# The Role of Monoclonal Antibodies in Preventing Infection



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**5th WAIDID Congress**

**Milan, Italy**

# Disclosures

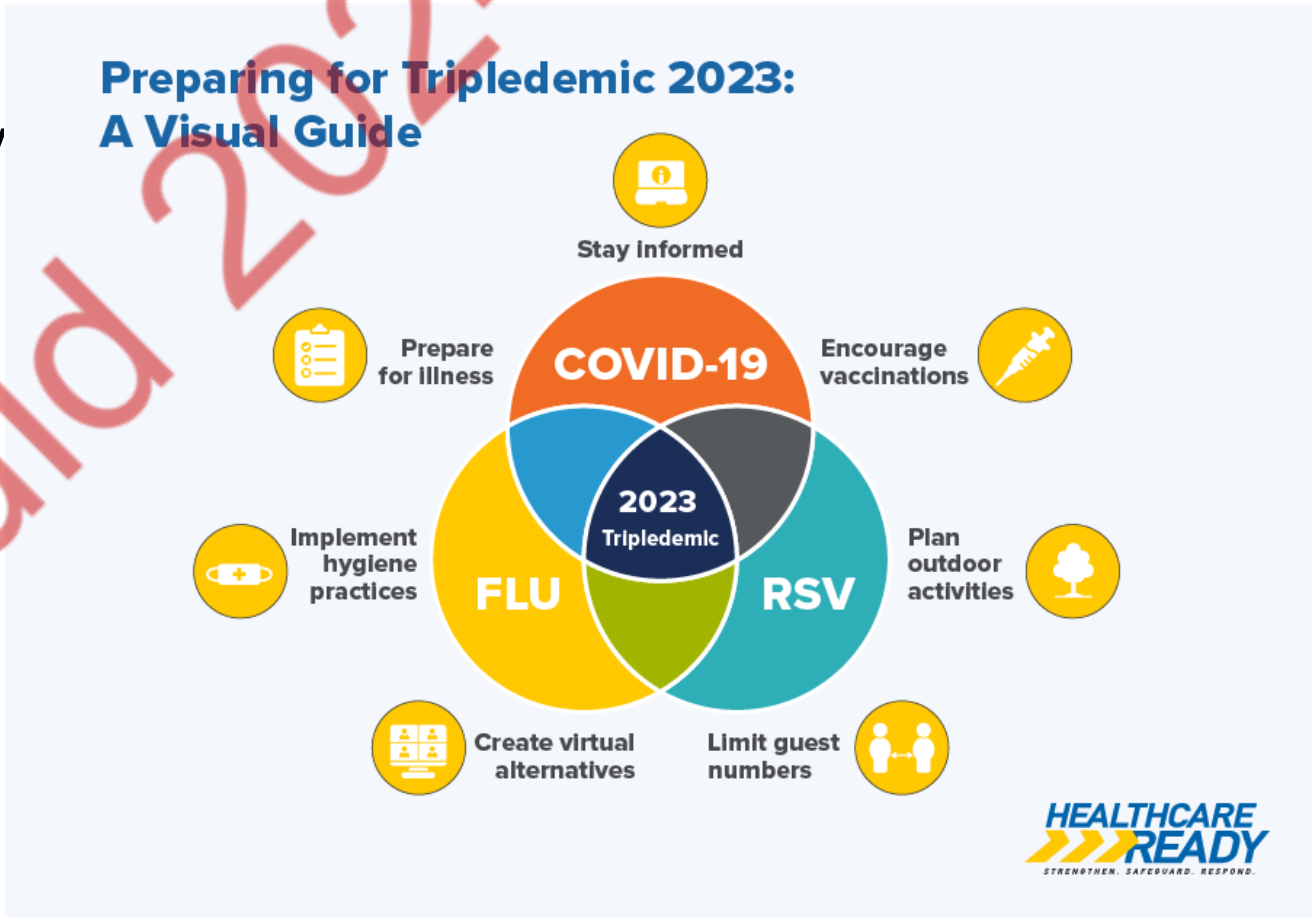
- Past investigator-initiated grant support from Sanofi and Quidel
- Current investigator-initiated support from Merck

# Objectives

- Discuss active versus passive immunization
- History and role of monoclonal antibodies
- How monoclonal antibodies were used during the COVID-19 pandemic

# Infectious Diseases Globally

- Infectious diseases leading cause of morbidity and mortality
- Pneumonia and sepsis
  - *Streptococcus pneumoniae*
  - MRSA/MSSA
  - Respiratory viruses
- Tripledemic
  - COVID-19
  - RSV
  - Influenza






https://healthcareready.org/2023-navigating-the-tripledemic-a-guide-to-preparing-your-family-for-a-safe-and-joyful-holiday-season/

# Groups at High Risk for Severe Respiratory Illness and Complications

- Birth through 59 months of age
- Adults 50 years old and older
- Chronic lung disease, asthma
- Chronic heart disease
- Metabolic diseases, e.g. diabetes
- Chronic renal disease
- High risk of aspiration
- **Immunosuppression**
- Pregnancy
- Chronic aspirin therapy: 18 years old and younger
- Obesity

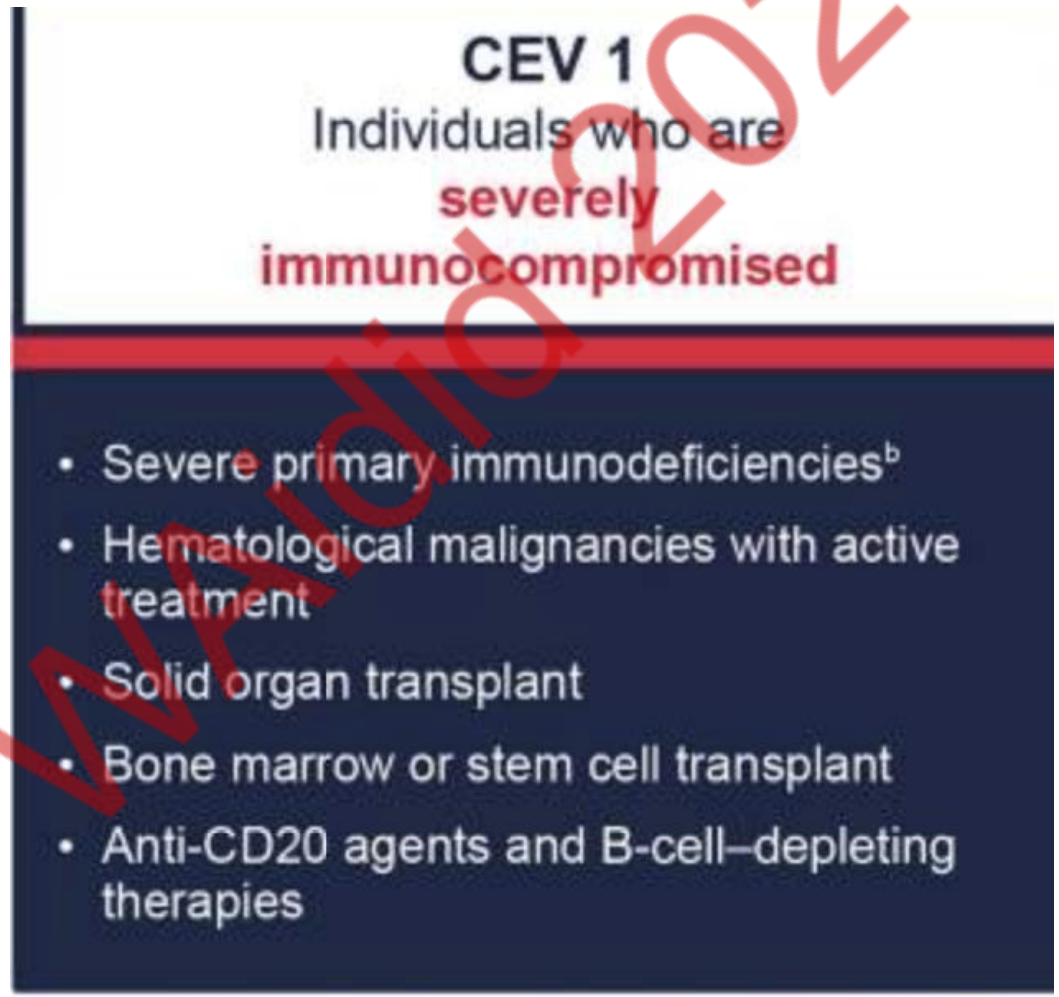

# Immunocompromised Individuals

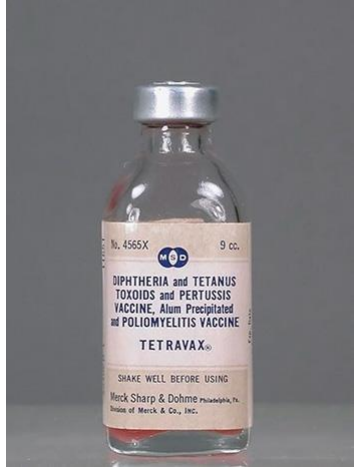
- Stem cell and solid organ transplant recipients
- Cancer
- HIV/AIDS
- Individuals taking immunosuppressive drugs
- Inherited immune system disorders



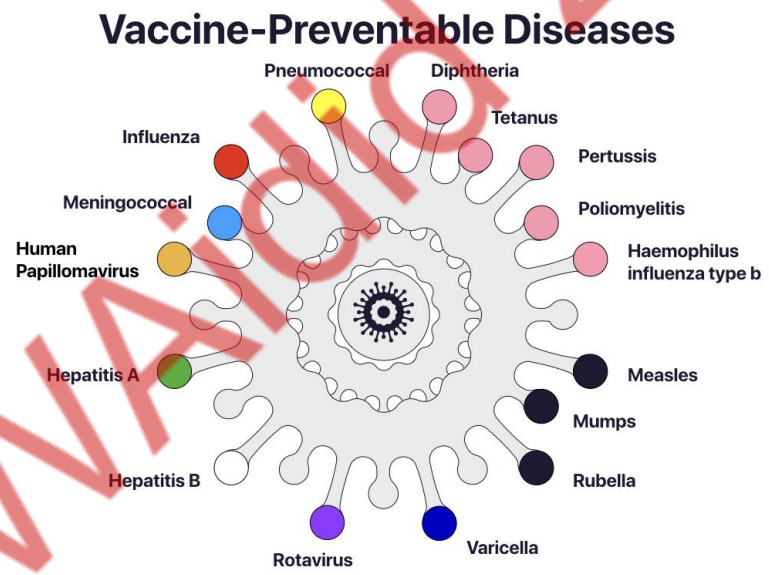
https://www.washingtonpost.com/brand-studio/wp/2022/01/12/protecting-immunocompromised-patients-in-the-covid-19-pandemic/

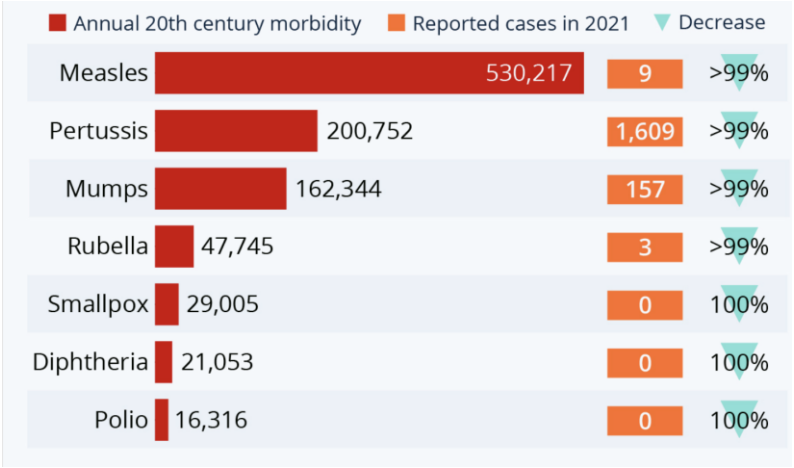
# Protection is Needed for Clinically Extremely Vulnerable (CEV)-1






