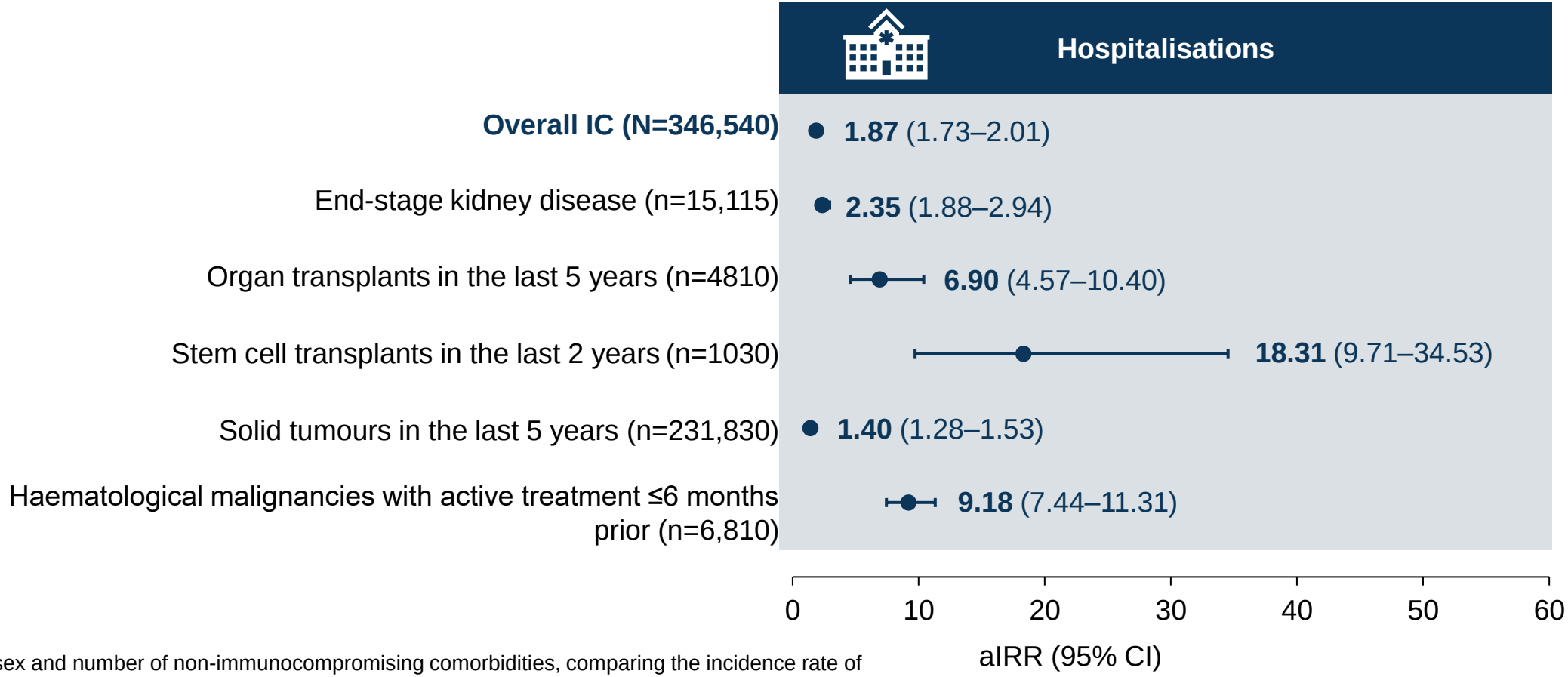
Hospitalisation
aIRR* (95% CI)
1.87
(1.73–2.01)

Death
aIRR* (95% CI)
1.64
(1.43–1.89)

*Adjusted for age, sex and number of non-immunocompromising comorbidities, comparing the incidence rate of individuals with the condition specified to the incidence rate in individuals who do not have the condition.
aIRR, adjusted incidence rate ratio; CI, confidence interval; IC, immunocompromised.
Dube S, et al. Abstract 2688. Poster presentation at the 34th ECCMID Congress; 27–30 April 2024; Barcelona, Spain.

Across all IC groups, the risk of COVID-19 hospitalisation was higher versus the overall population

aIRR* (95% CI) for COVID-19 hospitalisations in IC individuals vs the overall population receiving ≥4 vaccine doses (1 January–30 June 2023)



*Adjusted for age, sex and number of non-immunocompromising comorbidities, comparing the incidence rate of individuals with the condition specified to the incidence rate in individuals who do not have the condition.
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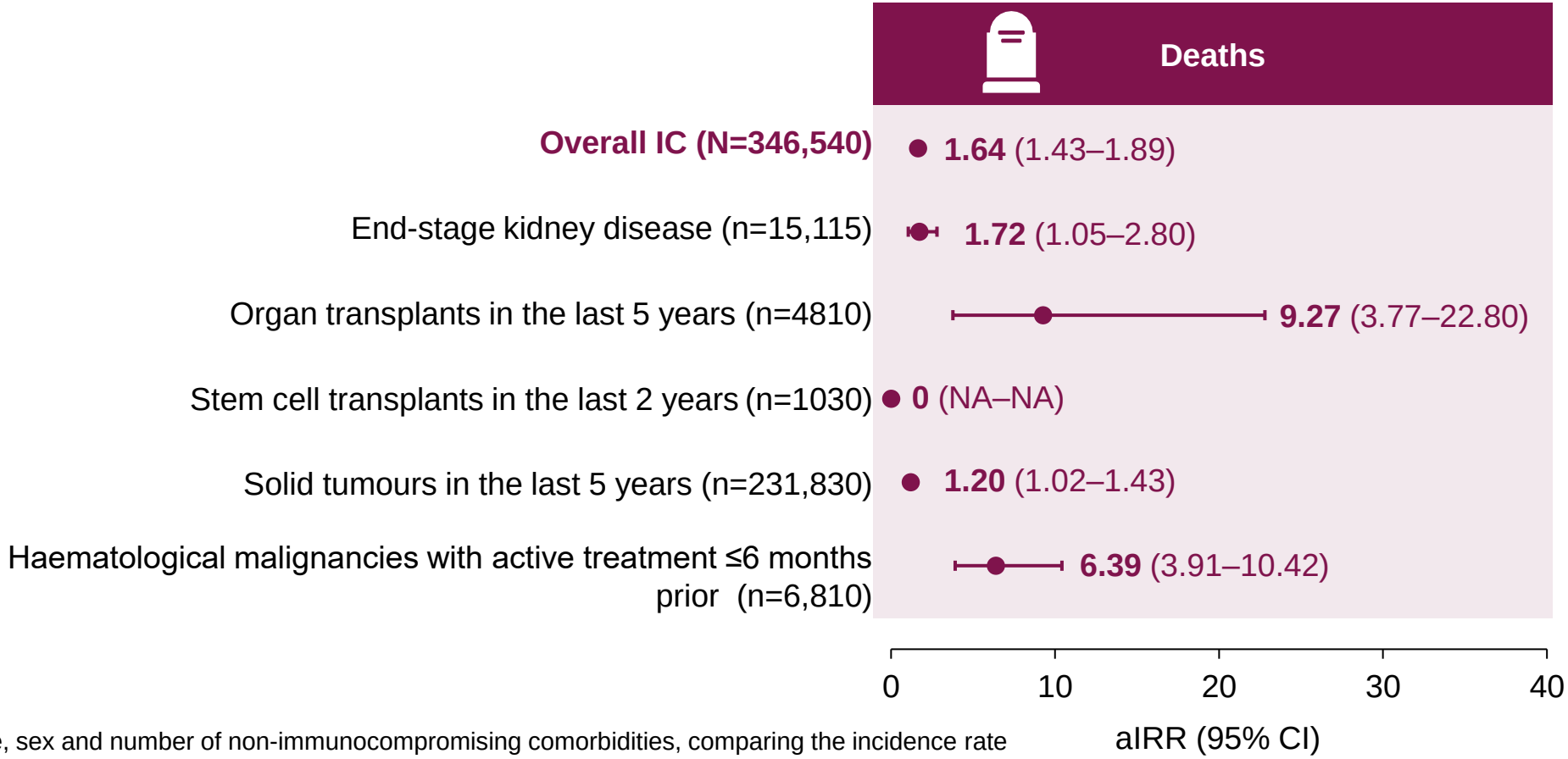
Dube S, et al. Abstract 2688. Poster presentation at the 34th ECCMID Congress; 27–30 April 2024; Barcelona, Spain.

Across all IC groups, the risk of COVID-19 death was higher versus the overall population

aIRR* (95% CI) for COVID-19 deaths in IC individuals vs the overall population receiving ≥4 vaccine doses (1 January–30 June 2023)



*Adjusted for age, sex and number of non-immunocompromising comorbidities, comparing the incidence rate of individuals with the condition specified to the incidence rate in individuals who do not have the condition.
aIRR, adjusted incidence rate ratio; CI, confidence interval; IC, immunocompromised; NA, not applicable.
Dube S, et al. Abstract 2688. Poster presentation at the 34th ECCMID Congress; 27–30 April 2024; Barcelona, Spain.

EPOCH-US: study overview

- **Aims:** to estimate the prevalence of patients with an immunocompromising condition at risk of COVID-19, to estimate COVID-19 cumulative incidence and incidence rate by immunocompromising condition, and to describe COVID-19–related HCRU and costs

Data sources

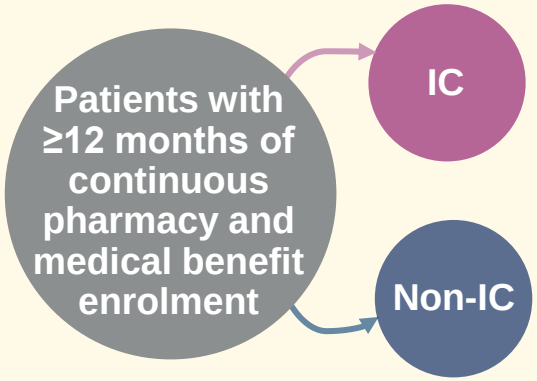
Healthcare Integrated Research Database (HIRD)®

25,080,848 US patients with commercial/Medicare Advantage coverage

Study period:
1 April 2018–31 December 2022

Infection period:
1 April 2020–31 December 2022

Study populations



Endpoints

- Prevalence of immunocompromising conditions
- Incidence of COVID-19 infection
- HCRU (hospitalisation length of stay)
- Costs associated with COVID-19 hospitalisation

EPOCH-US is an AstraZeneca-sponsored study.
HCRU, healthcare resource utilisation; IC, immunocompromised.
Ketkar A, et al. *Adv Ther.* 2024;41(3):1075–1102.

