

The Emerging Prevention Strategies for COVID-19 in Immunocompromised Patients

Outline

- A brief introduction of immunization
- The effects of vaccination in immunocompromised (IC) patients
- The clinical outcome of IC patients with confirmed COVID-19 infection
- Current prevention strategies and guideline for COVID-19 in Taiwan

Immune system

- The immune system is complex and pervasive
- There are **numerous cell types** that either **circulate** throughout the body or **reside** in a particular tissue
- Each cell type plays a **unique role**, with different ways of recognizing problems, communicating with other cells, and performing their functions

Response of the Immune System

Innate immune system	Adaptive immune system
Response is non-specific	Pathogen and antigen specific response
Composed of leukocytes	Composed of antigens, B cells, T cells
Exposure leads to immediate maximal response	Lag time between exposure and maximal response
Cell-mediated and humoral components	Cell-mediated and humoral components
No immunological memory	Exposure leads to immunological memory

Immunization

- **Active immunization** (vaccination)
 - Administering **Ag**, Ab generated by recipients and persisted for a long period
 - Classification: for **infectious diseases**, for allergy, for cancer
 - Further categorized into **prophylactic, abortive, therapeutic** vaccine
- **Passive immunization** (immunoglobulins)
 - Administering Ab via IM or IV, waning gradually

Passive Immunization Involves Antibodies

- Administered at or around the time of exposure, but short-term protection
- Indicated where:
 - One is unable to synthesize antibodies
 - **High-risk person** is susceptible to a disease he/she has been exposed to (or is likely to be exposed to)
 - **Disease already present** and the antibody may help to suppress the effects of a toxin or the inflammatory response

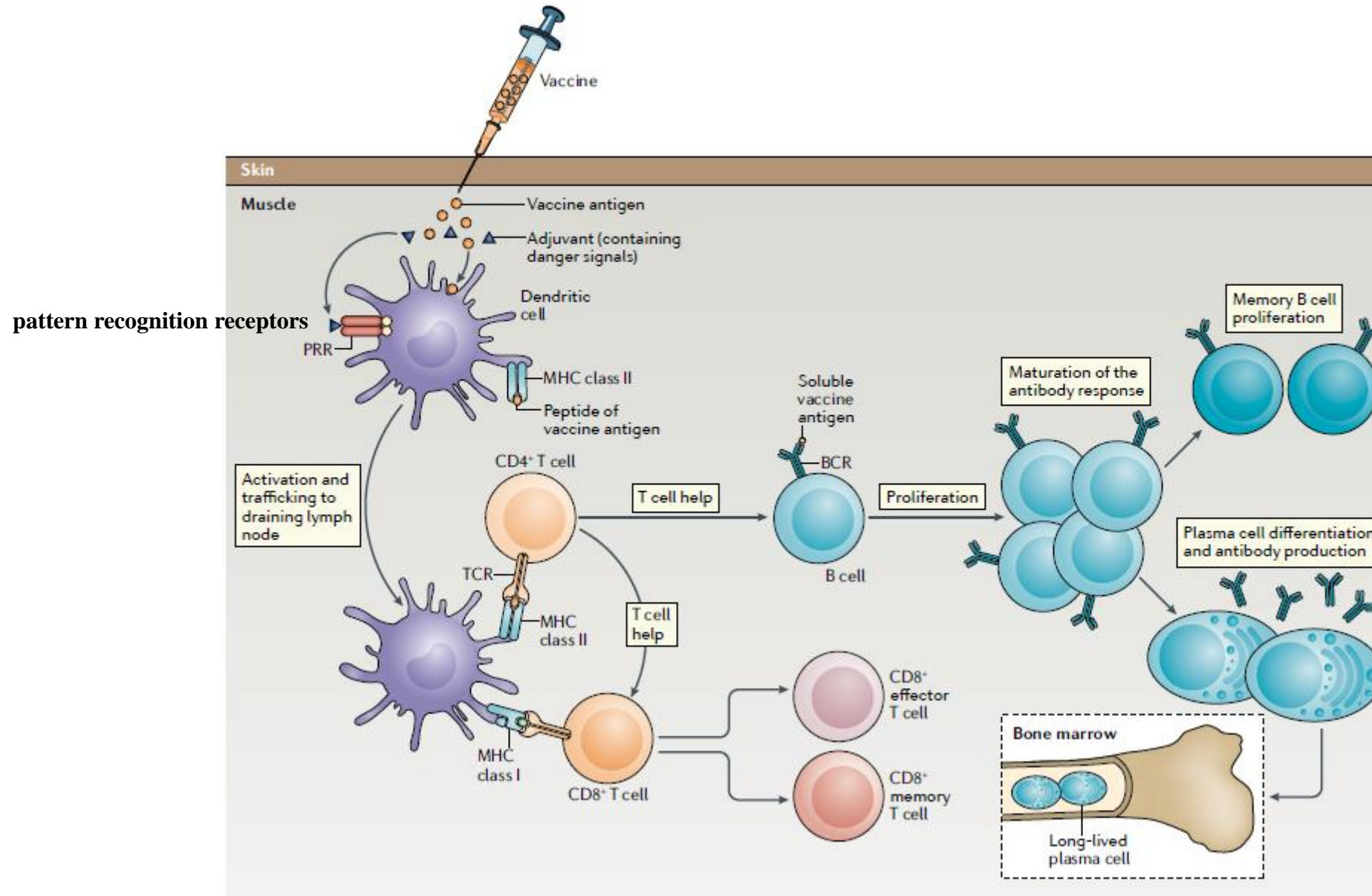
Passive Immunization: commercial preparations

- Immunoglobulins: non-specific
 - Intramuscular: for measles, hepatitis A virus
 - Intravenous: high antibody titer, **immunomodulation**
- **Hyperimmunoglobulins**: specific
 - HBIG: for hepatitis B virus
 - Cytogam: for cytomegalovirus
 - VZIG (ZIG): for varicella-zoster virus
 - RSV-IVIG: for respiratory syncytial virus (RSV)
- Recombination **monoclonal/ polyclonal** antibody
 - Palivizumab for RSV infection
 - Monoclonal/ polyclonal antibody for SARS-CoV-2

Vaccination

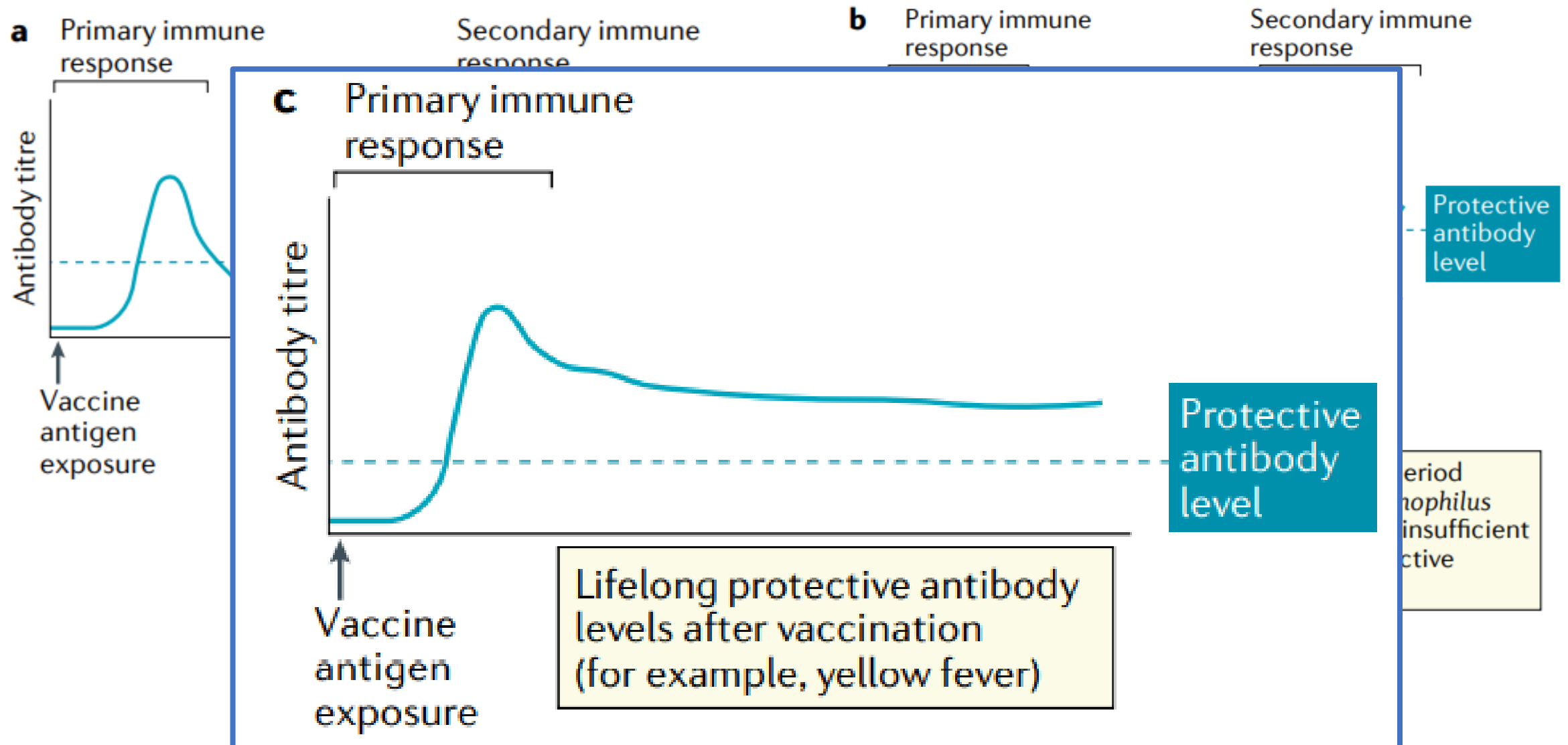
- A way to **train** your immune system against a **specific pathogen**
- Vaccination achieves **immune memory** without an actual infection, so the body is prepared when the virus or bacterium enters
- An effective **vaccine** will optimally **activate both** the **innate** and **adaptive** response
- An **immunogen** is used to activate the **adaptive** immune response so that specific memory cells are generated
- The goal of **vaccine design** is to select **immunogens** that will generate the most effective and efficient **memory response** against a particular pathogen
- Innate immunity recognizes broad patterns, and without innate responses, adaptive immunity cannot be optimally achieved

The generation of an immune response to a vaccine



(Pollard A et al Nat Rev Immunol 2021;21:83-100)

Immune memory is an important feature of vaccine-induced protection



Vaccine components





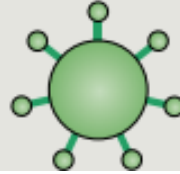
- **One or more antigens (immunogens)**
- Suspending fluids
 - sterile water
 - saline
- Residual cell culture materials
- Preservatives, stabilizers, antibiotics
- **Adjuvants**
 - aluminum compounds
 - **new adjuvants**

Several different adjuvants are used in U.S. vaccines

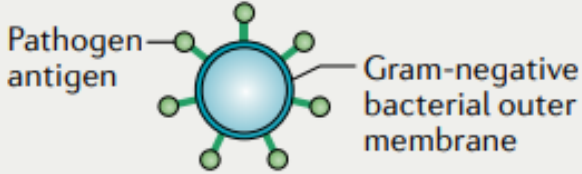
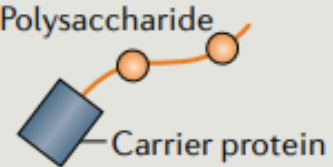
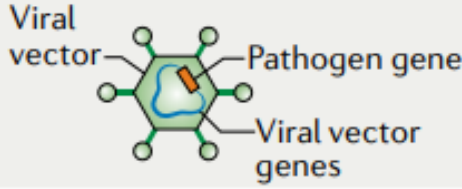

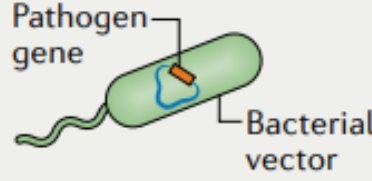
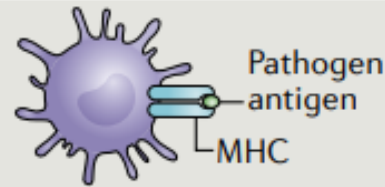
Adjuvant	Composition	Vaccines
Aluminum	One or more of the following: amorphous aluminum hydroxyphosphate sulfate (AAHS), aluminum hydroxide, aluminum phosphate, potassium aluminum sulfate (Alum)	Anthrax, DT, DTaP (Daptacel), DTaP (Infanrix), DTaP-IPV (Kinrix), DTaP-IPV (Quadracel), DTaP-HepB-IPV (Pediarix), DTaP –IPV/Hib (Pentacel), Hep A (Havrix), Hep A (Vaqta), Hep B (Engerix-B), Hep B (Recombivax), HepA/Hep B (Twinrix), HIB (PedvaxHIB), HPV (Gardasil 9), Japanese encephalitis (Ixiaro), MenB (Bexsero, Trumenba), Pneumococcal (Prevnar 13), Td (Tenivac), Td (Mass Biologics), Tdap (Adacel), Tdap (Boostrix)
AS04	Monophosphoryl lipid A (MPL) + aluminum salt	Cervarix
MF 59	Oil in water emulsion composed of squalene	Fluad
AS01 _B	Monophosphoryl lipid A (MPL) and QS-21, a natural compound extracted from the Chilean soapbark tree, combined in a liposomal formulation	Shingrix
CpG 1018	Cytosine phosphoguanine (CpG), a synthetic form of DNA that mimics bacterial and viral genetic material	Heplisav-B

(US CDC 2020 access)

Schematic representation of different types of vaccine against pathogens

Type of vaccine		Licensed vaccines using this technology	First introduced
Live attenuated (weakened or inactivated)		Measles, mumps, rubella, yellow fever, influenza, oral polio, typhoid, Japanese encephalitis, rotavirus, BCG, varicella zoster	1798 (smallpox)
Killed whole organism		Whole-cell pertussis, polio, influenza, Japanese encephalitis, hepatitis A, rabies	1896 (typhoid)
Toxoid		Diphtheria, tetanus	1923 (diphtheria)
Subunit (purified protein, recombinant protein, polysaccharide, peptide)		Pertussis, influenza, hepatitis B, meningococcal, pneumococcal, typhoid, hepatitis A	1970 (anthrax)
Virus-like particle		Human papillomavirus	1986 (hepatitis B)

Schematic representation of different types of vaccine against pathogens

Type of vaccine		Licensed vaccines using this technology	First introduced
Outer membrane vesicle		Group B meningococcal	1987 (group B meningococcal)
Protein-polysaccharide conjugate		<i>Haemophilus influenzae</i> type B, pneumococcal, meningococcal, typhoid	1987 (<i>H. influenzae</i> type b)
Viral vectored		Ebola	2019 (Ebola)
Nucleic acid vaccine		SARS-CoV-2	2020 (SARS-CoV-2)
Bacterial vectored		Experimental	–
Antigen-presenting cell		Experimental	–