# Active Immunization

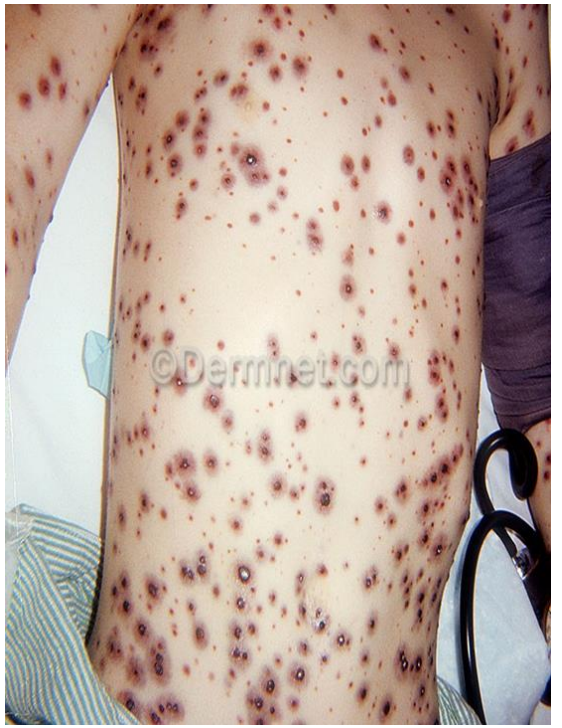


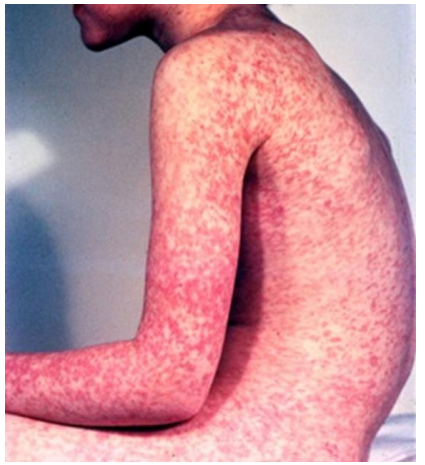



# Vaccines Responses in Immunocompromised Hosts



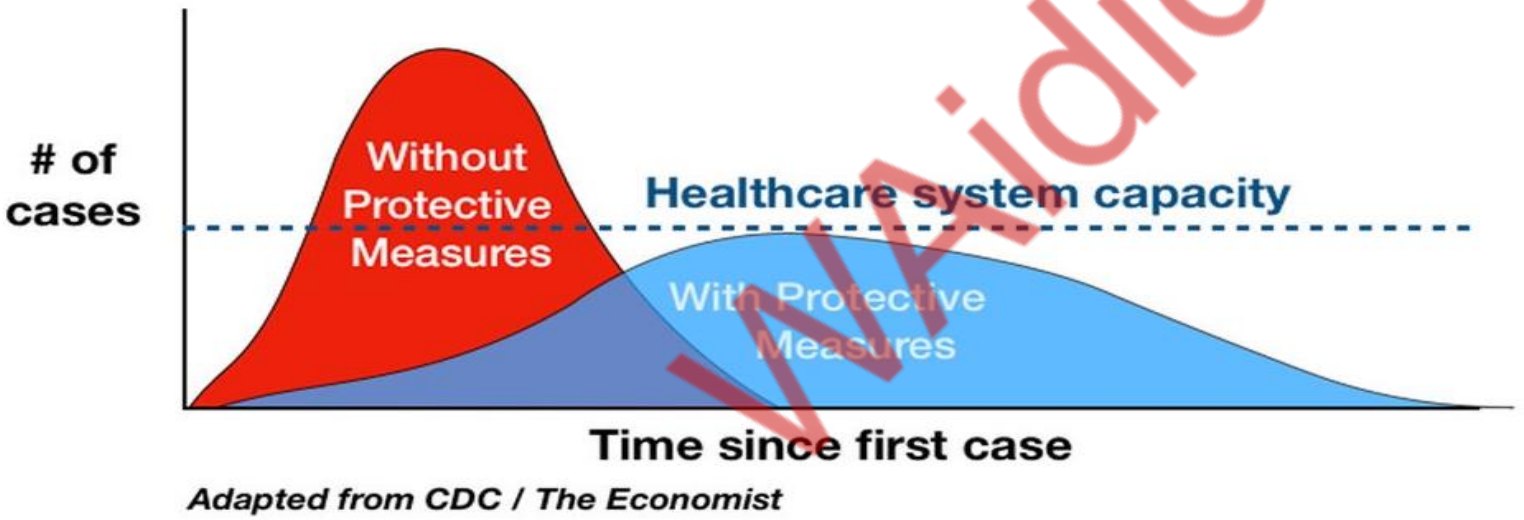
- Vaccine responses are lower when compared to age-match healthy controls
  - Underlying disease
  - Immunosuppressive drugs
  - Active GVHD
- Timing of vaccines
  - Post-SOT and HSCT transplant
  - Chemotherapy cycles
- Contraindication for live vaccines in most cases
- Excluded from clinical trials
  - Including during the COVID-19 pandemic



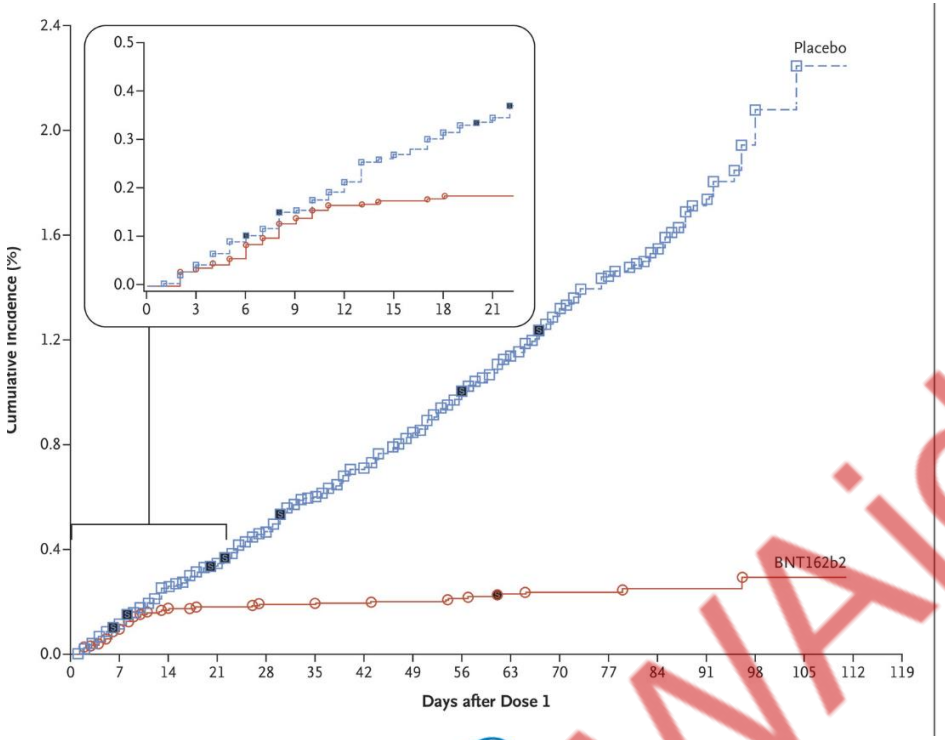



# COVID-19: Prevention of Transmission

- Social Distancing: Travel restrictions, school and business closures, meeting restrictions
- Hand hygiene
- Masks

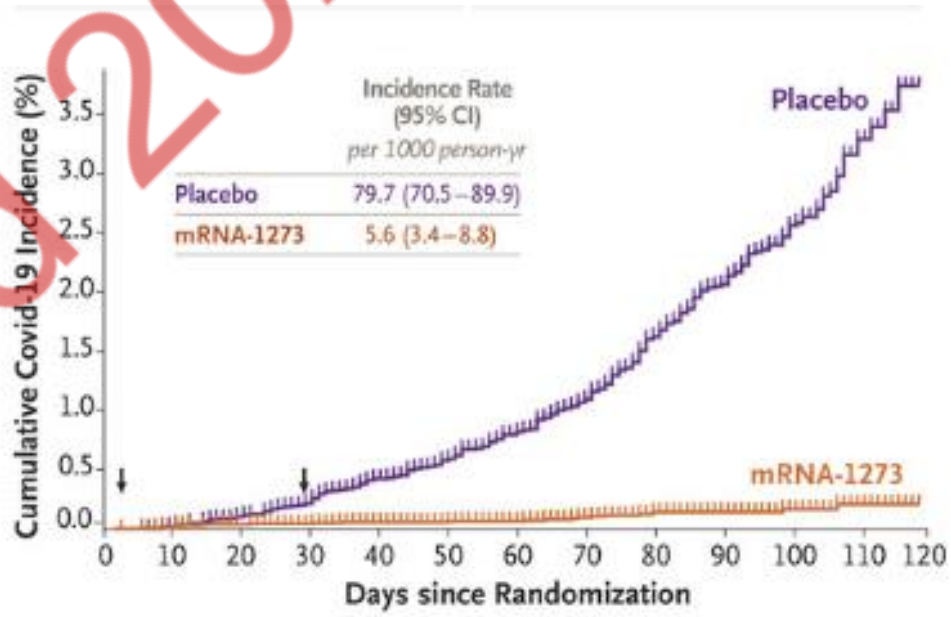



# COVID-19 Vaccine Efficacy Trials




Pfizer

**95% Efficacy**



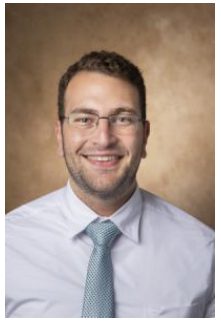

moderna

***EXCLUDED IMMUNOCOMPROMISED PATIENTS**



FP Polack · 2020 NEJM; LR Baden · 2021 ·NEJM

# COVID-19 Vaccine:
# Lower Antibody Responses in Solid Organ Transplant (SOT) Recipients Compared to Healthy Controls (HC)