In the US, immunocompromised patients continue to make up a disproportionate number of COVID-19 related hospitalisations

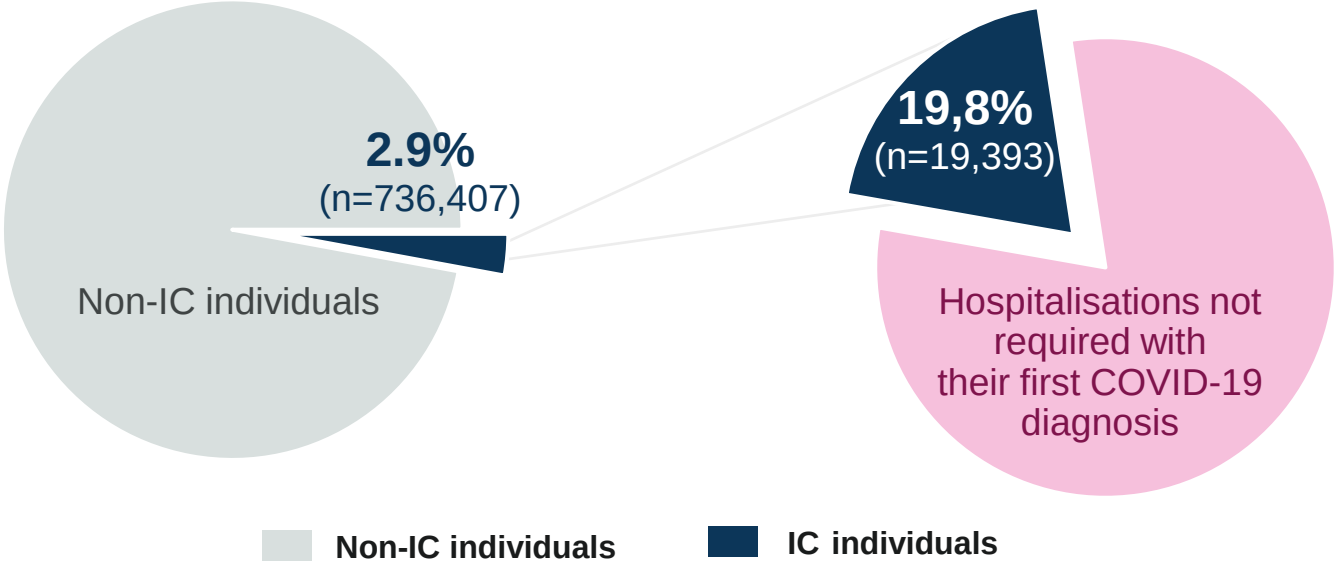
IC individuals

Prevalence of IC individuals of the EPOCH population

COVID-19-related hospitalisations

IC individuals had hospitalisations associated with their first COVID-19 diagnosis

COVID-19-related hospitalisation severity



Severe/critical/ Intensive care unit (ICU)

46%
(n=8992)

54%
(n=10,401)

Moderate/non-ICU

EPOCH-US is an AstraZeneca-sponsored study.
IC, immunocompromised; ICU, intensive care unit.
Ketkar A, et al. *Adv Ther.* 2024;41(3):1075–1102.

Hospitalisations and associated healthcare costs vary according to the underlying immunocompromising condition

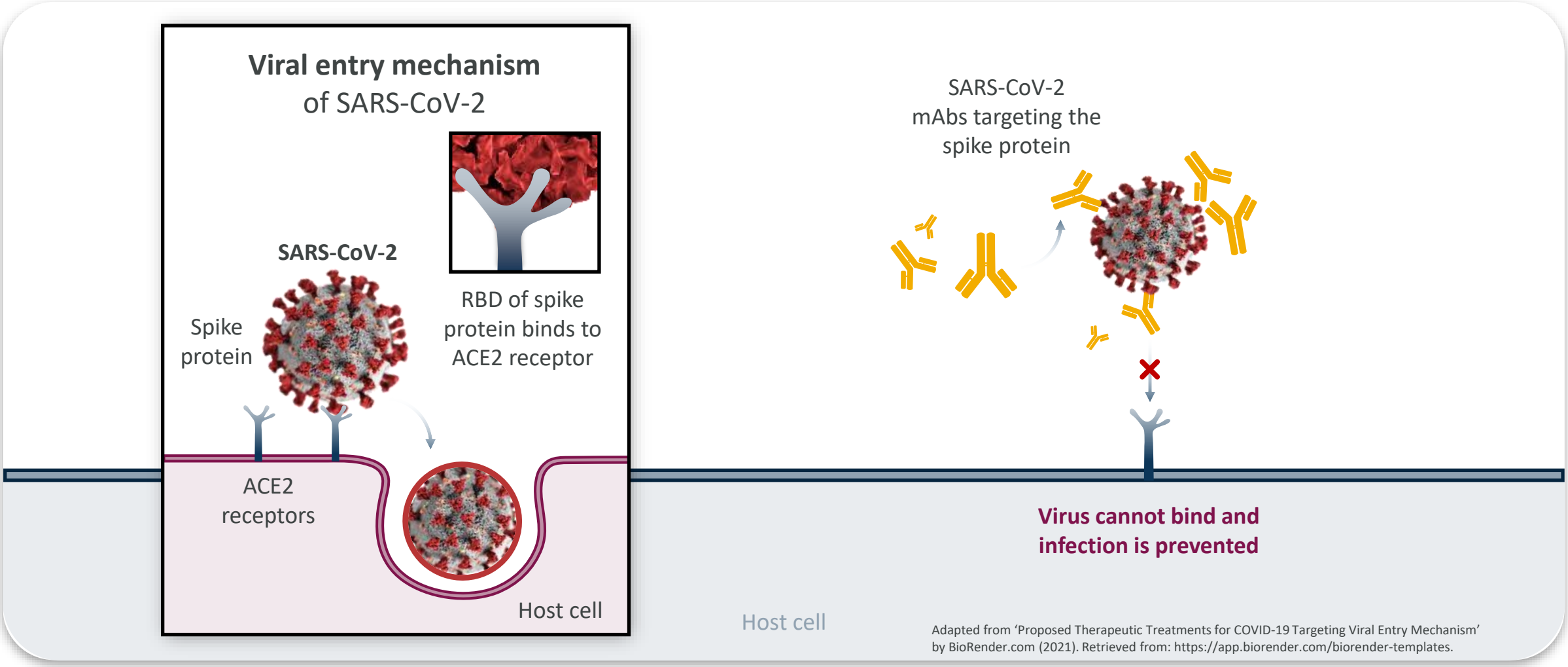
EPOCH-US

Patients hospitalised with first COVID-19 diagnosis

	General population (n=2,258,104)	HSTM (n=26,193)	HSCT/SOT (n=6474)	PID (n=22,001)	ESRD (n=12,891)	Immunosuppressive treatment (n=55,141)	Composite IC cohort (n=97,732)
Hospitalisation, %*	**4.7**	**20.4**	**29.0**	**23.8**	**59.1**	**13.8**	**19.8**
Mean (SD) length of hospital stay, days	**9.6** (15.8)	**9.4** (12.8)	**15.4** (27.8)	**12.5** (20.5)	**22.0** (30.6)	**10.5** (17.0)	**14.4** (23.3)
Mean (SD) all-cause total cost, USD	**$35,649** ($92,703)	**$30,257** ($69,582)	**$84,218** ($282,669)	**$55,513** ($183,496)	**$101,683** ($230,902)	**$42,840** ($132,037)	**$61,204** ($170,835)

*Proportion of patients with hospitalisation associated with first COVID-19 diagnosis.
EPOCH-US is an AstraZeneca-sponsored study.
ESRD, end-stage renal disease; HSCT, haematopoietic stem cell transplant; HSTM, haematologic or solid tumour malignancy; IC, immunocompromised; IQR, interquartile range; PID, primary immunodeficiency; SD, standard deviation; SOT, solid organ transplant; USD, US dollars.
Ketkar A, et al. *Adv Ther.* 2024;41(3):1075–1102.

mAbs target SARS-CoV-2 spike protein to prevent virus entry into host cells[1,2]



Adapted from 'Proposed Therapeutic Treatments for COVID-19 Targeting Viral Entry Mechanism' by BioRender.com (2021). Retrieved from: https://app.biorender.com/biorender-templates.

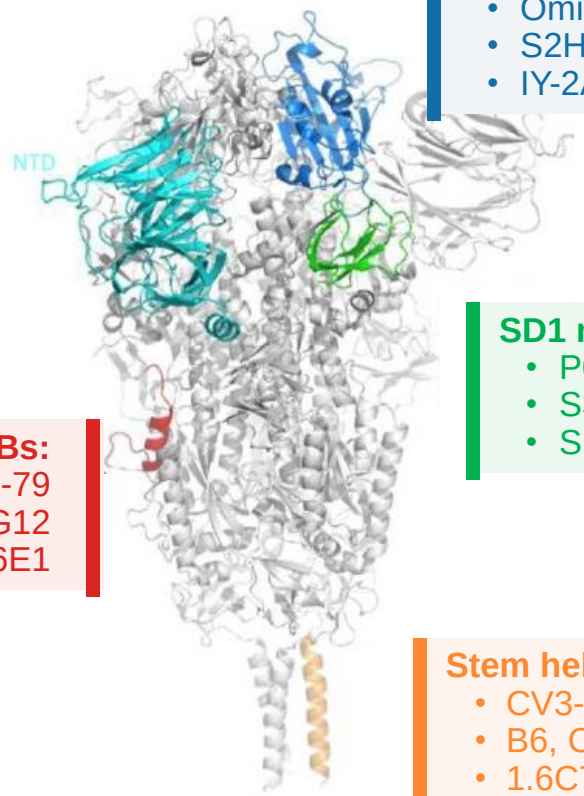
ACE2, angiotensin-converting enzyme 2; mAb, monoclonal antibody; RBD, receptor-binding domain.