Prevention strategy against COVID-19

Active immunization

Vaccines= the traditional approach to eliciting immunity



Stimulate immune response to induce both humoral and cellular immunity



Usually requires 2-3 immunization



Effective vaccine can provide long-lasting protection

Passive immunization

Direct administration of a broadly neutralizing antibody



Directly neutralize virus



Provide instant protection



Provide weeks to months protection and require maintenance injection

Outline

- A brief introduction of immunization
- **The effects of vaccination in immunocompromised(IC) patients**
- The clinical outcome of IC patients with confirmed COVID-19 infection
- Current prevention strategies and guideline for COVID-19 in Taiwan

Unmet Needs and Increased Burden on High-risk Populations¹⁻⁵

In the US of the adult population is moderately to severely immunocompromised, leading to increased vulnerability to COVID-19¹⁻³
about 3%



Hematologic malignancies^{2,3}



Active chemotherapy^{2,3}



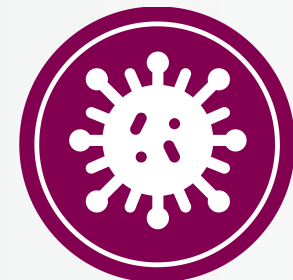
Transplant^{2,3}



Advanced or untreated HIV²



Taking immunosuppressants^{2,a}



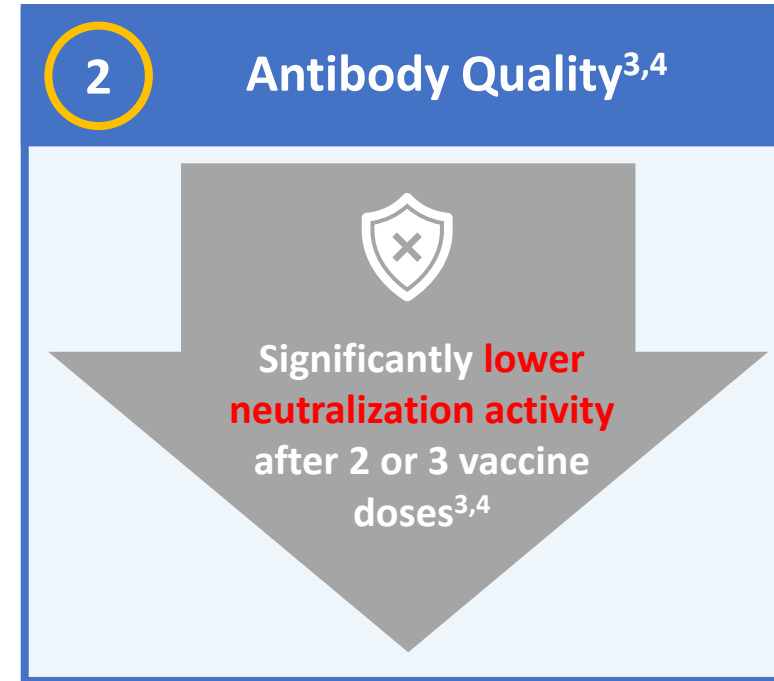
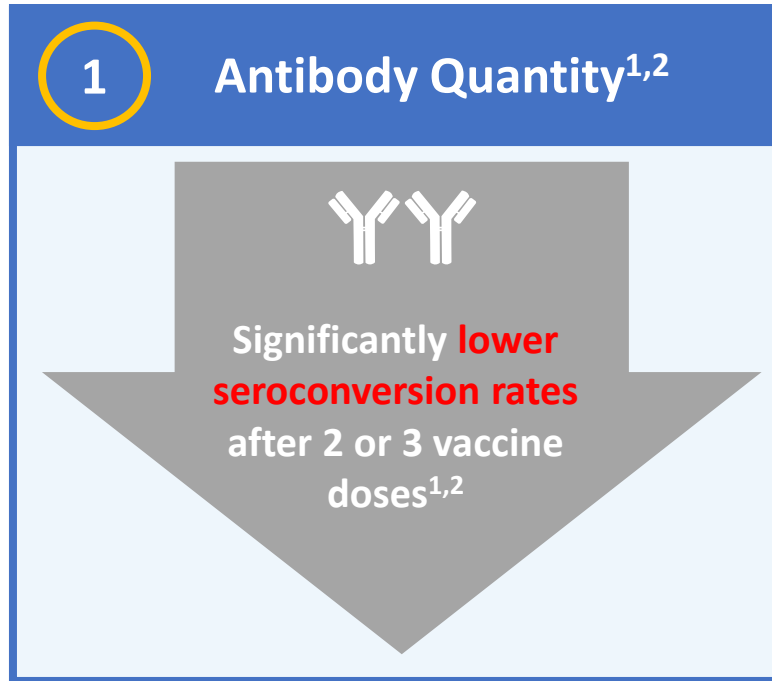
Primary moderate or severe immune deficiency²

^aImmunosuppressants could include medicines for non-Hodgkin's lymphoma, lupus, multiple sclerosis, rheumatoid arthritis.^{3,5}

COVID-19 = coronavirus disease 2019; HIV = human immunodeficiency virus; US = United States.

1. Harpaz R et al. Research letter. *JAMA*. 2016;316(23):2547-2448; 2. Centers for Disease Control and Prevention. COVID-19 vaccines for people who are moderately or severely immunocompromised; 3. Abbasi J. Medical news & perspectives. *JAMA*. 2021;325(20):2033-2035; 4. Rincon-Arevalo H et al. *Sci Immunol*. 2021;6(60):eabj1031; 5. Richard-Eaglin A et al. *Nurs Clin N Am*. 2018;53(3):319-334.

Immunocompromised Patients Have **Lower Seroconversion and Neutralization Responses** Than Healthy Individuals and Remain at High Risk of Severe COVID-19¹⁻⁴



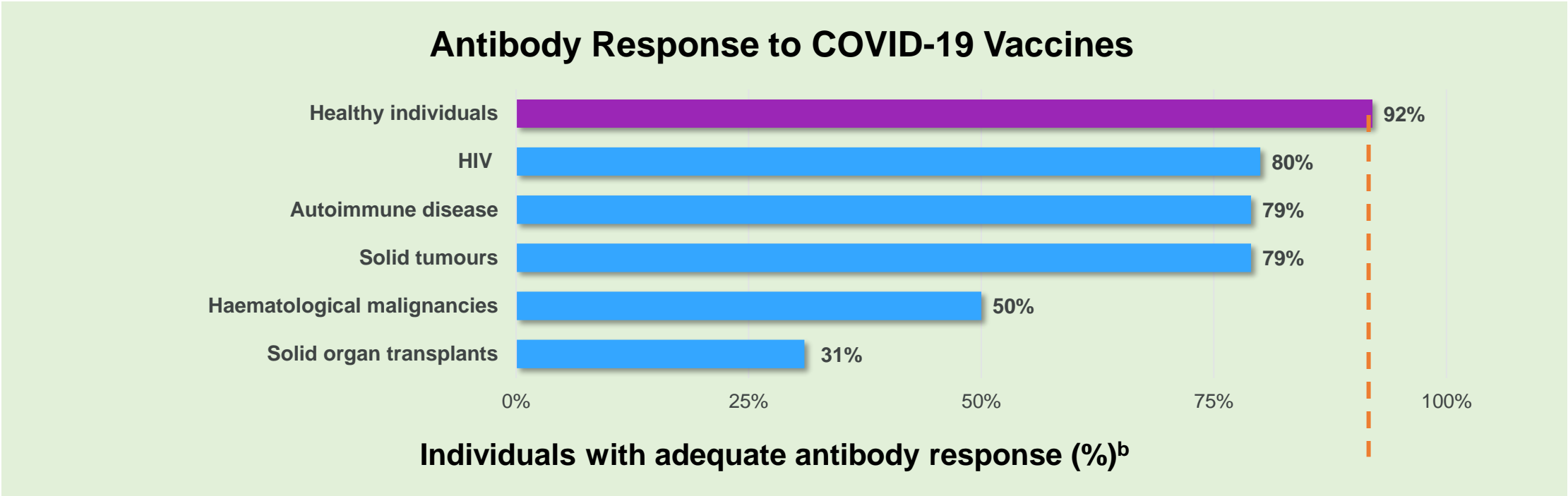
Immunocompromised patients remain at high risk of severe COVID-19 outcomes after full vaccination⁵

COVID-19 = coronavirus disease 2019.

1. Furer V et al. *Ann Rheum Dis.* 2021;80(10):1330-1338; 2. Yang LM et al. *J Clin Virol.* 2022;153:105217; 3. Chung DJ et al. *Blood Cancer Discov.* 2021;2(6):568-576;

4. Kim WJ et al. *Ann Rheum Dis.* 2022;81(11):1585-1593; 5. Singson JRC et al. *MMWR Morb Mortal Wkly Rep.* 2022;71(27):878-884.

Reduced immune response to COVID-19 vaccines was found in immunocompromised patients^a

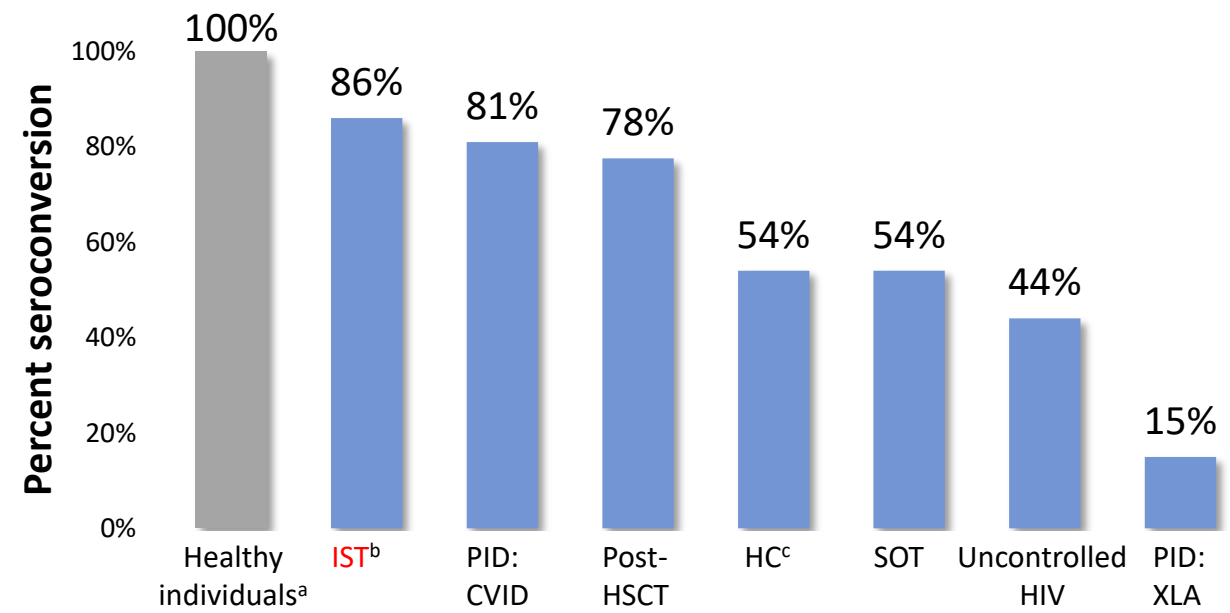


Antibody response in some immunocompromised groups was nearly half or lower than that of healthy adults.^a

^a172 healthy HCW and 1099 immunocompromised patients who had completed their COVID-19 vaccination series were enrolled. Compared with HCW, seropositivity was significantly lower ($P<0.01$) among immunocompromised patients; ^bSerum was collected to measure for the presence of IgG against the SARS-CoV-2 spike protein. COVID-19 = coronavirus disease 2019; IgG = immunoglobulin G; HCW = healthcare workers; HIV = human immunodeficiency virus; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2. Haidar G, et al. [Published online ahead of print]. *Clin Infect Dis*. 2022;ciac103. doi:10.1093/cid/ciac103

Immunocompromised Populations Are **Less Likely to Seroconvert** After Primary Series of COVID-19 Vaccination (vs. Healthy Controls)¹⁻⁷

Seroconversion Varies Across IC Population¹⁻⁷



Different Immunosuppressive Therapies Present Different Seroconversion Percentages²

Immunosuppressive therapy	Percent seroconversion
Methotrexate	84%
Glucocorticoids	66%
Mycophenolate mofetil	64%
Abatacept	62%
Anti-CD20	41%

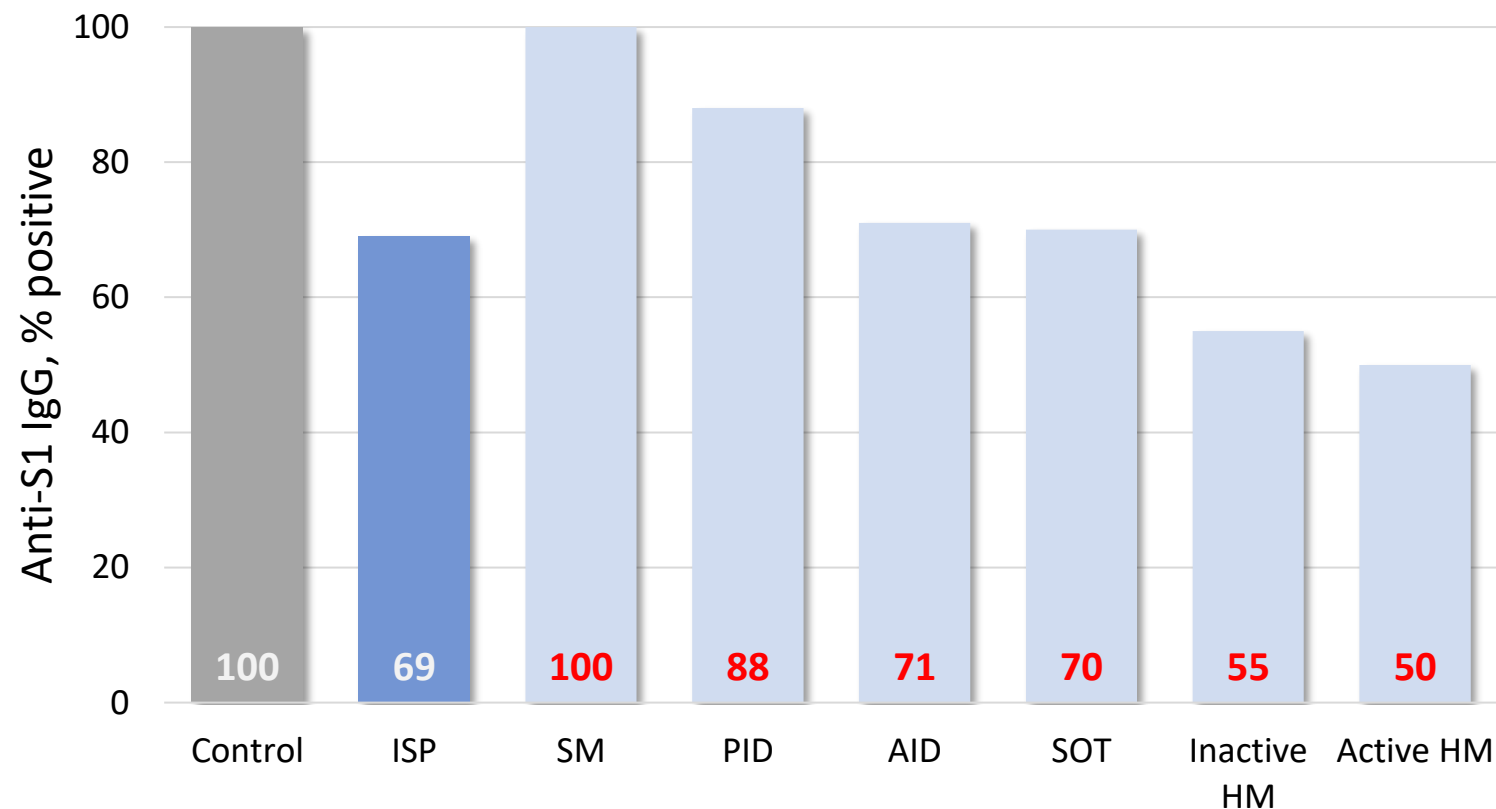
16% of CLL⁸ and 7% of NHL⁹ patients receiving active treatment seroconverted