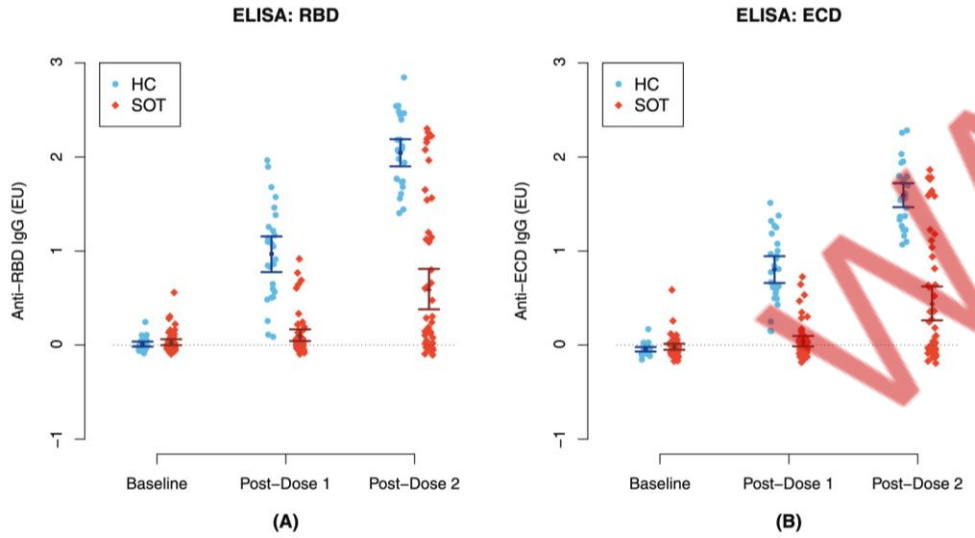
**54 SOT**

Mean – 72 years

- 7.2 years post-transplant
- 98% UMC

**26 HC**

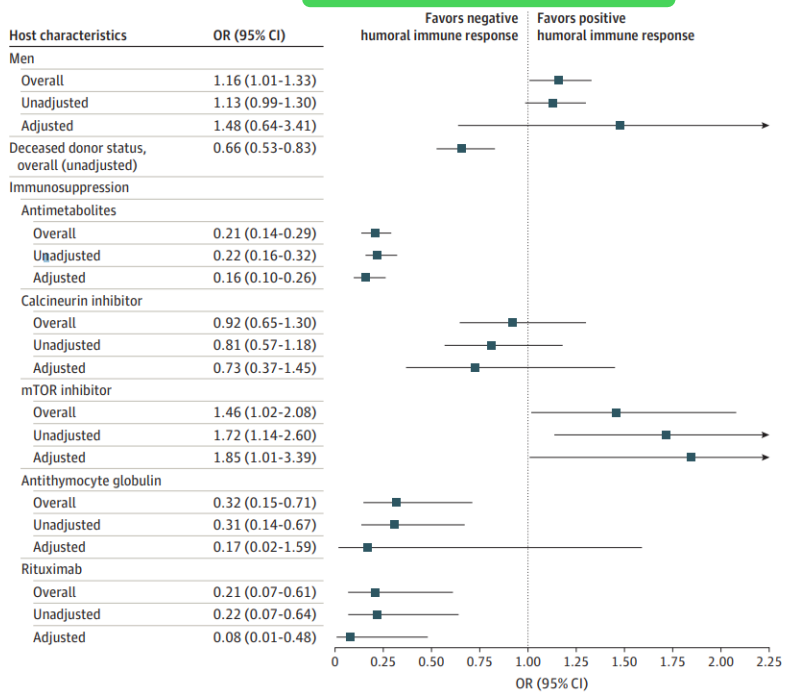
- Mean 62.4 years
- 69% UMC



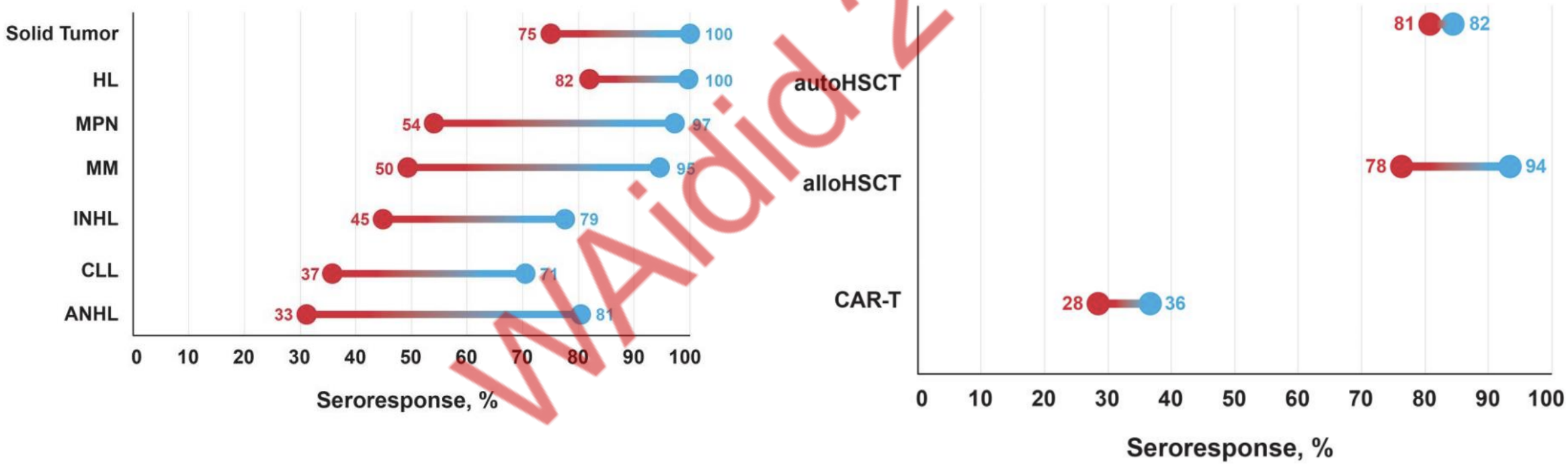

Yanis *TID* 2022; Manothummetha 2022 *JAMA Open Network*

- Older age
- Recent transplantation
- Deceased donor status
- Active use of antimetabolites
- Recent exposure to antithymocyte globulin or rituximab

**Meta-analysis**



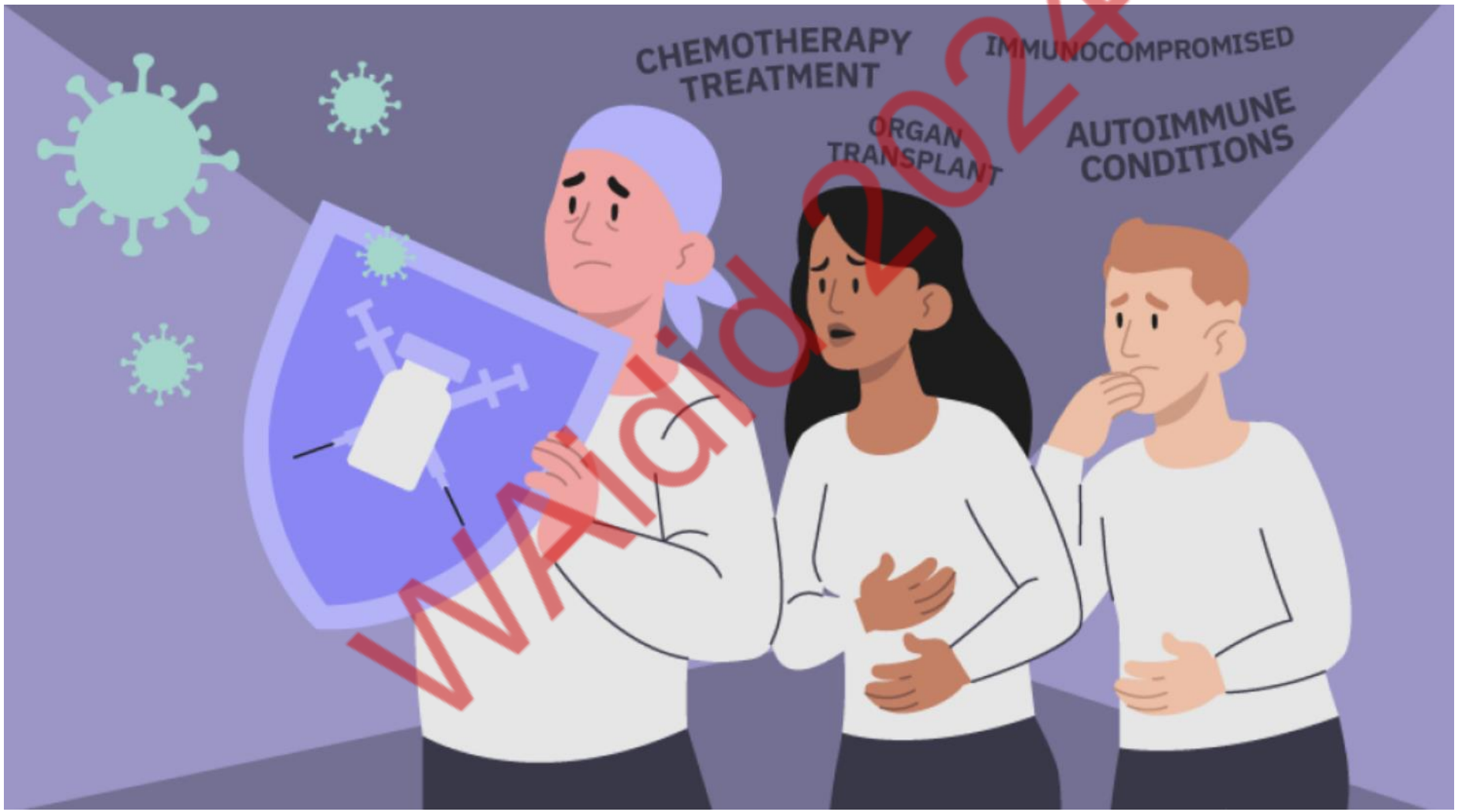
# COVID-19 Vaccine Seroresponse Varies among Cancer Patients and Transplant Recipients





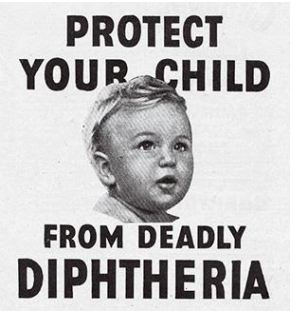

Hall, Teh *JID* 2023

# Other options for protection?





# PASSIVE IMMUNIZATION




# 19th century Anti-Diphtheria Serum


Emil von Behring - 1901 Nobel Prize

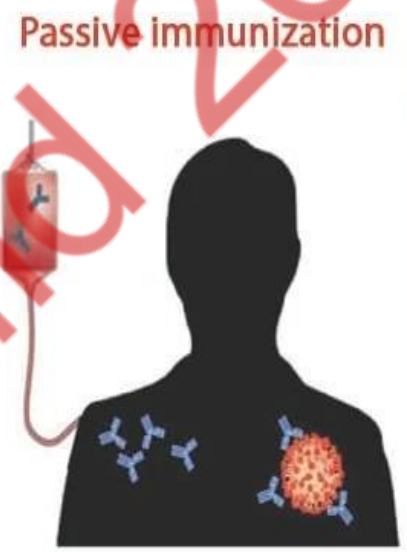
Antitoxin serum for diphtheria. Notice the hot pink fluff used to protect the glass ampule inside the wooden container.

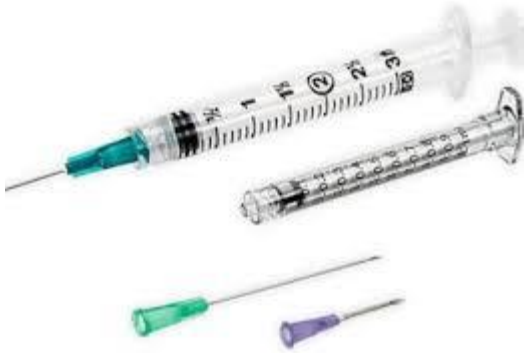



https://americanhistory.si.edu/explore/stories/how-horses-helped-cure-diphtheria#:~:text=In%201890%2C%20it%20was%20discovered,identify%20and%20fight%20foreign%20invaders.)

