Surviving SARS-CoV-2:
Lessons From 40+ Years of HIV Research

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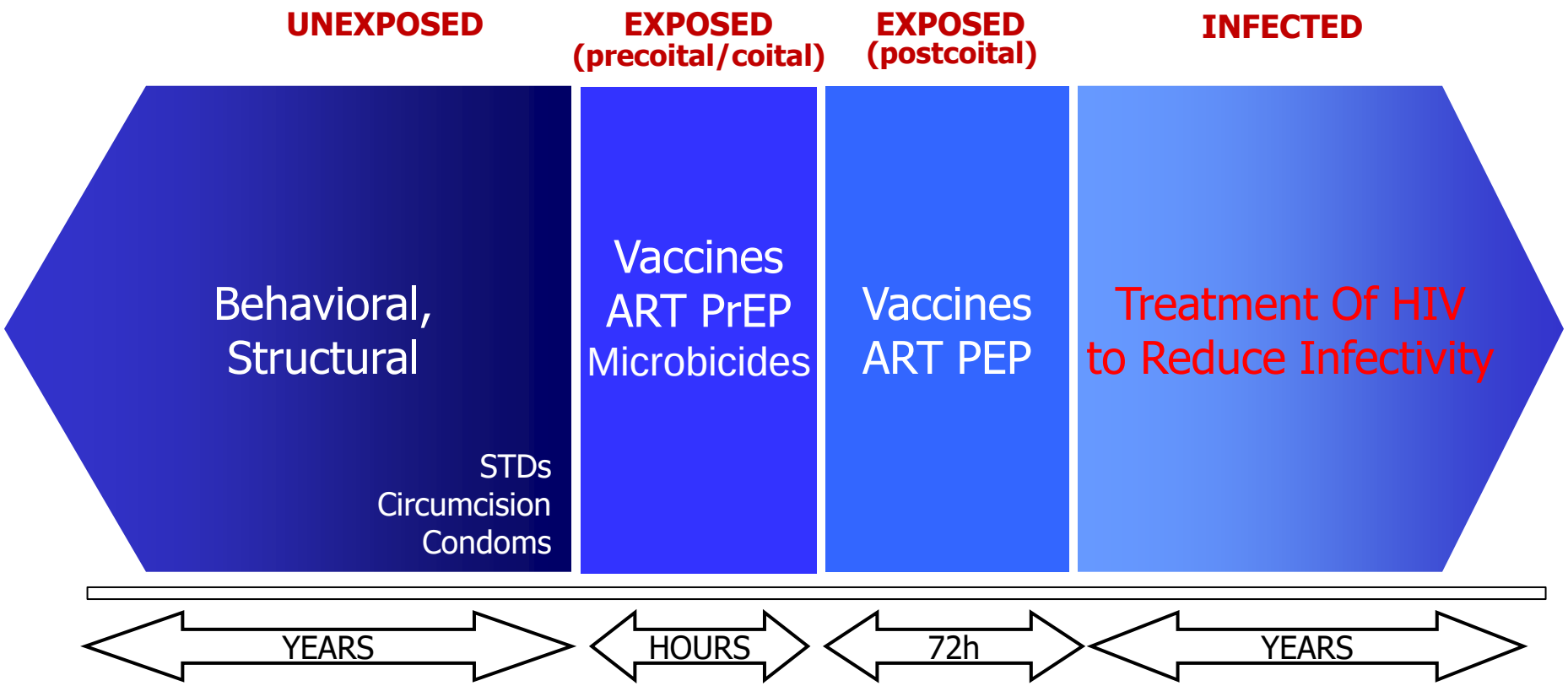
Four Prevention Opportunities

Cohen et al., JCI, 2008
Cohen et al., JIAS ,2008



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Current Guidelines

ART for Everyone…Urgently

- HIV replication has negative consequences
- Earlier ART prolongs survival (HPTN 052)
- ART blocks HIV transmission (HPTN 052)
- Early ART reduces the HIV latent reservoir

ART is recommended for virtually all HIV-infected individuals, as soon as possible after HIV diagnosis[a,b]

Saag MS, et al. *JAMA*. 2018;320:379-396; b. US DHHS Website.

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UNDETECTABLE = UNTRANSMITTABLE

Prevention Access Campaign

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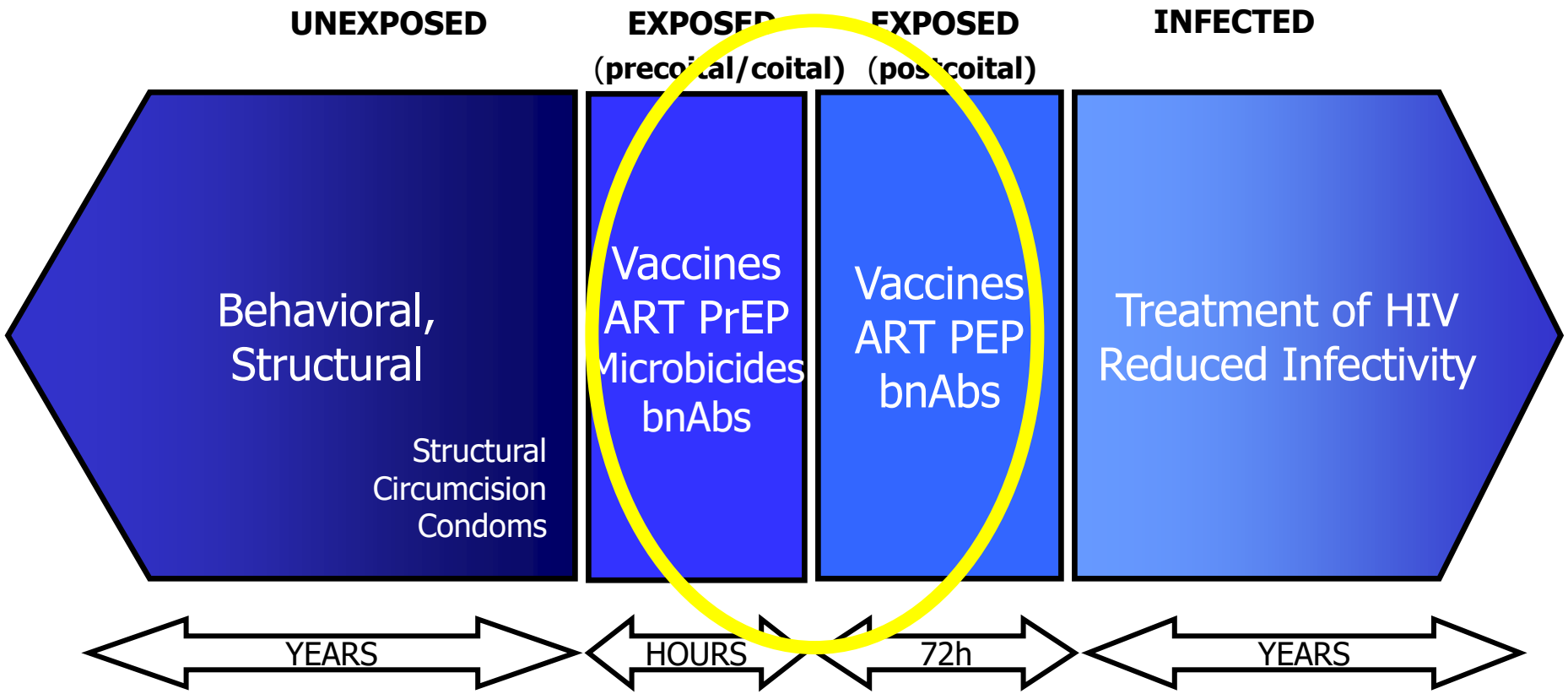