Anti-CD20 monotherapy significantly reduced vaccine-induced humoral response²

^aHealthy individuals after primary series of mRNA-1273; ^bIncluded glucocorticoids, conventional synthetic disease-modifying antirheumatic drugs (DMARDs), biologic DMARDs, and Janus kinase inhibitors; ^cIncluded multiple myeloma, lymphomas, B-cell chronic lymphocytic leukemia, and other myeloid malignancies. CD = cluster of differentiation; CLL = chronic lymphocytic leukemia; COVID-19 = coronavirus disease 2019; CVID = common variable immunodeficiency; HC = hematological cancer; HIV = human immunodeficiency virus; HSCT = hematopoietic stem cell transplant; IC = immunocompromised; IST = immunosuppressive therapy; mRNA = messenger ribonucleic acid; NHL = non-Hodgkin lymphoma; PID = primary immunodeficiency; SOT = solid organ transplant; XLA = X-linked agammaglobulinemia. 1. Jackson LA et al. *N Engl J Med.* 2020;383(20):1920-1931; 2. Furer V et al. *Ann Rheum Dis.* 2021;80(10):1330-1338; 3. van Leeuwen LPM et al. *J Allergy Clin Immunol.* 2022;149(6):1949-1957; 4. Shem-Tov N et al. *Br J Haematol.* 2022;196(4):884-891; 5. Agha ME et al. *Open Forum Infect Dis.* 2021;8(7):ofab353; 6. 204-2206; 6. Boyarsky BJ et al. *JAMA.* 2021;325(21):2204-2206; 7. Hassold N et al. *AIDS.* 2022;36(4):F1-F5; 8. Herishanu Y et al. *Blood.* 2021;137(23):3165-3173; 9. Perry C et al. *Blood Adv.* 2021;5(16):3053-3061.

Even After COVID-19 **Booster Vaccination**, Immunocompromised Patients Are **Less Likely to Seroconvert** Than Healthy Controls

A retrospective observational cohort study of immunocompromised patients (n=125) and healthy controls (n=12) after booster vaccination from January 1, 2021, through November 15, 2021:^a

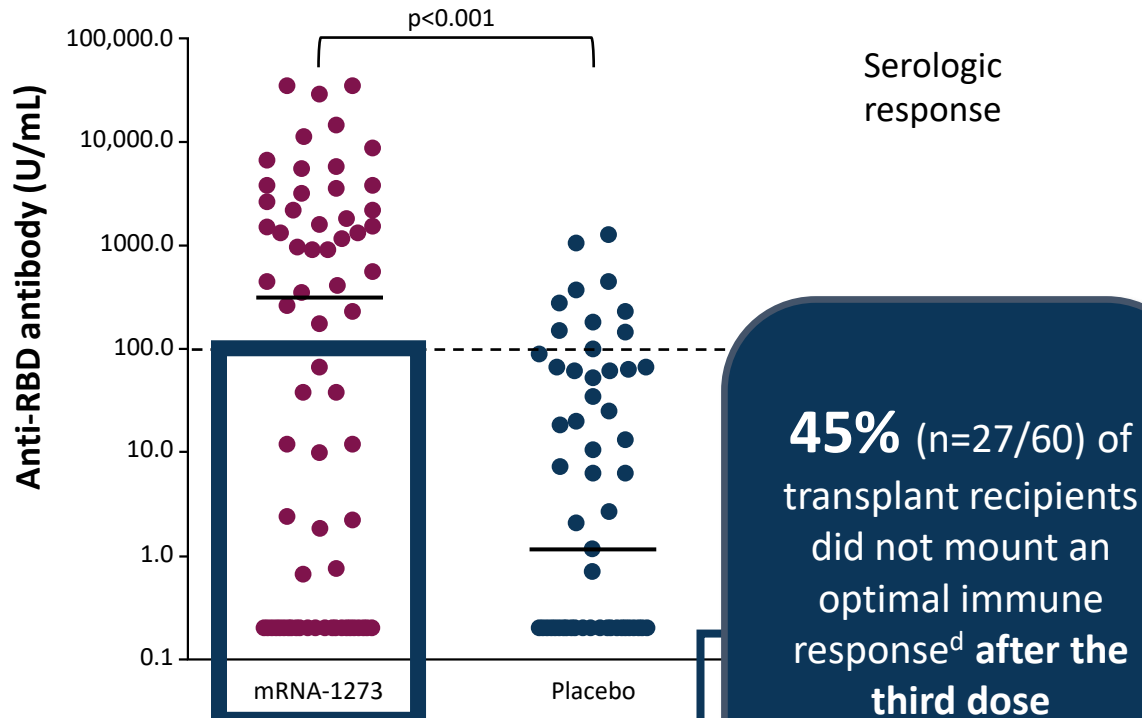


Only **69%** of all **immunosuppressed** patients seroconverted after booster vaccination compared with 100% of healthy controls

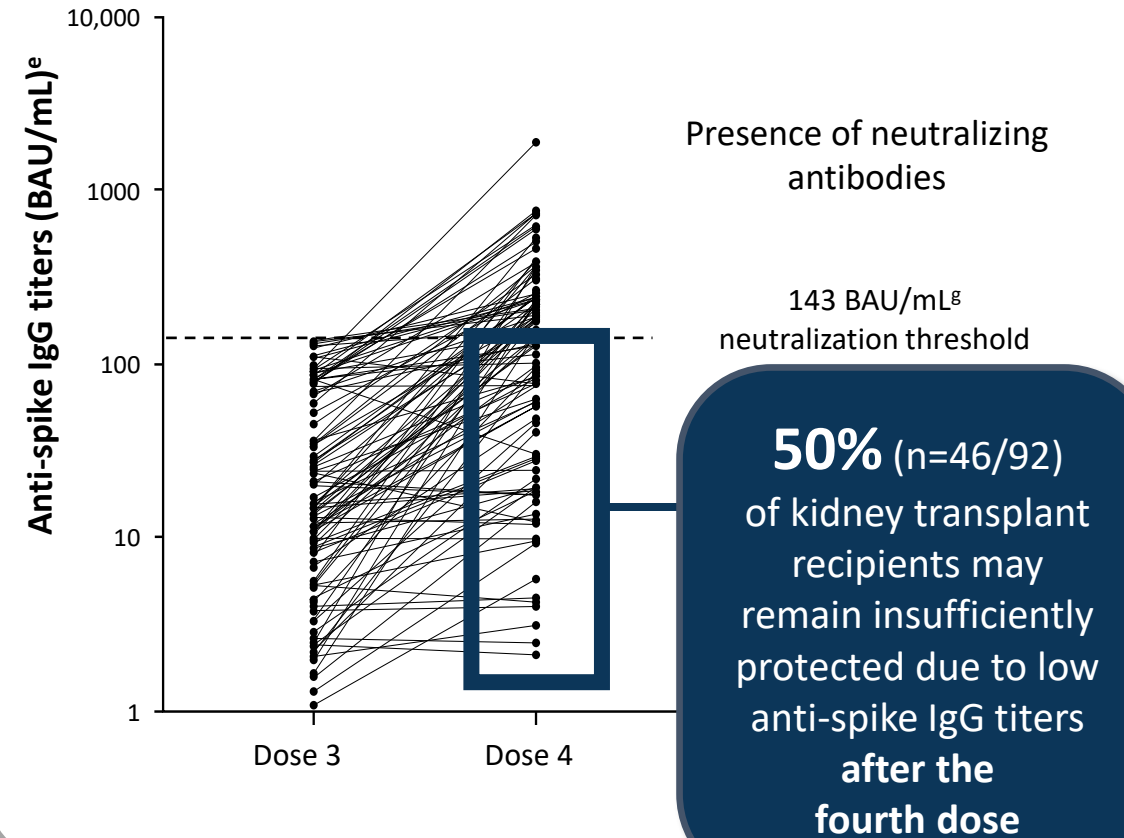
^aCohort consisted of immunocompetent healthcare workers and immunosuppressed patients who received a primary series of mRNA-1273, BNT162b2, or Ad26.COV2.S vaccine and a single booster dose of any of these three vaccines. AID = autoimmune disease; HM = heme malignancy; IgG = immunoglobulin G; ISP = immunosuppressed; PID = primary immune deficiency; SM = solid malignancy; SOT = solid organ transplant. Yang LM et al. *J Clin Virol.* 2022;153:105217.

Almost **Half** of Solid Organ Transplant Recipients Are Still **Not Protected** After Booster Doses^{1,2}

Antibody levels in transplant recipients^{1,a,b} after third mRNA vaccine dose^c



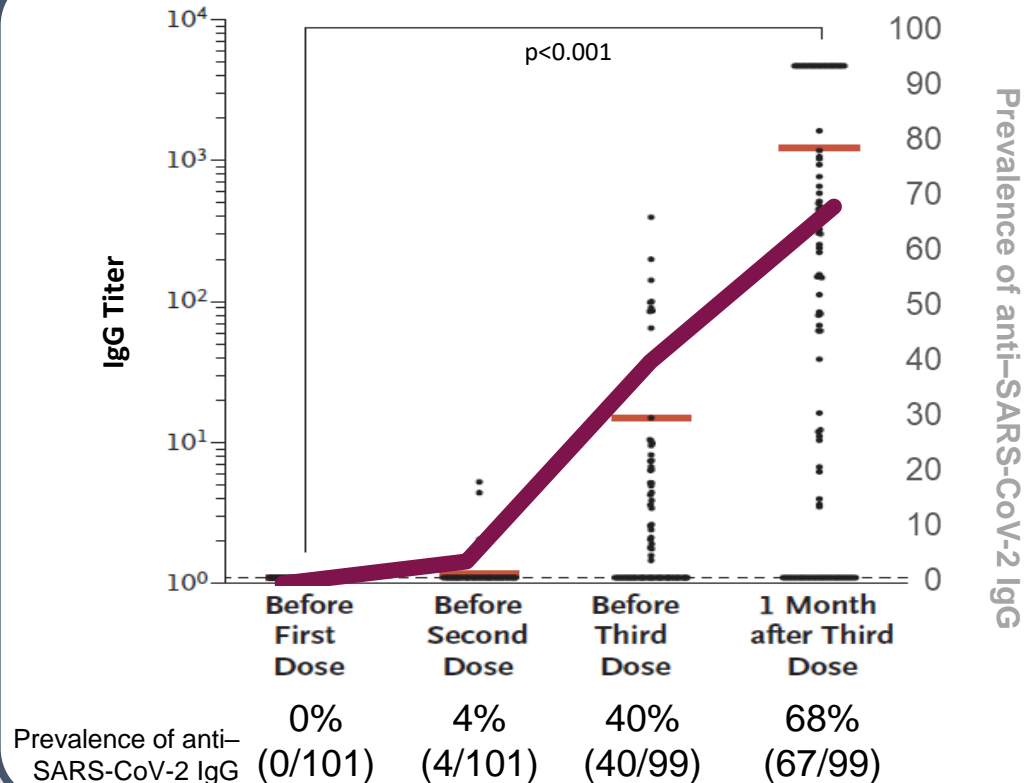
Antibody levels in kidney transplant recipients after fourth mRNA vaccine dose^{2,f}



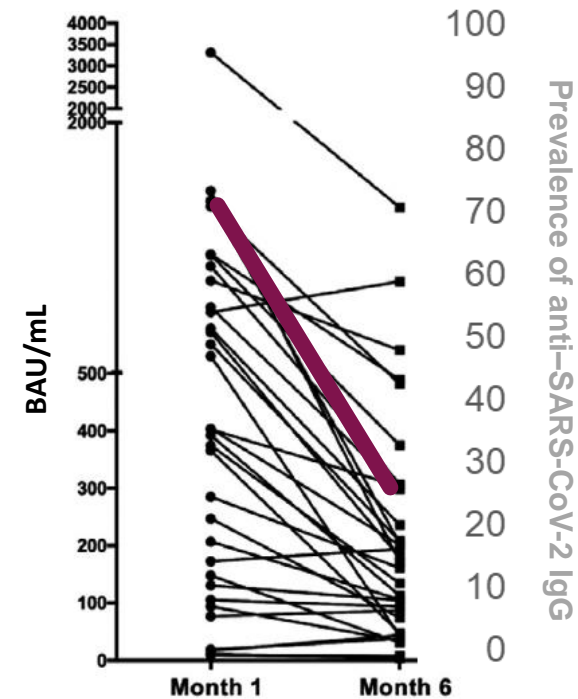
^aWho had received 2 doses of mRNA-1273, no previous COVID-19 diagnosis; ^bIncluded lung, heart, kidney, pancreas, and liver transplant patients; ^cmRNA-1273 vaccine (Moderna) received 2 months after the second dose of mRNA-1273; ^dAnti-receptor-binding domain (RBD) antibody level of at least 100 U per milliliter at Month 4; ^eTiters are expressed in BAU after calibration to the World Health Organization standard and measured 2-6 weeks after third and fourth mRNA vaccine; ^fA fourth dose of mRNA vaccine (BNT162b2 [Pfizer], n= 34; mRNA-1273 [Moderna], n= 58) was given to kidney transplant recipients who had anti-spike IgG titers less than 143 BAU/mL 1 month after a third dose; ^gAnti-spike IgG titers above 143 BAU/mL correlate with the presence of neutralizing antibodies against the wild-type virus and the Alpha, Beta, and Gamma variants, but neutralization of the Delta variant requires higher anti-spike IgG titers. BAU = binding antibody units; COVID-19 = coronavirus disease 2019; IgG = immunoglobulin G; mRNA = messenger ribonucleic acid; RBD = receptor-binding domain. 1. Hall VG et al. *N Engl J Med.* 2021;385(13):1244-1246; 2. Caillard S et al. *Ann Intern Med.* 2022;175(3):455-456.

The Humoral Response Among Immunocompromised Vaccine Responders Elicited by Booster Doses Quickly Declines^{1,2}

After the third dose, SOT patients showed an immune response^{1,a-c}



Seropositive^d kidney transplant recipients showed a decline over time²



63.8%
Median decrease
in IgG titers within
SOT responders
after the **third**
dose (n=33,
Month 1 vs. 6)

^aThe group included 78 kidney-transplant recipients, 12 liver-transplant recipients, 8 lung-transplant or heart-transplant recipients, and 3 pancreas-transplant recipients; ^bThe first two doses were given 1 month apart, and the third dose was administered 61±1 days after the second dose; ^cPatients received BNT162b2; ^dHad immune response 1 month after the third dose. BAU = binding antibody units; IgG = immunoglobulin G; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SOT = solid organ transplant.