# Passive Immunization in Infectious Diseases: Transfusions, IV, or IM

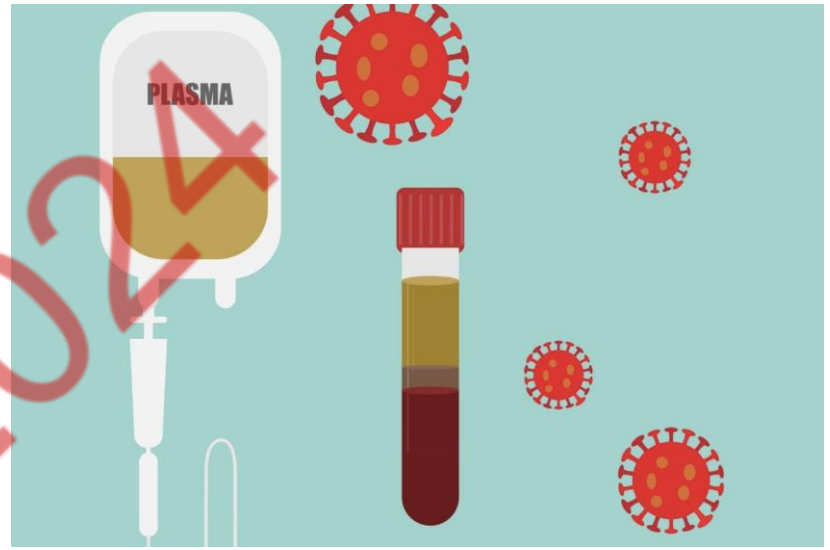
- Diphtheria
- Measles
- Varicella-Zoster
- 1918 Pandemic
- Ebola
- Rabies
- CMV
- Hepatitis A and B
- Vaccinia
- Varicella-zoster virus
- RSV
- West Nile



# COVID-19 and Convalescent Plasma (CCP)

- Hospitalization reduction was greatest
  - Early transfusion
  - High titer
- No significant reduction in hospitalization
  - >5 days after symptom onset
  - Receiving CCP with antibody titers below the median titer

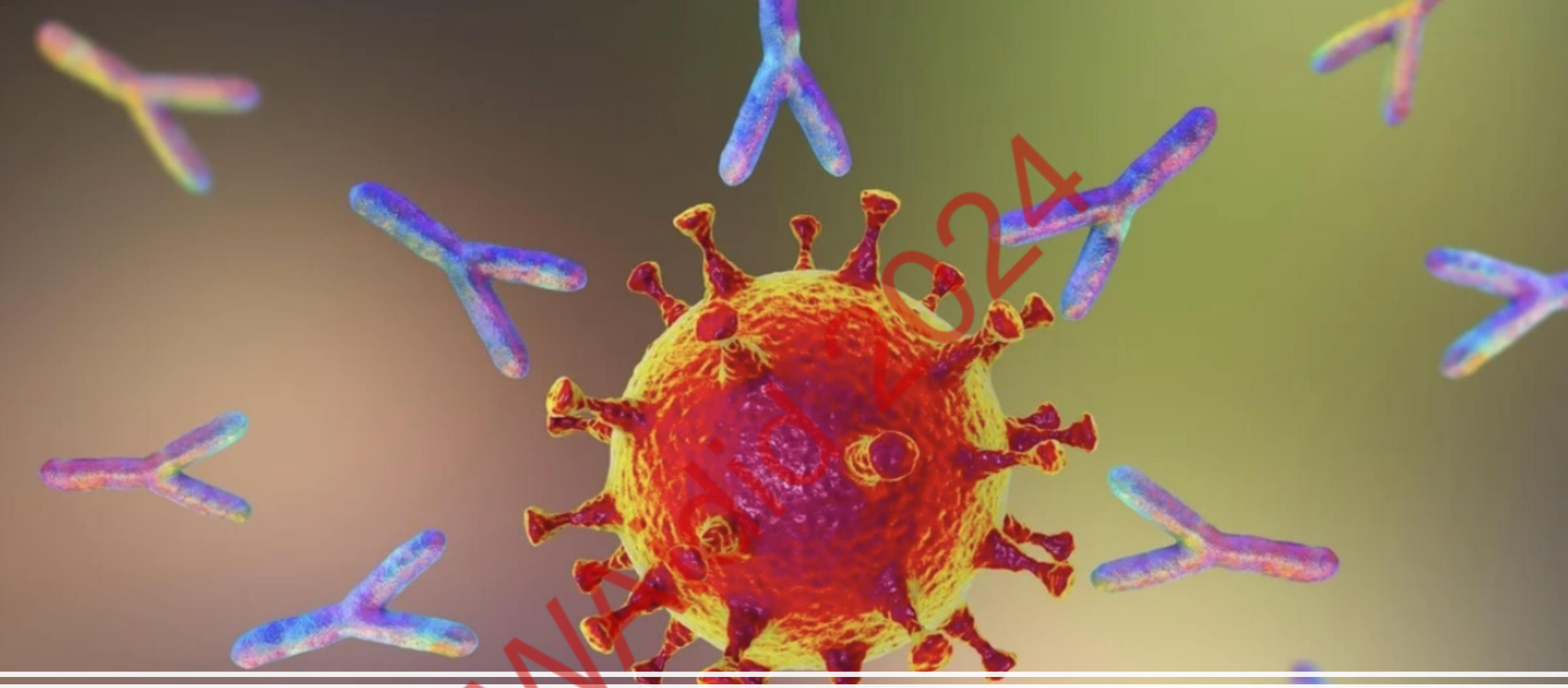



**Coronavirus Disease 2019 Convalescent Plasma Outpatient Therapy to Prevent Outpatient Hospitalization: A Meta-Analysis of Individual Participant Data From 5 Randomized Trials**

Adam C Levine [1], Yuriko Fukuta [2], Moises A Huaman [3], Jiangda Ou [4], Barry R Meisenberg [5], Bela Patel [6], James H Paxton [7], Daniel F Hanley [4], Bart J A Rijnders [8], Arvind Gharbharan [8], Casper Rokx [8], Jaap Jan Zwaginga [9 10], Andrea Alemany [11 12], Oriol Mitjà [11 12 13], Dan Ouchi [11 12], Pere Millat-Martinez [14], Valerie Durkalski-Mauldin [15], Frederick K Korley [16], Larry J Dumont [17 18], Clifton W Callaway [19], Romina Libster [20 21], Gonzalo Perez Marc [20], Diego Wappner [20], Ignacio Esteban [20], Fernando Polack [20 21], David J Sullivan [22]

# Limitations of Serum Derived Immunoglobulins

- Includes all epitopes
- Not all are neutralizing
- Risk of pathogen transmission
- Batch-to-batch variation
- Difficult to find donors during a pandemic
- Side effects and anaphylaxis



# Monoclonal Antibodies

https://www.news-medical.net/news/20211001/Structure-of-monoclonal-antibody-that-can-potently-neutralize-SARS-CoV-2-and-variants-of-concern.aspx

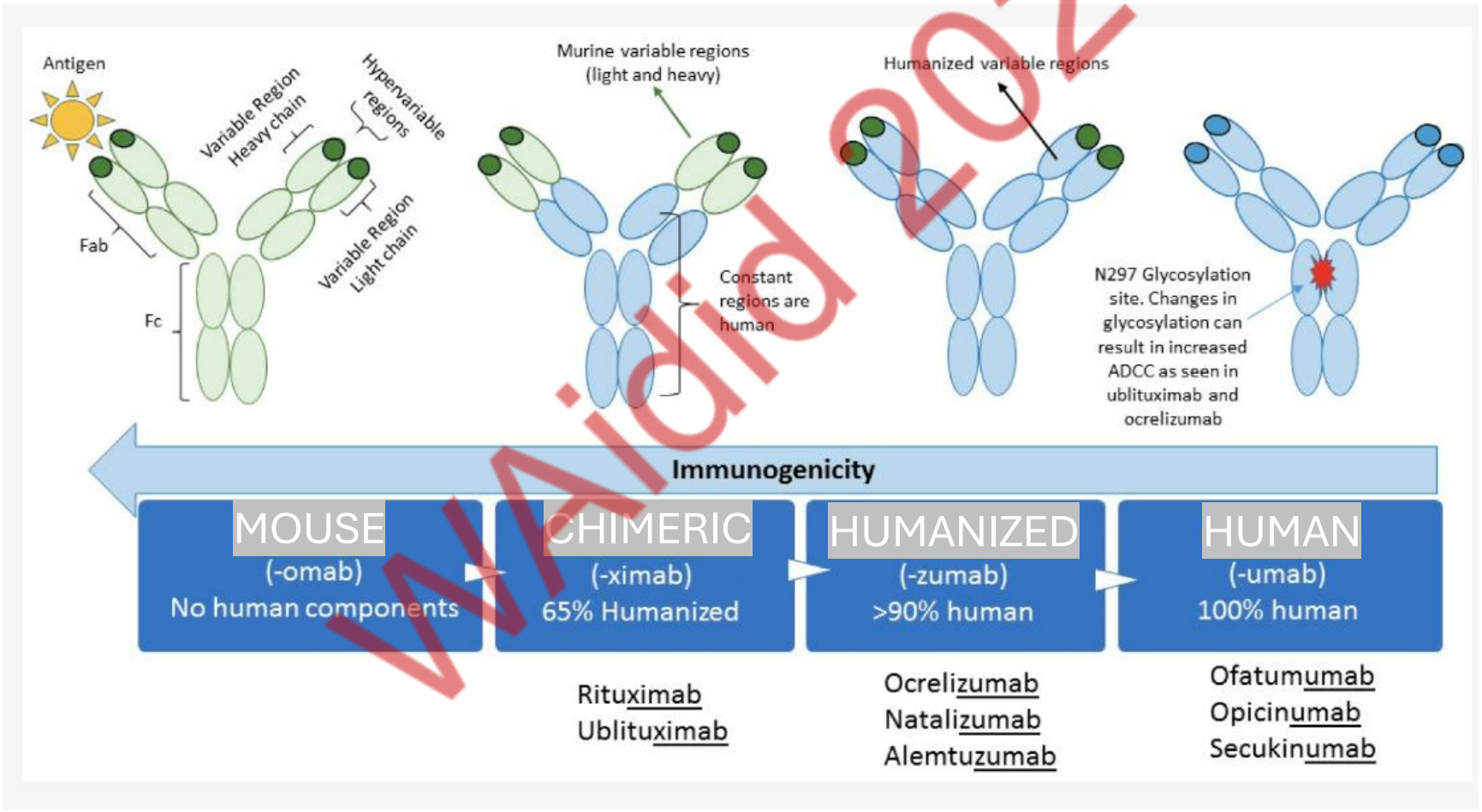
# Monoclonal Antibodies

- “mono” meaning they are a pure, single type of antibody targeted at a single site on a pathogen
- “clonal” because they are produced from a single parent cell
- Generated first time in 1975 in mice using hybridoma technology
  - Antibody-producing B lymphocytes are isolated from mice after immunizing the mice with specific antigen and are fused with immortal myeloma cell lines to form hybrid cell

César Milstein and Georges Köhler together in 1984, the year they were awarded the Nobel Prize in physiology or medicine, jointly with Niels Jerne. Credit: Photo reproduced courtesy of the MRC Laboratory of Molecular Biology, Cambridge, UK.

