Georgian Implementation Science Fogarty Training (GIFT) Program : Ilia State University and Yale U.

Accelerating Impact: Immersive Summer Bootcamp in Implementation Science and Biostatistics

11 July, 2024

How might one assess community effectiveness of vaccines? The test-negative case-control study and a case study of COVID-19

Sten H. Vermund, MD, PhD

Yale School of Public Health

Global Virus Network

Yale SCHOOL OF PUBLIC HEALTH

GVN GLOBAL VIRUS NETWORK

Outline

Yale

- **Introduction to translational research**
- Virology translational research example from a vaccine effectiveness study in the Dominican Republic
- Use of networks as a vehicle for translational research: Global Virus Network example
- Need for translational research in pandemic preparedness

Why do we need Implementation and Translational Science?

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Discovery does not always quickly lead to knowledge

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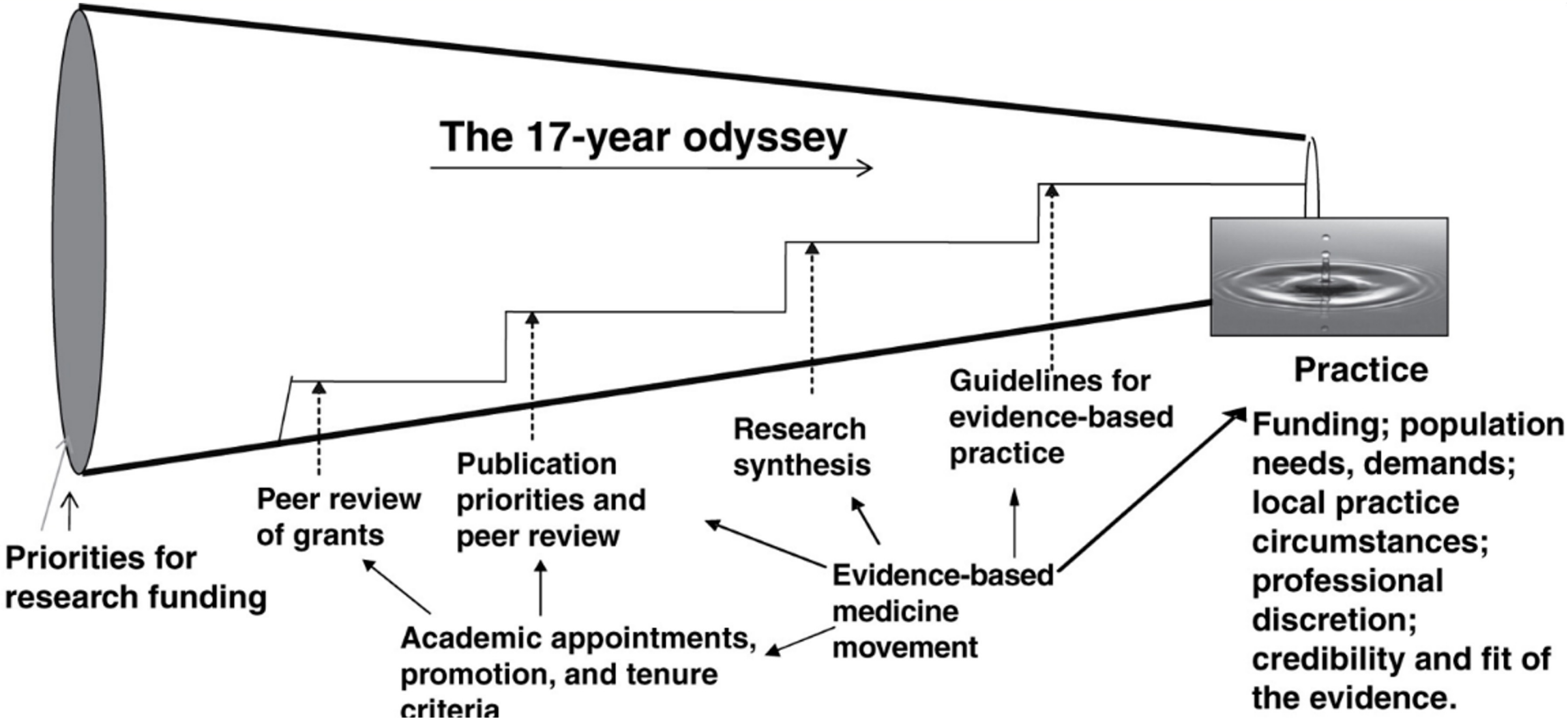

Green LW, et al. *Annu Rev Public Health* 2009; Morris ZS, et al. *J R Soc Med* 2011

Historical examples of slow and fast implementation

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Smallpox Vaccination
50+ years

Lady Montague, Edward Jenner

Peni cillin
15+ years

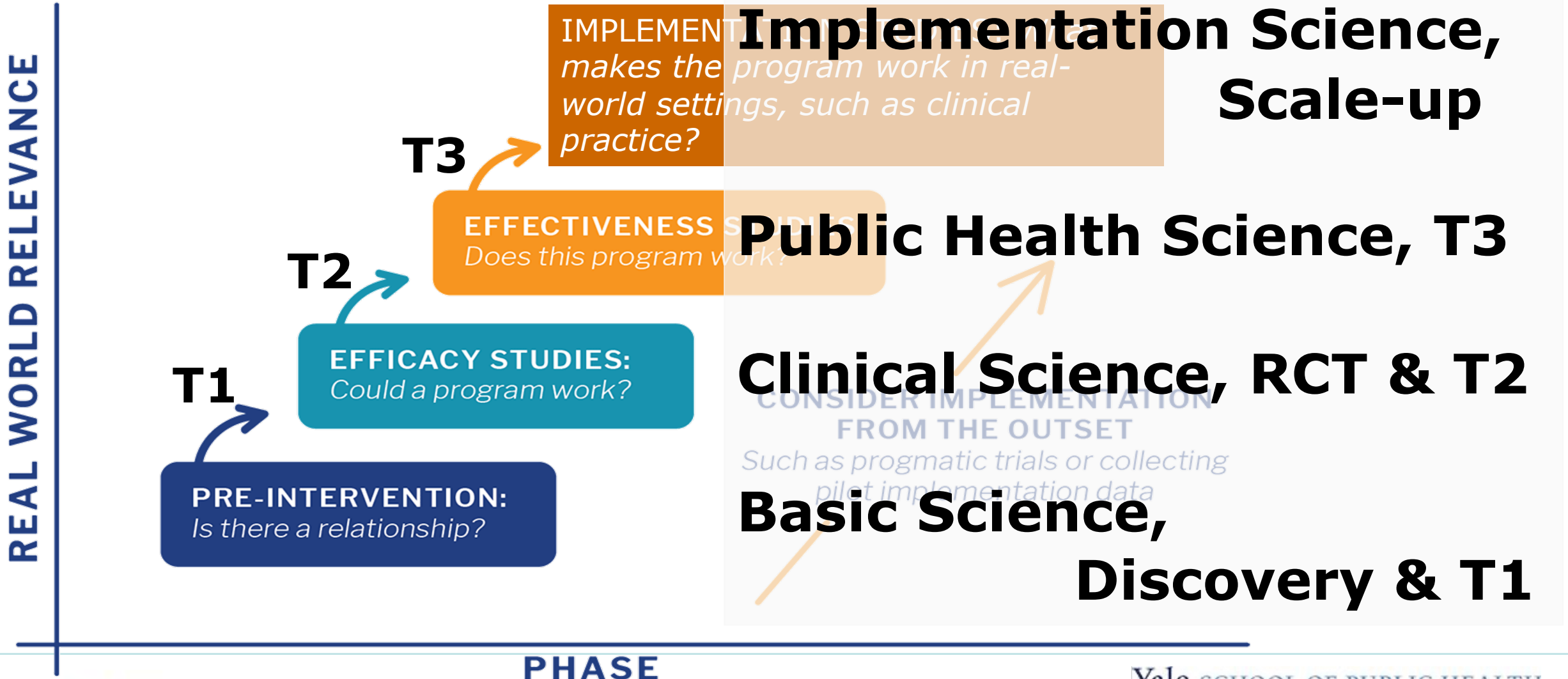
Fleming, Chain, Florey

Insuli n
6 months

Banting & Best

Translational research at many levels

Source: https://catalyst.harvard.edu/community-engagement/implementation-science/



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What is translational research?

Translation

Translation

Basic research in medicine, engineering, economics and the life, physical, computer and social sciences

Improved or novel **treatments and interventions**

Community application, penetration and cooperation

VCU Center for Clinical and Translational Research

VIRGINIA COMMONWEALTH UNIVERSITY

Translational research in microbiology

What do we mean by translational research?

- Laboratory and animal research to clinic
- Clinic to community
- Clinic/Community to scale for impact at a clinical/public health level (Implementation Science)

When is basic research ready for translation?