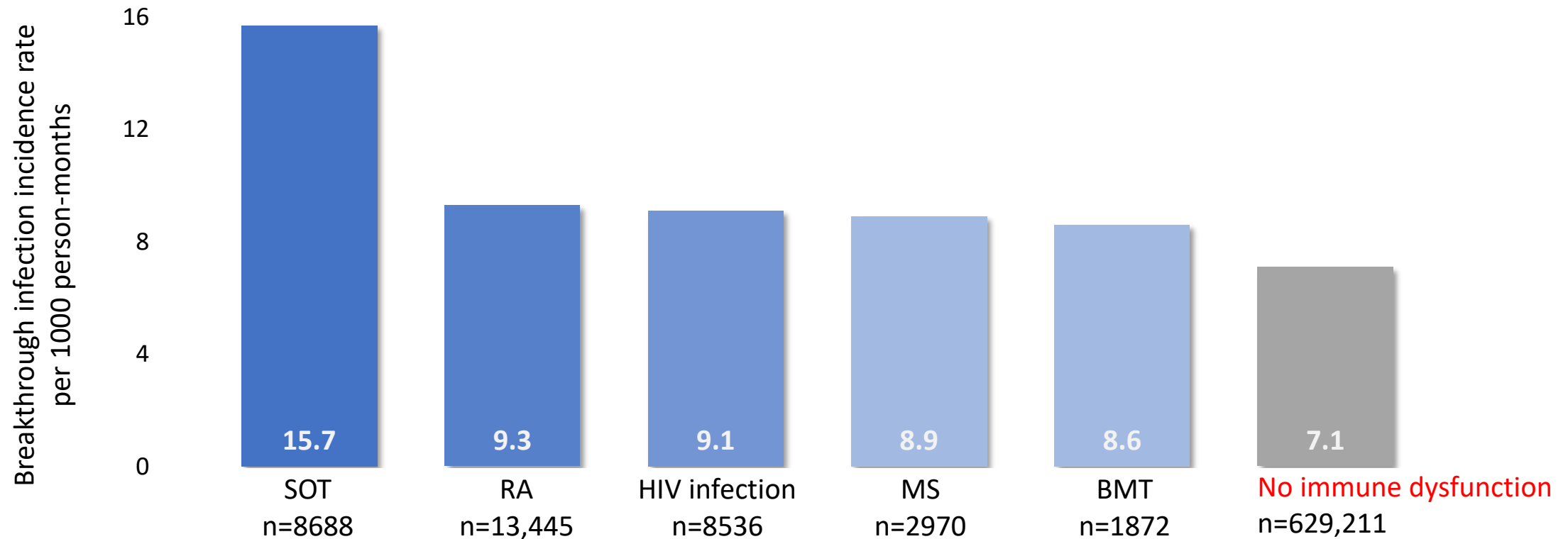
1. Kamar N et al. *N Engl J Med.* 2021;385(7):661-662; 2. Bertrand D et al. Letter. *Am J Transplant.* 2022;22(5):1498-1500.

Outline

- A brief introduction of immunization
- The effects of vaccination in immunocompromised(IC) patients
- **The clinical outcome of IC patients with confirmed COVID-19 infection**
- Current prevention strategies and guideline for COVID-19 in Taiwan

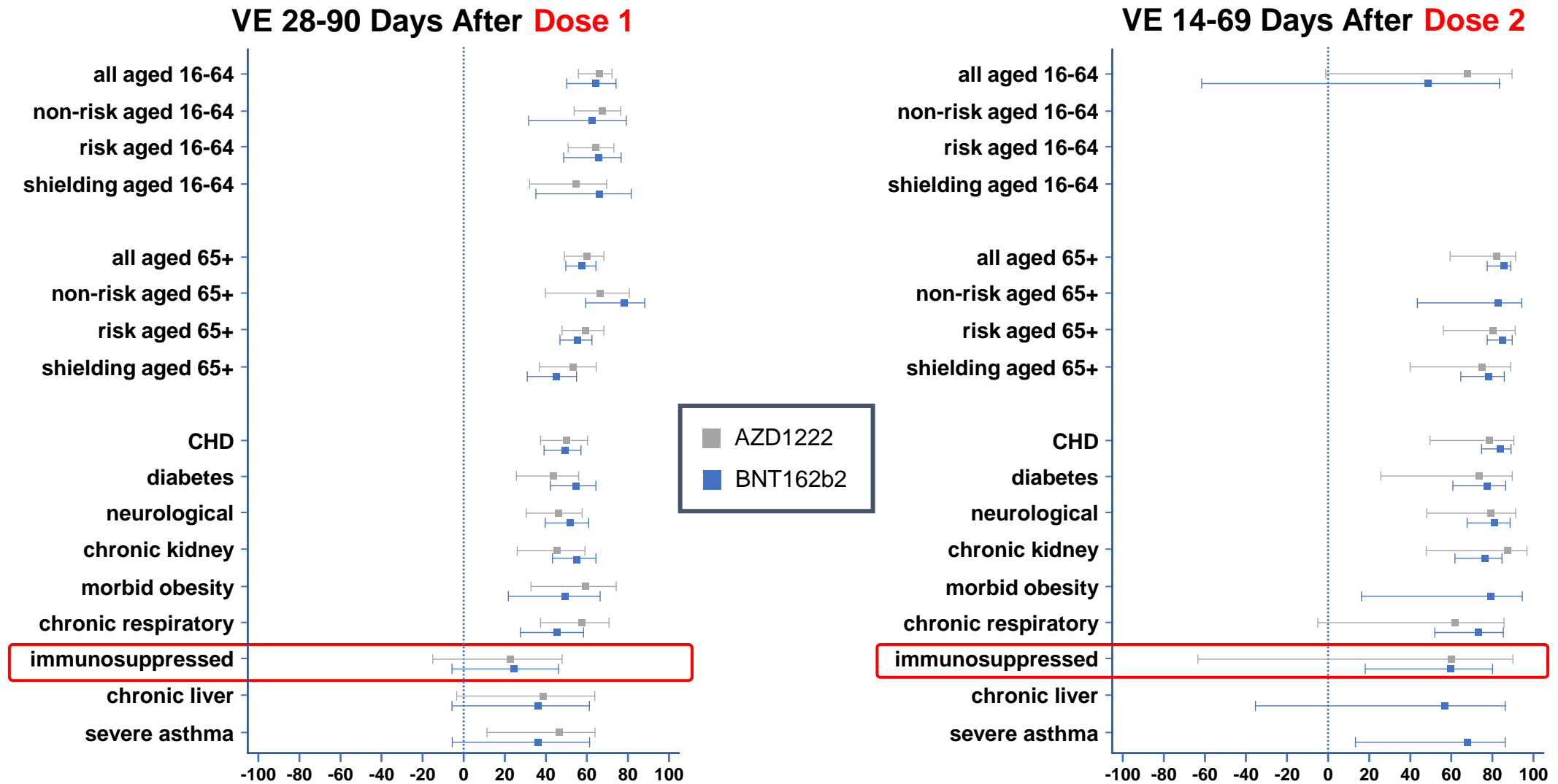
Immunocompromised Patients Are at an Increased Risk of COVID-19 Breakthrough Infections

Breakthrough infections were more common in vaccinated patients with immune dysfunction than in those without immune dysfunction^a



^aA retrospective analysis of 664,722 patients from the National COVID Cohort Collaborative who received at least 1 dose of a vaccine between December 10, 2020, and September 16, 2021. BMT = bone marrow transplantation; COVID-19 = coronavirus disease 2019; HIV = human immunodeficiency virus; MS = multiple sclerosis; RA = rheumatoid arthritis; SOT = solid organ transplant. Sun J et al. *JAMA Intern Med.* 2022;182(2):153-162.

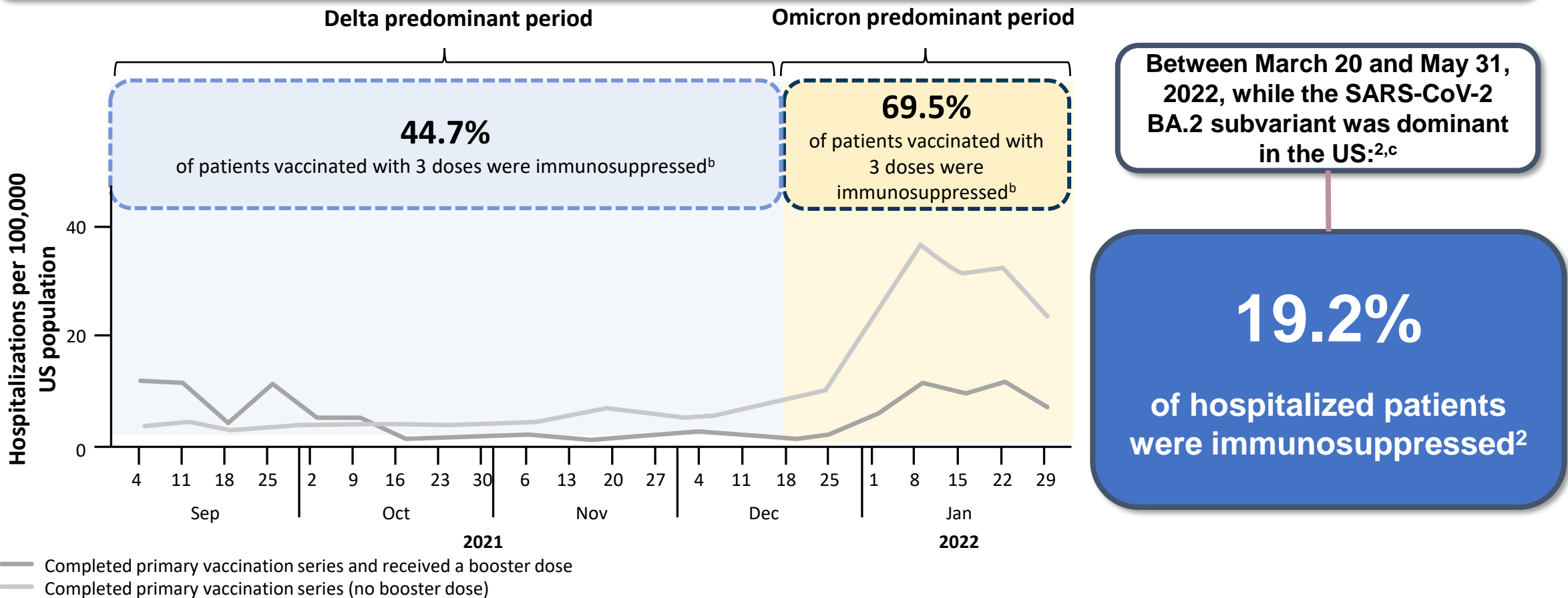
Reduced Vaccine Effectiveness Is Seen in Immunosuppressed Individuals After 1 and 2 COVID-19 Vaccine Doses^{a,b}



^aData collected by the Oxford- Royal College of General Practitioners Research and Surveillance Centre between December 7, 2021, and May 16, 2022 (N=7,480,272; immunosuppressed group, n=987); ^bVaccine effectiveness was against acute, symptomatic COVID-19 confirmed by a positive PCR test. CHD = chronic heart disease and vascular disease; COVID-19 = coronavirus disease 2019. PCR = polymerase chain reaction; VE = vaccine effectiveness.
Whitaker HJ et al. *J Infect.* 2022;84(5):675-683.

Immunocompromised Individuals Continue to Remain Vulnerable Throughout Surges of VOCs^{1,2}

During the Delta and Omicron Surges, **Hospitalized Patients** Were Disproportionately Immunocompromised^{1,a}



^aData from the US COVID-19–Associated Hospitalization Surveillance Network (COVID-NET) were analyzed to compare COVID-19–associated hospitalization rates among adults aged ≥18 years;

^bIncludes current treatment of recent diagnosis of an immunosuppressive condition or use of an immunosuppressive therapy during the preceding 12 months; ^cAmong hospitalized patients, 27.8% were unvaccinated during this period. SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; US = United States; VOCs = variants of concern.

1. Taylor CA et al. *MMWR Morb Mortal Wkly Rep.* 2022;71(12):466-473; 2. Havers FP et al. *MMWR Morb Mortal Wkly Rep.* 2022;71(34):1085-1091.

Among Adults **Hospitalized** for COVID-19, Immunocompromised Patients Are at Higher Risk of **Severe Outcomes** Than Immunocompetent Patients

Once hospitalized for COVID-19, immunocompromised patients had **higher risk of ICU admission and death** than immunocompetent patients – and this did not differ by vaccination status^a



Among **vaccinated** patients, immunocompromised individuals were at:

1.40x

Higher risk of
ICU
admission

(95% CI, 1.01-1.92; p<0.05)

1.87x

Higher risk of
in-hospital
death

(95% CI, 1.28-2.75; p<0.01)



Among **unvaccinated** patients, immunocompromised individuals were at:

1.26x

Higher risk of
ICU
admission

(95% CI, 1.08-1.49; p<0.01)

1.34x

Higher risk of
in-hospital
death

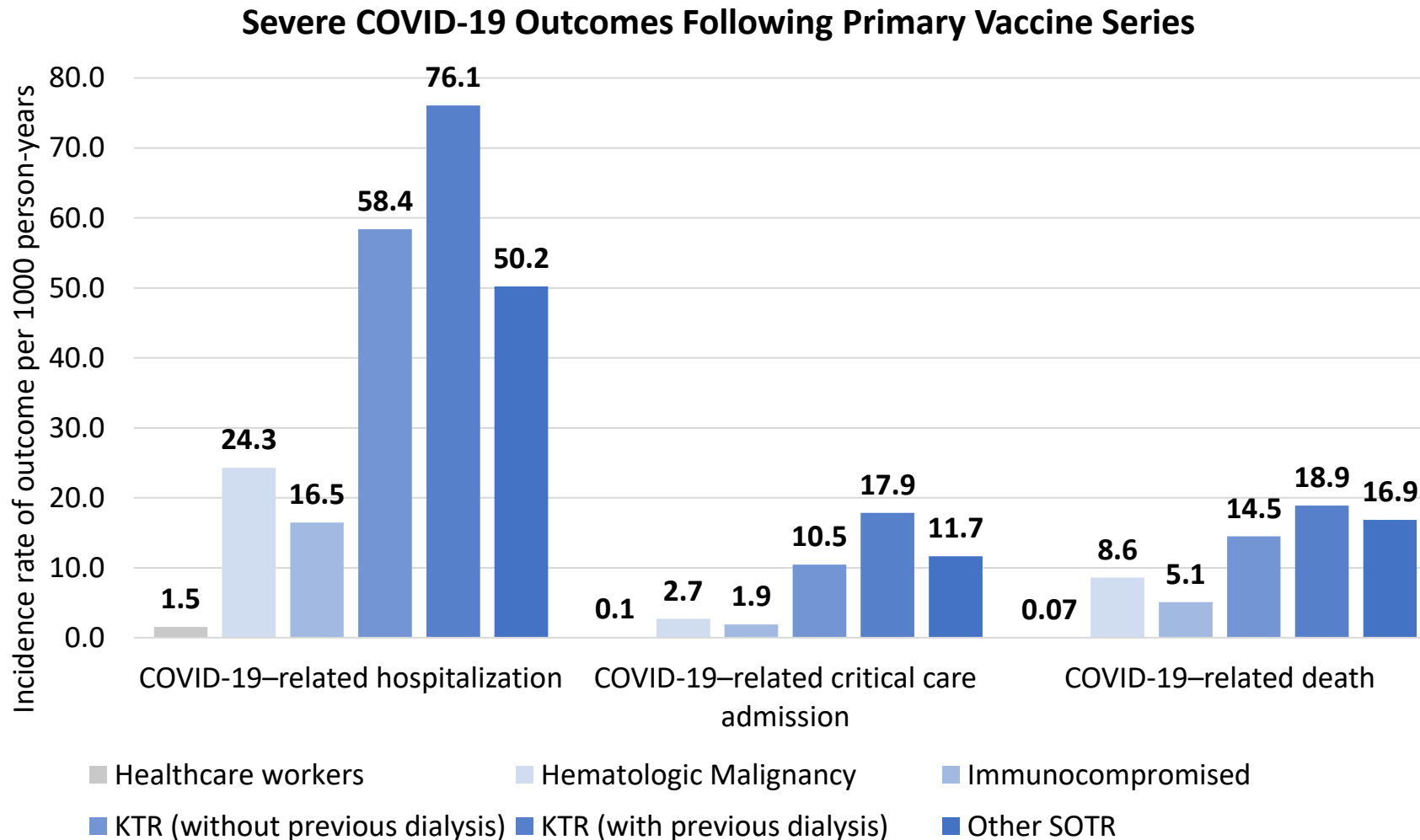
(95% CI, 1.05-1.70; p<0.05)

^aData on adults hospitalized with COVID-19 from 10 US states in the COVID-19-Associated Hospitalization Surveillance Network were analyzed to assess ICU admission and in-hospital death from March 1, 2020, to February 28, 2022.