Cohen MS, et al. J Clin Invest. 2008;118:1244-1254
Cohen IAS 2008

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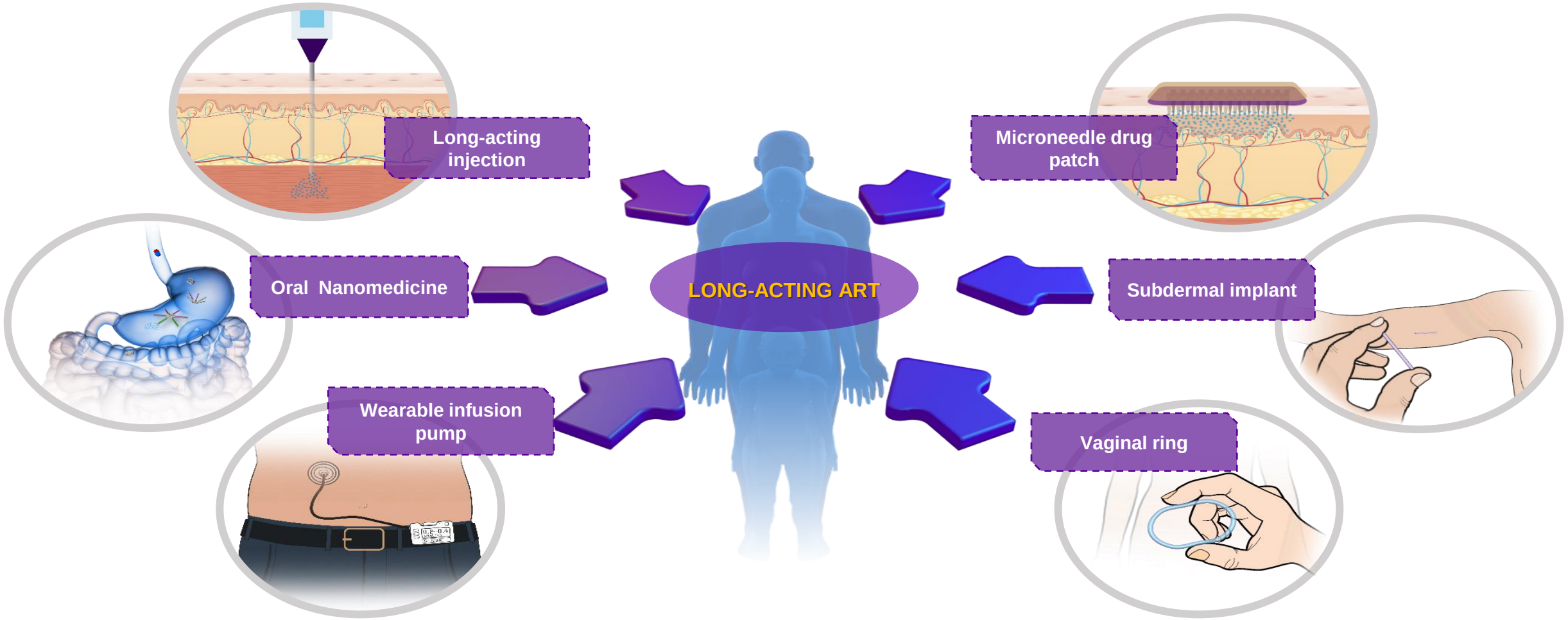
New Technologies in HIV PrEP



Adapted from Scarsi K, International Workshop on HIV & Women 2019.

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Alternative Long-Acting ARV Strategies

- Once a month pill (Merck, Islatravir)
- Implants (Islatravir, Cabotegravir)
- Needles and Patches (Academic Centers)
- Sub Q Capsid Inhibitors (Gilead, Lencapravir)

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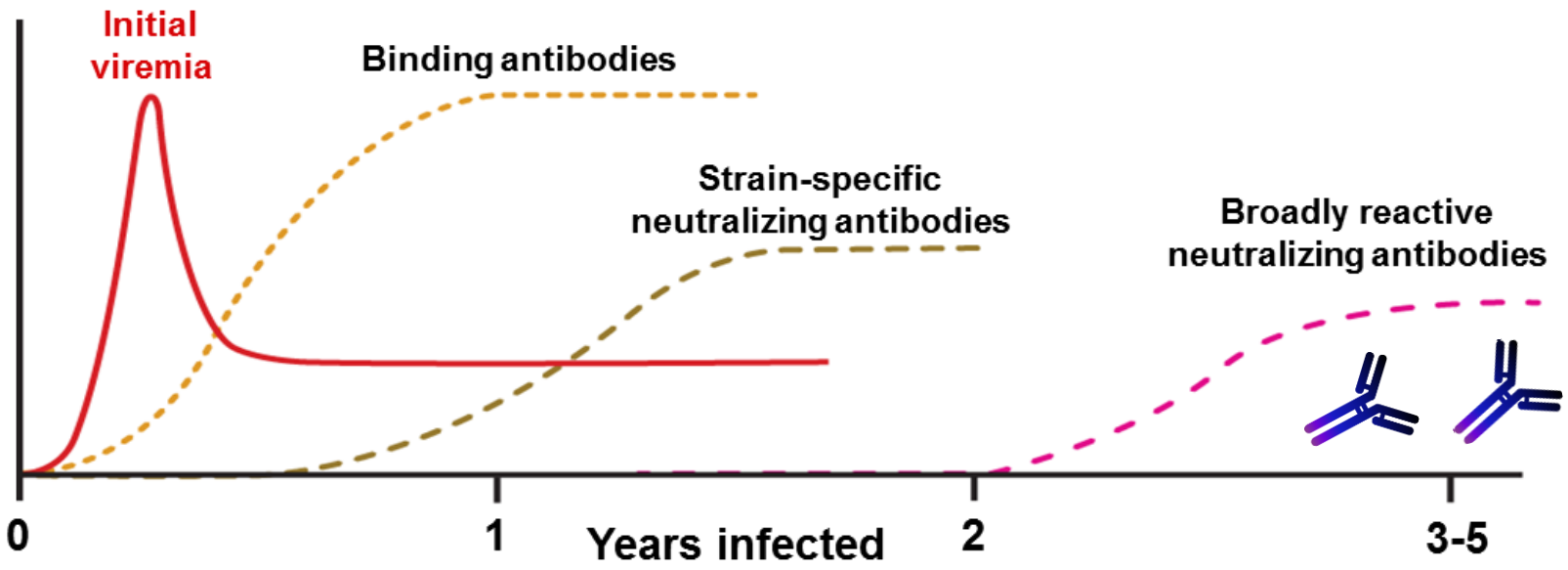
Natural Infection:
Development of Broadly Neutralizing Antibodies