- Cell culture and appropriate animal model testing
- Efficacy and safety are demonstrated
- There are no clear, established guidelines

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What factors are needed to design basic experimental work to plan for later translation?

- Cell cultures and animal models that are appropriate for human translation
- Assess advantages of a drug, immunotherapeutic, vaccine, or other biologic of interest
- Document the mechanism of action with assessment of potential side effects and interactions
- Collect data with FDA/CTSA guidance to prepare for Phase I human clinical trials

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Why is translational research in virology so elusive?

Obstacles

- Suitable cell cultures and animal models
- No NIH criteria for translational work in grants
- Gap in physician-scientist workforce
- Failure of PhD and MD scientists to engage

How to overcome them

 Right model to ask the right questions

 Scientists promote best lab and practice standards

 Centers to create collaborative dynamics/incentives; K23 awards

 Nurtured interactive meetings, seminars, and projects (e.g., GIFT, CIRA)

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How do we design clinical trials to better inform further basic science (feedback loops)?

- Basic scientists can join clinical researchers in the design, follow up, and interpretation of clinical trials
  - Influence on the quantity, type, and costs of sample collections
  - Subsidies from research grants for satellite research, indirect cost returns, enlightened trial sponsors
- Plan what we can learn from negative trials

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New platforms of Big data, Artificial intelligence, Machine learning, Integrative structural biology

- CTSAs provide a platform where scientists can examine clinical trials to consider important ancillary studies
  - Conscientious efforts for universities to nurture MD and PhD engagement
- Open access to data between networks
  - Easy to find and understand the trial, the specimens, and the data, including beyond one's own institution

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GLOBAL VIRUS NETWORK

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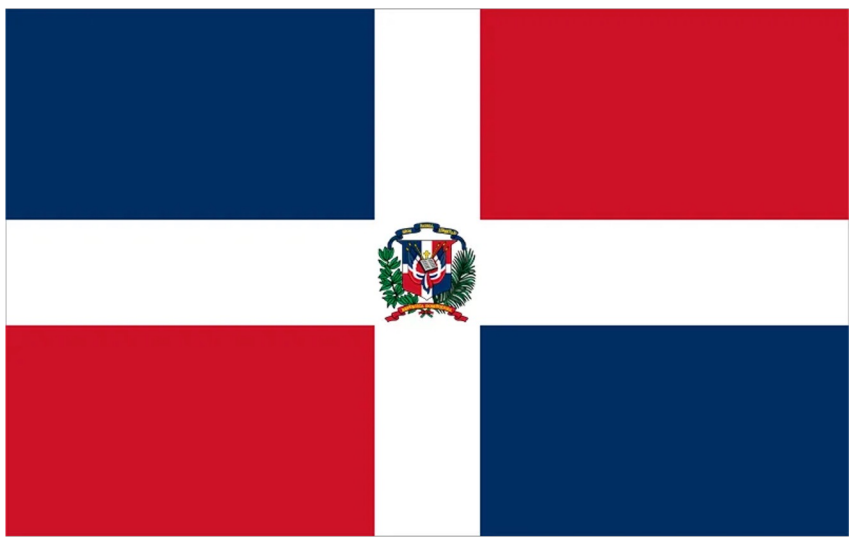
Studies of COVID-19 Vaccine Effectiveness in the Dominican Republic: 2021-2022

- To determine the effectiveness of the vaccine in real world field conditions in the Dominican Republic
- Important, since the inactivated SARS-CoV-2 vaccine is not as immunologically potent as the mRNA vaccine and 8+ billion doses have been given
  - Some argue “wait for the better vaccine”
  - Others say, “use what we have available to us”
  - But all agree to answer, “were these worthwhile or a waste of time?”

Methods (August to November 2021)

- A test-negative case-control study to assess the real-world effectiveness of nationwide COVID-19 vaccination program using an inactivated SARS-CoV-2 vaccine (CoronaVac™) on reducing symptomatic SARS-CoV-2 infections, hospitalizations, and deaths
- Participants suspected as having COVID-19 recruited from 10 hospitals in 5 provinces (+PCR were cases; others were controls)
- Estimated the effectiveness of full immunization (≥14 days after receipt of the second dose) and partial immunization
- Vaccine effectiveness estimated with multivariable adjustment for individual demographic and clinical characteristics

Dominican Republic



Effectiveness of CoronaVac against **symptomatic COVID-19 illness**

Variable	N = 1078	Hospitalized n = 395 (36.6%)	Crude OR (95% CI)	Adjusted OR (95% CI)	Vaccine effectiveness (1-adjusted OR, %)
Age, years					
18-59	905	308 (34.0)	1.0	1.0	
≥60	173	87 (50.3)	1.96 (1.41, 2.72)	**1.88 (1.35, 2.62)**	
Sex					
Male	409	157 (38.4)	1.0		
Female	669	238 (35.6)	0.89 (0.69, 1.14)	-	
Obesity: Body Mass Index ≥30kg/m^2					
No	810	288 (35.6)	1.0		
Yes	268	107 (39.9)	1.21 (0.91, 1.60)	-	
Comorbidities					
0	656	224 34.1)	1.0		
≥ 1	422	171 (40.5)	1.31 (1.02, 1.69)	-	
Vaccination status					
Unvaccinated	255	114 (44.7)	1.0	1.0	
Partially	93	26 (28.0)	0.48 (0.29, 0.80)	**0.51 (0.30, 0.86)**	**49 (14-70)**
Fully	730	255 (34.9)	0.66 (0.50, 0.89)	**0.69 (0.52, 0.93)**	**31 (7-48)**

Effectiveness of CoronaVac vaccine against **hospitalization**

Variable	N = 1078	Hospitalization n = 142 (13.2%)	Crude OR (95% CI)	Adjusted OR (95% CI)	Vaccine effectiveness (1-adjusted OR, %)
Age, years					
18-59	905	85 (9.4)	1.0	1.0	
≥60	173	57 (32.9)	4.74 (3.22, 6.99)	**4.06 (2.62, 6.28)**	
Sex					
Male	409	59 (14.4)	1.0	-	
Female	669	83 (12.4)	0.84 (0.59, 1.20)		
Obesity (BMI≥30 kg/m^2)					
No	810	93 (11.5)	1.0	1.0	
Yes	268	49 (18.3)	1.73 (1.18, 2.52)	**1.82 (1.20, 2.74)**	
Comorbidities					
0	656	60 (9.1)	1.0	1.0	
≥ 1	422	82 (19.4)	2.40 (1.67, 3.43)	**1.53 (1.02, 2.30)**	
Vaccination status					
Unvaccinated	255	71 (27.8)	1.0	1.0	
Partially	93	8 (8.6)	0.24 (0.11, 0.53)	**0.30 (0.13, 0.66)**	**70 (34-87)**
Fully	730	63 (8.6)	0.25 (0.168, 0.36)	**0.26 (0.17, 0.38)**	**74 (62-83)**

Conclusions

- The inactivated SARS-CoV-2 vaccine was highly effective in preventing hospitalization and death from COVID-19 in the time of ancestral and delta strain transmission
- The DR findings support other studies (Chile, Brazil, Indonesia, Turkey) that indicate that **lives were saved, and hospitalizations avoided with the early deployment of this vaccine**
- Widespread use of vaccination is a major tool for reducing serious COVID-19 disease and death

Pérez-Then E, Miric M, Qian HZ, et al, Vermund SH; DR Vaccine Study Team. **Population-Level Effectiveness of an Inactivated Whole-Virion COVID-19 Vaccine: A Test Negative Case-Control Study in the Dominican Republic.** *Open Forum Infect Dis* 2023;10(3):ofad075.