1. Cevik M, et al. *BMJ*. 2020;371:m386; 2. Taylor PC, et al. *Nat Rev Immunol*. 2021;21(6):382–393.

Broadly Neutralizing mAbs Against COVID-19

RP

Regions of SARS-CoV-2 spike protein targeted by 4 types of broadly neutralizing mAbs characterized as binding nAbs



RBD mABs:
- Omi-42 (AZD3152) is a highly potent Ab
- S2H97 is a promising pansarbecovirus-neutralizing Ab
- IY-2A is strongly active

SD1 mABs:
- P008_60
- S3H3
- SD1.040

→ Neutralize relatively **weakly** vs potent ACE2-blocking RBD-binding mAbs

FP mABs:
- COV44-62, COV44-79
- VN01H1, C77G12
- 76E1

← Broadly neutralize the currently dominant SARS-CoV-2 variants

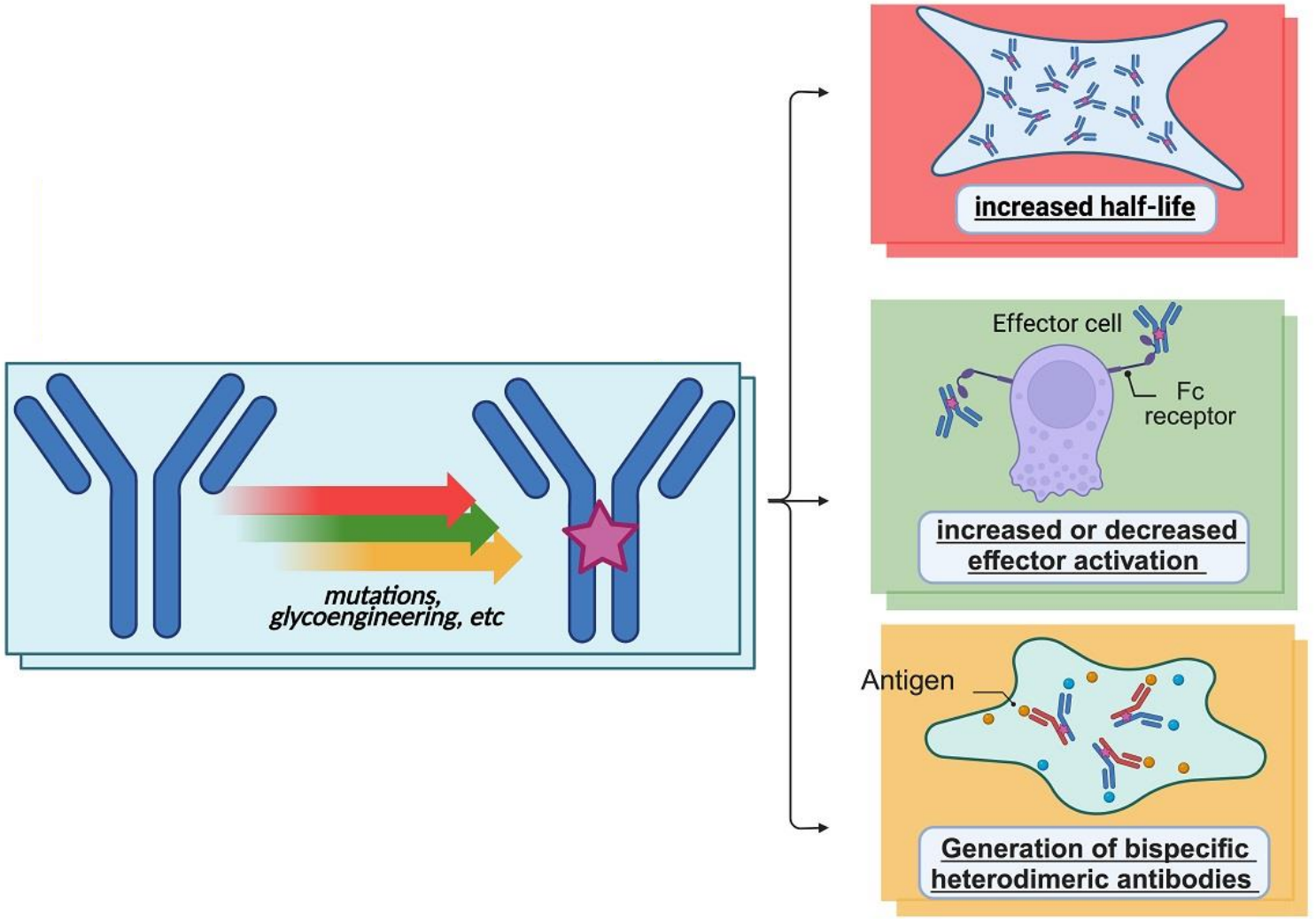
Stem helix mABs:
- CV3-25, S2P6
- B6, CC40.8
- 1.6C7, 28D9

→ Broadly neutralized in pseudovirus neutralization assay or animal models, but their potency was weak

FP, fusion peptide; NTD, N-terminal domain; RBD, receptor-binding domain; SD1, subdomain 1; and (RBD) all characterized as binding neutralizing antibodies

Zhou D, et al. Curr Opin Virol. 2023;61:101332.

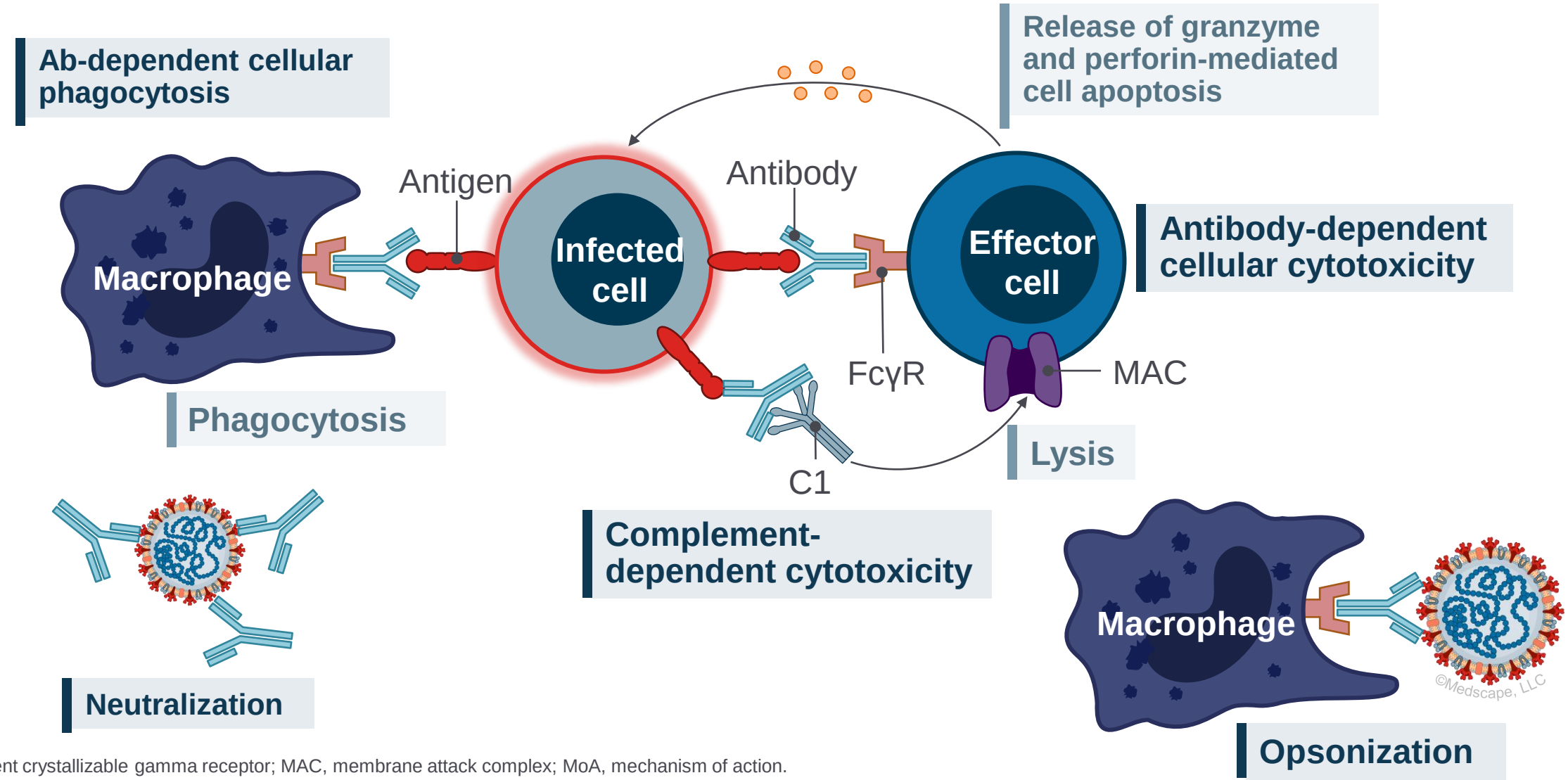
Fc Engineering Strategies in Next-Generation mAbs



Abdeldaim DT, et al. Pharmaceutics. 2023;15:2402.