- 50% of those infected develop NAbs
- 20% are broadly cross-reactive (bNAbs)

Mascola, Montefiori Ann Rev Imm (2010)

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JOURNAL of MEDICINE

ORIGINAL ARTICLE

Two Randomized Trials of Neutralizing Antibodies to Prevent HIV-1 Acquisition

L. Corey, P.B. Gilbert, M. Juraska, D.C. Montefiori, L. Morris, S.T. Karuna, S. Edupuganti, N.M. Mgodi, A.C. deCamp, E. Rudnicki, Y. Huang, P. Gonzales, R. Cabello, C. Orrell, J.R. Lama, F. Laher, E.M. Lazarus, J. Sanchez, I. Frank, J. Hinojosa, M.E. Sobieszczyk, K.E. Marshall, P.G. Mukwekwerere, J. Makhema, L.R. Baden, J.I. Mullins, C. Williamson, J. Hural, M.J. McElrath, C. Bentley, S. Takuva, M.M. Gomez Lorenzo, D.N. Burns, N. Espy, A.K. Randhawa, N. Kochar, E. Piwowar-Manning, D.J. Donnell, N. Sista, P. Andrew, J.G. Kublin, G. Gray, J.E. Ledgerwood, J.R. Mascola, and M.S. Cohen, for the HVTN 704/HPTN 085 and HVTN 703/HPTN 081 Study Teams*

N Engl J Med. 2021 Mar 18;384(11):1003-1014

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EDITORIAL

Combination prevention for COVID-19

The coronavirus disease 2019 (COVID-19) pandemic has produced the fear and disorder inevitably provoked by emerging pathogens. As such, it should also inspire consideration of our experience with HIV over the past 40 years. As with HIV, the road to reducing infections with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2, the cause of COVID-19), and attendant morbidity and mortality, requires medical and nonmedical strategies. The most important lesson learned from tackling HIV is to use a combination of prevention strategies.

The first step to stopping the spread of SARS-CoV-2 has already been taken—behavioral changes. This reflects a rapid but imperfect understanding of the transmission of this virus. At the beginning of the AIDS epidemic, changes in sexual behavior, condom promotion, and government interventions (closing "hotspots" of HIV transmission such as bathhouses) made a difference. For SARS-CoV-2, masks and gloves, hand hygiene, and "shelter in place" mandates have already demonstrated benefits. More efficient behavioral intervention requires better understanding of the rules governing SARS-CoV-2 transmission. What are the risks from exposure to respiratory droplets, airborne virus, and surface contamination? What concentration of SARS-CoV-2 is required for transmission? Evidence suggests that SARS-CoV-2 transmission is greatest very early in infection prior to development of symptoms—the same lesson learned from HIV. Given this rule [illegible] biomedical prevention strategies that [illegible] become [illegible] reliable [illegible]

tiviral agents reduce the HIV viral load to a point where infected people no longer transmit. This approach, which uses combinations of powerful antiretroviral agents, is now the mainstay of HIV prevention worldwide.

For SARS-CoV-2, we have leapt into a cacophony of clinical trials of drug candidates with differing degrees of plausibility. Preliminary results from a large randomized controlled trial show that the antiviral drug remdesivir substantially reduced the duration of hospitalization for COVID-19. To date, COVID-19 testing results have been used primarily for patient isolation, contact tracing, and quarantine. But effective therapies will lend great urgency for the universal availability of rapid and reliable testing for SARS-CoV-2 infection, so that treatment can be provided when indicated.

Long-acting antiviral agents and monoclonal antibodies that neutralize SARS-CoV-2 may become important nonvaccine pharmacologic tools for prevention. Antiviral agents that prevent replication of SARS-CoV-2 could be used as pre-, peri-, or postexposure prophylaxis. Several different potent monoclonal antibody combinations designed to treat and prevent SARS-CoV-2 will enter clinical trials in June 2020.

Ultimately, a safe and effective vaccine is crucial for preventing COVID-19. Vaccine efforts started immediately after the discovery of SARS-CoV-2. Numerous vaccine candidates have been identified, and early-phase vaccine studies of several are underway. Proof of vaccine efficacy will require large trials with 6000 to [illegible]000 participants [illegible] more in each [illegible] is moving

"HIV has taught us that multiple concomitant prevention strategies are essential."

Science. 2020 May 8;368(6491):551.

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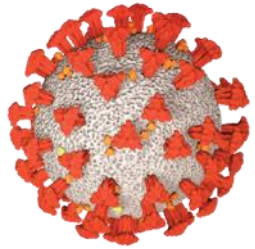
Three Entities with Distinct Roles in COVID-19 Response

Operation Warp Speed

USG body responsible for strategic approach, coordination and resource allocation

Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV)

NIH established Public-private partnership for coordinating COVID-19 response



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NIH Funded networks - Phase 3 trial execution