1984 Nobel Prize in Physiology or Medicine:
César Milstein and Georges J. F. Köhler

# Monoclonal Antibodies have Wide-ranging Potential Applications to Infectious Diseases, Immunological, and Cancer

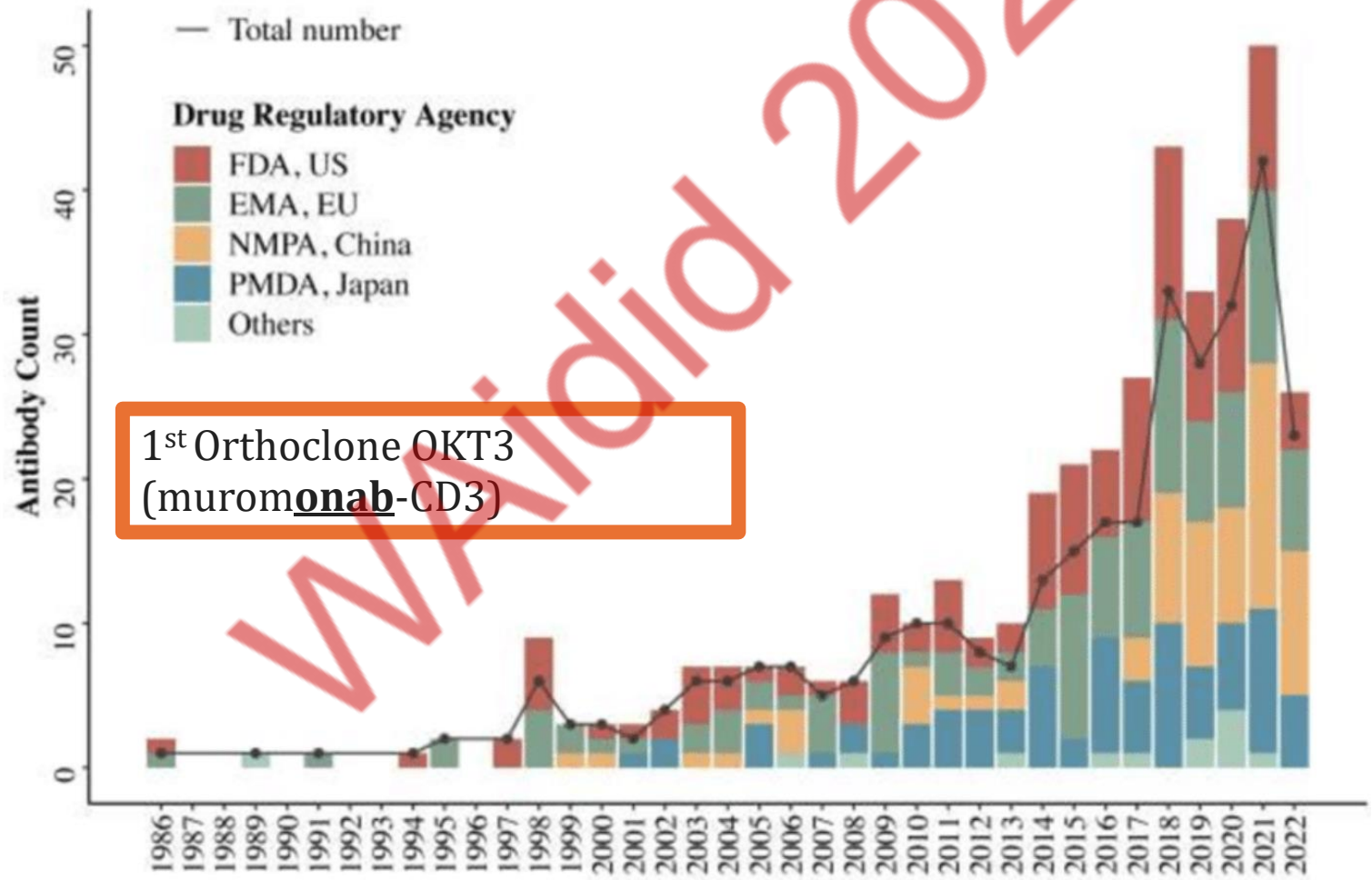





Otsubo Pharmacology and Therapeutics 2022; Vogue Biomedicines 2019

***complementarity-determining regions (CDR)**

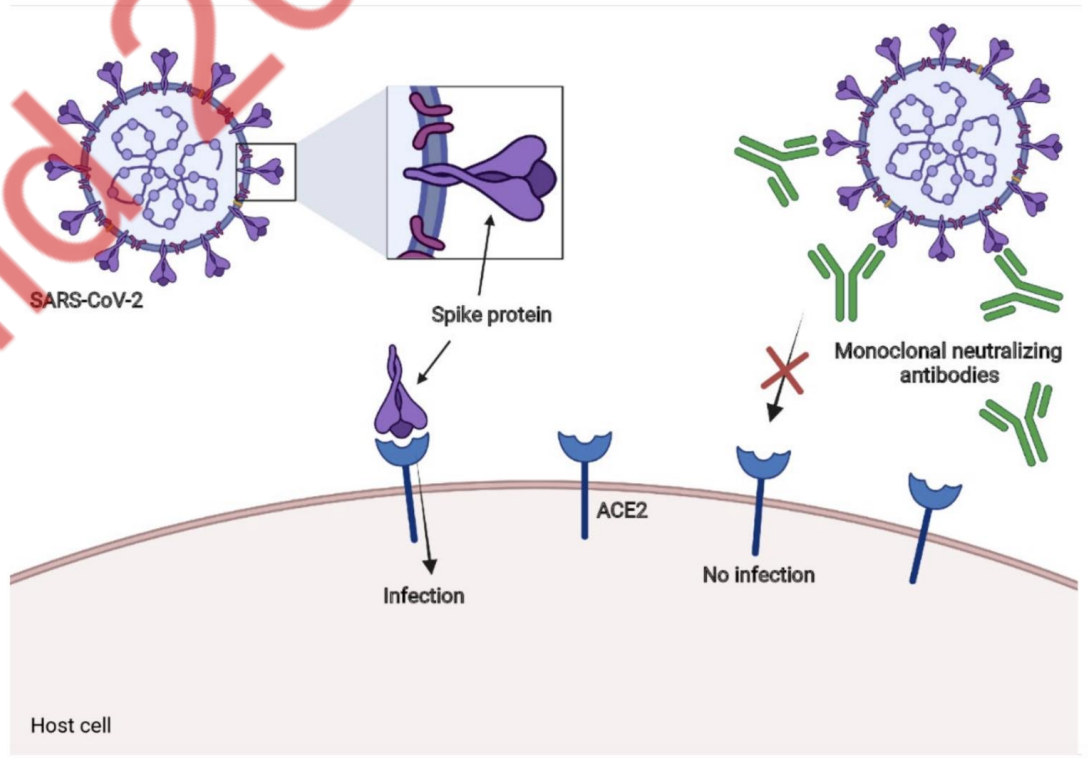
# Monoclonal Antibodies
# First approved in 1986




1st Orthoclone OKT3
(muromonab-CD3)

# Multiple Mechanisms of Monoclonal Neutralizing Antibody for Viral Infections

- Direct blocking of viral entry
- mAb-mediated effector functions
- Indirect blocking over viral entry by cross-linking virions
- Inactivating the viral entry of glycoprotein
- Prevent egress of virus from infected cells
- Blocking cell-to-cell spread of the virus






Corti Cell 2021

# Indications for Monoclonal Antibodies for Infection

- Pre-exposure prevention
- Post-exposure prophylaxis
- Treatment for mild disease
- Treatment for severe disease

# Prevention

| Drug | Target | Format | Technology | Year Approved by FDA |
|---|---|---|---|---|
| Palivizumab | RSV | Humanized IgG1 | Hybridoma | 1998 |
| Bezlotoxumab | *Clostridioides difficile* enterotoxin B | Human IgG1 | Transgenic mice | 2016 |
| Obiltoxaximab | *Bacillus anthracis* PA | Chimeric IgG1 | Hyridoma | 2016 |
| Ansuvimab | Ebola glycoprotein | Human IgG1 | Human | 2020 |
| Atoltivimab, maftivimab, and odesivimab | Ebola glycoprotein | Human IgG1 | Transgenic mice | 2020 |
| Nirsevimab | RSV | Humanized IgG1 | Human | 2023 |



Pantaleo Nature Reviews 2022

# Treatment

| Drug | Target | Format | Technology | Indication | Year Approved by FDA |
|---|---|---|---|---|---|
| Raxibacumab | *Bacillus anthracis* PA | Human IgG1 | Human scFv phase display library | Anthrax infection | 2012 |
| Ibalizumab | CD4 receptor (domain 2) | Humanized IgG4 | Mice | Treatment of HIV-1 infection | 2018 |



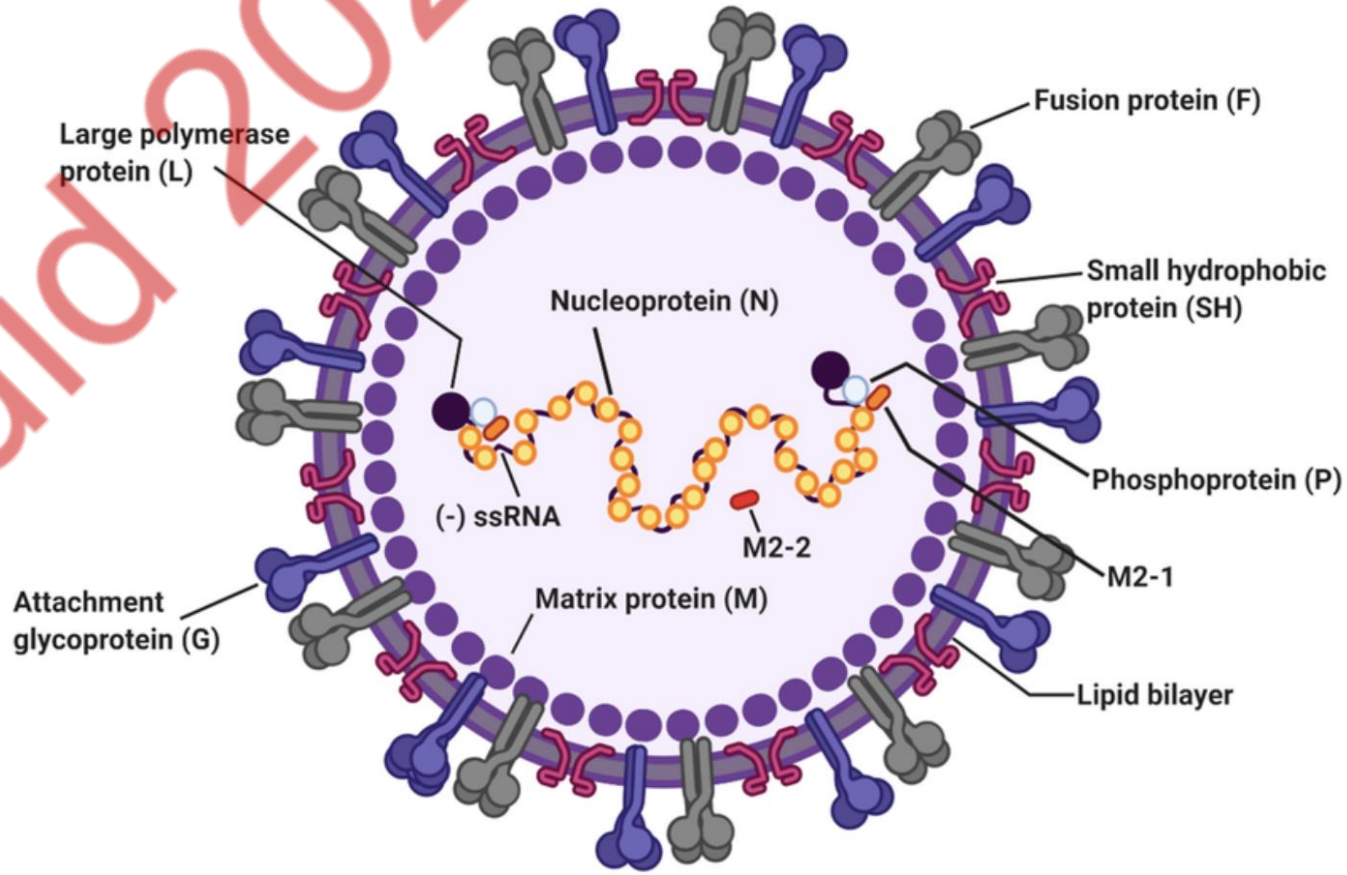
Pantaleo Nature Reviews 2022

## Factors to Consider with Monoclonal Antibodies

- Frequency of administration - ideally want to prolong ½ life
- Risk of antigenic escape in infections due to mutations
- Can be used when vaccines are not effective
- Waiting for vaccine to take effect