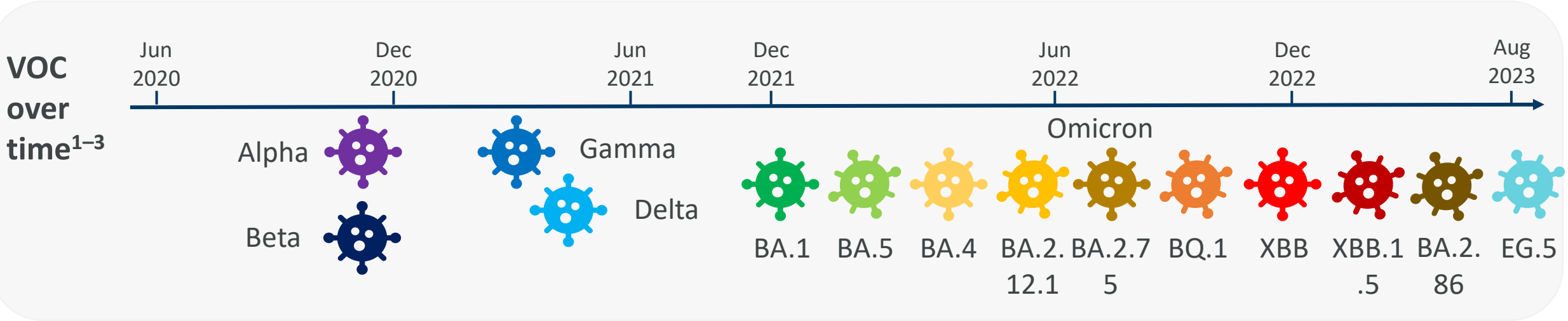
MoA of mAbs for the Treatment of COVID-19

AU



FcγR, fragment crystallizable gamma receptor; MAC, membrane attack complex; MoA, mechanism of action.
Taylor PC, et al. Nat Rev Immunol. 2021;21:382-393.

VOC mutations are associated with immune escape and may result in a decrease in neutralisation



Some VOCs are resistant to neutralisation by mAbs[4]

	B.1	BA.1	BA.4–5	BA.4.6	BA.2.75.2	BQ.1.1
mAb 1	37	2658	88	24,200	>50,000	>50,000
mAb 2	7	173	10,090	27,740	>50,000	>50,000
mAb 3	21	1890	>50,000	>50,000	>50,000	>50,000

EC_{50} (ng/mL)

EC_{50}, half maximal effective concentration; mAb, monoclonal antibody; VOC, variant of concern.

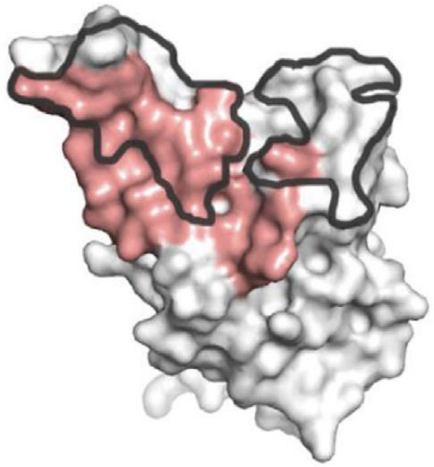
1. Nextstrain. Genomic epidemiology of SARS-CoV-2 with subsampling focused globally since pandemic start. Available at: https://nextstrain.org/ncov/gisaid/global/all-time?dmax=2022-08-08&dmin=2020-10-17 (last accessed: September 2023); 2. CoVariants. Overview of Variants/Mutations. Available at: https://covariants.org/variants (last accessed: September 2023); 3. World Health Organization. Tracking SARS-CoV-2 variants. Available at: https://www.who.int/activities/tracking-SARS-CoV-2-variants (last accessed: September 2023); 4. Arora P, et al. *Lancet Infect Dis*. 2023;23(1):22–23.

Novel mAbs Against COVID-19 Are Being Developed
AZD3152: Origin and MoA

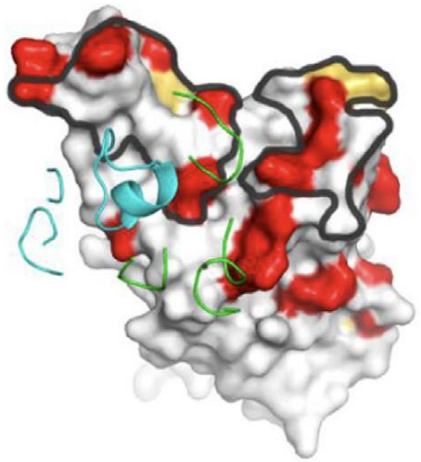
RP

Omi-42[1]

- Isolated from a patient infected by BA.1
- The overlapping binding footprints on the RBD do not allow for mutation to occur



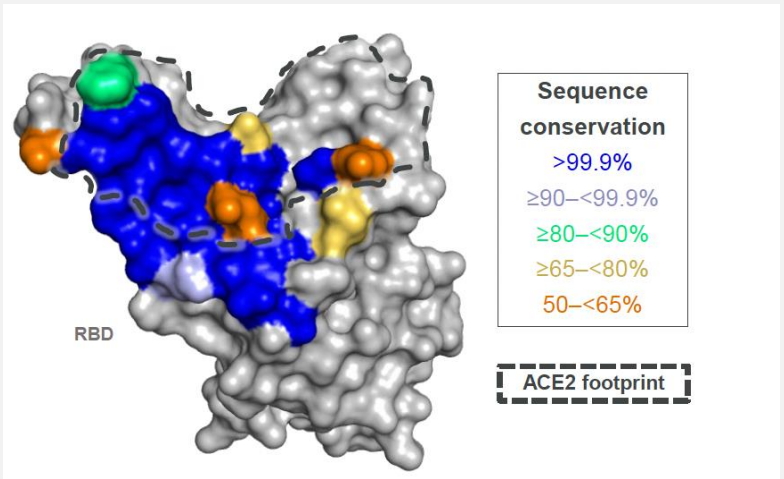
Omi-42 (red) and ACE2 (black lines) have substantially overlapping binding footprints on the RBD



Binding of the CDRs of Omi-42 with the RBD

AZD3152

- Is a **slightly modified version of Omi-42**[1]
- Targets the conserved region of the RBD and blocks binding to ACE2[2,3]



Residues on the RBD are colored according to their percentage conservation within the GISAID database. There are no residues in the ≥ 90% to < 99.9% conservation category

CDR, complementarity-determining region; GISAID, Global Initiative on Sharing Avian Influenza Data.

1. Zhou D, et al. Curr Opin Virol. 2023;61:101332; 2. Francica JR, et al. Presented at: ECCMID; April 15-18, 2023; Copenhagen, Denmark. Poster P2636; 3. Haars J, et al. Microorganisms. 2023;11:2417.

Novel mAbs Are Being Developed
AZD3152: Origin and MoA

RP

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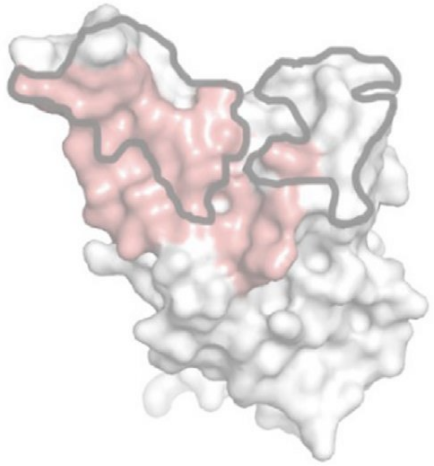

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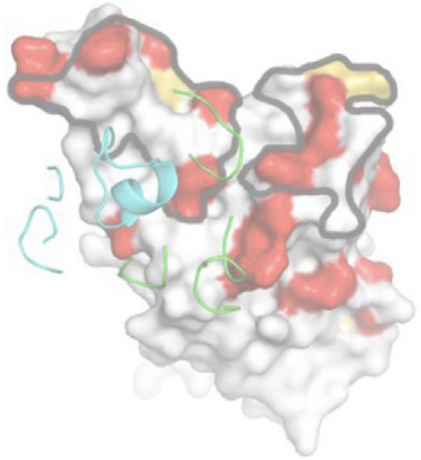
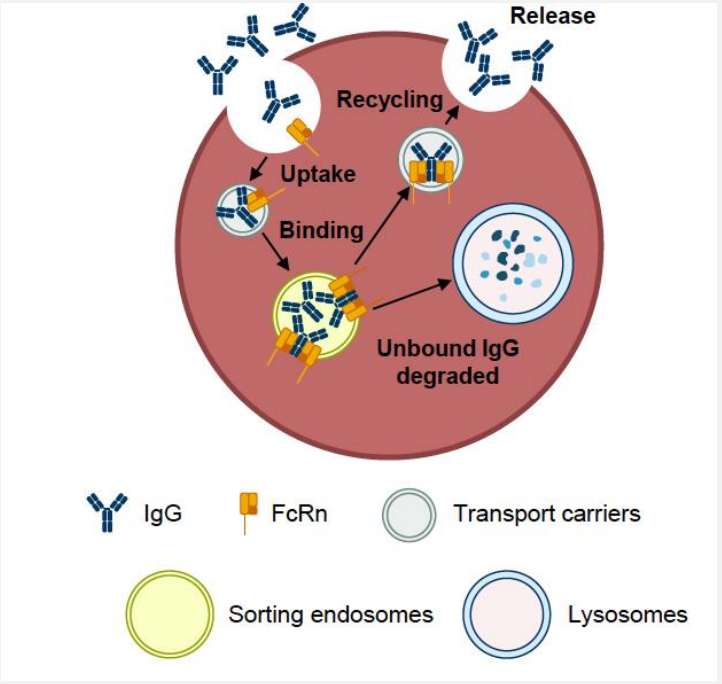


Binding of the CDRs of Omi-42 with the RBD

AZD3152

- Has Fc modifications to extend pharmacokinetics and reduce effector functions[2]

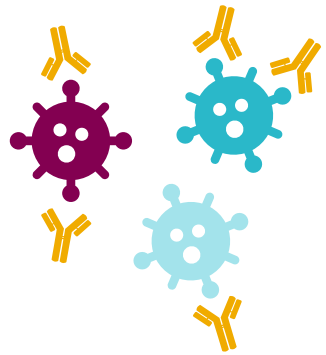


FcRn, neonatal Fc receptor; IgG, immunoglobulin G.

1. Zhou D, et al. Curr Opin Virol. 2023;61:101332; 2. Francica JR, et al. Presented at: ECCMID; April 15-18, 2023; Copenhagen, Denmark. Poster P2636.