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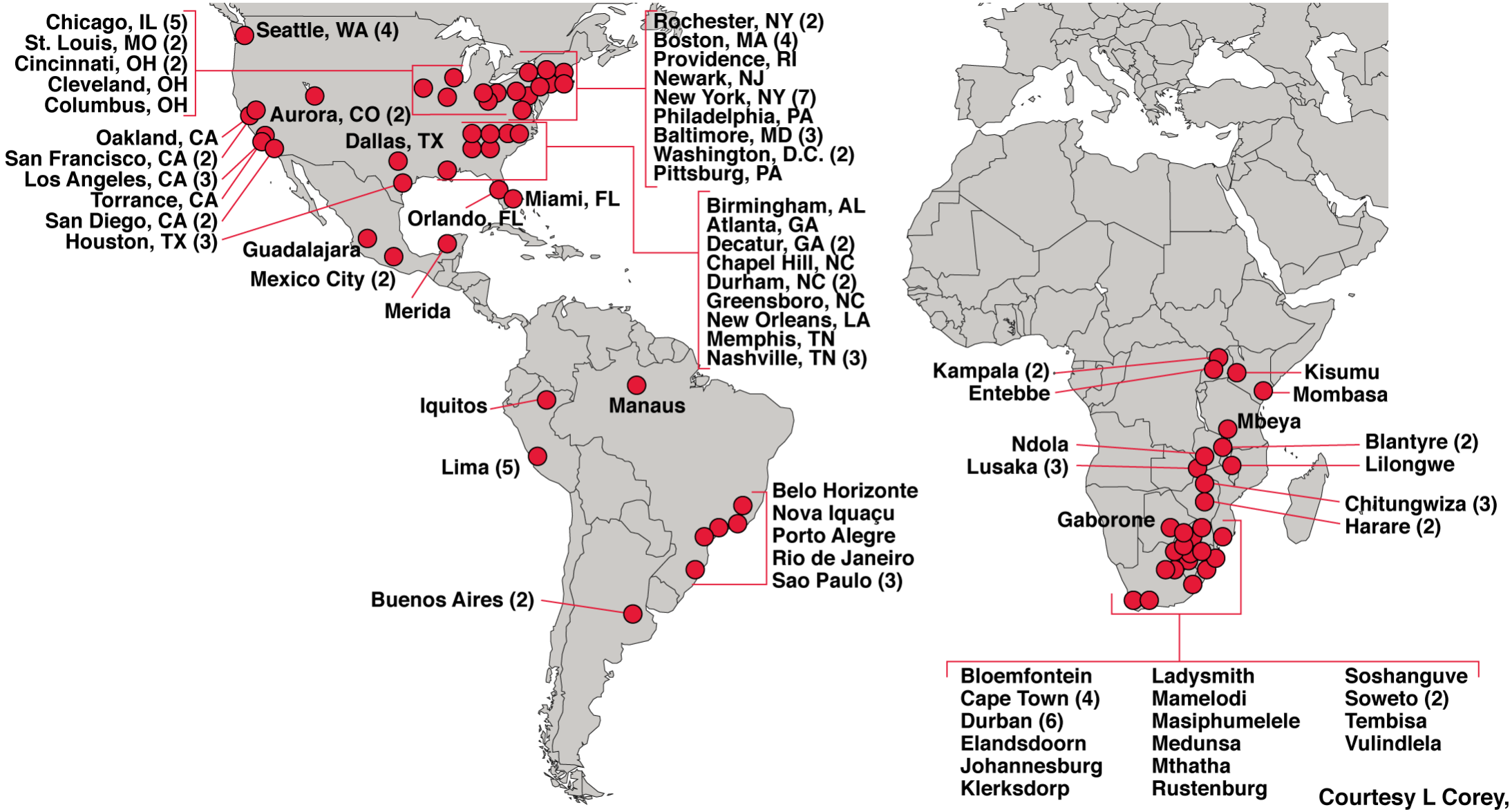
CoVPN Clinical Sites



Courtesy L Corey, HVTN

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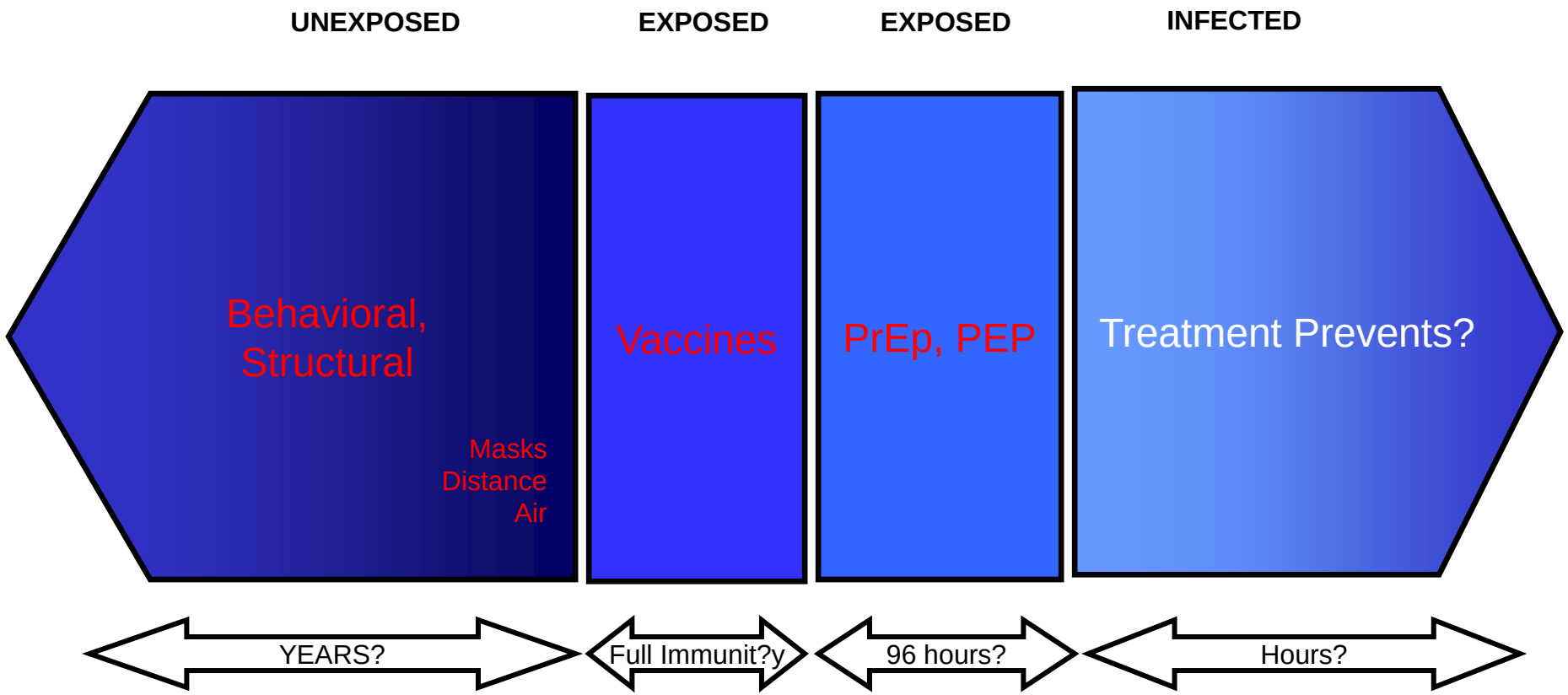
COVID-19: Four Prevention Opportunities



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637 million people travelled in National Day holiday (Oct. 1 - 8) in all parts of China