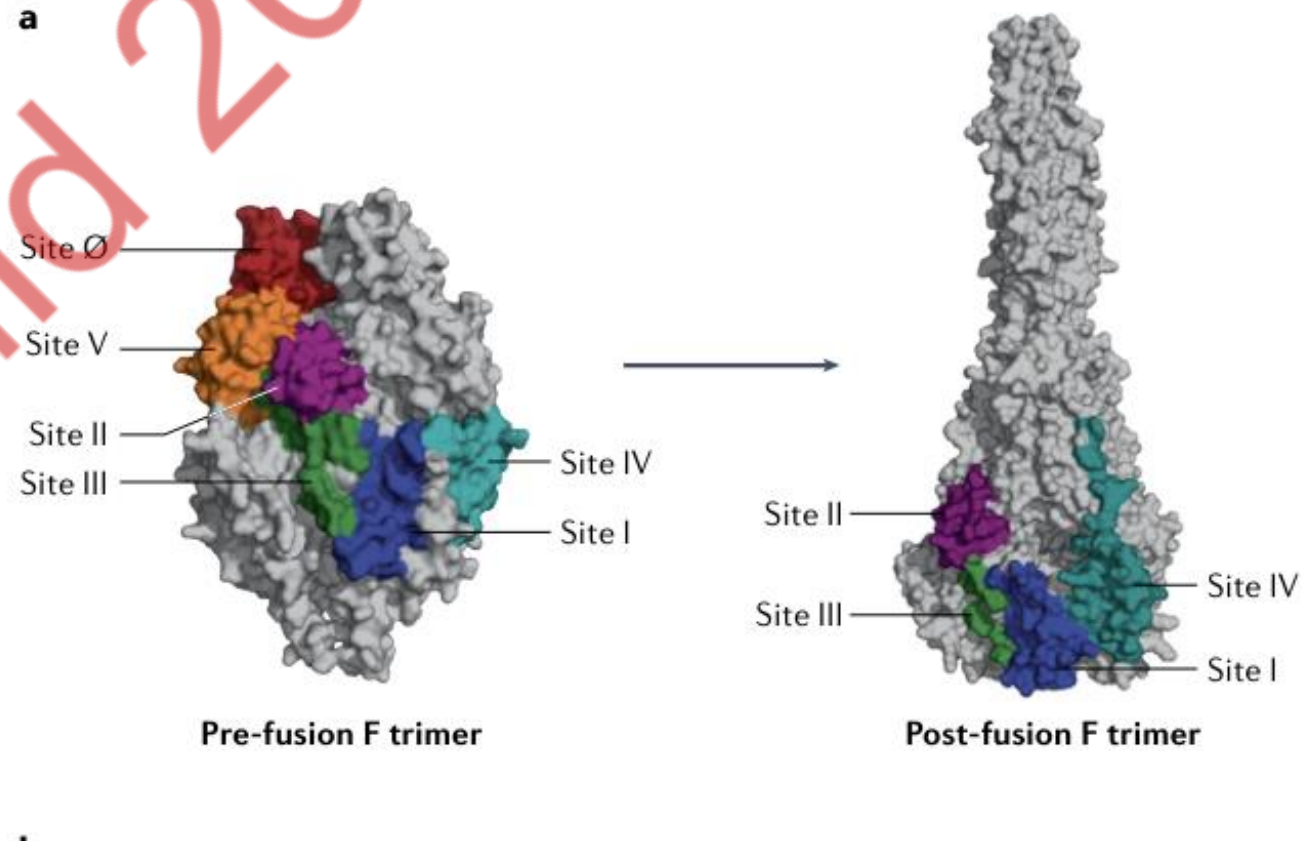
# RSV

- Important cause of respiratory illness in young children, older adults, and immunocompromised patients
- Enveloped, nonsegmented negative-strand RNA
- Two antigenic subgroups, A and B
- Fusion protein (F) important Ag target
- 1st Passive Therapy
  - RespiGam prophylaxis by IV



# Palivizumab

- 1998
- Humanized mouse immunoglobulin G1 (IgG1κ)
- Recombinant DNA technology
- Antibody is directed against a conserved epitope
  - **Site II** of the prefusion and postfusion (F) protein
- Demonstrates both neutralizing and fusion inhibitory activity






Caserta *Pediatrics* 2023

# Palivizumab – Limitations

- Administered IM at a dosage of 15 mg/kg once a month - up to 5 months
- The drug is packaged in single-dose liquid solution and does not contain preservative
- A vial cannot be stored once it is opened
  - So, a vial-sharing scheme is important to minimize wastage
- Limited to high-risk infants and children
- High cost  - mostly in developed country
- At-risk adults not feasible cost (based on body weight in children)

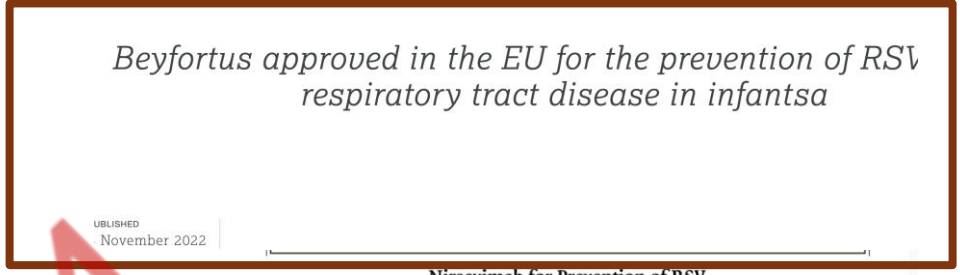

FDA NEWS RELEASE

FDA Approves New Drug to Prevent RSV in Babies and Toddlers

Share Post Linkedin Email Print

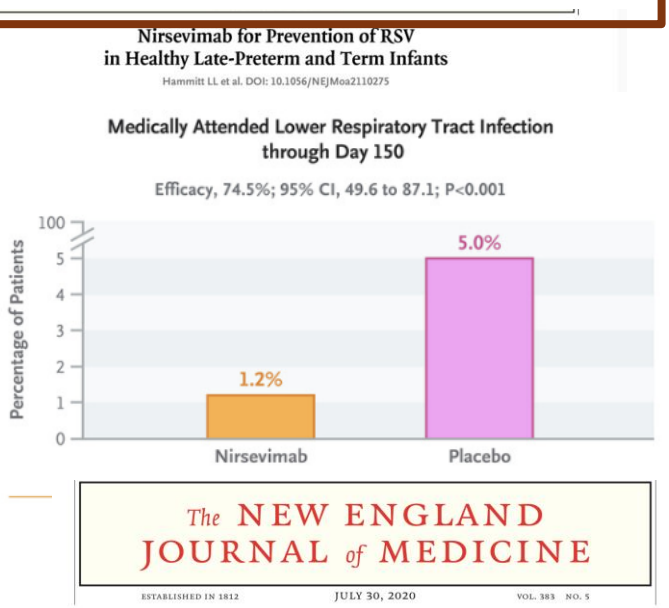
For Immediate Release: July 17, 2023

# Nirsevimab


*Beyfortus approved in the EU for the prevention of RSV respiratory tract disease in infantsa*

UBLISHED
November 2022

- Recombinant human immunoglobulin G1 kappa monoclonal antibody
- Binds the F1 and F2 subunits of the RSV fusion (F) protein at the highly conserved antigen site Ø
- Extended half-life
  - **<u>Mutation YTE Fc region</u>**
- Single injection
- Target all infants
- Mostly being used in developed countries for now


Nirsevimab for Prevention of RSV in Healthy Late-Preterm and Term Infants

Hammitt LL et al. DOI: 10.1056/NEJMoa2110275

Medically Attended Lower Respiratory Tract Infection through Day 150

Efficacy, 74.5%; 95% CI, 49.6 to 87.1; P<0.001

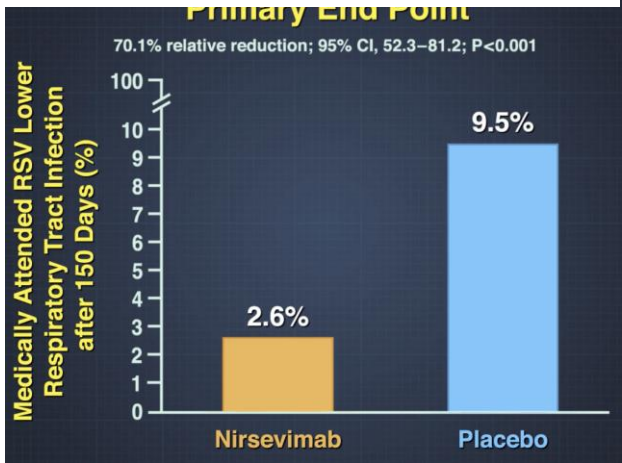


The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 30, 2020 VOL. 383 NO. 5

Single-Dose Nirsevimab for Prevention of RSV in Preterm Infants

M. Pamela Griffin, M.D., Yuan Yuan, Ph.D., Therese Takas, B.S., Joseph B. Domachowske, M.D., Shabir A. Madhi, M.B., B.Ch., Ph.D., Paolo Manzoni, M.D., Ph.D., Eric A.F. Simões, M.D., Mark T. Esser, Ph.D., Anis A. Khan, Ph.D., Filip Dubovsky, M.D., Tonya Villafana, Ph.D., and John P. DeVincenzo, M.D., for the Nirsevimab Study Group*






Hammit NEJM 2022; Griffin NEJM 2020

# Early High Estimates of Nirsevimab Effectiveness from Spain

- Universal immunization program began late September
  - coverage range: 79–99%
- 70% effective in preventing hospitalizations in infants with lower respiratory tract infections positive for RSV
- Oct 2023–Jan 2024

Euro Surveill. 2024 Feb 8; 29(6): 2400046.
doi: 10.2807/1560-7917.ES.2024.29.6.2400046
PMCID: PMC10853977
PMID: 38333937

Journal Article

Early estimates of nirsevimab immunoprophylaxis effectiveness against hospital admission for respiratory syncytial virus lower respiratory tract infections in infants, Spain, October 2023 to January 2024

Mónica López-Lacort, [1,2,*] Cintia Muñoz-Quiles, [1,2,*] Ainara Mira-Iglesias, [1,2] F Xavier López-Labrador, [2,3,4] Beatriz Mengual-Chuliá, [2,3] Carlos Fernández-García, [1] Mario Carballido-Fernández, [5,6] Ana Pineda-Caplliure, [7] Juan Mollar-Maseres, [8] Maruan Shalabi Benavent, [9] Francisco Sanz-Herrero, [10] Matilde Zornoza-Moreno, [11] Jaime Jesús Pérez-Martín, [11] Santiago Alfayate-Miguelez, [11] Rocío Pérez Crespo, [12] Encarnación Bastida Sánchez, [12] Ana Isabel Menasalvas-Ruiz, [13] Mª Cinta Téllez-González, [13] Samuel Esquiva Soto, [13] Carlos Del Toro Saravia, [14] Iván Sanz-Muñoz, [15] José María Eiros, [15] Vanesa Matías Del Pozo, [16] Marina Toquero-Asensi, [16] Eliseo Pastor-Villalba, [17] José Antonio Lluch-Rodrigo, [17] Javier Díez-Domingo, [1,2,18] and Alejandro Orrico-Sánchez [1,2,18]

Author information ▸ Article notes ▸ Copyright and License information PMC Disclaimer

# New Vaccine Surveillance Network


CDC Morbidity and Mortality Weekly Report (*MMWR*)