Opportunity: DR chose to boost with heterologous vaccine, and we could look at SARS-CoV-2 Variants and Vaccine induced-Immunity

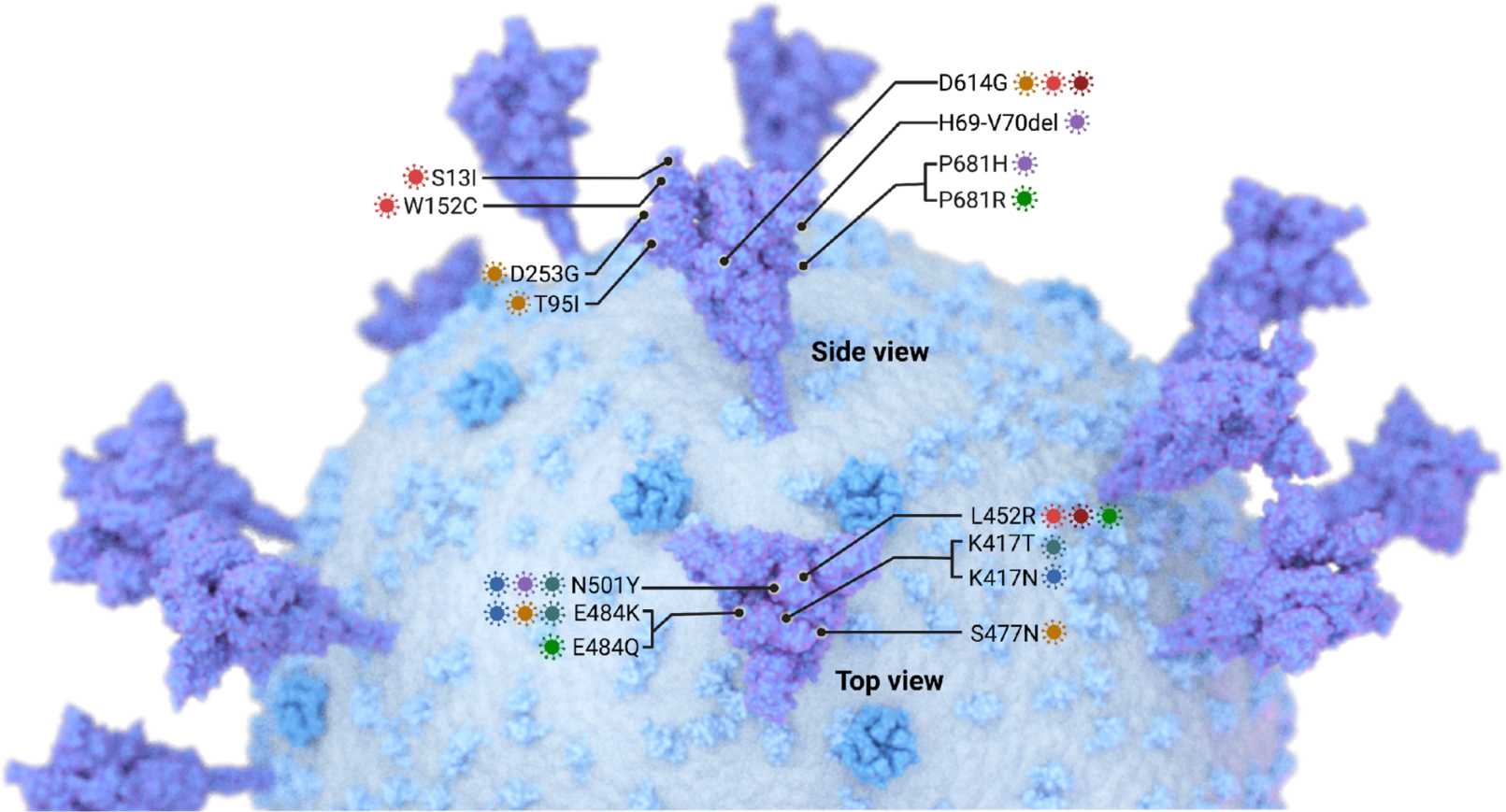
Variants of Concern:

Transmissibility

Severity

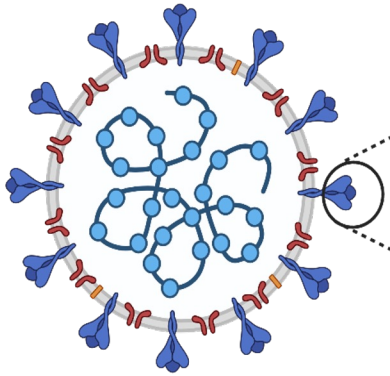
Vaccine efficacy

B.1.1.7	B.1.351	P.1	B.1.526	B.1.427	B.1.429	B.1.617
Discovered: Dec. 14 2020	Discovered: Dec. 18 2020	Discovered: Dec. 4 2020	Discovered: Nov. 2020	Discovered: Dec. 2020	Discovered: Nov. 2020	Discovered: Oct. 2020



SARS-CoV-2 spike protein

1



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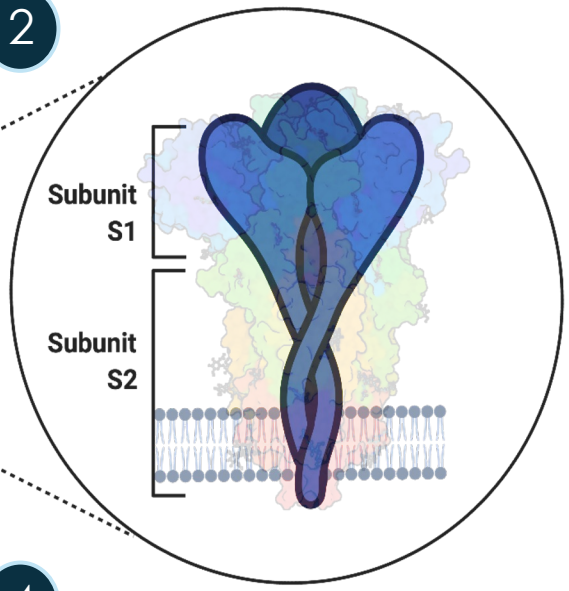

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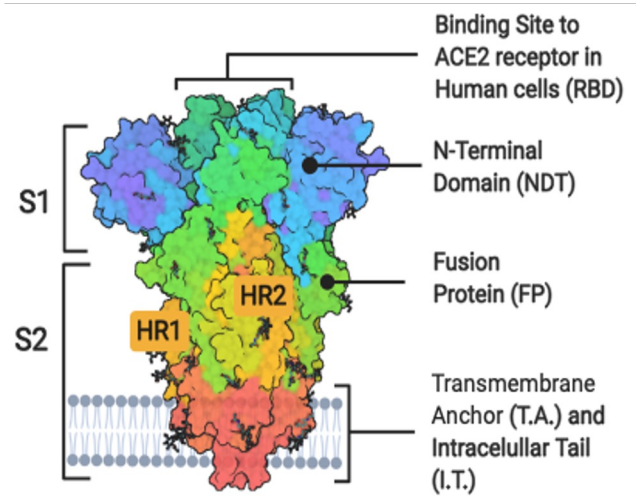

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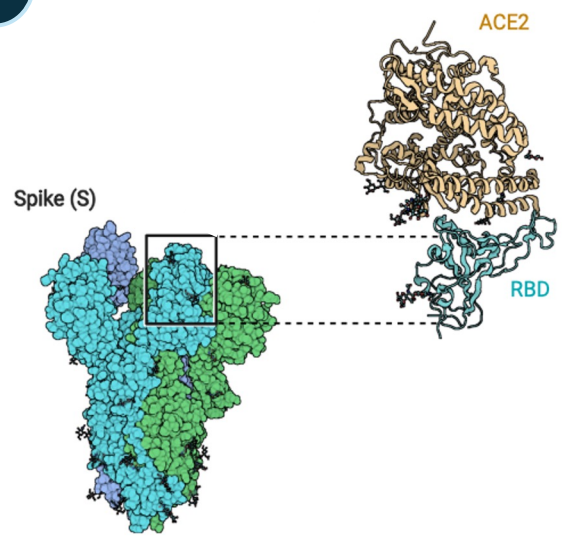
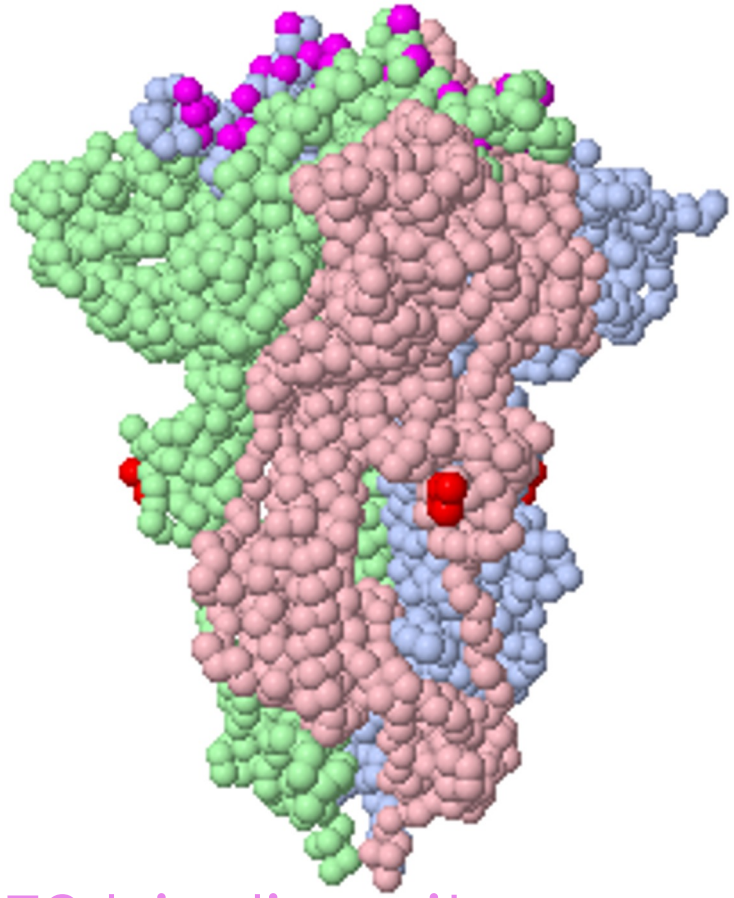