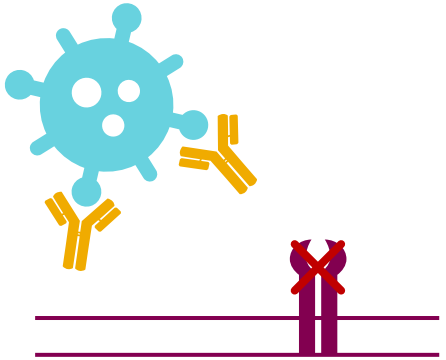
Key features of a mAb proposed to resist constant viral evolution and provide extended protection

Retained RBD binding affinity between variants



Reduces the chances of immune escape

High potency



Strong neutralisation response evoked at low concentrations

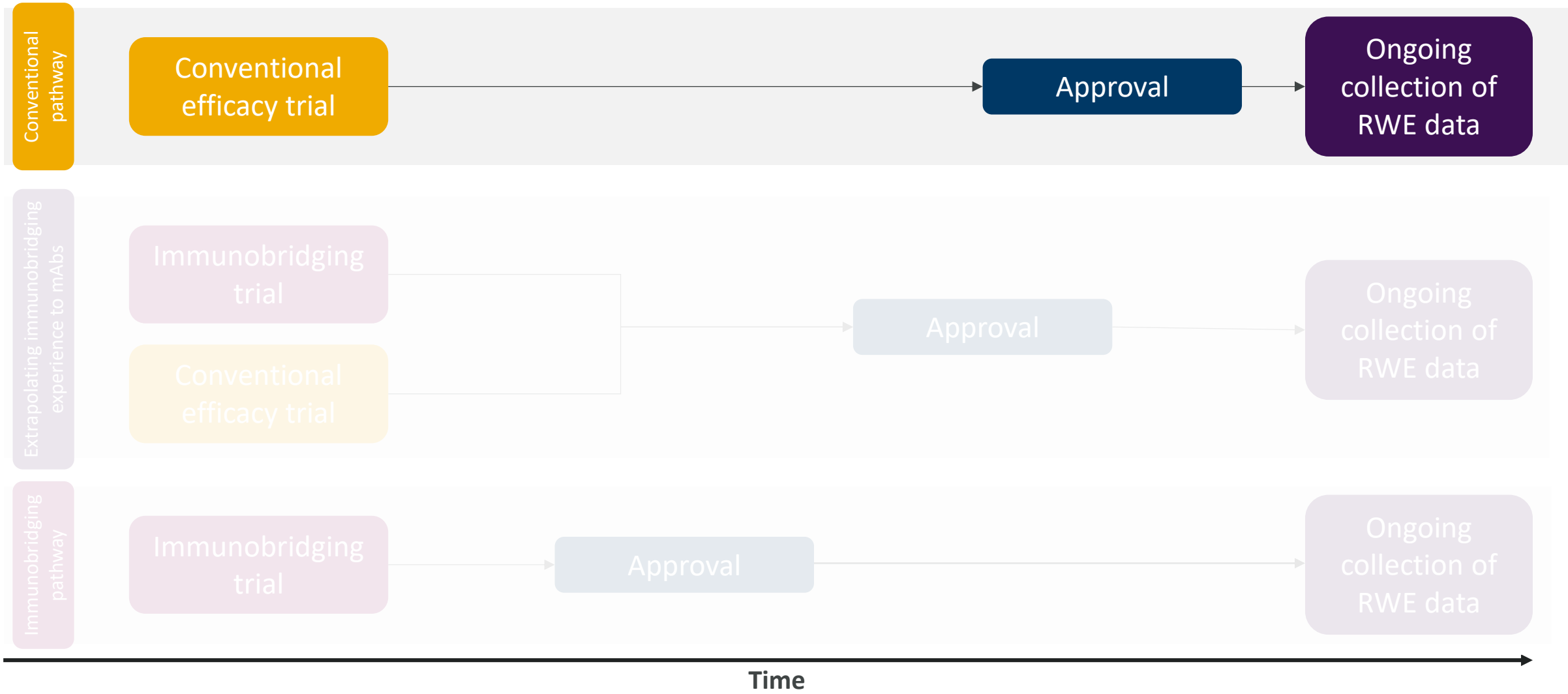
Extended half-life

Long duration of protection

mAb, monoclonal antibody; RBD, receptor-binding domain.

Strohl WR, et al. *BioDrugs.* 2022;36(3):231–323.

Pathways to approval for a next-generation mAb[1,2]



mAb, monoclonal antibody; RWE, real-world evidence.

1. Simpson S, et al. *NPJ Vaccines*. 2020;5:101; 2. Van Norman G. *JACC Basic Transl Sci.* 2016;1(3):170–179.

Conventional approval pathway for a mAb[1,2]

Robust clinical studies performed sequentially to demonstrate efficacy and safety

Duration depends on endpoints required, recruitment speed, etc.

Market approval granted following completion of all clinical trials

Accelerated approval options are available with both FDA and EMA if it is determined there is a public health emergency and urgent need for the intervention

2–3 years	~2 years	3–4 years	FDA: 10 months EMA: 210 days
~$15 million	*~$25 million*	*~$90 million*	

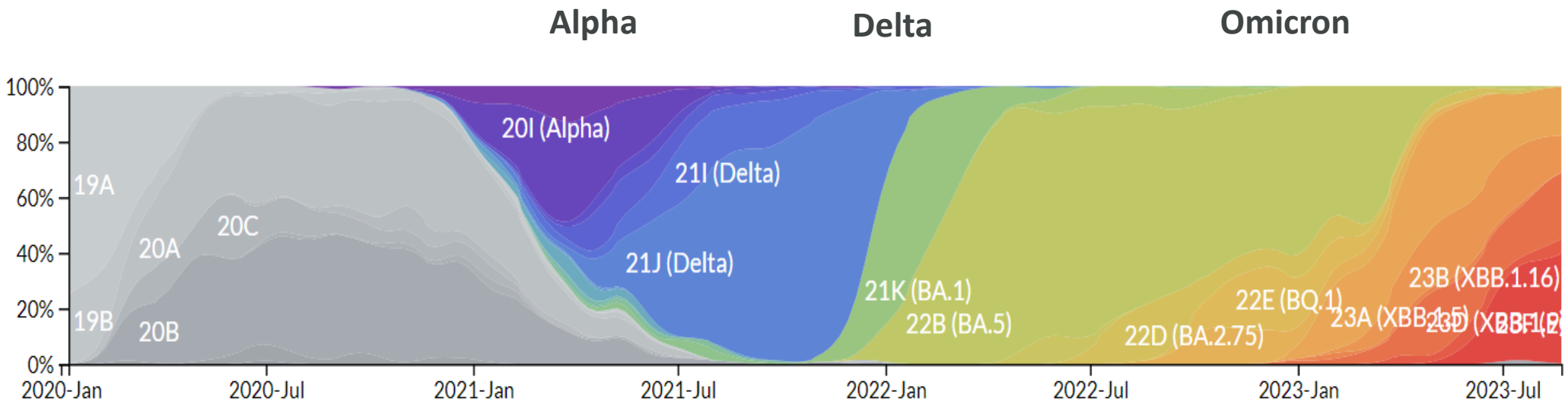
Total: 10–15 years

>$1 billion

EMA, European Medicines Agency; FDA, U.S. Food and Drug Administration; mAB, monoclonal antibody.

1. Simpson S, et al. *NPJ Vaccines.* 2020;5:101; 2. Van Norman G. *JACC Basic Transl Sci.* 2016;1(3):170–179.

The dominant viral variant of SARS-CoV-2 has changed over time[1]



New VOC?

Figure adapted from Nextstrain data, which are available under the Creative Commons Attribution 4.0 International License.

- The dominant SARS-CoV-2 strain changes every few months[1]
- Randomised control trial efficacy data cannot be generated against rapidly emerging newer SARS-CoV-2 variants due to the length of time required to undertake the trial[2]

EMA, European Medicines Agency; FDA, U.S. Food and Drug Administration; VOC, variant of concern.

1. Nextstrain. Genomic epidemiology of SARS-CoV-2 with subsampling focused globally since pandemic start. Available at: https://nextstrain.org/ncov/gisaid/global/all-time?dmax=2022-08-08&dmin=2020-10-17 (last accessed: September 2023); 2. European Medicines Agency. Summary report of the Joint EMA-FDA workshop on the efficacy of monoclonal antibodies in the context of rapidly evolving SARS-CoV-2 variants. Available at: https://www.fda.gov/media/165344/download (last accessed: September 2023).

Regulators agree new mAbs for SARS-CoV-2 management are urgently required

There is an overall agreement by the FDA and EMA to **expedite the development of new mAb products** against emerging VOC

Regulators stated there is a **strong scientific basis for using evidence from first-generation mAbs to support development of second-generation mAbs**

Selected mAbs have demonstrated a **consistent and predictable safety profile**

Next-generation mAbs are developed using the **same established platforms and technologies** as previous first-generation mAbs