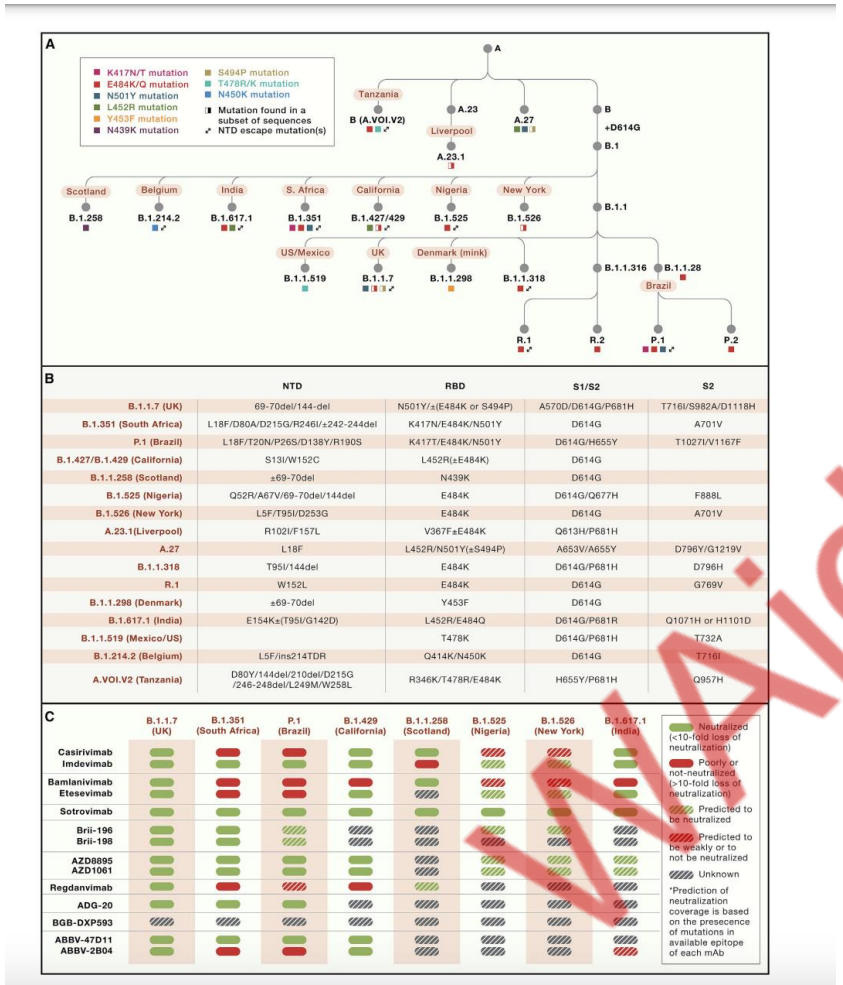
## Early Estimate of Nirsevimab Effectiveness fo Prevention of Respiratory Syncytial Virus–Associated Hospitalization Among Infants Entering Their First Respiratory Syncytial Viru Season — New Vaccine Surveillance Network October 2023–February 2024

*Weekly* / March 7, 2024 / 73(9);209–214

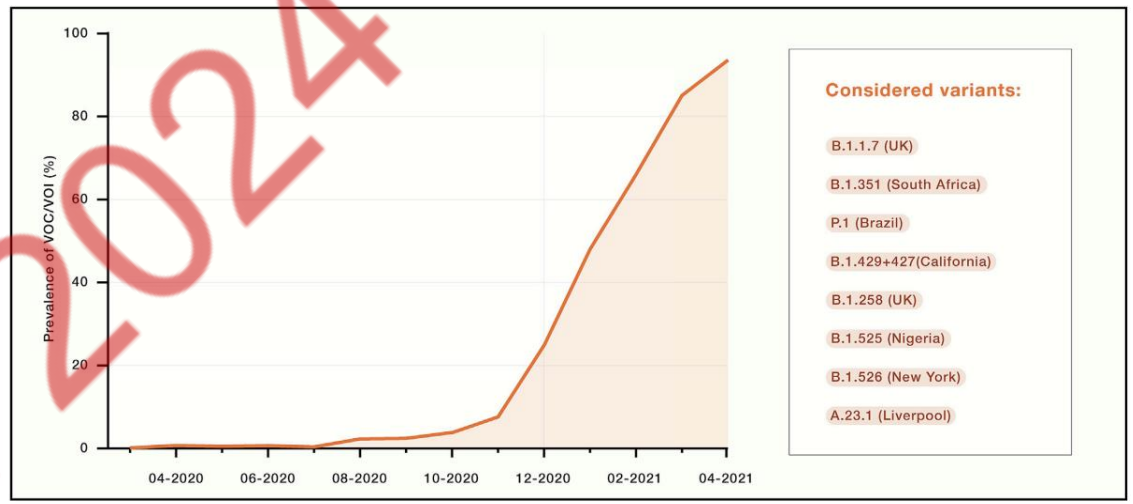
Print

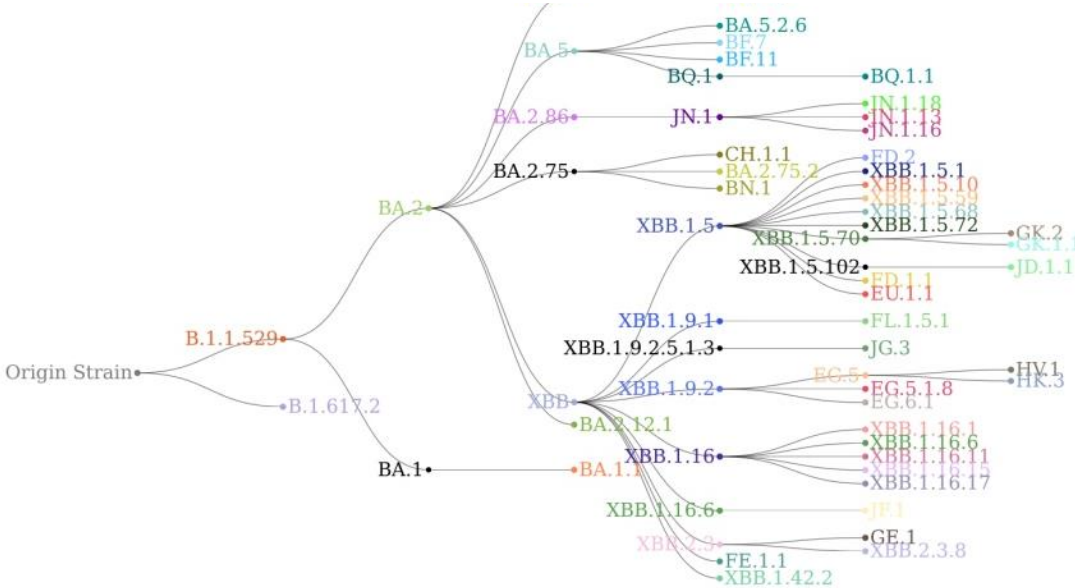
***Please note:*** This report has been corrected.

# COVID-19 Variants of Concern



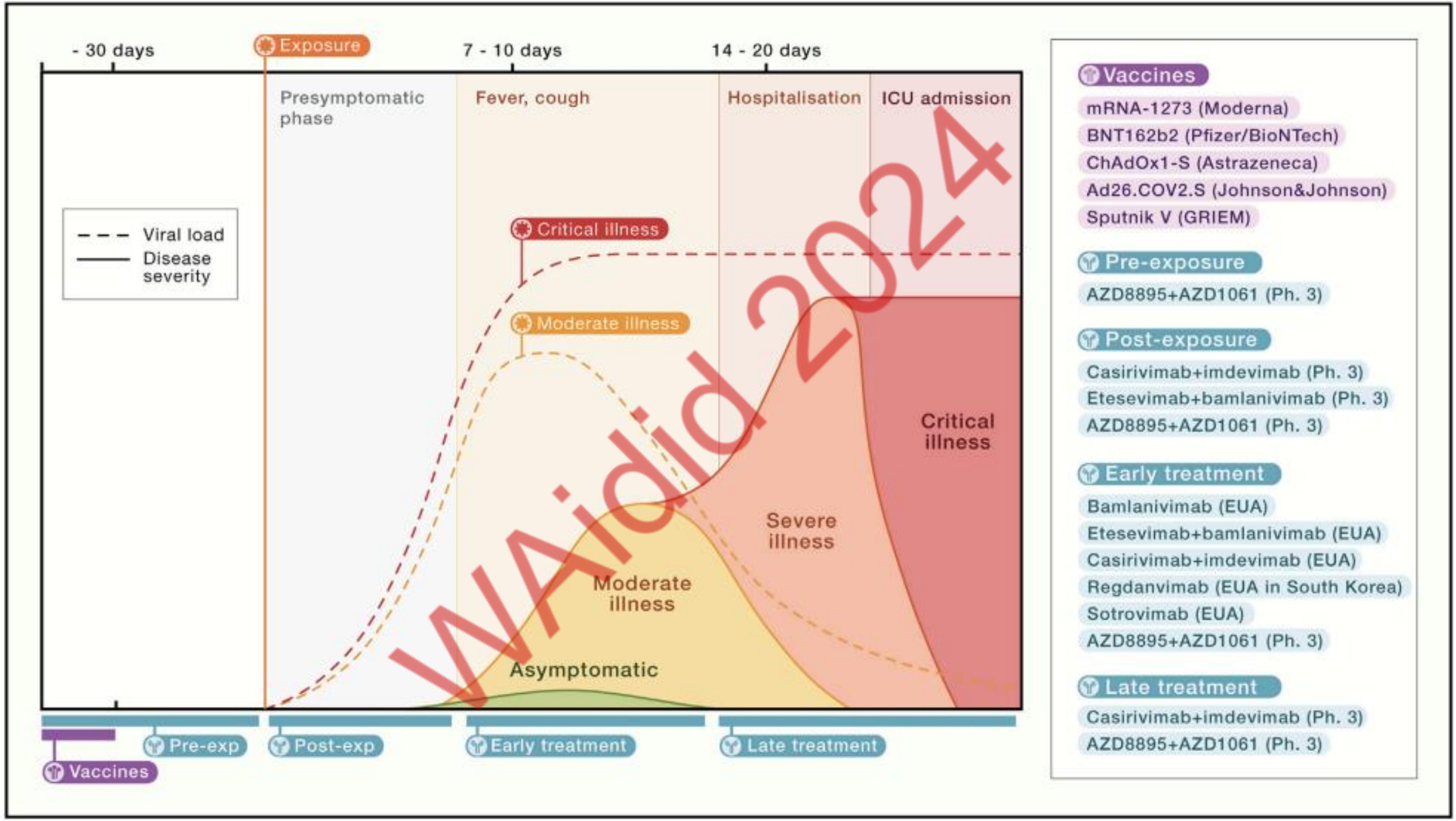

| | NTD | RBD | S1/S2 | S2 |
|---|---|---|---|---|
| B.1.1.7 (UK) | 69-70del/144-del | N501Y/±(E484K or S494P) | A570D/D614G/P681H | T716I/S982A/D1118H |
| B.1.351 (South Africa) | L18F/D80A/D215G/R246I/±242-244del | K417N/E484K/N501Y | D614G | A701V |
| P.1 (Brazil) | L18F/T20N/P26S/D138Y/R190S | K417T/E484K/N501Y | D614G/H655Y | T1027I/V1167F |
| B.1.427/B.1.429 (California) | S13I/W152C | L452R(±E484K) | D614G | |
| B.1.1.258 (Scotland) | ±69-70del | N439K | D614G | |
| B.1.525 (Nigeria) | Q52R/A67V/69-70del/144del | E484K | D614G/Q677H | F888L |
| B.1.526 (New York) | L5F/T95I/D253G | E484K | D614G | A701V |
| A.23.1(Liverpool) | R102I/F157L | V367F±E484K | Q613H/P681H | |
| A.27 | L18F | L452R/N501Y(±S494P) | A653V/A655Y | D796Y/G1219V |
| B.1.1.318 | T95I/144del | E484K | D614G/P681H | D796H |
| R.1 | W152L | E484K | D614G | G769V |
| B.1.1.298 (Denmark) | ±69-70del | Y453F | D614G | |
| B.1.617.1 (India) | E154K±(T95I/G142D) | L452R/E484Q | D614G/P681R | Q1071H or H1101D |
| B.1.1.519 (Mexico/US) | | T478K | D614G/P681H | T732A |
| B.1.214.2 (Belgium) | L5F/ins214TDR | Q414K/N450K | D614G | T716I |
| A.VOI.V2 (Tanzania) | D80Y/144del/210del/D215G /246-248del/L249M/W258L | R346K/T478R/E484K | H655Y/P681H | Q957H |






https://covid.cdc.gov/covid-data-tracker/#variant-proportions






Corti Cell 2021

# COVID-19 in Immunocompromised Host

- Continue to be at increased risk of COVID-19 hospitalization and death in immunocompromised individuals
- Breakthrough COVID-19 infections occur despite vaccination
- Best strategies of when to use monoclonal antibodies
  - Pre-exposure
  - Post-exposure
  - Treatment of mild, moderate or severe disease
  - Combination therapy