The Bund of Shanghai

The West Lake of Hangzhou

The Forbidden City of Beijing

The Beach of Qingdao

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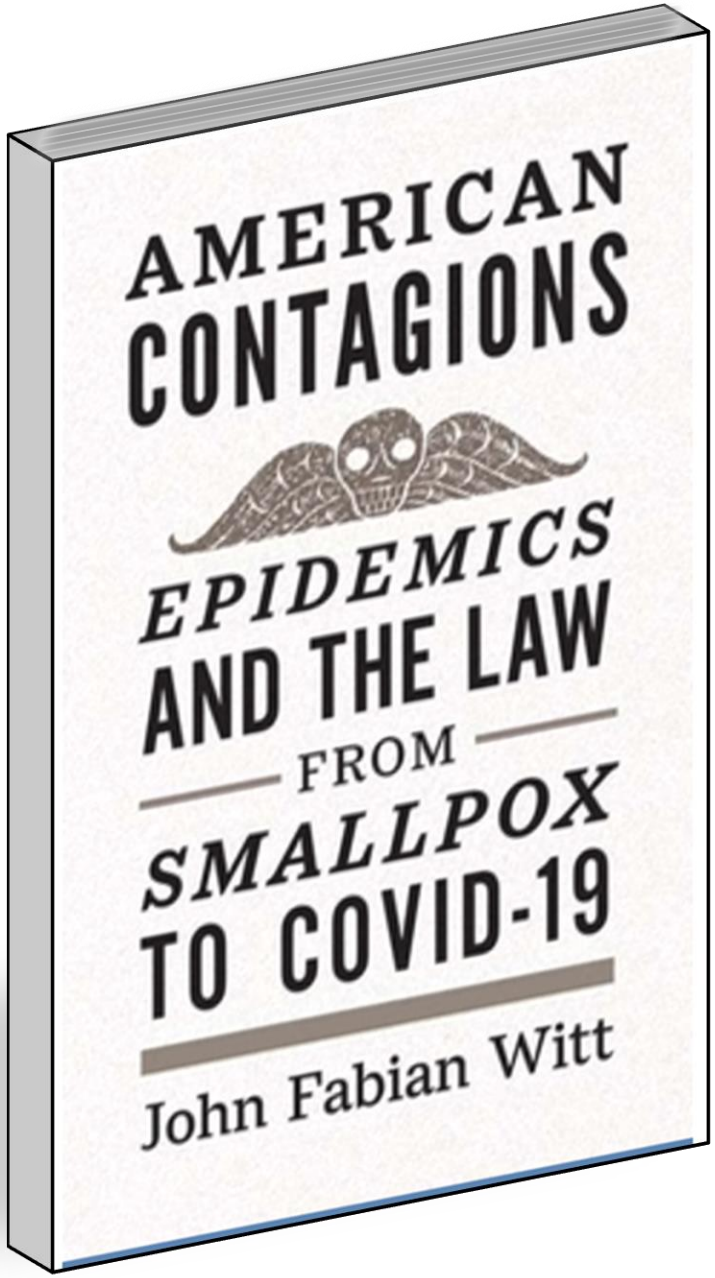

Fabian Witt, John. Yale University Press, 2020. https://doi.org/10.2307/j.ctv15wxn74. Accessed Dec. 20, 2020.

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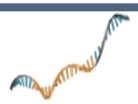
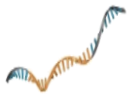
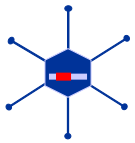
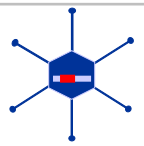
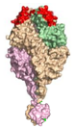
COVID-19 Vaccines in the US

Company	Platform	Product	Vaccination dose/schedule	Status
moderna	 mRNA	mRNA: encodes 2P-stabilized Spike, TM, FI	2 doses at 100 µg (0, 28 days)	EUA
BIONTECH Pfizer	 mRNA	mRNA: encodes stabilized SARS-CoV-2 Spike	2 doses at 30µg (0, 21 days)	EUA
UNIVERSITY OF OXFORD AstraZeneca	 Ad Vector	Replication incompetent ChAdOx1 wild type Spike; △F; TM	2 doses at 5 × 10^{10} vp, (0, 28 days)	Under Review
janssen PHARMACEUTICAL COMPANIES of Johnson & Johnson	 Ad Vector	Replication Incompetent Ad26; stabilized Spike; △F; TM	1 dose at 5 × 10^{10} vp	EUA
NOVAVAX Creating Tomorrow's Vaccines Today	 Recombinant protein Adjuvanted	Baculovirus Expressed trimeric Stabilized Spike, △F; TM; trimerization domain; Matrix M	2 doses at 5 µg with Matrix M (0, 21 days)	Under Review
gsk SANOFI	 Recombinant protein Adjuvanted	Baculovirus Expressed trimeric Stabilized Spike, △F; TM; trimerization domain; AS03	5/15 µg +AS03 (0, 21 days)	??

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Perspective

Scaling Up Covid-19 Vaccination in Africa — Lessons from the HIV Pandemic

Jean B. Nachega, M.D., Ph.D., M.P.H., Nadia A. Sam-Agudu, M.D., John W. Mellors, M.D., Alimuddin Zumla, M.D., Ph.D., and Lynne M. Mofenson, M.D.

Concerns regarding access to Covid-19 vaccines in Africa are reminiscent of concerns raised about responding to the HIV pandemic in the mid-1990s and early 2000s, when highly active antiretroviral treatment (ART) was accessible in high-income and ensure rapid and equitable access to vaccines in both high-

In addition to access to Covid-19 vaccines and therapies, countries require sufficient infrastructure to receive and administer these interventions, which may be logistically challenging in rural and remote areas. Local resources for addressing these requirements,

N Engl J Med. 2021 Mar 31.

Lessons from HIV Pandemic Response Applicable to Covid-19 Vaccine Scale-Up.