ACE2 binding site

Furin cleavage site

Jmol

Emergency of Omicron and Vaccine induced-Immunity

Variants of Concern (VOCs)

B.1.17 (α)

First reported:
Sept 2020 in the
United Kingdom

B.1.351 (β)

First reported:
Oct 2020 in
South Africa

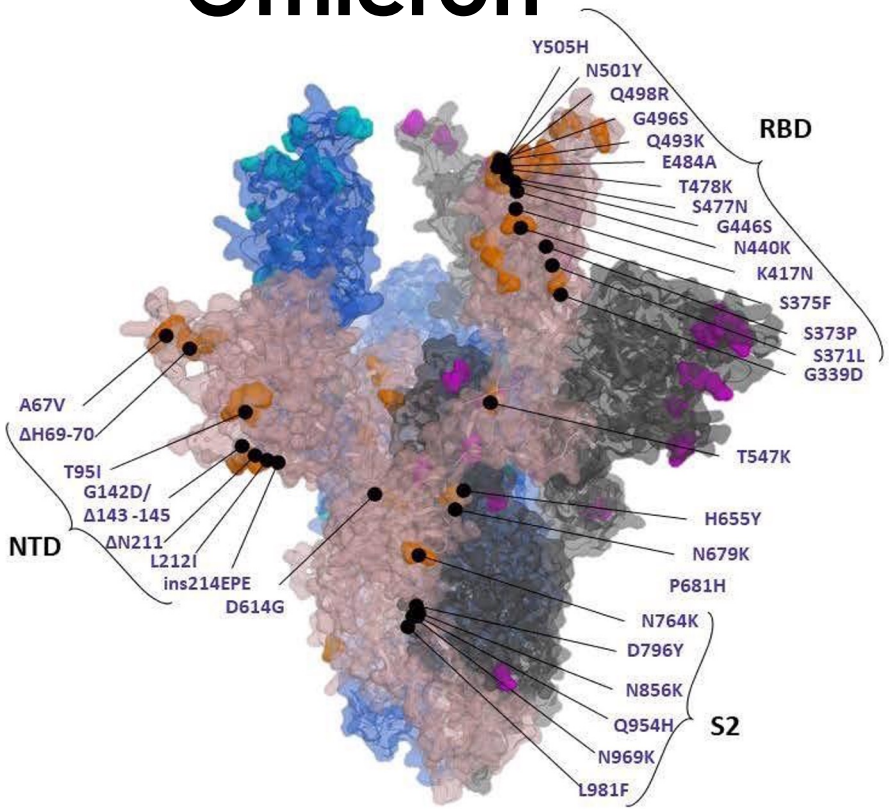
P.1 (γ)

First reported:
Dec 2020 in
Brazil

B.1.617.2 (δ)

First reported
Oct 2020 in
India

Omicron



Nov. 2021 in South Africa and Botswana

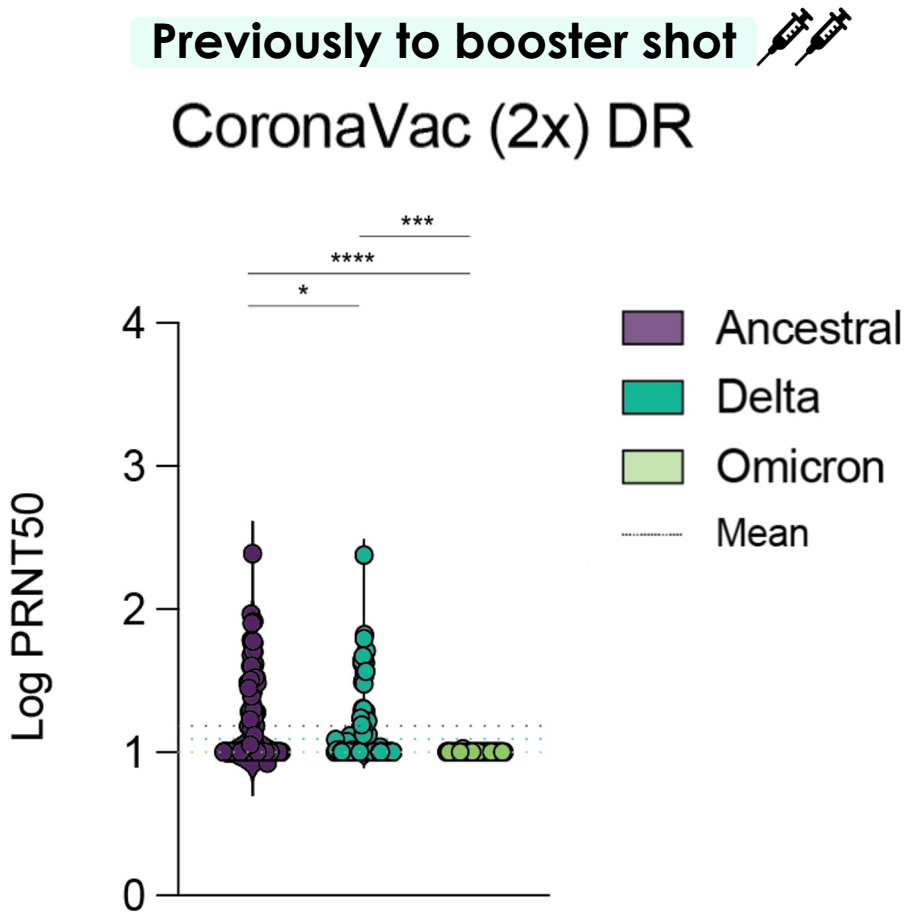
Shah M, Woo HG. **Omicron: A Heavily Mutated SARS-CoV-2 Variant Exhibits Stronger Binding to ACE2 and Potently Escapes Approved COVID-19 Therapeutic Antibodies**. *Front Immunol* 2022;12:830527.

Additional COVID-19 vaccine study - I

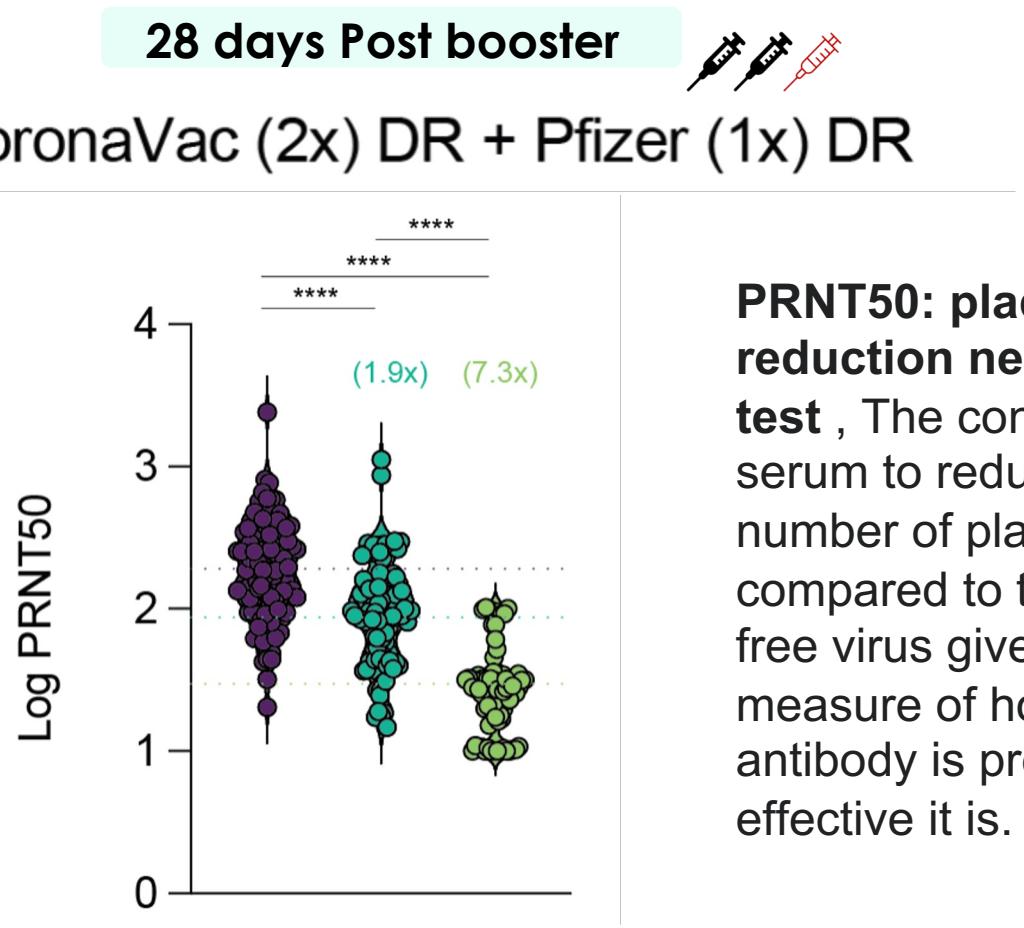
- What is the effect of mRNA vaccine boosting in persons who have received two doses of inactivated vaccine (primary series)? (DR government purchased Pfizer/BioNTech mRNA vaccine for SARS-CoV-2 boosting in 2021)
- We collected blood specimens before the mRNA dose and periodically after boosting (inactivated vaccine as prime doses)
- Results: Two inactivated vaccines followed by one mRNA booster were just as immunogenic as two mRNA vaccines, using phone reactivity to spike protein and receptor binding domain by ELISA
  - **Vital information for all nations using inactivated vaccines!**

Neutralization titers against Omicron were significantly reduced compared to ancestral virus and Delta variant post booster

Previously to booster shot



28 days Post booster



PRNT50: plaque reduction neutralization test , The concentration of serum to reduce the number of plaques by 50% compared to the serum free virus gives the measure of how much antibody is present or how effective it is.