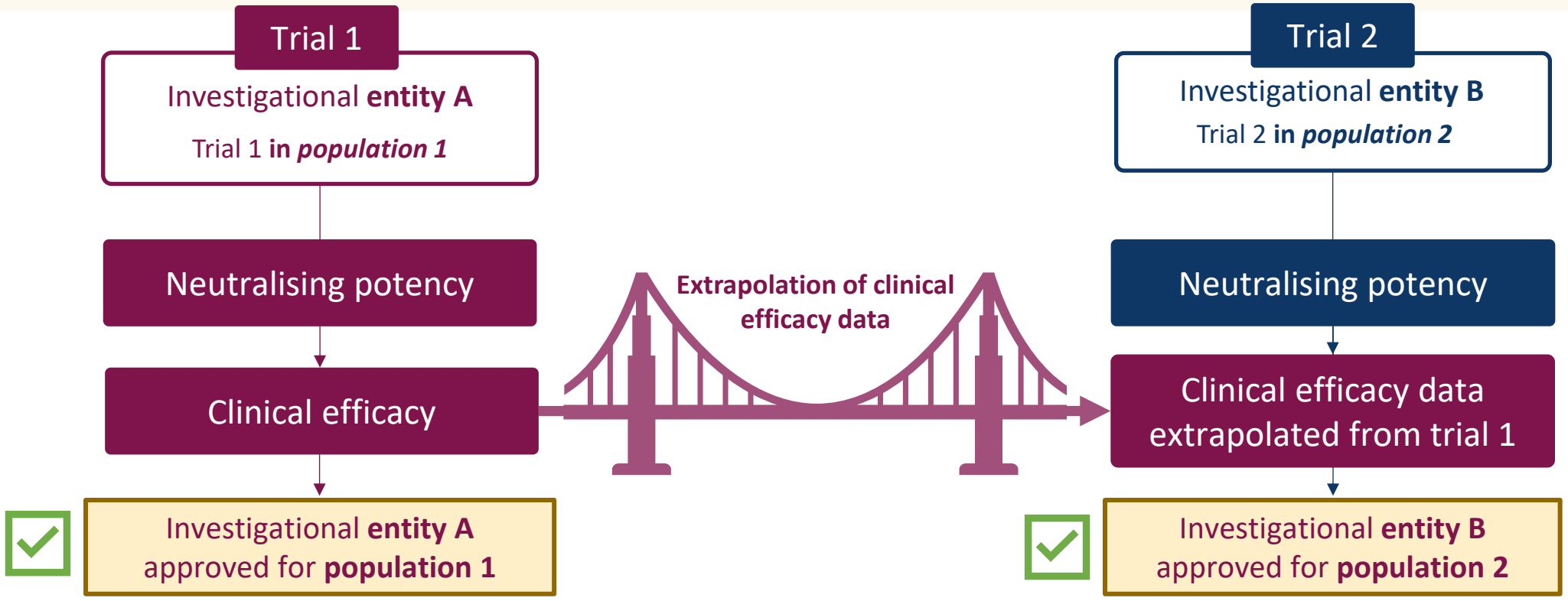
Immunobridging trials are an established approach used when there is an urgent need for important, new medicines, but full-scale efficacy trials may not be feasible within the timeframe required

EMA, European Medicines Agency; FDA, U.S. Food and Drug Administration; mAbs, monoclonal antibodies; VOC, variants of concern.

European Medicines Agency. Summary report of the Joint EMA-FDA workshop on the efficacy of monoclonal antibodies in the context of rapidly evolving SARS-CoV-2 variants. Available at: https://www.fda.gov/media/165344/download (last accessed: September 2023).

Immunobridging enables extrapolation of clinical efficacy data[1]

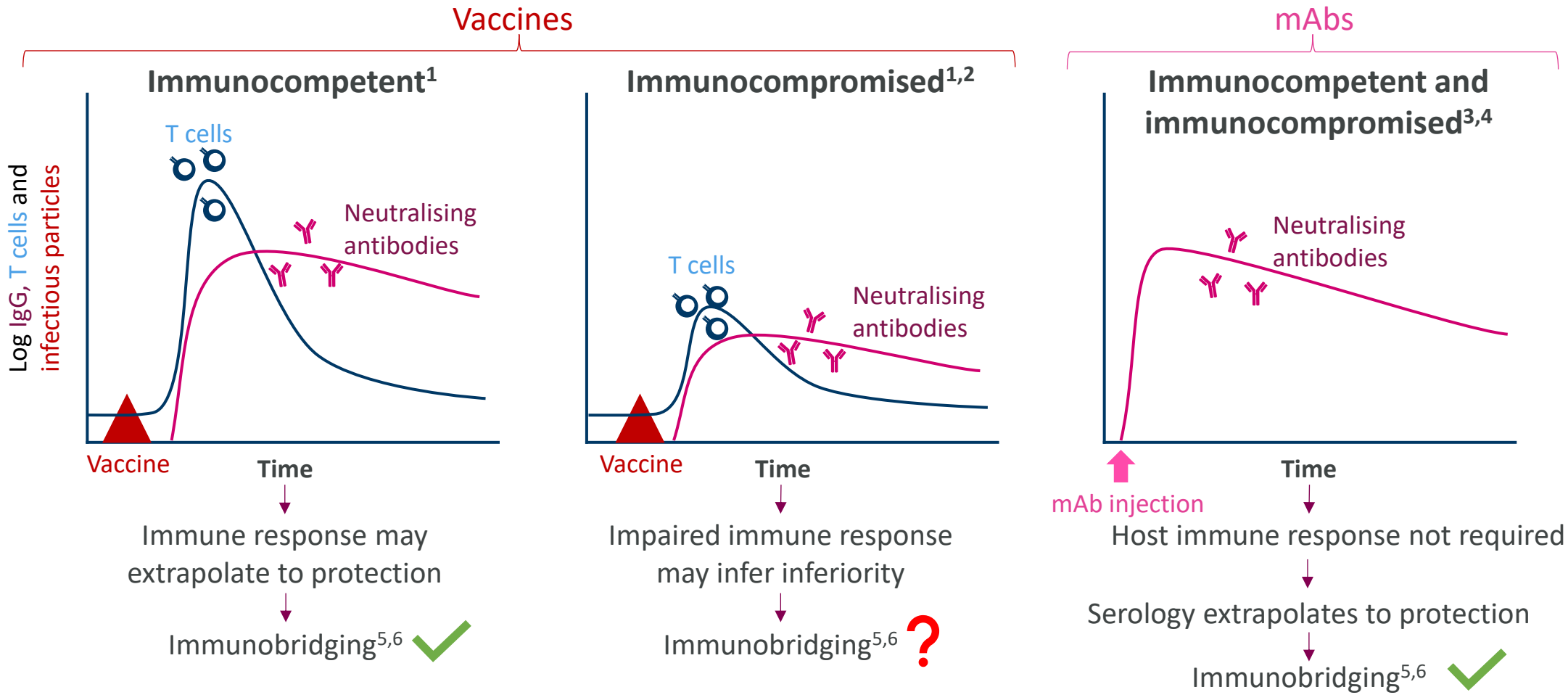
The immunobridging model[1–3]



Safety in a bridging trial may be measured or bridged to the original trial depending on the study design.[1–3]

1. World Health Organization. Annex 9 – Guidelines on clinical evaluation of vaccines: regulatory expectations. Available at: https://www.who.int/publications/m/item/WHO-TRS-1004-web-annex-9 (last accessed: Septemb er 2023); 2. European Medicines Agency. Guideline on clinical evaluation of vaccines. Available at: https://www.ema.europa.eu/en/clinical-evaluation-new-vaccines-scientific-guideline (last accessed: September 2023); 3. European Medicines Agency. ICH Topic E 5 (R1): Ethnic factors in the acceptability of foreign clinical data. Available at: https://www.ema.europa.eu/en/ich-e5-r1-ethnic-factors-acceptability-foreign-clinical-data-scientific-guideline#current-effective-version-section (last accessed: September 2023).

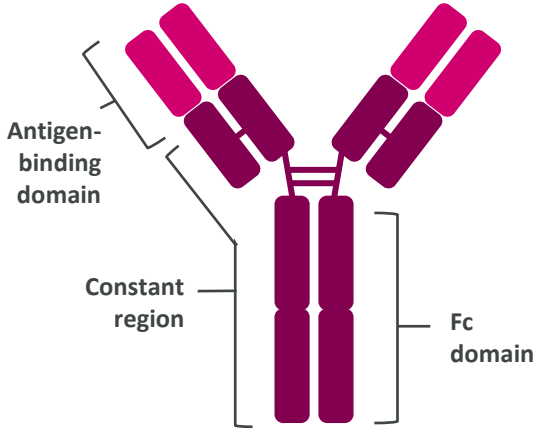
Immunobridging for mAbs bypass the requirement for an immune response and facilitates the extrapolation of efficacy



IgG, immunoglobulin; mAb, monoclonal antibody.

1. Jiskoot W, et al. *Pharm Biotechnol.* 2019:281–304; 2. Azzolini E, et al. *Life Sci Alliance.* 2022;5(6):e202201381; 3. Wu W-L, et al. *JCI Insight.* 2022;7(8):e157597; 4. Hwang YC, et al. *J Biomed Sci.* 2022;29:1; 5. European Medicines Agency. ICH E 5 (R1): Ethnic factors in the acceptability of foreign clinical data. Available at: https://www.ema.europa.eu/en/ich-e5-r1-ethnic-factors-acceptability-foreign-clinical-data-scientific-guideline#current-effective-version-section (last accessed: September 2023); 6. Stadler E, et al. *medRxiv.* 2022 [preprint].

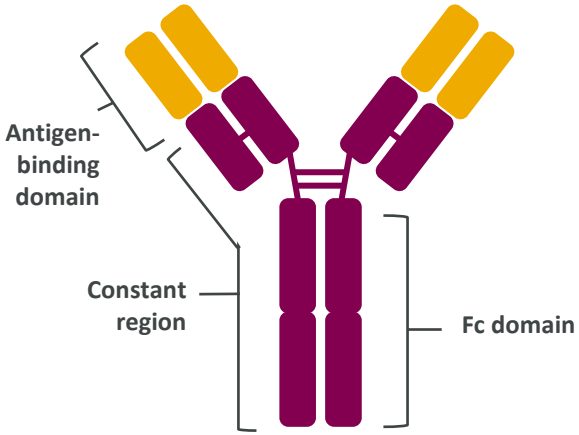
Next-generation mAbs are manufactured using the same platform processes as previous generations[1,2]



mAb 1

Established safety profile through RCTs[2]

Novel antigen-binding domain but **optimised structural and functional characteristics remain**[1,2]



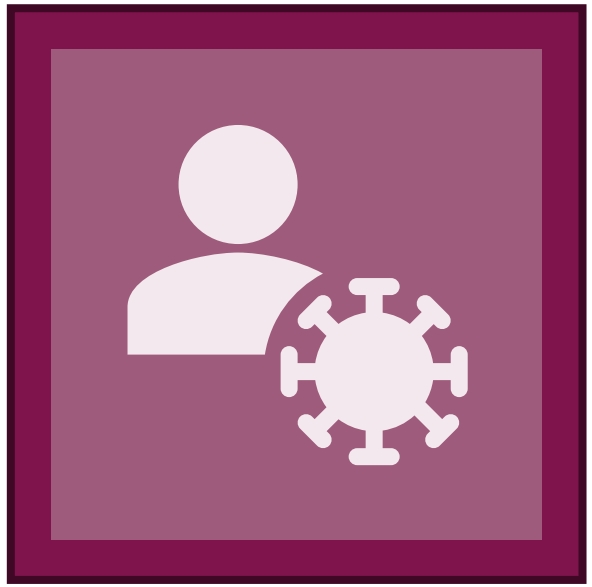
mAb 2

Safety profile from **mAb 1** used to support safety profile of **mAb 2**[2]

mAbs, monoclonal antibodies; RCTs, randomised controlled trials.