Area of Need	Lessons from HIV Response	Potential Applications in Covid-19 Pandemic
Health infrastructure and supply needs	Global Fund and PEPFAR funding were critical for HIV clinical care and local capacity building. Educating and training health care providers in HIV care and ART was essential. Community health and lay workers were indispensable for enhancing HIV testing, ART adherence, and retention in care in hard-to-reach communities.	Appropriate vaccine storage and transport Protective equipment for health care workers in clinic settings Adequate numbers of trained health care workers to safely provide injections and address patient concerns Engagement and compensation of community health workers Tracking systems for vaccines requiring multiple doses to ensure vaccine series completion
Key populations and local epidemiology	Targeted programs were needed to identify groups at highest risk for HIV. Testing, treatment, and prevention had to be provided to difficult-to-reach populations.	Targeting limited vaccine supply toward populations at greatest risk Tailoring response according to geographic region, infrastructure, and culture Conducting surveillance to identify and reach high-risk populations (WHO Expanded Program on Immunization)
Prevention and treatment reluctance	Sustained and improved risk communication and education from trusted persons and institutions helped overcome fear and stigma surrounding contagion and ART side effects. Misconception that there is no reason for treatment if there are no symptoms had to be corrected. Convenience and side-effect profiles of ART regimens had to be improved. Misinformation, including from political leaders and media, had to be corrected.	Reducing stigma and fear of disease, isolation, and adverse effects of vaccines Eliminating misconception that there is no reason for isolation if there are no symptoms Addressing misinformation and disinformation about vaccines, including from political leaders, media, and social media Recognizing the importance of risk communication by trusted voices in the community
Communication and community involvement and engagement	Mobile testing units, community health workers (CHWs), community-based care, and efficient drug provision for treatment and prevention were implemented.	Tailoring education and risk communication to needs of local communities Understanding community structures for vaccine communication and distribution. Involving CHWs for rapid, wide-scale, effective, and equitable vaccination
Prevention and treatment in pregnant women and children	Years-long delays for inclusion in HIV drug studies and in access could have been minimized. Social determinants of health had to be identified.	Conducting timely trials of Covid-19 vaccines in pregnant women and children Social determinants of infection disease and of vaccine acceptance and access will be important to identify and address.

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Scaling Up Covid-19 Vaccination in Africa — Lessons from the HIV Pandemic

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N Engl J Med. 2021 Mar 31.

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COVID-19 mAb Applications for Prevention

Monoclonal Abs (mAbs):

- Offer immediate protection for those exposed or unvaccinated in high-risk settings
- Can be provided to people unlikely to respond to a vaccine, or allergic
- **They could stop viral replication and block progression of disease**
- *Can help predict requirements for a vaccine by identifying required titers of neutralizing antibodies*

Target Populations for mAbs:

- Nursing homes, both residents and attendants
- High incidence workplaces (e.g. meat packing plants)
- Index case contacts (e.g. household contacts)

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Emergency Use Authorization (EUA) Monoclonal Antibody Rx for COVID-19

Adults

<u>At least one of the following</u>:

- **Are ≥65 years of age**
- **A body mass index (BMI) ≥35**
- **Chronic kidney disease**
- **Diabetes**
- **Immunosuppressive disease**
- **Receiving immunosuppressive treatment**

<u>≥55 years of age AND have one of the following</u>:

- **Cardiovascular disease**
- **Hypertension**
- **Chronic obstructive pulmonary disease**
- **Other chronic respiratory disease**

Pediatrics

<u>Between 12-17 years of age AND at least one of the following</u>:

- **BMI ≥85th percentile for their age and gender based on CDC growth charts**
- **Sickle cell disease**
- **Congenital or acquired heart disease**
- **Neurodevelopmental disorders, for example, cerebral palsy**
- **A medical-related technological dependence, (e.g., tracheostomy, gastrostomy, or positive pressure ventilation)**
- **Asthma, reactive airway or other chronic respiratory disease that requires daily medication for control.**

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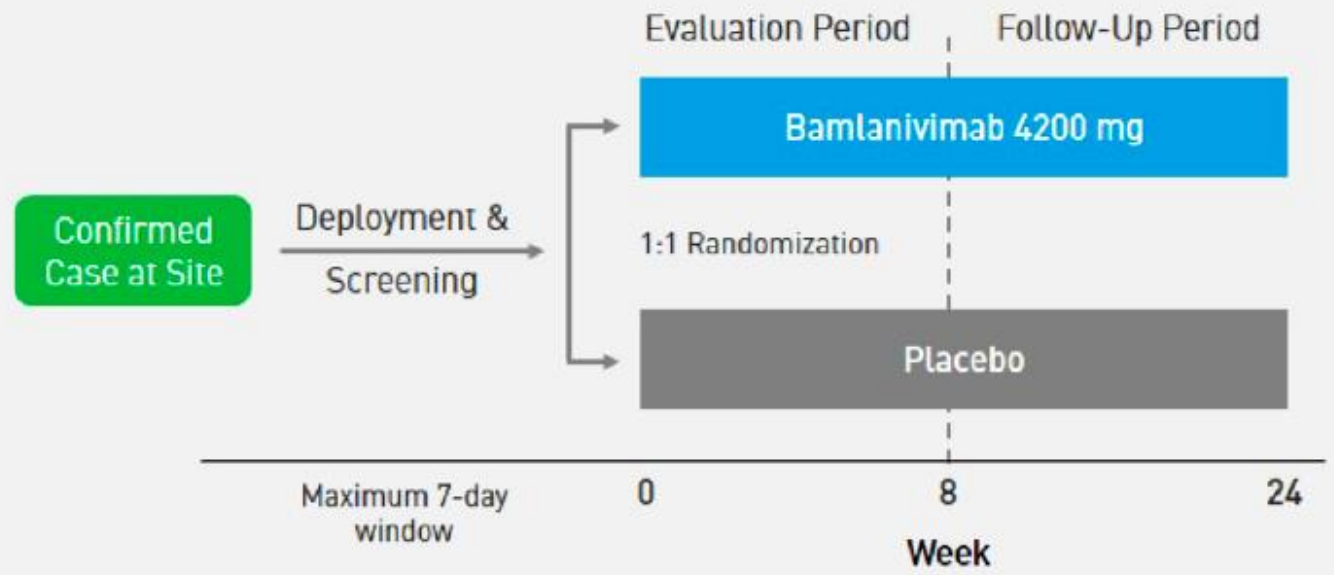
BLAZE-2: POST-EXPOSURE PROPHYLAXIS

N=966 (666 staff; 300 residents)