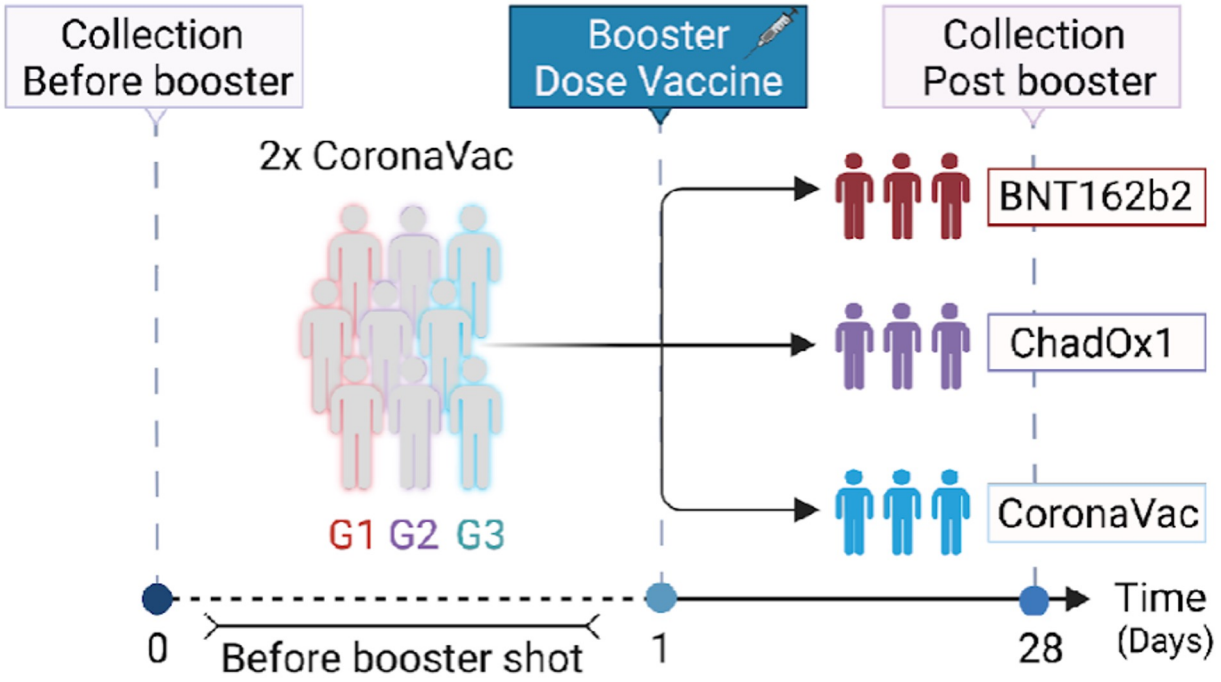
Pérez-Then E, Lucas C, Monteiro VS, et al, Vermund SH, Iwasaki A. **Neutralizing antibodies against the SARS-CoV-2 Delta and Omicron variants following heterologous CoronaVac plus BNT162b2 booster vaccination.** *Nat Med* 2022;28:481-5.

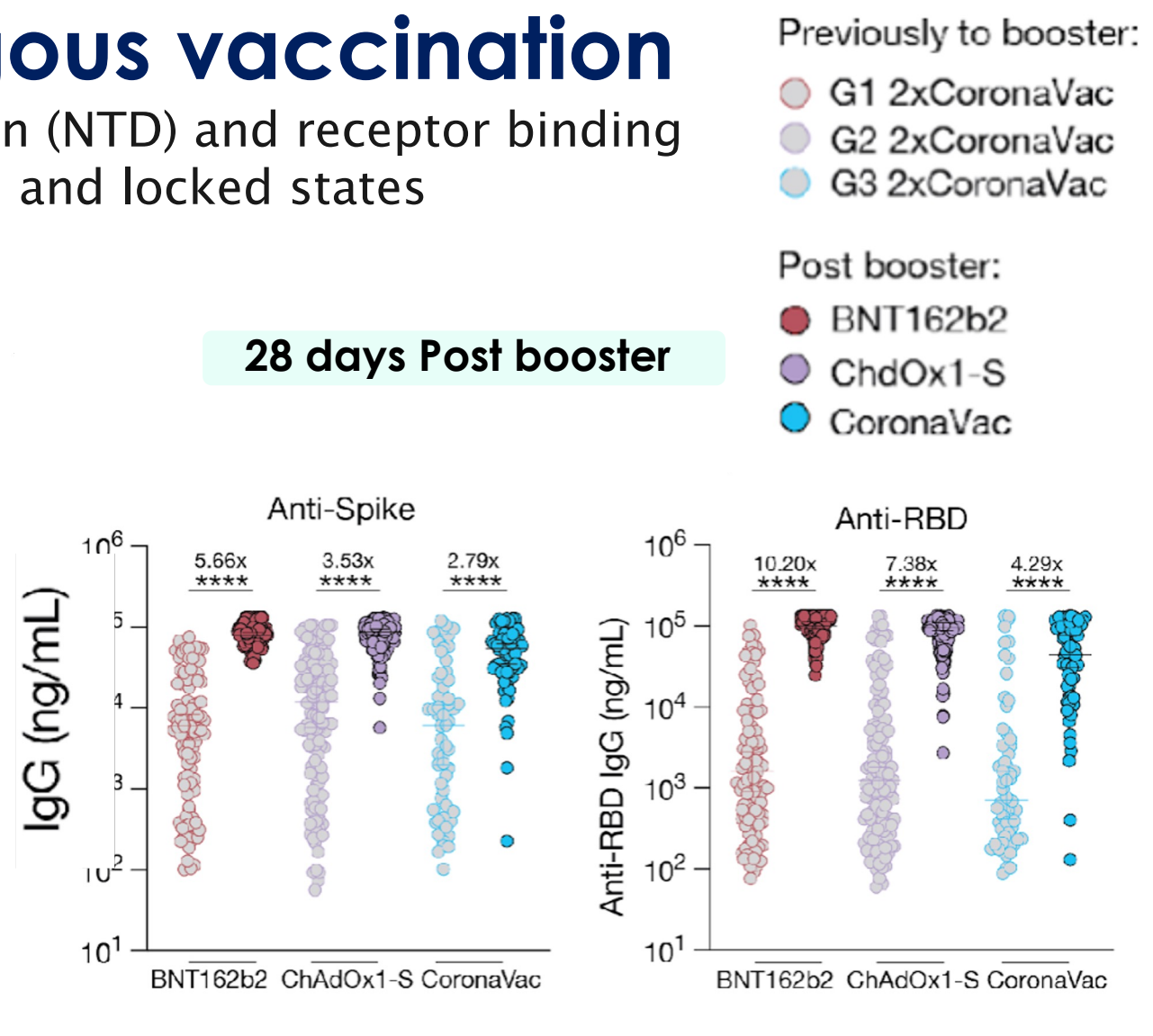
Additional COVID-19 vaccine study - II

- Do homologous versus heterologous booster doses in those fully vaccinated with CoronaVac induce distinct humoral responses? Do responses vary across age groups?
- Results: IgG against SARS-CoV-2 spike or receptor binding domain, and neutralization titers against Omicron sublineages were **substantially reduced** in participants receiving homologous CoronaVac™ vs. heterologous BNT162b2 or ChAdOx1 booster, esp. in recipients >50 yrs old
  - **A second study confirming the wisdom of heterologous boosting!**