CI = confidence interval; COVID-19 = coronavirus disease 2019; ICU = intensive care unit; US = United States.

Singson JRC et al. *MMWR Morb Mortal Wkly Rep.* 2022;71(27):878-884.

Immunocompromised Patients **in the UK** Have Higher Rates of **Severe** COVID-19 Outcomes After Vaccination (vs. Healthcare Workers)

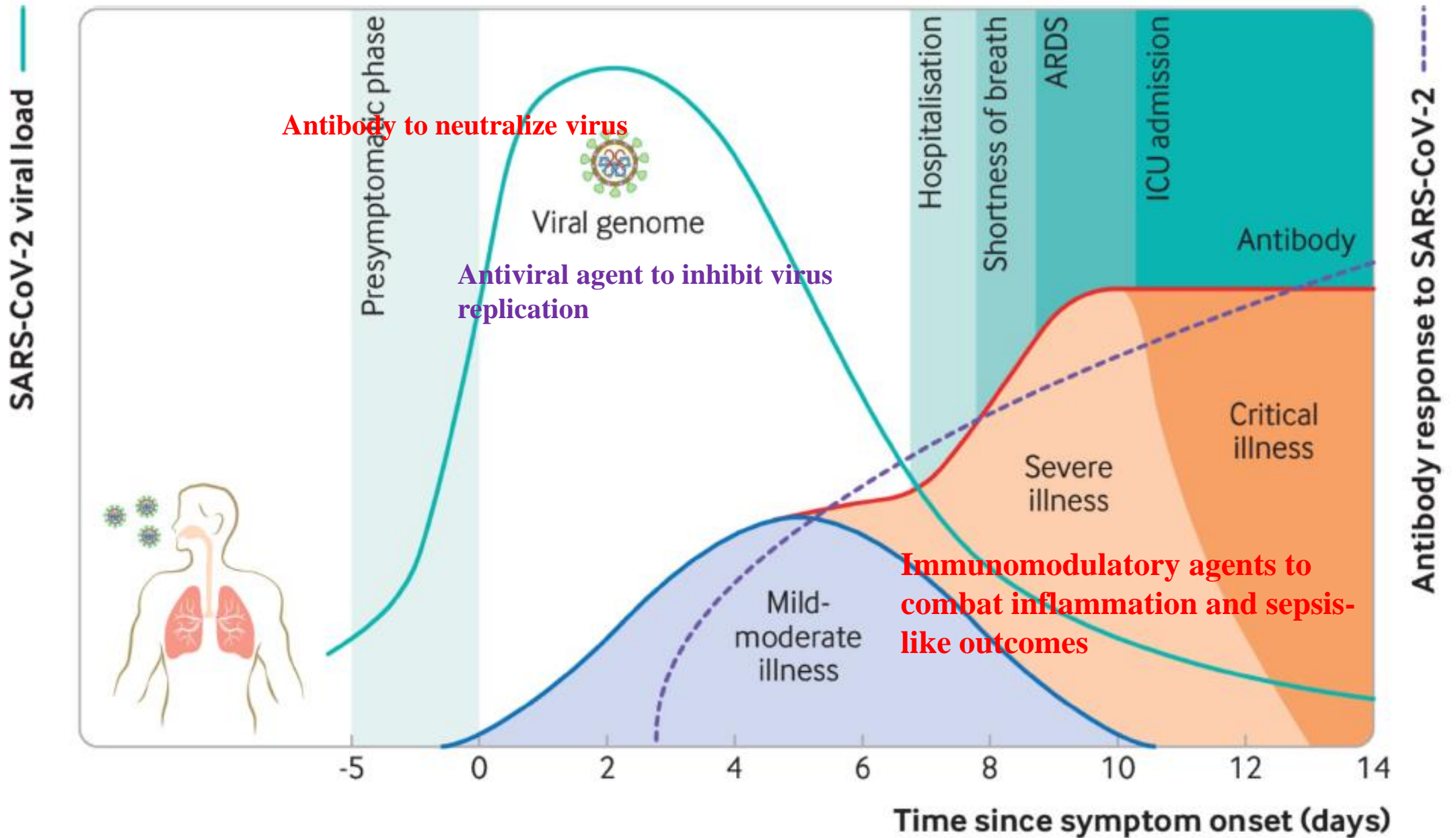


In an analysis of 15,501,550 **fully vaccinated individuals** in the UK between December 2020 and November 2021, immunocompromised patients had higher rates of COVID-19-related **hospitalization, critical care admission, and death** than healthcare workers^a

^aVaccines administered were the BNT162b2, mRNA-1273, and ChAdOx1 nCoV-19 vaccines.
COVID-19 = coronavirus disease 2019; KTR = kidney transplant recipients; SOTR = solid organ transplant recipients; UK = United Kingdom.
OpenSAFELY Collaborative et al. *BMC Med.* 2022;20(1):243.

Outline

- A brief introduction of immunization
- The effects of vaccination in immunocompromised(IC) patients
- The clinical outcome of IC patients with confirmed COVID-19 infection
- **Current prevention strategies and guideline for COVID-19 in Taiwan**



(Cevik M et al BMJ 2020;371:m3862)

新型冠狀病毒SARS-CoV-2 感染臨床處置指引第二十一版

針對 SARS-CoV-2 之預防性藥物

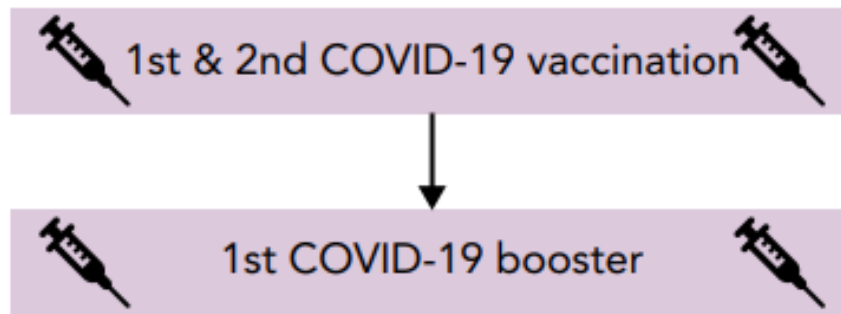
- Tixagevimab + Cilgavimab (Evusheld)用於暴露前預防 SARS-CoV-2 感染

針對 SARS-CoV-2 之抗病毒與其他治療

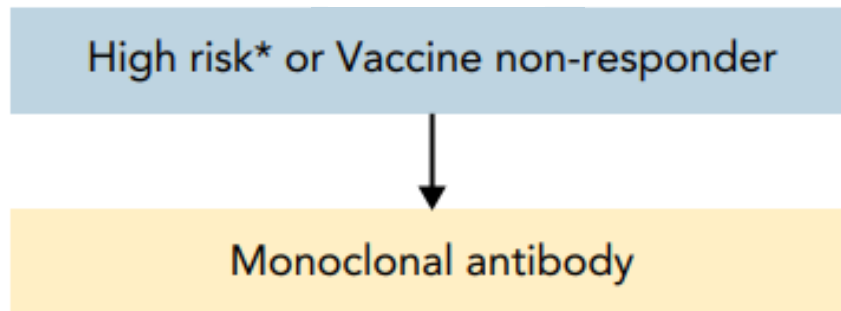
	不需用氧且具重症風險因子者	需吸氧治療	高流量氧或非侵襲性呼吸器	插管
可降低死亡率 建議使用	下列藥物任一# Nirmatrelvir + ritonavir ; Remdesivir ; Tixagevimab + cilgavimab* ; molnupiravir	Dexamethasone		
		Baricitinib 或/及 tocilizumab		
		Remdesivir		

COVID-19 prevention strategy

Active
immunization



Passive
immunization



第二次追加劑開放對象

- ◆ 50歲以上成人
- ◆ 18歲以上因外交、公務、洽商等工作需求需出國民衆
- ◆ 18歲以上免疫不全及免疫力低下且病情穩定者，包括：
 - 目前正進行或1年內曾接受免疫抑制治療之癌症患者
 - 器官移植患者/幹細胞移植患者
 - 中度/嚴重先天性免疫不全患者
 - 洗腎患者
 - 長照機構住民
 - HIV陽性患者
 - 目前正使用高度免疫抑制藥物者
 - 過去6個月內接受化學治療或放射線治療者
 - 其他經醫師評估因免疫不全或免疫力低下，可接種基礎加強劑者

* High risk population

- Receipt of solid organ transplant or hematopoietic stem cell transplant within 1 year
- Solid organ transplant or hematopoietic stem cell transplant recipients who had acute rejection
- Receipt of chimeric antigen receptor (CAR)-T-cell or B-cell depletion therapy within 1 year
- Severe primary immunodeficiency disease

The challenge of monoclonal antibody in treatment

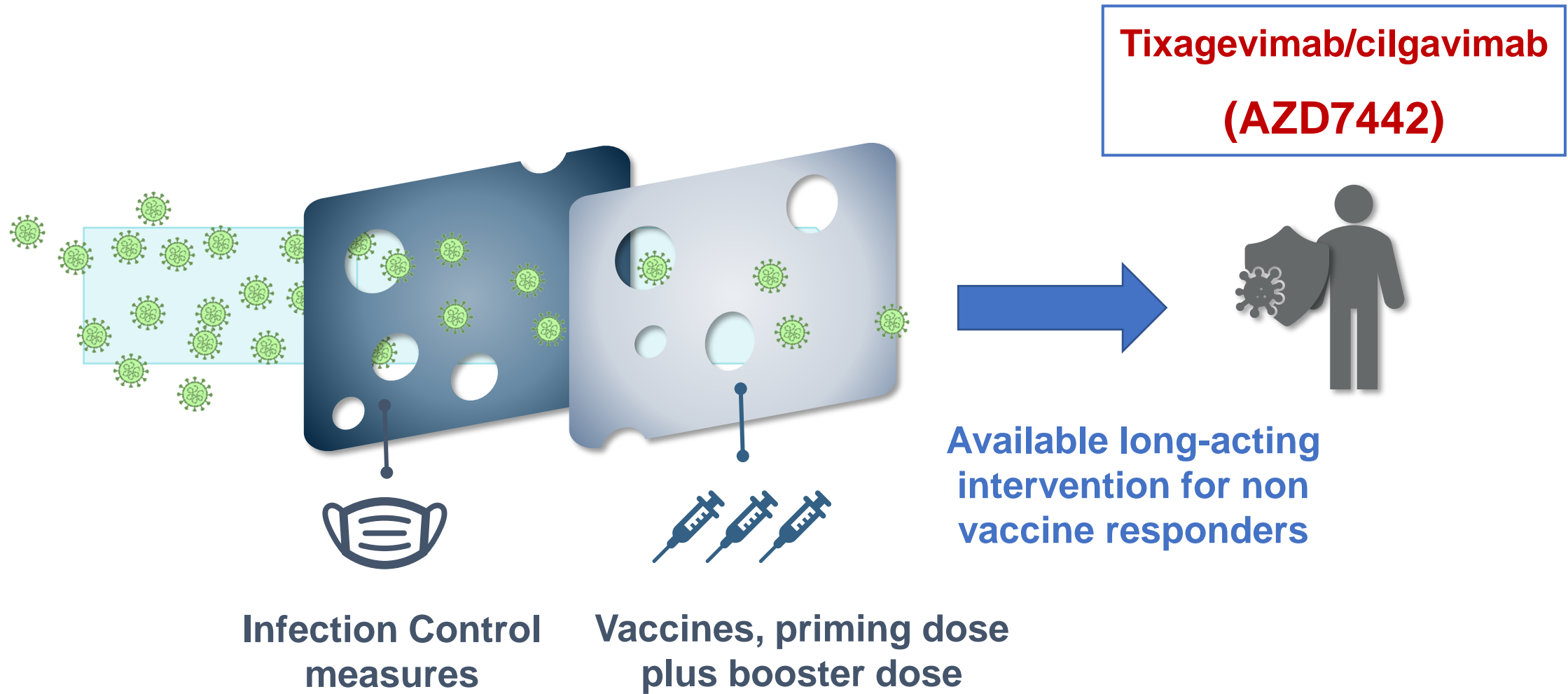
Omicron sub-lineage		我國現有單株抗體			尚未引進				
		Casirivimab + Imdevimab	Bamlanivimab+ Etesevimab	Tixagevimab + cilgavimab	Regdanvimab	Sotrovimab	Bamlanivimab	Etesevimab	Bebtelovimab
目前流行株	BA.1	X	X	O	X	O	X	X	O
	BA.1.1	X	X	O	X	O	X	X	O
	BA.2	X	X	O	X	X	X	X	O
	BA.2.12.1	X	X	O	X	X	X	X	O
	BA.2.75	X	X	O	X	X	X	X	O
	BA.3	X	X	O	NA	X	NA	NA	NA
	BA.4	X	X	O	X	X	X	X	O
	BA.4.6	X	X	X	NA	O	X	X	O
	BA.5	X	X	O	X	X	X	X	O
	BQ.1	NA	NA	X	NA	NA	NA	NA	X
	BQ.1.1	NA	NA	X	NA	NA	NA	NA	X
	BF.7	NA	NA	X	NA	NA	NA	NA	NA
	XBB	X	NA	X	NA	NA	NA	NA	X

註1：O 有效；X 無效(unlikely to be active, >100 fold reduction in susceptibility of authentic or pseudovirus test)；NA表無資料。

註2：根據體外試驗與藥物動力學模擬，建議Omicron變異株流行期間，Tixagevimab + cilgavimab用於暴露前預防時加倍劑量(300 → 600mg)。