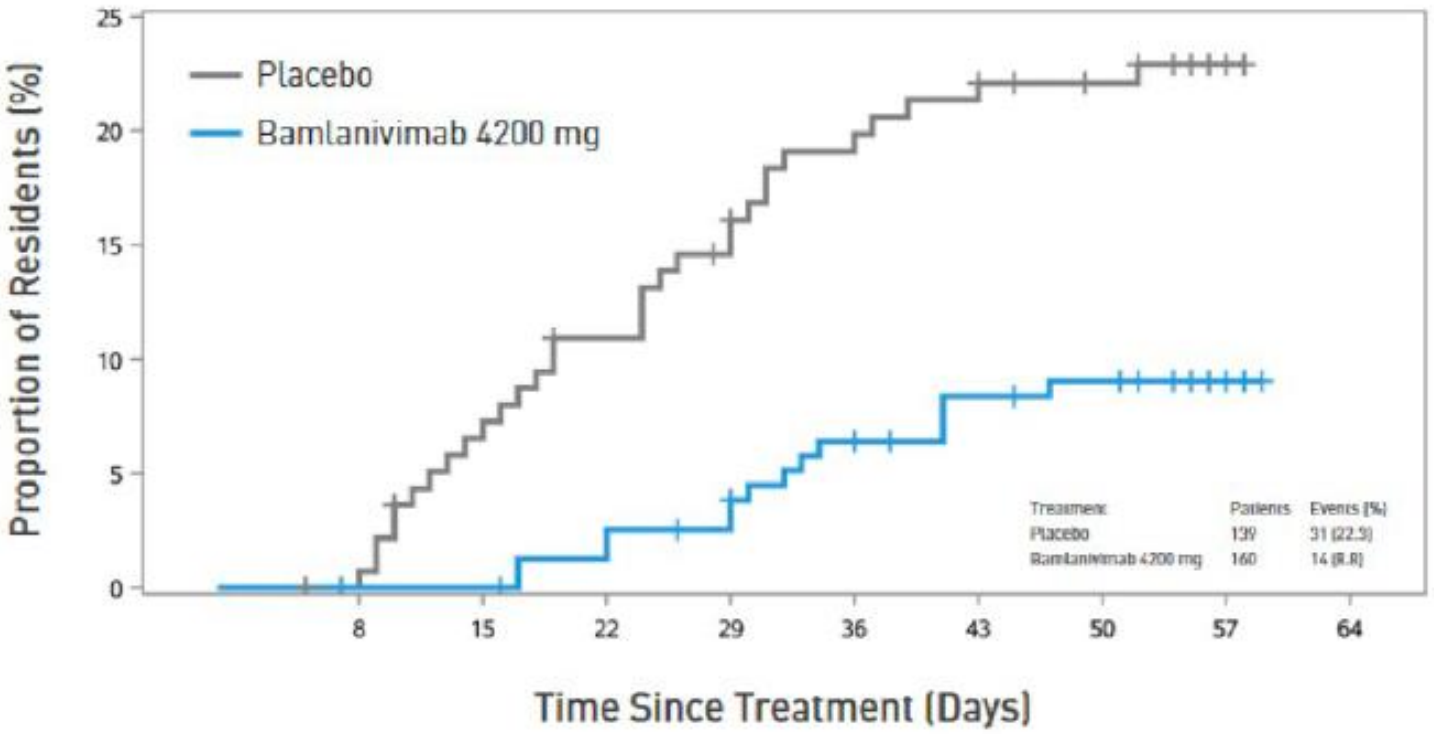
STUDY DESIGN



To facilitate rapid prophylaxis and treatment of residents and facility staff, participants were enrolled prior to assessment of baseline SARS-CoV-2 status. This allowed for separate **prevention** and **treatment** analysis populations.

MOBILE RESEARCH UNITS

RESIDENTS WITH SYMPTOMATIC COVID-19 (Prevention Population)



COVID-19 PREVENTION

Odds ratio: 0.20
p-value: 0.00026

Up to 80% reduction in risk

DEATH DUE TO COVID-19

Placebo: 4 of 139 residents
Bamlanivimab: 0 of 160 residents

No deaths due to COVID-19 on bamlanivimab

Notes:

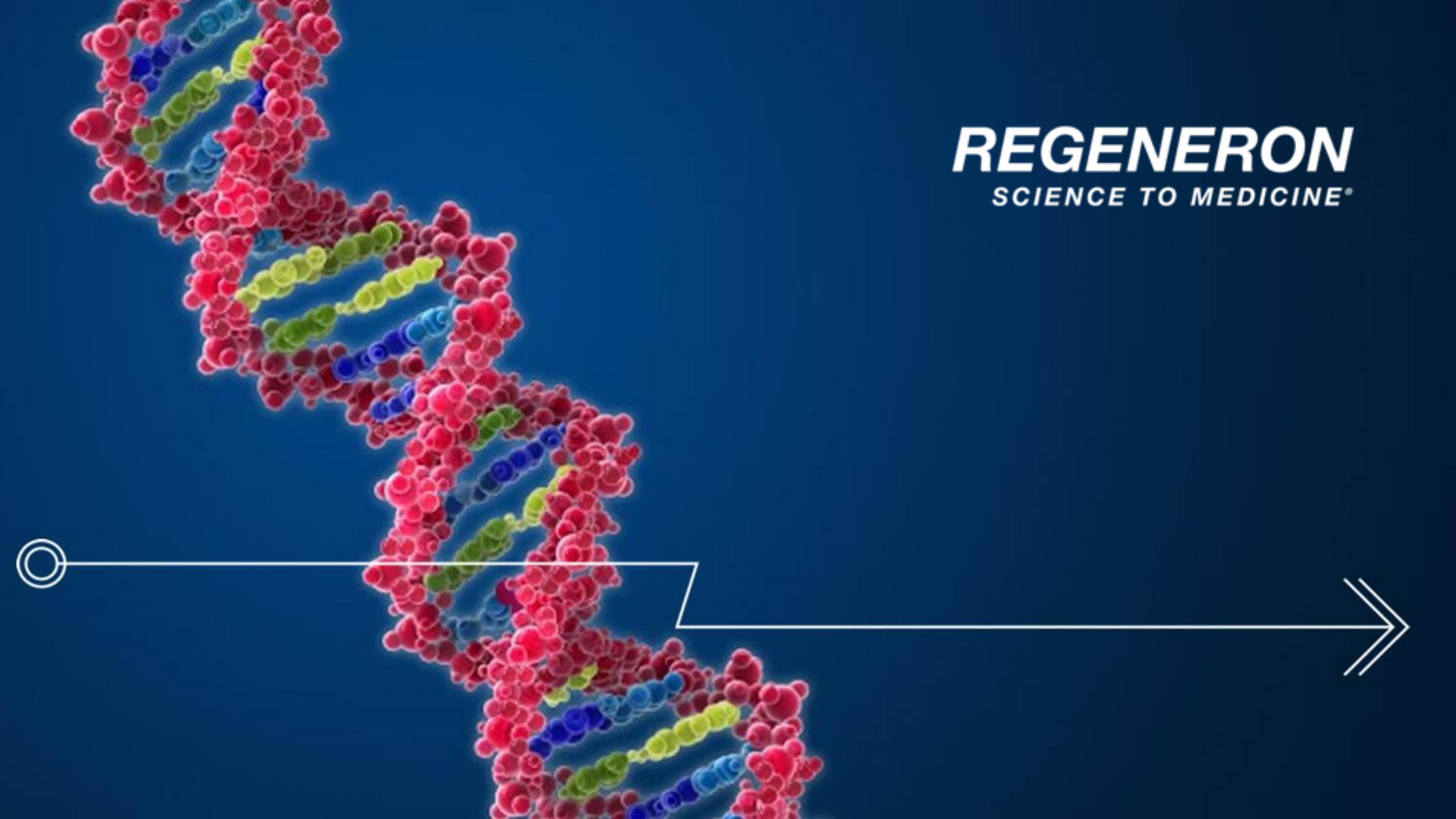
No significant effect in rate of COVID-19 diagnosis, which was relatively low, in staff.