Homologous *vs.* heterologous vaccination

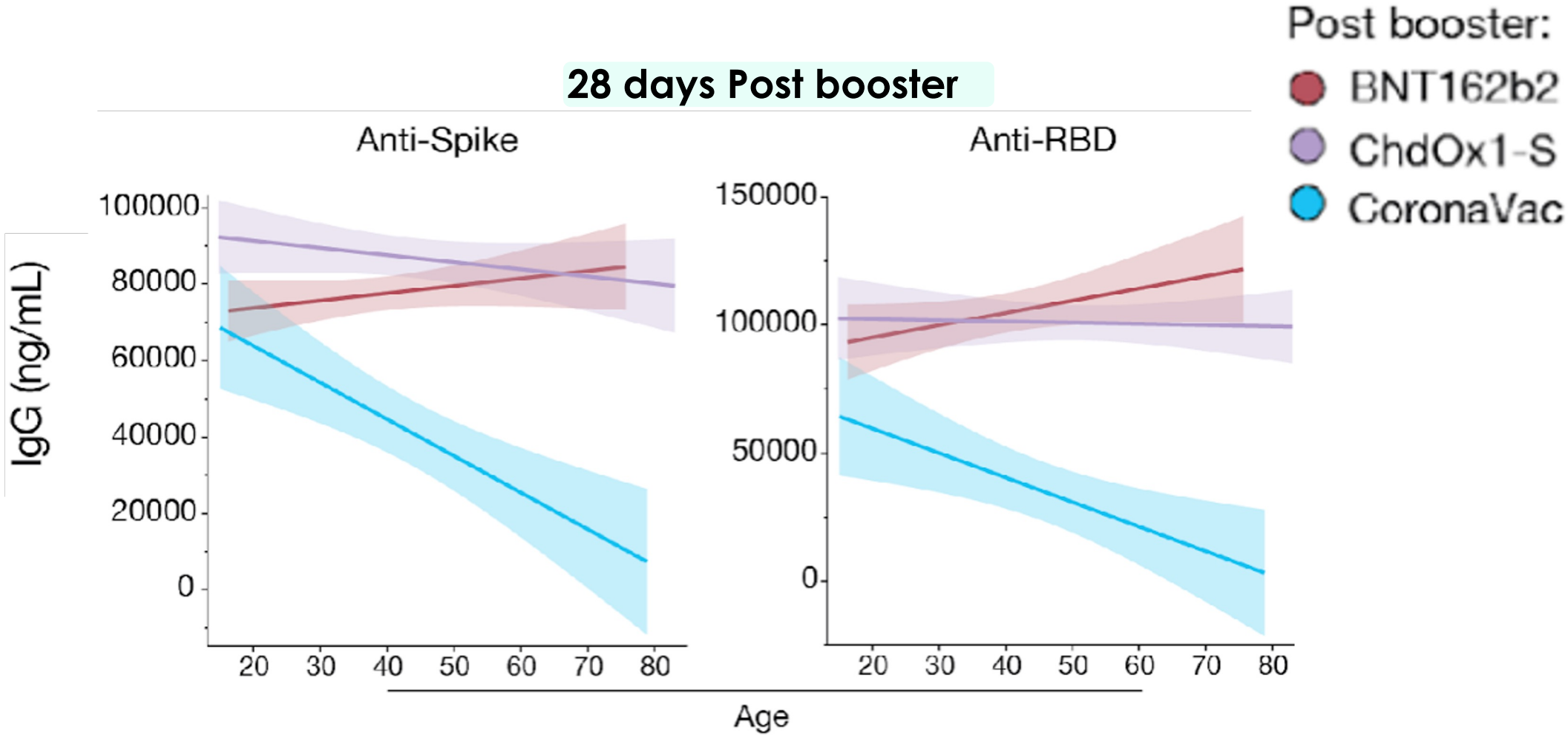
Conformational states of the N-terminal domain (NTD) and receptor binding domain (RBD) can move between open, closed, and locked states





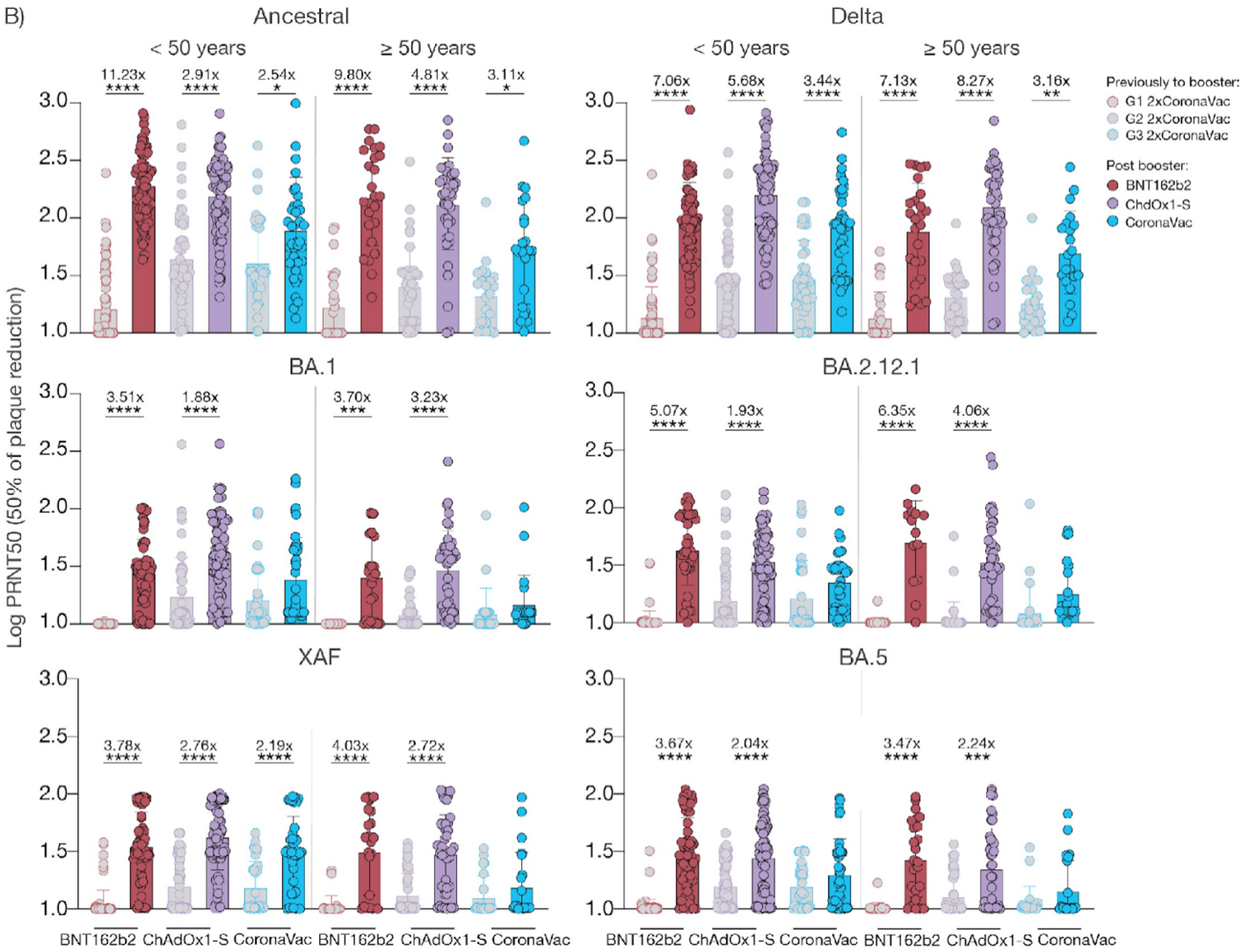
Filardi BA, Monteiro VS, Schwartzmann PV, et al. **Age-dependent impairment in antibody responses elicited by a homologous CoronaVac booster dose.** *Sci Transl Med* 2023;15(683): eade6023

Defective age-associated SARS-CoV-2 antibody response post CoronaVac homologous, but not heterologous vaccination-booster regimen



Filardi BA, et al. *Sci Transl Med* 2023; 15(683): eade6023

3 Emergency of Omicron and Vaccine induced-Immunity



Homologous regimen induces lower virus-specific antibody responses with a remarkable impact in older participants

Lower antibody response is vaccine-specific, rather than resulting from an aging-associated impaired immune response.

Homologous CoronaVac boosters do not improve neutralization responses against Omicron sub-lineages in older adults

Filardi BA, et al. *Sci Transl Med* 2023; 15(683): eade6023

Additional COVID-19 vaccine study - III

- Do mRNA vaccines cause fetal defects of anti-syncytin-1 Ab production?
- Answer: No (multiple cohorts including the D.R.)

Ref: Lu-Culligan A, Tabachnikova A, Pérez-Then E, et al, Iwasaki A. **No evidence of fetal defects or anti-syncytin-1 antibody induction following COVID-19 mRNA vaccination**. *PLoS Biol* 2022; 20(5):e3001506.