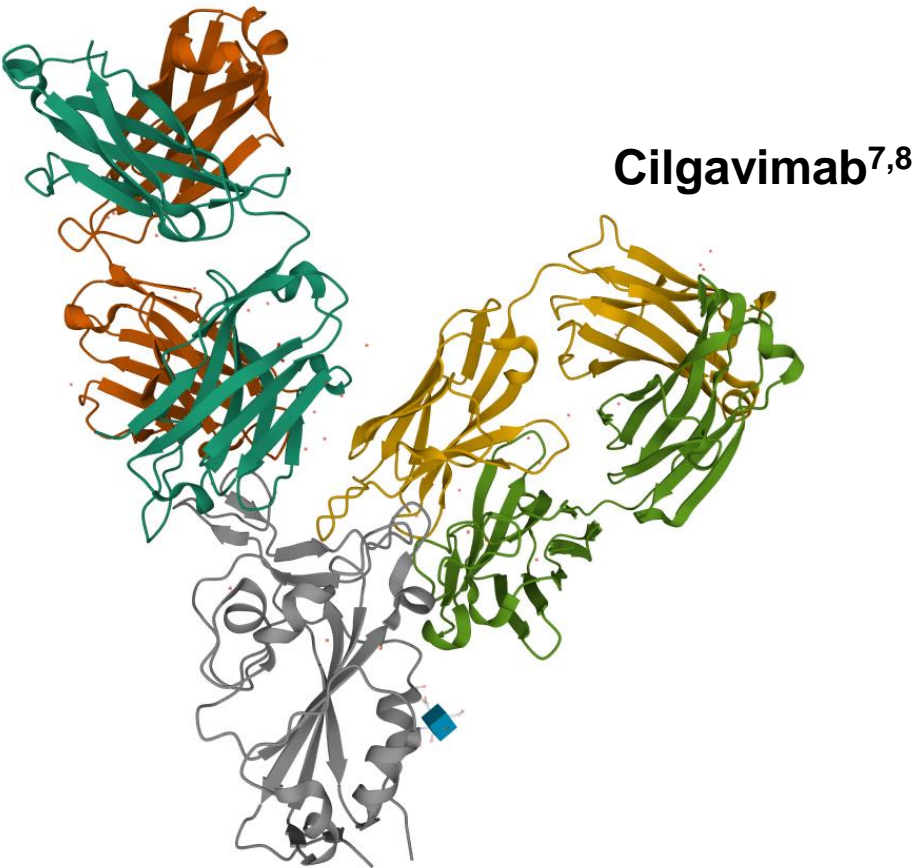
註3：灰底表示非美國FDA公布資料。

A Multilayered Approach in Immunocompromised Patients



Tixagevimab/Cilgavimab is a combination of 2 human long acting monoclonal antibodies¹

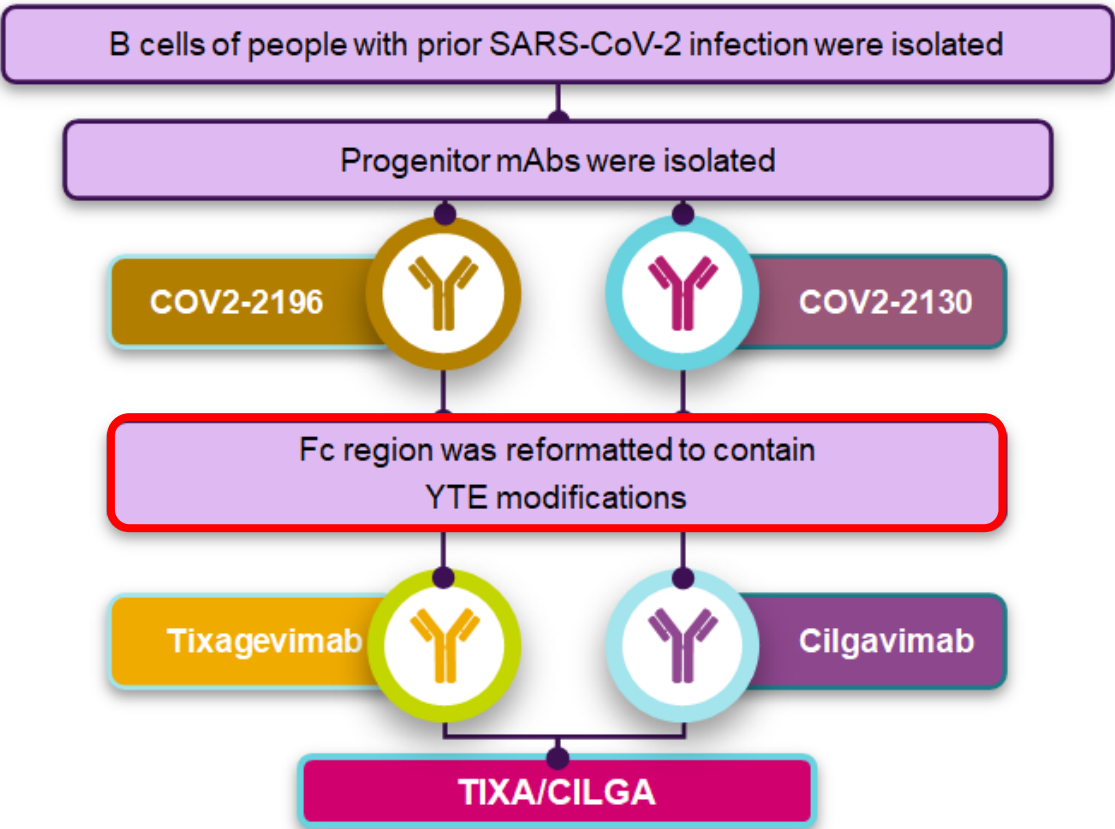
Tixagevimab^{7,8}



Cilgavimab^{7,8}

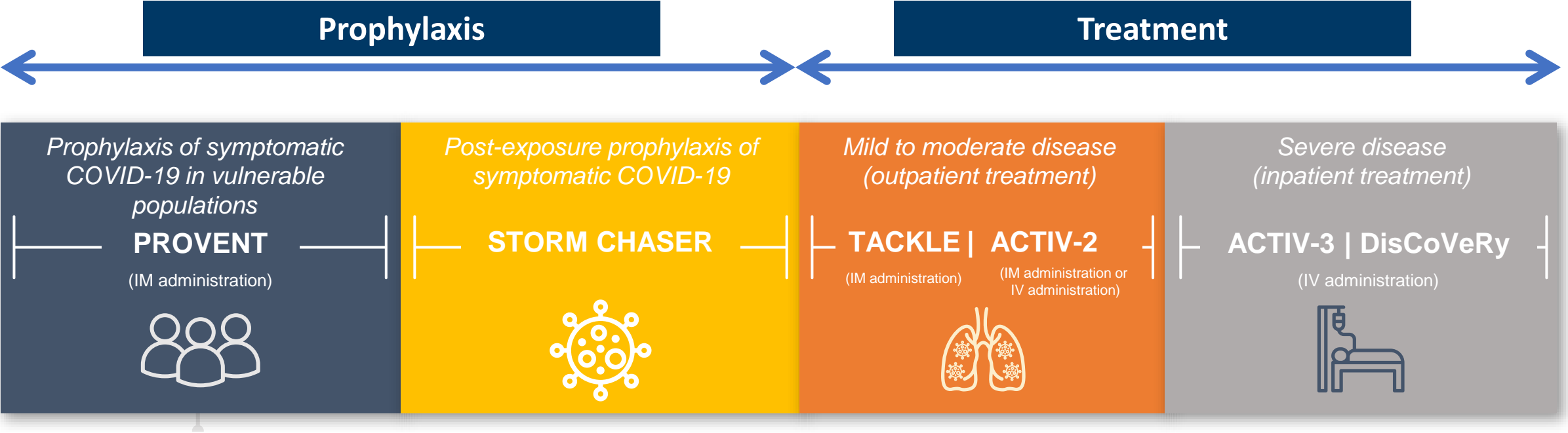
SARS-CoV-2 Spike RBD^{7,8}

TIXA/CILGA Discovery Workflow²⁻⁶



Some of the information provided is based off a preprint research paper that has not been peer reviewed.
Fc = fragment crystallizable region; LAAB = long-acting antibody; mAb = monoclonal antibody; RBD = receptor-binding domain; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; TIXA/CILGA = tixagevimab/cilgavimab; YTE = M253Y/S254T/T256E.
1. Fact sheet for healthcare providers. Emergency Use Authorization (EUA) of EVUSHELD™ (tixagevimab co-packaged with cilgavimab). 2021; 2. Zost SJ et al. Nature. 2020;584:443-449; 3. Zost SJ et al. Nat Med. 2020;26:1422-1427; 4. Kaplon H et al. MAb. 2021;13:1860476. <https://dx.doi.org/10.1080/19420862.2020.1860476>. Accessed September 24, 2021; 5. Robbie GJ et al. Antimicrob Agents Chemother. 2013;57:6147-6153; 6. Loo YM et al. Preprint published online. medRxiv. 2021; 7. Sehna D et al. Nucleic Acids Res. 2021;49:W431-W437; 8. Protein Data Bank. <https://www.rcsb.org/>. 7L7E. Accessed November 10, 2021

Pre-exposure Prophylaxis and Treatment Strategies for Tixa/Cilga



ORIGINAL ARTICLE

Intramuscular AZD7442 (Tixagevimab–Cilgavimab) for Prevention of Covid-19

M.J. Levin, A. Ustianowski, S. De Wit, O. Launay, M. Avila, A. Templeton, Y. Yuan, S. Seegobin, A. Ellery, D.J. Levinson, P. Ambery, R.H. Arends, R. Beavon, K. Dey, P. Garbes, E.J. Kelly, G.C.K.W. Koh, K.A. Near, K.W. Padilla, K. Psachoulia, A. Sharbaugh, K. Streicher, M.N. Pangalos, and M.T. Esser, for the PROVENT Study Group*

NEJM, 2022 April

Efficacy and safety of intramuscular administration of tixagevimab–cilgavimab for early outpatient treatment of COVID-19 (TACKLE): a phase 3, randomised, double-blind, placebo-controlled trial

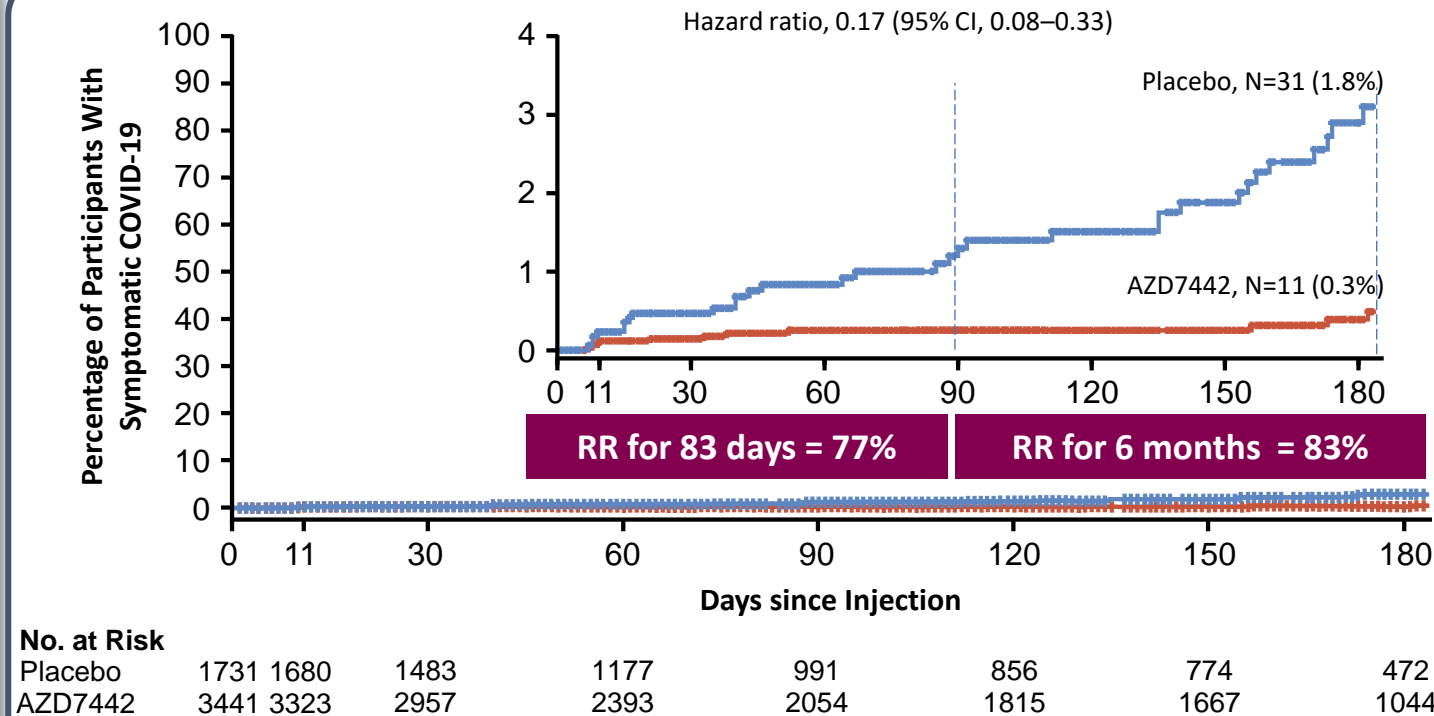
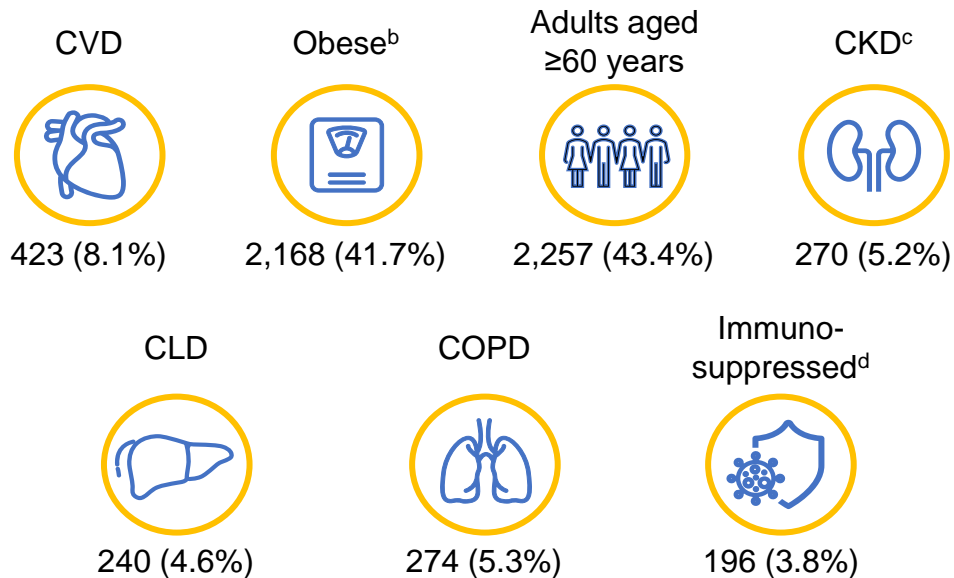
Hugh Montgomery, FD Richard Hobbs, Francisco Padilla, Douglas Arbetter, Alison Templeton, Seth Seegobin, Kenneth Kim, Jesus Abraham Simón Campos, Rosalinda H Arends, Bryan H Brodek, Dennis Brooks, Pedro Garbes, Julieta Jimenez, Gavin C K W Koh, Kelly W Padilla, Katie Streicher, Rolando M Viani, Vijay Alagappan, Menelas N Pangalos, Mark T Esser, on behalf of the TACKLE study group