1. FDA-EMA. Considerations Regarding Assessment of A Modified Monoclonal Antibody (mAb) Product Related to A Prototype mAb Product in Addressing Emerging SARS-COV-2 Variants – A CMC Perspective. Available at: https://www.ema.europa.eu/en/documents/presentation/presentation-10-considerations-regarding-assessment-modified-monoclonal-antibody-mab-product-related_en.pdf (last accessed: September 2023); 2. FDA-EMA. Development Approach for Anti-Spike Monoclonal Antibodies to Keep Pace with SARS-CoV-2 Variants. Available at: https://www.ema.europa.eu/en/documents/presentation/presentation-11-development-approach-anti-spike-monoclonal-antibodies-keep-pace-sars-cov-2-variants_en.pdf (last accessed: September 2023).

Bridging has been used to expand use or receive approval of several vaccines

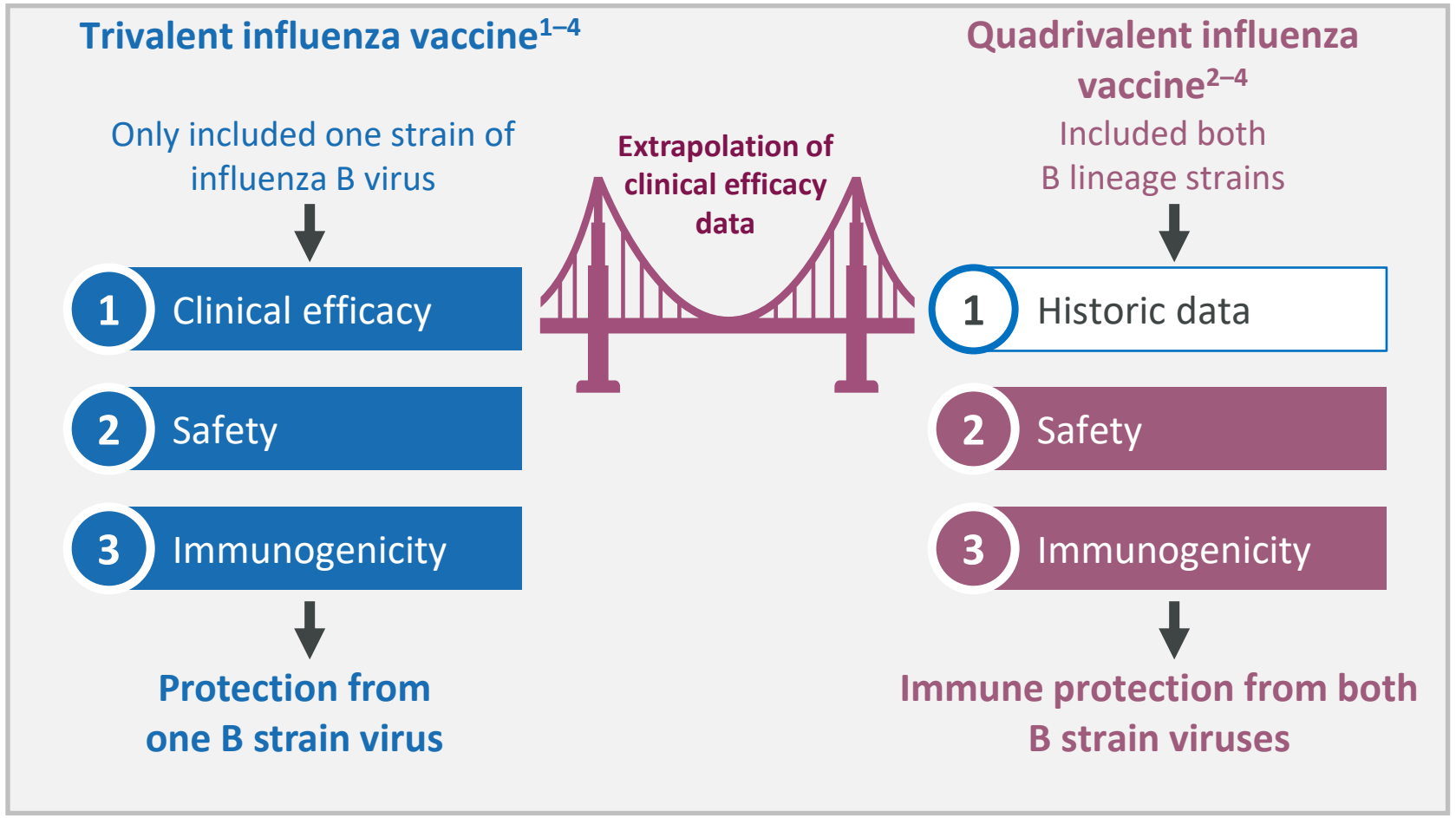


1. Expand eligible age group for an approved COVID-19 vaccine **BNT162b2** in both the EU and US[1,2]
2. EMA approval in June 2022 of a vaccine for COVID-19 based on bridging data to an approved vaccine[3]
3. Approval of a quadrivalent influenza vaccine based on bridging data to a trivalent vaccine in the US[4]
4. Expansion of eligibility for an approved HPV vaccine from young adults to mid-adults[5]

EMA, European Medicines Agency; HPV, human papillomavirus.

1. European Medicines Agency press release. Published 28 May 2021; 2. U.S. Food and Drug Administration press release. Published 10 May 2021; 3. European Medicines Agency press release. Published 23 June 2022; 4. Centers for Disease Control and Prevention. Immunogenicity, efficacy, and effectiveness of influenza vaccines. Available at: https://www.cdc.gov/flu/professionals/acip/immunogenicity.htm (last accessed: September 2023); 5. Centers for Disease Control and Prevention. Grading of Recommendations Assessment, Development and Evaluation (GRADE) for use of HPV vaccine in adults 27 through 45 years of age. Available at: https://www.cdc.gov/vaccines/acip/recs/grade/HPV-adults.html (last accessed: September 2023).

A quadrivalent influenza vaccine was made available based on bridging data to a trivalent vaccine[1]



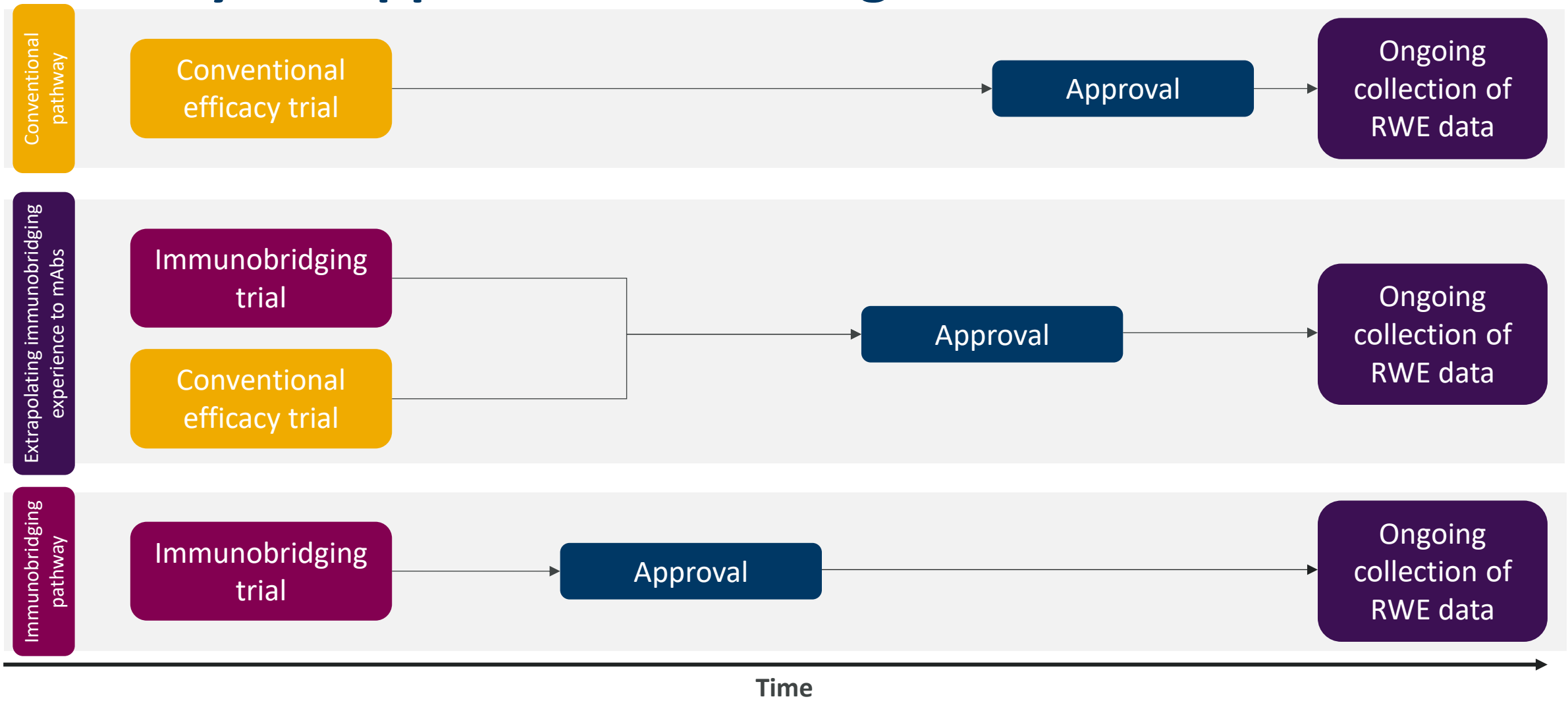
Randomised non-inferiority clinical trials comparing immunogenicity of IIV3 with IIV4 were performed[2–5]

The quadrivalent vaccine demonstrated superior immunogenicity for IIV4 for the added influenza B virus that is not included in IIV3, without interfering with immune responses to the remaining three vaccine viruses[1]

IIV3, trivalent inactivated influenza vaccine; IIV4, quadrivalent inactivated influenza vaccine.