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- **Global Virus Network as a vehicle for translational research**
- Need for translational research in pandemic preparedness

The Global Virus Network

- 80+ Centers of Excellence and Affiliated Institutions
- 10 Senior Advisors
- 40+ Countries on 6 continents

“All Regions, All People”

- GVN Centers of Excellence (CoE)
- GVN Affiliate Centers
- GVN CoE in the Institut Pasteur Network

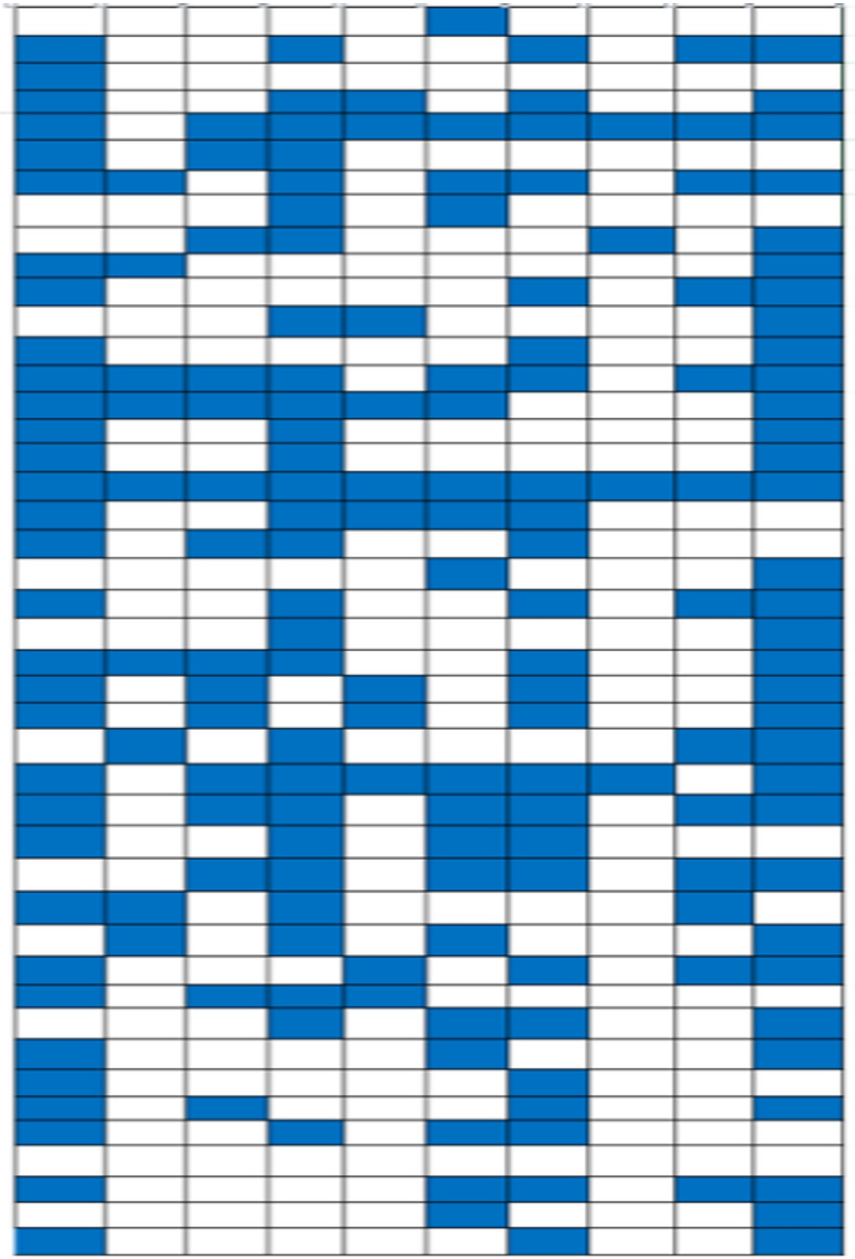
GVN Mission

- To combat viral diseases through international collaborative research, surveillance, healthcare and public health solutions, professional training, public information-sharing, and policy guidance.

- To partner and collaborate with agencies, businesses, and other organizations dedicated to advancing global health.

Virus Expertise: GVN Centers of Excellence and Affiliates

Countries	Institutions
Argentina	IBBM, Universidad Nacional de La Plata
Australia	Peter Doherty Institute University of Melbourne
Belgium	Gembloux Agro-Bio Tech
China	National Centre for AIDS/STD Control & Prevention, China CDC
France	Institut Pasteur
Germany	Institute of Virology, Technical University of Munich
Germany	Robert Koch Institute, Berlin
Germany	Institute for Virology, Philipps-Universität Marburg
Germany	University of Veterinary Medicine Hannover
Grenada	St. George's University, Grenada, West Indies
India	Amrita Institute of Medical Sciences & Research Centre
India	Rajiv Gandhi Centre for Biotechnology (RGCB)
Ireland	Univ. College, Dublin
Israel	Tel Aviv University
Italy	University of Padova
Jamaica	University of West Indies
Japan	National Institute of Infectious Diseases
Netherlands	Erasmus University Hospital Rotterdam
Nigeria	Institute for Human Virology -Nigeria
Russia	Moscow Center for HIV/AIDS Prevention and Treatment
South Africa	NICD of the National Health Laboratory Service
South Korea	International Vaccine Institute
Spain	CReSA, Barcelona
Spain	Centro de Biología Molecular Severo Ochoa (CBMSO), Madrid
Sweden	Karolinska Inst. and Univ. Hospital, Stockholm
Estonia	University of Tartu
UK-England	The Pirbright Institute Pirbright
UK-Scotland	Scotland, United Kingdom, Medical Research Council, (MRC) Glasgow
USA	Johns Hopkins University
USA	The Scripps Research Institute, La Jolla
USA	J. Craig Venter Institute
USA	Univ. of Rochester Medical Center, School of Medicine and Dentistry
USA	University Texas Medical Branch, UTMB, Galveston
USA	Center for Global Health (CGH), University of Michigan
USA	University of Pittsburgh Cancer Institute
USA	Icahn School of Medicine at Mount Sinai
USA	Colorado State University, Fort Collins
USA	Gladstone Institute of Virology and Immunology
USA	Univeristy of Miami
USA	University of Buffalo
USA	Institute of Human Virology, UMD School of Medicine
USA	Emory University
USA	Tulane University School of Medicine
Vietnam	Vietnamese NIHE, Laboratory of Molecular Diagnostics



GVN Drs. Pan Zhang & Yang Liu Academy Program

- GVN Short Course in Translational Virology
- GVN Postdoctoral Fellowship Training Program
- GVN Rising Star Mentorship Program
- GVN Alumni Networking Series
- GVN Highschool Research Internships
- GVN Online Short Course


NIH


Pandemic Preparedness
• VRC had a partnership with Moderna to test a Nipah virus mRNA vaccine as a Pandemic Preparedness demonstration project