Phase III (PROVENT): AZD7442 significantly reduced 83% COVID-19 infection risk and no severe COVID-19 or death case during 6 month follow up period^{1,2}

Subjects with inadequate response to COVID-19 vaccination

Time to first SARS-CoV-2 RT-PCR-positive symptomatic illness, median 6-month data cut



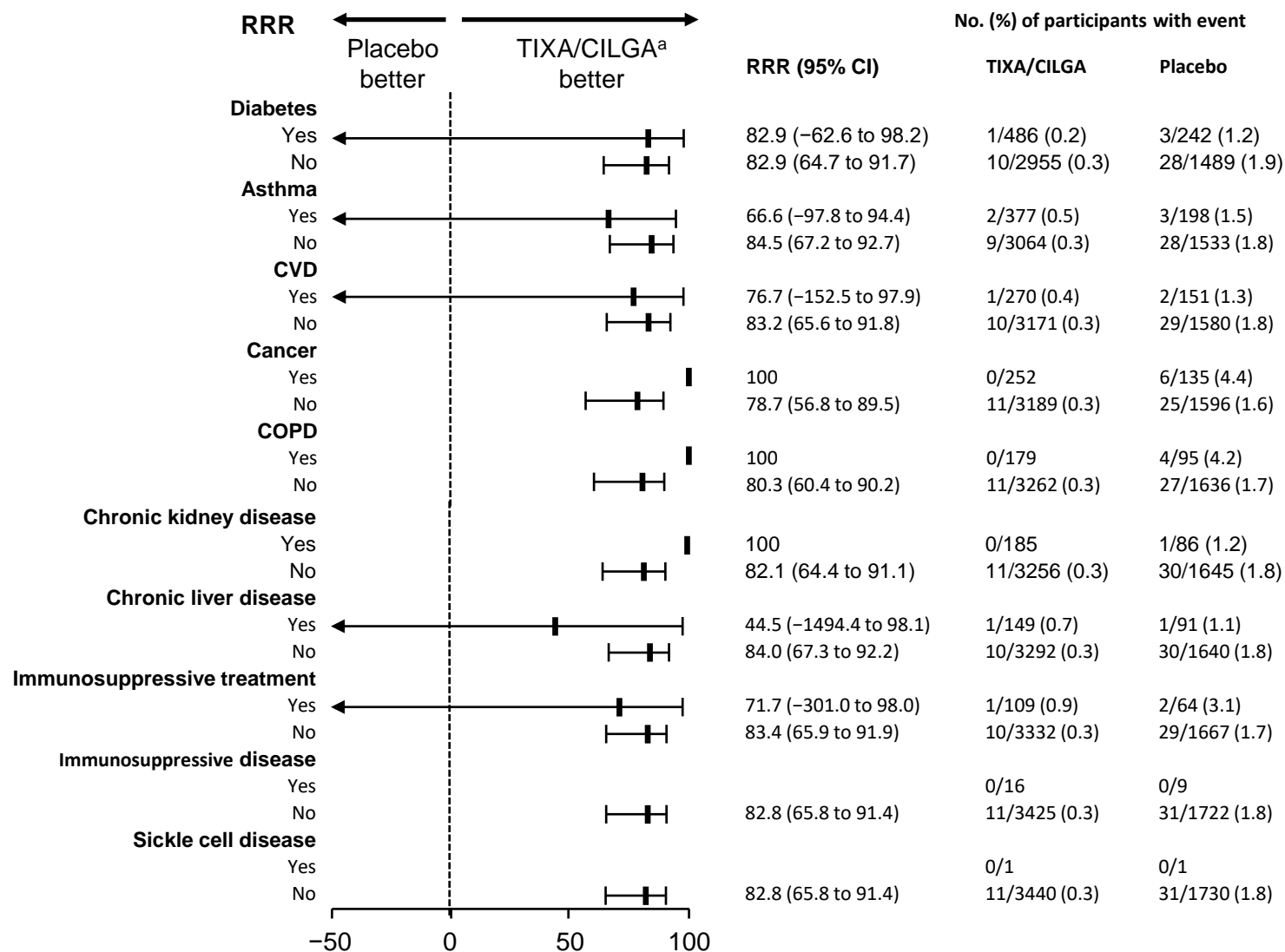
^aBody mass index ≥30 kg/m²; ^bCaused by underlying/chronic disease or treatments.²

CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; COVID-19 = coronavirus disease 2019; CVD = cardiovascular disease.; RR = Risk reduction.

1. Study NCT04625725. ClinicalTrials.gov website; 2. Levin MJ et al. Online ahead of print. *N Engl J Med*. 2022.

Phase III PROVENT study: Subgroup analysis for efficacy of AZD7442

Efficacy of TIXA/CILGA was consistent across participant subgroups where evaluable



TIXA/CILGA has a favorable AE profile

- AEs were balanced between the TIXA/CILGA and placebo groups
- Most AEs were of mild or moderate severity
- There were two COVID-19–related deaths in the placebo group^a
- No COVID-19–related deaths occurred in the TIXA/CILGA group^a

No. (%) of participants with:	TIXA/CILGA (n=3461)	Placebo (n=1736)	No. (%) of:	TIXA/CILGA (n=3461)	Placebo (n=1736)
≥1 AE	1221 (35.3)	593 (34.2)	Participants with mild AEs	761 (22.0)	369 (21.3)
≥1 SAE	50 (1.4)	23 (1.3)	Participants with moderate AEs	387 (11.2)	191 (11.0)
≥1 Treatment-related SAE	1 (<0.1) ^b	0	Participants with severe AEs	64 (1.8)	27 (1.6)
≥1 AE leading to study withdrawal	1 (<0.1) ^c	0	Deaths ^d	4 (0.1)	4 (0.2)
≥1 AESI	93 (2.7)	37 (2.1)	Myocardial infarction	1 (<0.1)	0
Injection site reaction	82 (2.4)	36 (2.1)	Illicit drug overdose	2 (0.1)	2 (0.1)
Anaphylaxis	1 (<0.1)	0	Renal failure	1 (<0.1)	0
Immune complex disease	1 (<0.1)	0	COVID-19/ARDS^a	0	2 (0.1)
Other	9 (0.3)	2 (0.1)			

Safety Analysis Set (all participants who have received at least one dose of study drug; one participant was randomized to placebo and incorrectly received AZD7442). ^aCOVID-19–related deaths were adjudicated by Morbidity Adjudication Committee and concurred with investigator assessment. ^bMesenteric artery thrombosis. ^cParticipant who died of end-stage renal disease; the investigator characterized the death as the AE leading to study discontinuation: this is not consistent with usual practice. ^dAll deaths were assessed by the investigator to be unrelated to study treatment.

AESI, AE of special interest; ARDS, acute respiratory distress syndrome; SAE, serious AE.

Myron J Levin et al. N Engl J Med. 2022 Apr 20. doi: 10.1056/NEJMoa2116620

Tixa/Cilga Reduced COVID-19 related Composite Outcome in Immunocompromised or High-risk Population during Omicron Outbreak

Study period

2022/02 to 2022/05

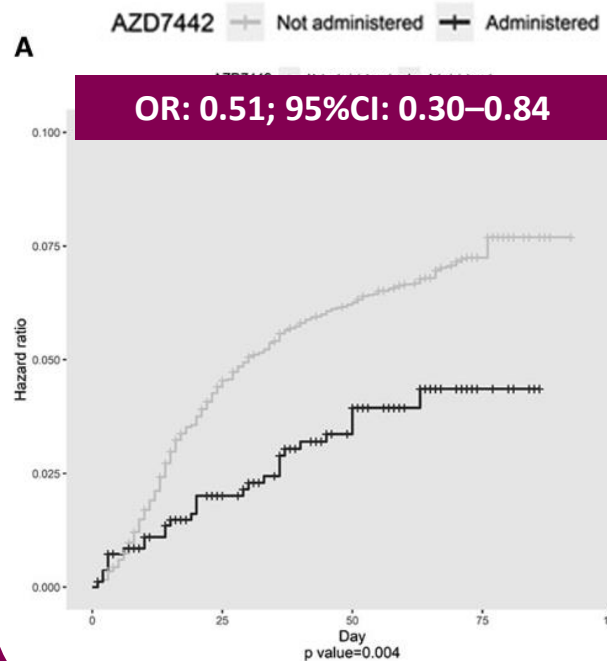
Predominantly BA.1 between 2022.2-2022.3 (BA.1), with the BA.2 variant becoming the most prevalent from Apr 2022

Medication

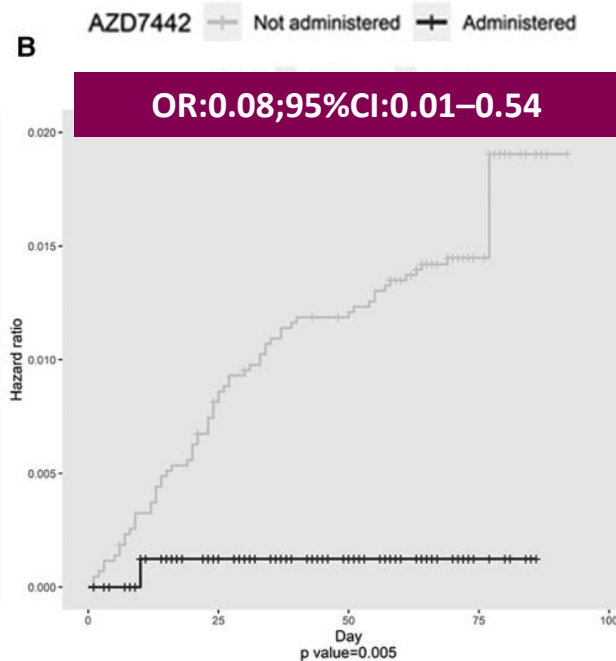
Tixa/Cilga

300 mg (150+150)

COVID-19 infection



COVID-19 Hospitalization or Death



Infection rate in IC population

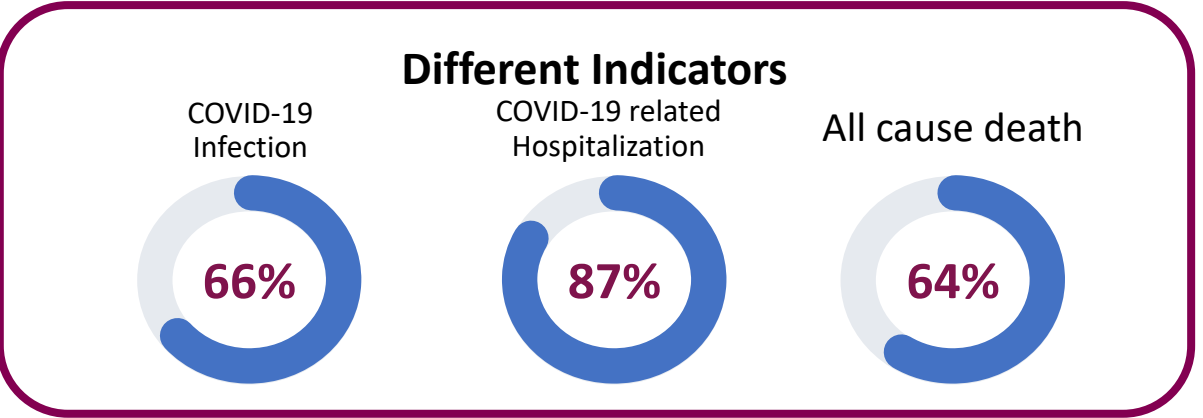
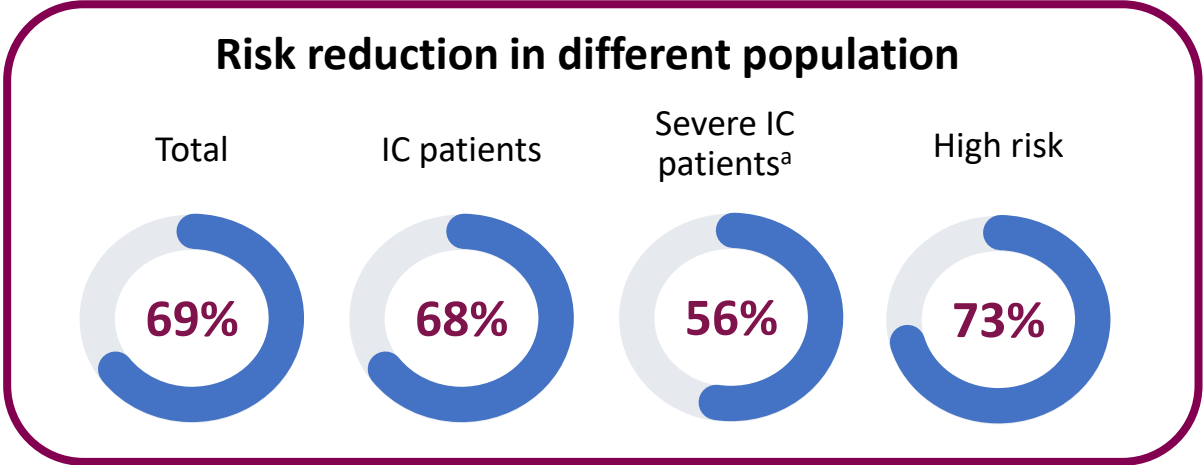
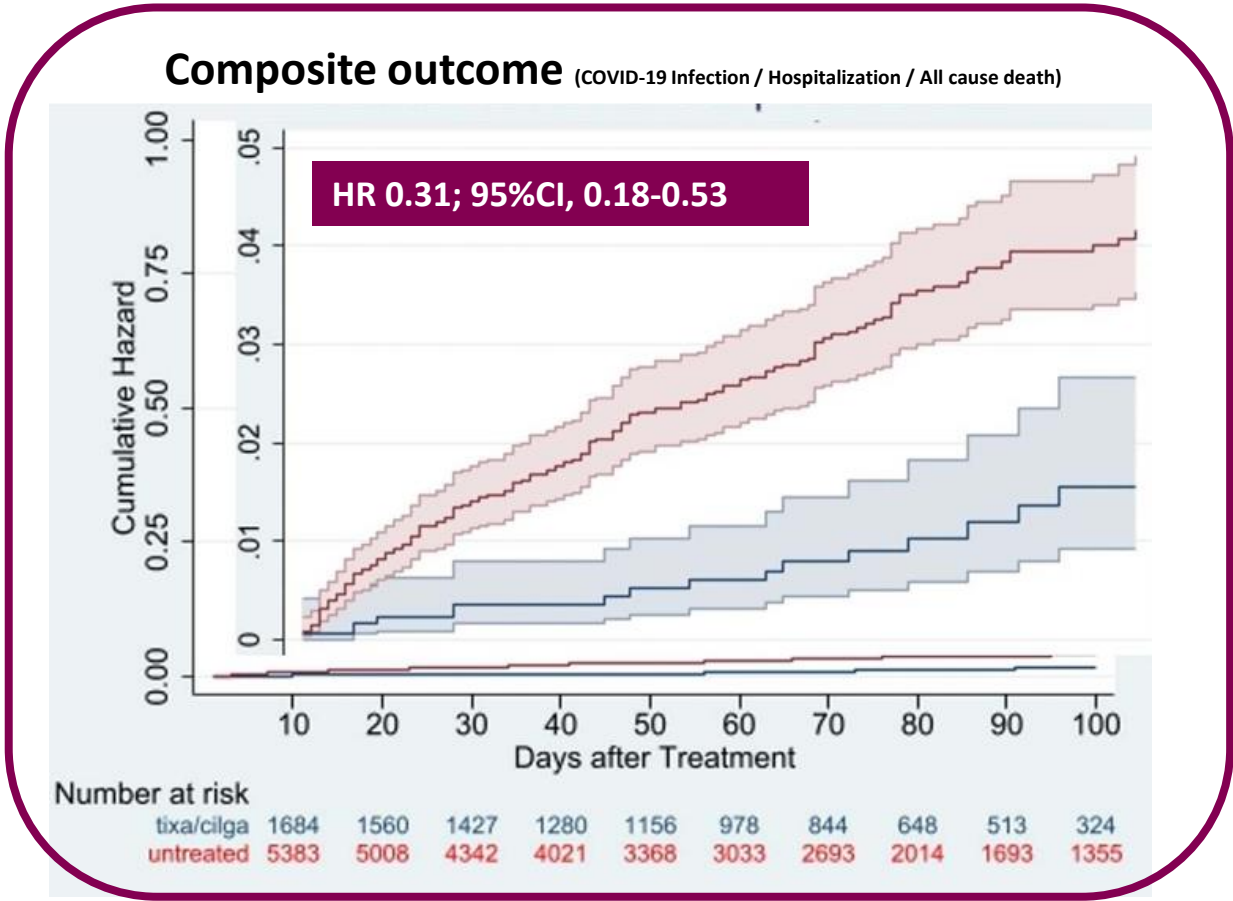
Sub-group	Administration vs. Not administration
Anti-CD20 Rx in last 6 months*	65 (9.2%) vs. 913 (23%)
Solid-organ transplant*	116 (9.5%) vs. 1574 (20.5%)
Lymphoma	132 (6.8%) vs. 1892 (10.3%)
Multiple myeloma	32 (12.5%) vs. 647 (20.9%)
All other	17 (11.8%) vs. 252 (30.2%)