1. Centers for Disease Control and Prevention. Immunogenicity, efficacy, and effectiveness of influenza vaccines. Available at: https://www.cdc.gov/flu/professionals/acip/immunogenicity.htm (last accessed: September 2023);
2. Treanor JT, et al. *Vaccine*. 2017;35(15):1856–1864; 3. Kieninger D, et al. *BMC Infect Dis*. 2013;13:343; 4. Pépin S, et al. *Vaccine*. 2013;31(47):5572–5578; 5. Tinoco JC, et al. *Vaccine*. 2014;32(13):1480–1487.

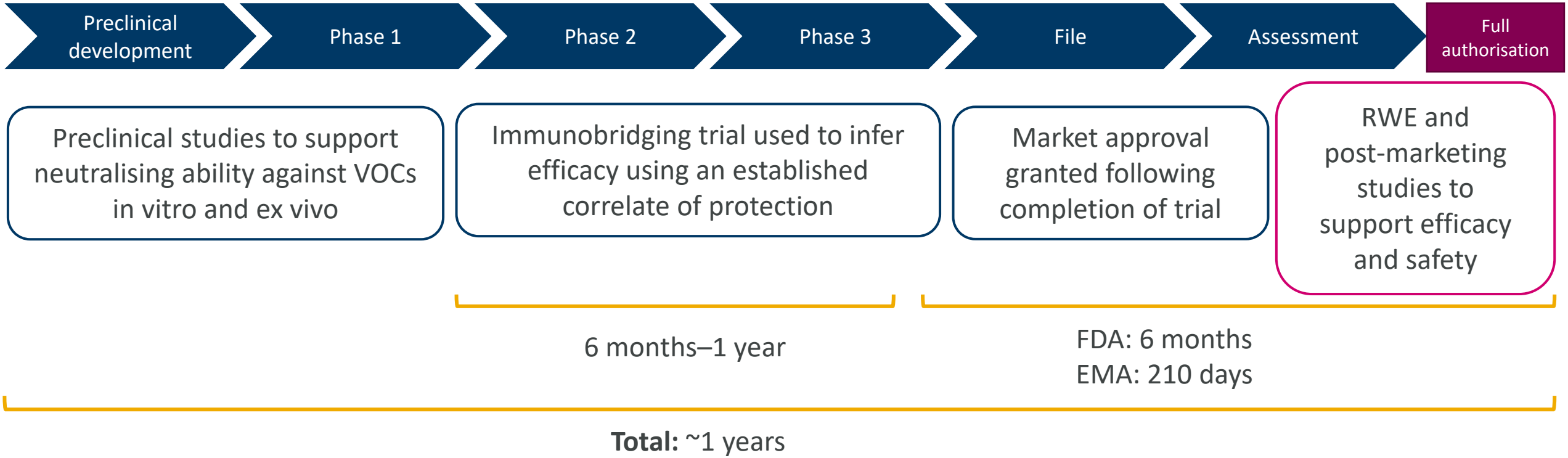
Pathways to approval for a next-generation mAb[1–5]



mAb, monoclonal antibody; RWE, real-world evidence.

1. Simpson S, et al. *NPJ Vaccines.* 2020;5:101; 2. Van Norman G. *JACC Basic Transl Sci.* 2016;1(3):170–179; 3. World Health Organization. Annex 9 – Guidelines on clinical evaluation of vaccines: regulatory expectations. Available at: https://www.who.int/publications/m/item/WHO-TRS-1004-web-annex-9 (last accessed: September 2023); 4. European Medicines Agency. Guideline on clinical evaluation of vaccines; 5. European Medicines Agency. ICH Topic E 5 (R1): Ethnic factors in the acceptability of foreign clinical data. Available at: https://www.ema.europa.eu/en/ich-e5-r1-ethnic-factors-acceptability-foreign-clinical-data-scientific-guideline#current-effective-version-section (last accessed: September 2023).

Pathway to approval through immunobridging[1–4]

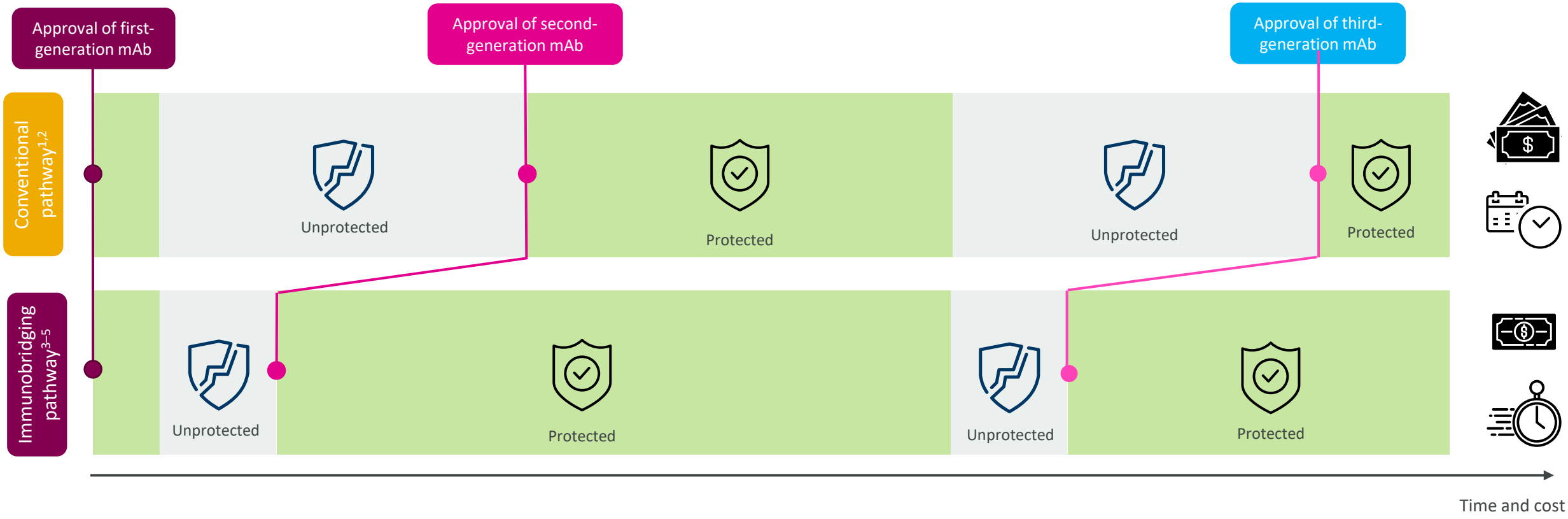


Immunobridging trials can help **reduce development time** and **accelerate access** to new medicines

EMA, European Medicines Agency; FDA, U.S. Food and Drug Administration; RWE, real-world experience; VOCs, variants of concern.

1. Simpson S, et al. *NPJ Vaccines.* 2020;5:101; 2. Van Norman G. *JACC Basic Transl Sci.* 2016;1(3):170–179; 3. European Medicines Agency. Summary report of the Joint EMA-FDA workshop on the efficacy of monoclonal antibodies in the context of rapidly evolving SARS-CoV-2 variants. Available at: https://www.fda.gov/media/165344/download (last accessed: September 2023); 4. Cox EM, et al. *Clin Transl Sci*. 2020;13(3):451–461.

Immunobridging may enable protection from COVID-19 sooner than conventional efficacy trials[1–5]



mAb, monoclonal antibody.

1. Simpson S, et al. *NPJ Vaccines.* 2020;5:101; 2. Van Norman G. *JACC Basic Transl Sci.* 2016;1(3):170–179; 3. World Health Organization. Annex 9 – Guidelines on clinical evaluation of vaccines: regulatory expectations. Available at: https://www.who.int/publications/m/item/WHO-TRS-1004-web-annex-9 (last accessed: September 2023); 4. European Medicines Agency. Guideline on clinical evaluation of vaccines. Available at: https://www.ema.europa.eu/en/clinical-evaluation-new-vaccines-scientific-guideline (last accessed: September 2023); 5. European Medicines Agency. ICH Topic E 5 (R1): Ethnic factors in the acceptability of foreign clinical data. Available at: https://www.ema.europa.eu/en/ich-e5-r1-ethnic-factors-acceptability-foreign-clinical-data-scientific-guideline#current-effective-version-section (last accessed: September 2023).

Summary

- Immunobridging is an approach within clinical trials to infer effectiveness of a new drug candidate through an accepted surrogate for efficacy[1–3]
- There is a need to expedite the development of new mAbs due to the evolving nature of SARS-CoV-2[4]
- Immunobridging trials can help reduce development time and accelerate access to new medicines for people with immunocompromising conditions[4]
- The prevention of COVID-19 in people with immunocompromising conditions should be prioritised[4]

EMA, European Medicines Agency; FDA, U.S. Food and Drug Administration; mAbs, monoclonal antibodies.

1. World Health Organization. Annex 9: Guidelines on clinical evaluation of vaccines: regulatory expectations. Available at: https://cdn.who.int/media/docs/default-source/prequal/vaccines/who-trs-1004-web-annex-9.pdf?sfvrsn=9c8f4704_2&download=true (last accessed: September 2023); 2. European Medicines Agency. Guideline on clinical evaluation of vaccines. Available at: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-evaluation-vaccines-revision-1_en.pdf (last accessed: September 2023); 3. European Medicines Agency. ICH E 5 (R1). Available at: https://www.ema.europa.eu/en/ich-e5-r1-ethnic-factors-acceptability-foreign-clinical-data-scientific-guideline#current-effective-version-section (last accessed: September 2023); 4. European Medicines Agency. Summary report of the Joint EMA-FDA workshop on the efficacy of monoclonal antibodies in the context of rapidly evolving SARS-CoV-2 variants. Available at: https://www.fda.gov/media/165344/download (last accessed: September 2023).