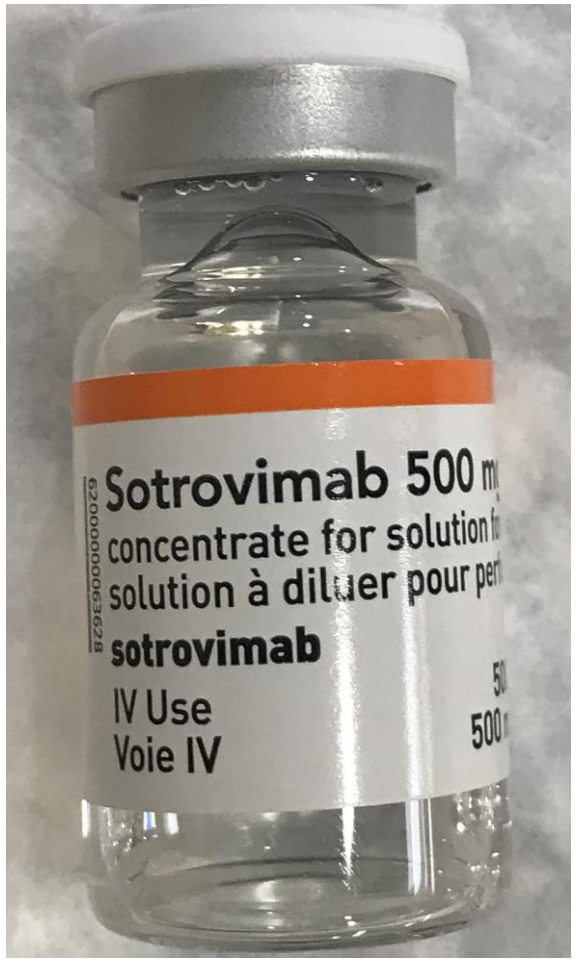
# COVID-19 in Immunocompromised Host

- Continuation of monitoring for VOC – with currently approved monoclonal antibody per each country
- Monoclonal antibodies are limited to children and adults 12 years and older
- Global access
- Important to include them in clinical trials
  - Especially with future monoclonals (e.g. influenza, CMV, etc.)

# THANK YOU --
# QUESTIONS?




# May 2021
# FDA issued an emergency use authorization (EUA) Early Treatment






JAMA

**QUESTION** Among patients at risk of disease progression, does early treatment of mild to moderate COVID-19 with the neutralizing antibody sotrovimab prevent progression to severe disease?

**CONCLUSION** The findings support sotrovimab as a treatment option for nonhospitalized, high-risk patients with mild to moderate COVID-19, although efficacy against SARS-CoV-2 variants that have emerged since the study was completed is unknown.

**POPULATION**

572 Women
485 Men

Adults with symptomatic SARS-CoV-2 infection

Median age: 53 years

**LOCATIONS**

57 Clinic sites worldwide

**INTERVENTION**

1057 Patients analyzed

528 **Sotrovimab**
Single intravenous infusion with 500 mg of sotrovimab given over 1 hour on day 1

529 **Placebo**
Equal volume of saline placebo given over 1 hour on day 1

**PRIMARY OUTCOME**

All-cause hospitalization longer than 24 hours for acute illness management or death through day 29

**FINDINGS**

All-cause hospitalization or death

**Sotrovimab** 1% (6 of 528 patients)

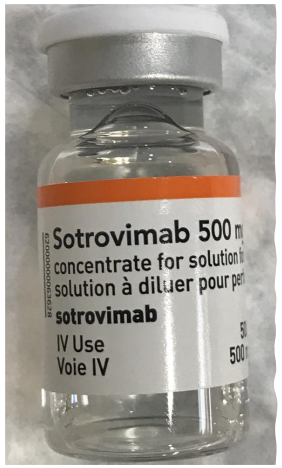
**Placebo** 6% (30 of 529 patients)

Sotrovimab vs placebo was significant:

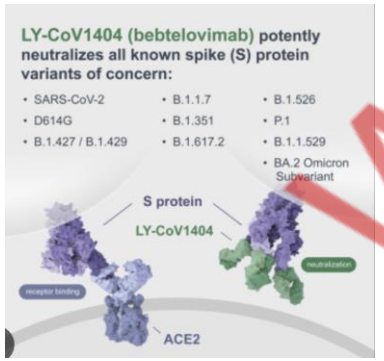
Adjusted relative risk, 0.21
(95% CI, 0.09 to 0.50)

Absolute difference, −4.53%
(95% CI, -6.70% to -2.37%)

# Risk of Antigenic Escape in Infections due to Mutations




**April 2022, the FDA withdrew the EUA**

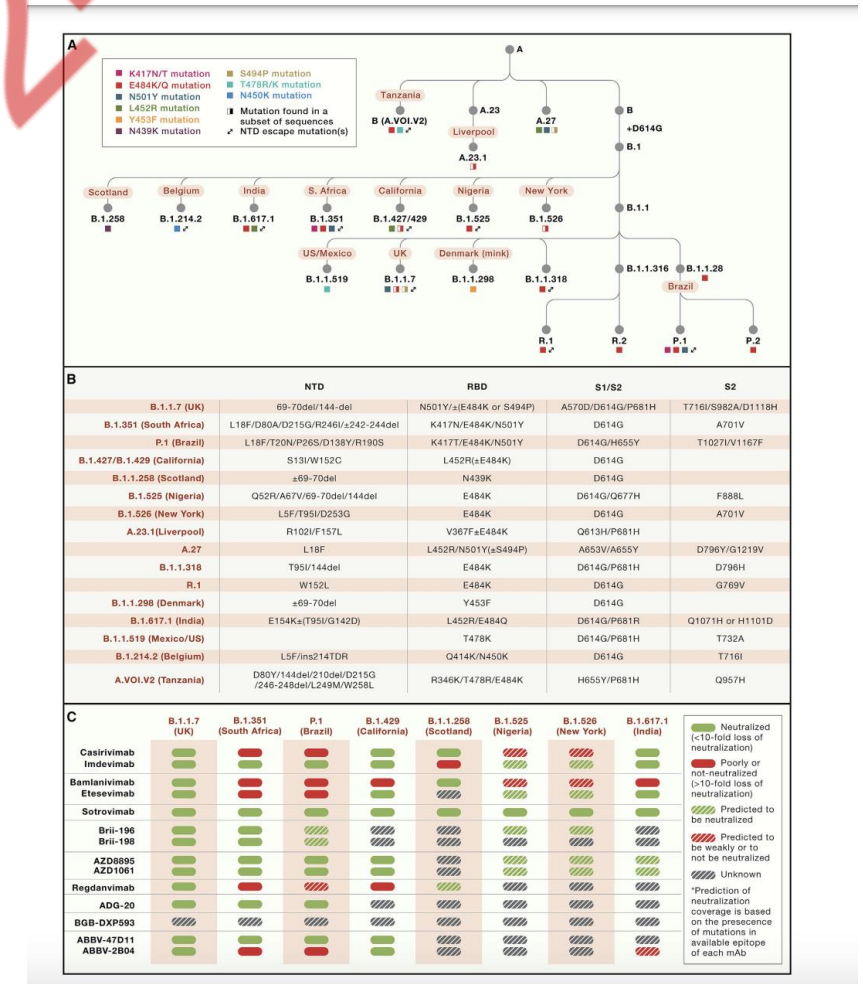




**February 2022**

Medical use in the United States via an emergency use authorization

**November 2022**

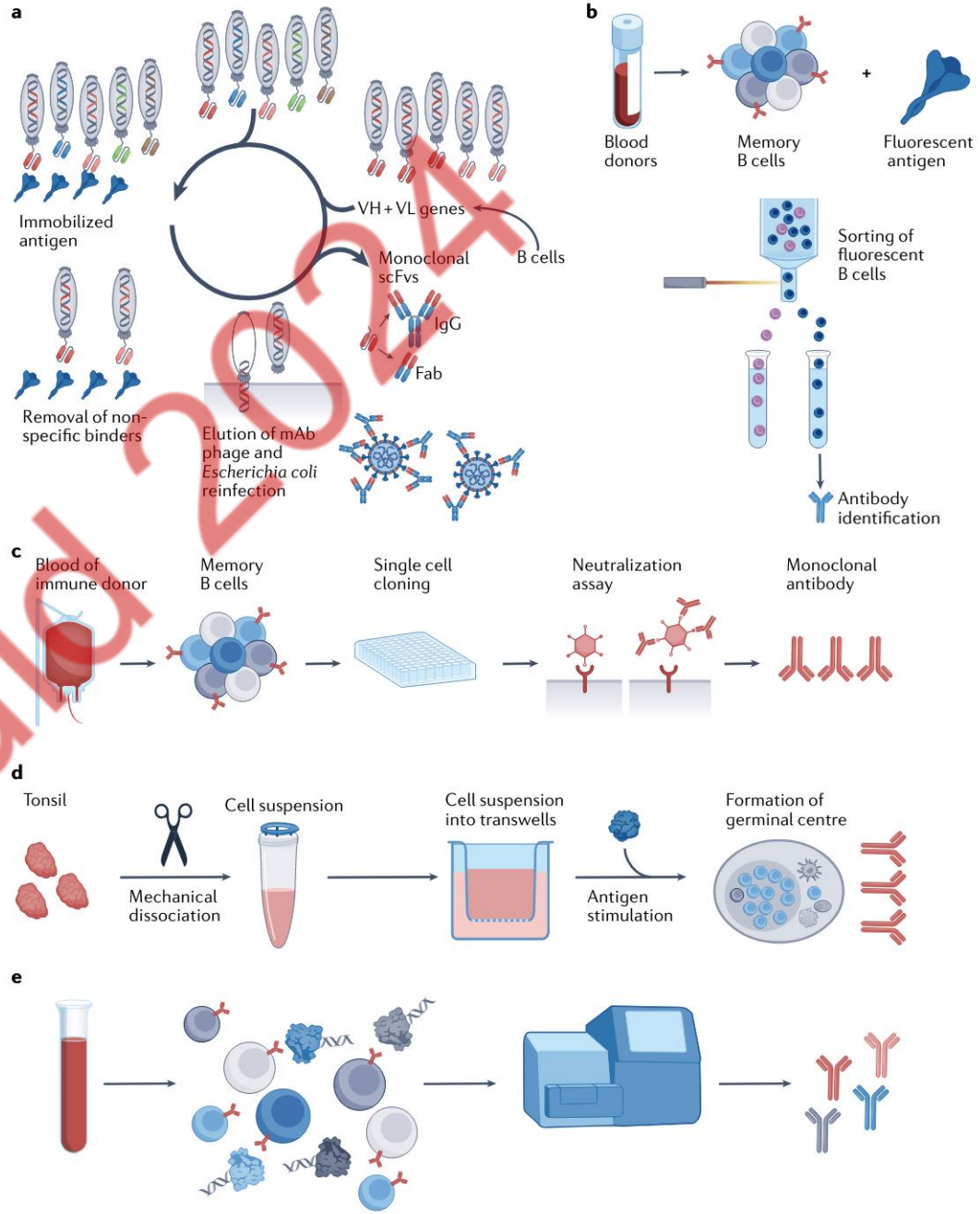
Not authorized for emergency use in the US because it is not expected to neutralize Omicron subvariants BQ.1 and BQ.1.1






Corti Cell 2021

# Antibody Discovery






Pantaleo Nature Reviews 2022

# Sipavibart for COVID-19 Pre-Exposure Prophylaxis SUPERNOVA Study

- Sipavibart was derived from B-cells donated by convalescent patients after SARS-CoV-2 infection.
- Sipavibart has been engineered using the same antibody scaffold as Evusheld and was optimised with the same half-life extension and reduced Fc effector function and complement C1q binding platform.
- The reduced Fc effector function aims to minimize the risk of antibody-dependent enhancement of disease - a phenomenon in which virus-specific antibodies promote, rather than inhibit, infection and/or disease.