*p<0.05

<US real world evidence>

Tixa/Cilga Reduced COVID-19 related Composite Outcome in Immunocompromised or High-risk Population during Omicron Outbreak

Study period	2022/01 to 2022/04	Predominantly BA.1
Medication	Tixa/Cilga	300 mg (150+150)

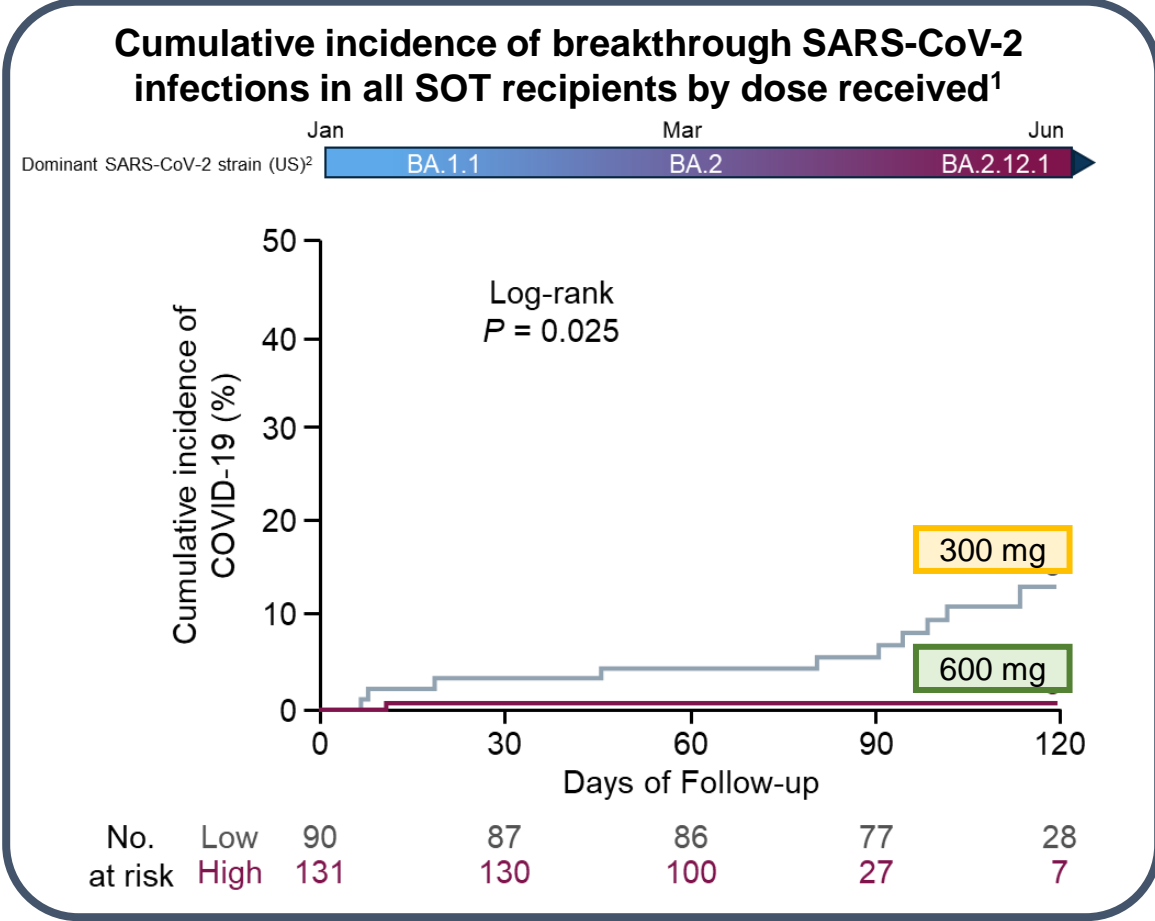
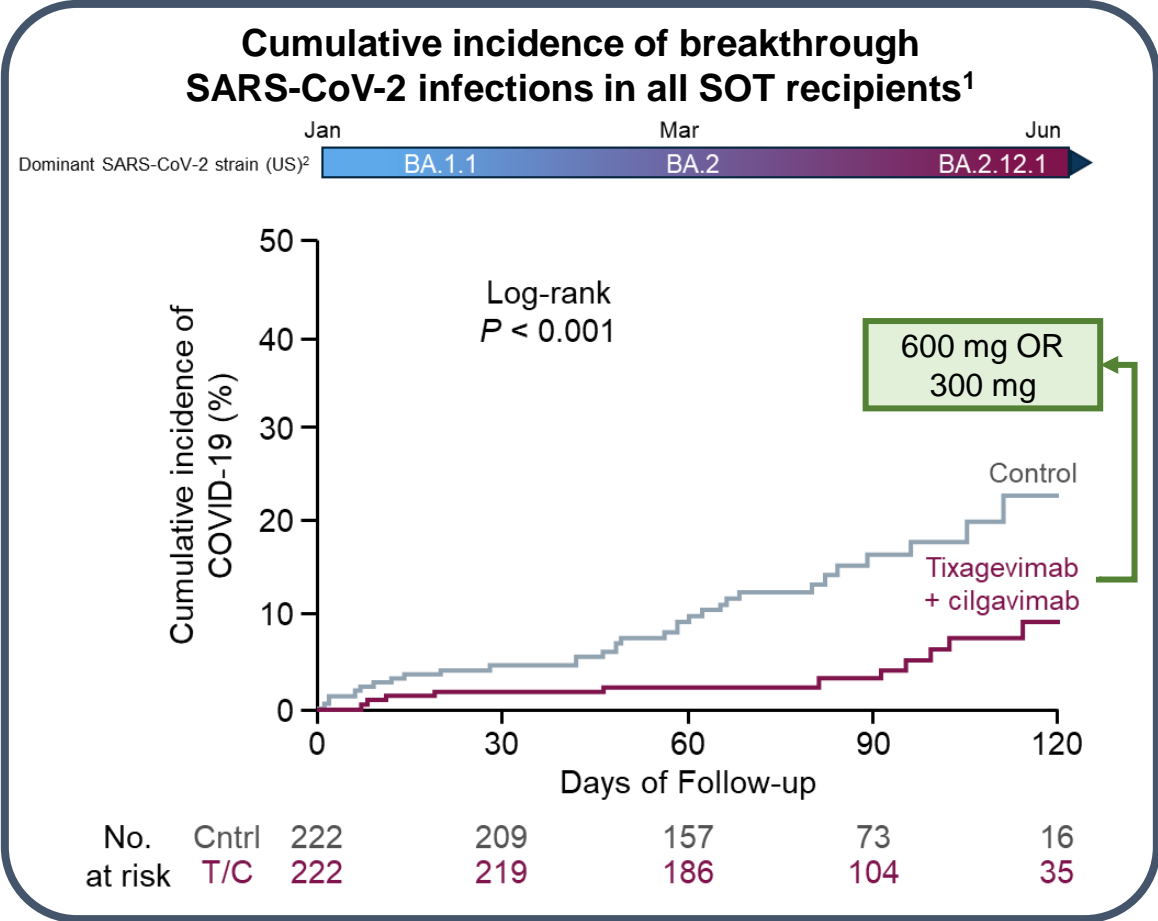


FDA Authorizes Revisions to TIXA/CILGA Dosing



FDA: Escalate the dose from 300mg to 600mg according to Pharmacokinetic modeling and current variant neutralizing ability

RWE: PrEP With Tixa/Cilga 300 mg or 600 mg IM was Associated With Significantly Lower Risk of Breakthrough SARS-CoV-2 Infections in SOT Recipients



During the omicron wave, SOT recipients who received Tixa/Cilga 600 mg had fewer breakthrough cases compared to those who received Tixa/Cilga 300 mg¹

PrEP = pre-exposure prophylaxis; RWE = real-world effectiveness; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SOT = solid organ transplant; US = United States; VOCs = variants of concern.
1. Al Jurdi A et al. Online ahead of print. *Am J Transplant*. 2022;10.1111/ajt.17128; 2. Hodcroft EB. Overview of variants in countries. <https://covariants.org/per-country>. Accessed July 12, 2022.


44

NIH Guideline Recommendation for Pre-exposure Prophylaxis

- Aged ≥ 12 years and weighing ≥ 40 kg
- Without SARS-CoV-2 infection,
- Without recently exposed to an individual with SARS-CoV-2 infection

PLUS

- Moderately to severely immunocompromised

- 
1. Active treatment for solid tumors and hematologic malignancies,
 2. Received a SOT and are receiving immunosuppressive therapy,
 3. CAR-T cell therapy or HSCT (< 2 years of transplantation or receiving immunosuppression therapy),
 4. Have a moderate or severe PID (e.g., DiGeorge syndrome...),
 5. Have advanced or untreated HIV infection,
 6. Immunosuppression therapy% (e.g., B cell depleting agents)

SOT: solid organ transplantation, CAR-T: Chimeric antigen receptor T-cell therapy, HSCT: Haematopoietic Stem Cell Transplant, PID: Primary immunodeficiency %Active treatment with high-dose corticosteroids, alkylating agents, antimetabolites, transplant-related immunosuppressive drugs, cancer chemotherapeutic agents classified as severely immunosuppressive, tumor-necrosis blockers, or other immunosuppressive or immunomodulatory biologic agents (e.g., B cell-depleting agents)

台灣現行建議與臨床處置指引(2022.11.29 updates)



建議使用族群(暴露前預防)

1. 12歲以上且體重40公斤以上，且；
2. 六個月內無感染SARS-CoV-2，且；
3. 一週內與SARS-CoV-2感染者無已知的接觸史，且；
4. 符合下列條件任一者：
 1. 曾在一年內接受器官移植或血液幹細胞移植；
 2. 接受實體器官或血液幹細胞移植後任何時間有急性排斥現象；
 3. 曾在一年內接受 CAR-T 治療或 B 細胞清除治療(B cell depletion therapy)；
 4. 具有有效重大傷病卡之嚴重先天性免疫不全病患

用法用量

1. 單次肌肉注射: 300mg Tixagevimab + 300mg Cilgavimab
2. 交互作用: 未曾進行藥物交互作用研究，目前無已知的藥物交互作用研究證實會與 TIXA/CILGA產生交互作用

台灣現行建議與臨床處置指引(2022.11.29 updates)



建議使用族群(治療)

1. 具任一重症風險因子*，
2. 未使用氧氣且於發病五天內之成人或 ≥ 12 歲且體重 ≥ 40 公斤輕症病患

*重症風險因子

年齡 ≥ 65 歲、氣喘、癌症、糖尿病、慢性腎病、心血管疾病(不含高血壓)、慢性肺疾(間質性肺病、肺栓塞、肺高壓、氣管擴張、慢性阻塞性肺病)、結核病、慢性肝病(肝硬化、非酒精性脂肪性肝炎、酒精性肝病與免疫性肝炎)、失能(注意力不足及過動症、腦性麻痺、先天性缺陷、發展或學習障礙、脊髓損傷)、精神疾病(情緒障礙、思覺失調症)、失智症、吸菸(或已戒菸者)、BMI ≥ 30 (或 12–17 歲兒童青少年 BMI 超過同齡第 95 百分位)、懷孕(或產後六周內)、影響免疫功能之疾病(HIV 感染、先天性免疫不全、實體器官或血液幹細胞移植、使用類固醇或其他免疫抑制劑)。吸菸或已戒菸者需同時具有其他重症風險因子方可開立藥物。

用法用量

1. 單次肌肉注射: **300mg** Tixagevimab + **300mg** Cilgavimab
2. 交互作用: 未曾進行藥物交互作用研究，目前無已知的藥物交互作用研究證實會與 TIXA/CILGA 產生交互作用

注意事項

1. EVUSHELD不能取代疫苗接種
2. EVUSHELD成分含有 polysorbate 80與 polyethylene glycol(PEG)結構相似。Novavax COVID-19疫苗成分包括 polysorbate 80；mRNA COVID-19疫苗則含有 PEG，因此可能引發交叉過敏反應。建議若要對 COVID-19疫苗曾有嚴重過敏者給予 Evusheld，應諮詢免疫專家
3. 建議注射 EVUSHELD後仍需維持其他防疫措施
4. 應於接種 COVID-19疫苗後至少兩週再給予 EVUSHELD，若在 EVUSHELD後接種疫苗，則無時間間隔限制
5. 不建議於免疫低下族群進行常規血清抗體檢驗，或以抗體檢驗結果決定是否給予 Evusheld

新型冠狀病毒SARS-CoV-2 感染臨床處置指引. <https://www.cdc.gov.tw/Category/Page/xCSwc5oznwcqunujPc-qmQ>

FACT SHEET FOR HEALTHCARE PROVIDERS: EMERGENCY USE AUTHORIZATION FOR EVUSHELD™ (tixagevimab co-packaged with cilgavimab) <https://www.fda.gov/media/154701/download> assessed on 2022/09/14

Take Home Message

Unmet Needs

Despite the availability of vaccines, there remains an unmet need for immunocompromised patients

Mechanism of Action

Tixa/Cilga is a combination of long- acting antibodies with proven neutralizing ability against all variants in vitro by binding the RBD.

Phase III Trial

PROVENT trial showed that Tixa/Cilga provided an 83 % risk reduction of symptomatic SARS-COV-2 infection.

Real World Evidence

Tixa/Cilga maintained effectiveness for immunocompromised patients during omicron era and vaccinated patients based on current RWE.

Thanks!!