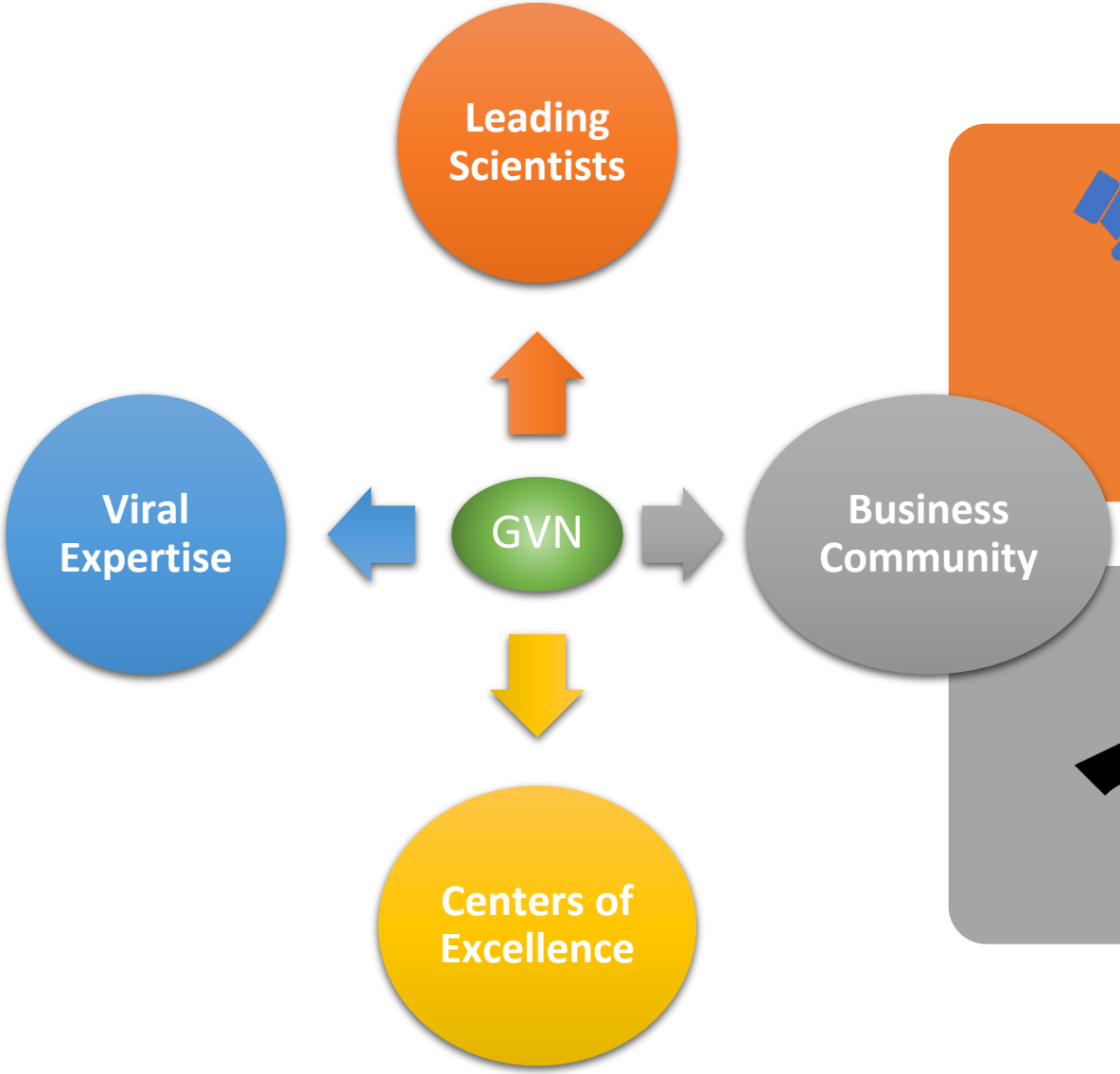

EXIT


zation summary groups

Action Committees

- Emerging Pathogens
- Hemorrhagic fever viruses
- Arboviruses
- Respiratory viruses, e.g., SARS-CoV-2, RSV, measles
- Viral detection and control
- Poxviruses
- Emerging Pathogens
- Post-Acute Infection Virus Syndromes, e.g., long-COVID

GVN Healthcare & Pharma Centers of Excellence Coalition (GHPC)



A **platform** for partnerships to strengthen international viral preparedness and response between business community and leading medical virologists

To support research, training activities and increased awareness of medical virology issues, and address the risks and impacts of human viral diseases, including SARS- CoV -2

Corporate Partnerships Activities Highlights

- Marburg Project
- Biobanking
- Emerging Pathogens Discovery Network Action Committee
- Postdoctoral Fellowship Training Program
- Testing Product Effectiveness against SARS-CoV-2
- Developing Product Testing Protocols
- Clinical and Genome Sequencing
- Validation of Diagnostic Testing Kits

- **Operationalize the Action Items for the GVN Strategic Plan for the Next 5 Years**
  --Use New Regional Representations and CoEs
  --Surveillance Program, incl. Wastewater
  --Expand online educational programs, e.g., short course
  --Bioinformatics; Bioanalytics; Artificial intelligence for pandemic preparedness

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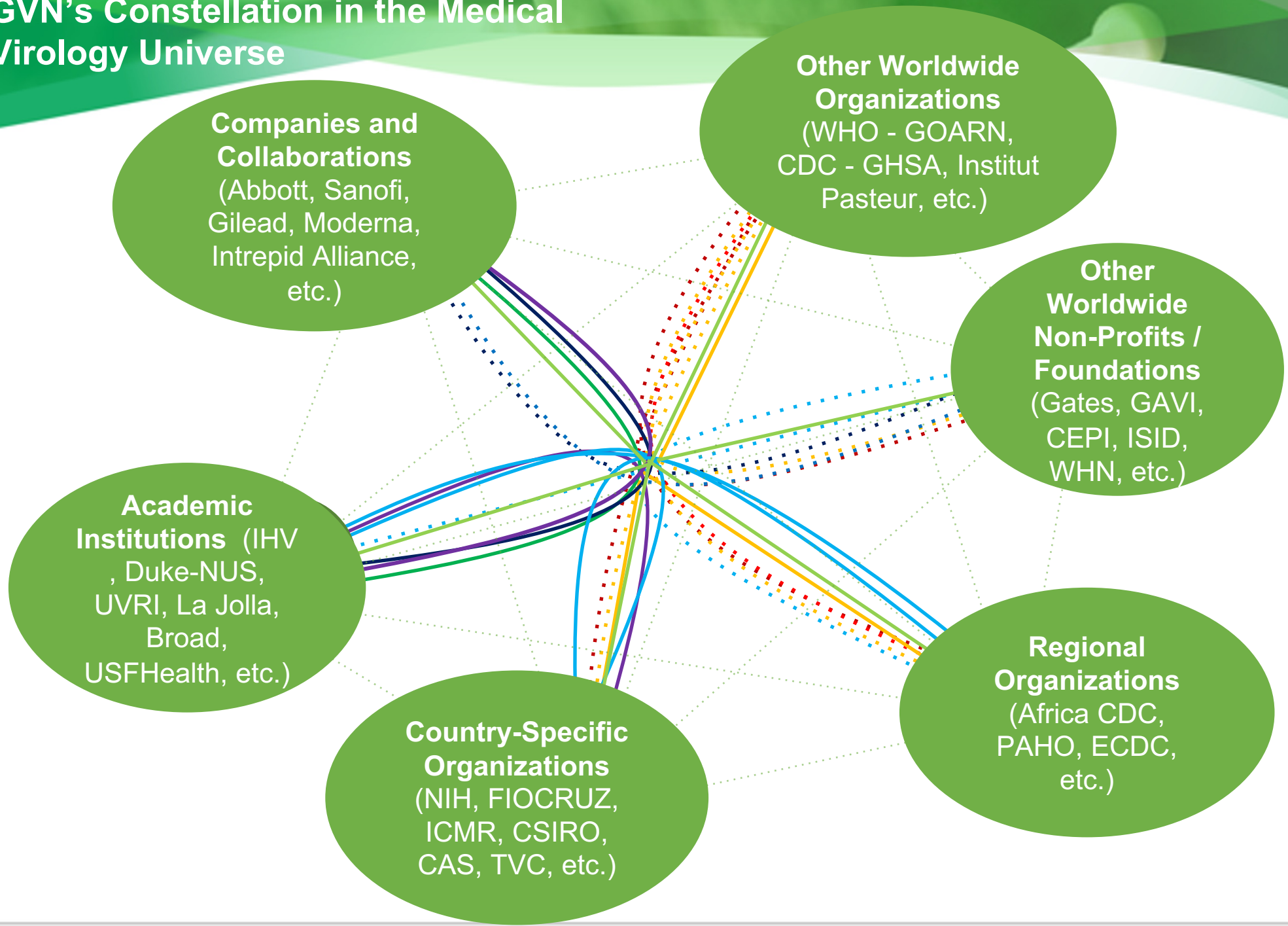
GLOBAL VIRUS NETWORK

GVN's Constellation in the Medical Virology Universe



GVN Present/Future Connections

- Viral Surveillance
- Responding to Outbreaks
- Stopping Epidemics/Pandemics
- Task Forces and Watch Groups
- Developing Vaccines
- Viral Research Projects
- Clinical Trials
- Developing Antiviral Therapies

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Epidemic: serious outbreak in a single community, population or region

Pandemic: multi-continent epidemic, likely infecting thousands or millions of persons

Pandemic flu: pandemic from an influenza virus strain that humans have not been previously exposed to ☐ genetic REASSORTMENT of an animal strain with a human strain

Pandemic	Dates	Estimated Deaths
“Asiatic” Flu	1889-1890	1 million
“Spanish” Flu	1918-1920	40 -100 million
“Asian” Flu	1957-1958	1 - 1.5 million
“Hong Kong” Flu	1968-1969	0.75 - 1 million

Today

- Modern travel such that 95% of humanity can visit each other within 48 hours
- Densely populated urban areas
- Population exceeds 8 billion

1918

- WW I
  - civilian/military overcrowding
  - Public information withheld
- Population approximately 1.8 billion

Pandemics of influenza

- Pandemic influenza: Reassortant virus to which humans have no significant immunologic memory or protection; Highly transmissible; Incubation period within travel times.
  - H5N1 is not yet sufficiently adapted for human transmission, but it can get there.
- Surveillance/recognition; Vaccine and treatment discovery and production capacities; Public health infrastructures; Global cooperation; Political will; Funding; Respiratory disease mitigation with masks, hygiene, ventilators in hospitals, workforce deployment

- The World Health Organization correctly predicts periodic influenza and other pandemics.

- Unknown when it will occur or how severe it will be

- Unknown what the organism will be

Collaborative allies can address a host of global disease surveillance, control, and prevention activities to respond to pandemic and epidemic threats: Georgia and the U.S. can collaborate with international partners in translational and implementation science research!

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