Lower viral loads at time of detection among those getting the mAb

DEATH DUE TO ANY CAUSE (RESIDENTS)

	N	Deaths	Rate
Placebo	24	4	17%
Bamlanivimab 4200 mg	17	0	0%

https://investor.lilly.com/news-releases/news-release-details/lillys-neutralizing-antibody-bamlanivimab-ly-cov555-prevented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Phase 3 Clinical Trial of Casirivimab And Imdevimab as Passive "Vaccine" to Prevent COVID-19 in Household Contacts

- Household contacts of COVID-19 case (N=400 prelim analysis) randomized to CASI+IMDE 1,200 mg subQ vs Placebo

- Passive vaccination with CASI+IMDE resulted in 100% prevention of symptomatic infection (8/223 placebo vs. 0/186 CASI+IMDE), and approximately 50% lower overall rates of infection (symptomatic and asymptomatic) (23/223 placebo vs. 10/186 CASI+IMDE)
- Infections occurring with CASI+IMDE therapy were all asymptomatic
  - Infections occurring in the placebo group had, on average, more than 100-fold higher peak viral load.
  - Infections in the CASI+IMDE group lasted no more than 1 week, while approximately 40% of infections in the placebo group lasted 3-4 weeks.
  - No infected individuals in the CASI+IMDE group had high viral loads (>10^4 copies/mL) compared to 62% of the infected placebo group (13/21 placebo vs. 0/9 CASI+IMDE).

https://newsroom.regeneron.com/news-releases/news-release-details/regeneron-reports-positive-interim-data-regen-covtm-antibody.

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Variants: They're Here

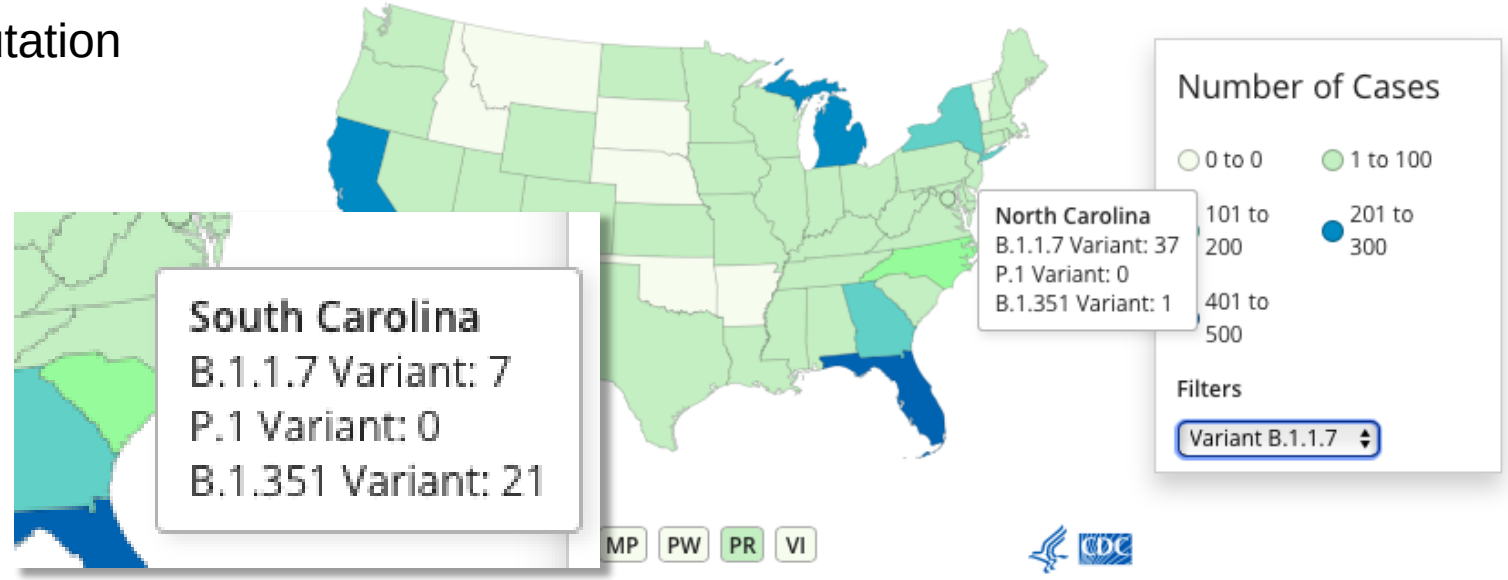
- Major variants
  - **B.1.1.7** – UK -> More infectious, Maybe more severe disease
  - **B.1.351** – South Africa -> Reduced protection by some vaccines (not Moderna or Pfizer), reduced effect of some COVID-19 antibody treatments
  - **P.1** – Brazil -> shares E484K mutation with B.1.351

US COVID-19 Cases Caused by Variants

Updated Feb. 23, 2021 Languages Print

Variant	Reported Cases in US	Number of States Reporting
B.1.1.7	1881	45
B.1.351	46	14
P.1	5	4

Emerging Variant Cases in the United States*†



https://www.cdc.gov/coronavirus/2019-ncov/transmission/variant-cases.html

Epidemiology in India

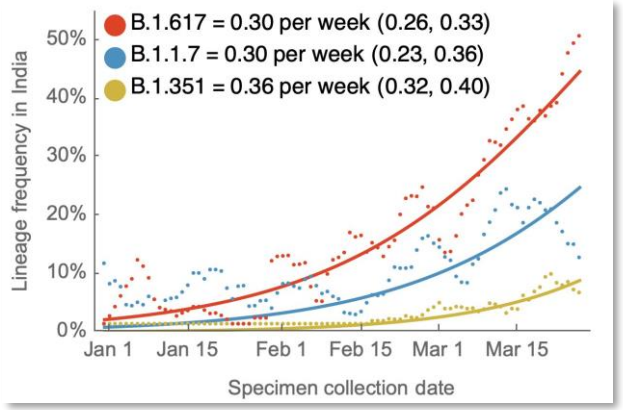
Reported cases: ~22.7M **Deaths**: ~246K

Vaccine coverage: 9.4% received 1 dose; 2.1% fully vaccinated

Vaccines available: Majority of vaccine administered (10:1) has been Covishield (Serum Institute of India, ChAdOx1), followed by Covaxin (Bharat Biotech, inactivated w/ Alhydroxiquim-II adjuvant)

<u>Variants in India:</u> B.1.617 > B.1.1.7 > B.1.351

Preliminary reports that B.1.617 growing at a rate similar to B.1.1.7 in India, suggesting that it may be more transmissible than ancestral variants. More data needed.



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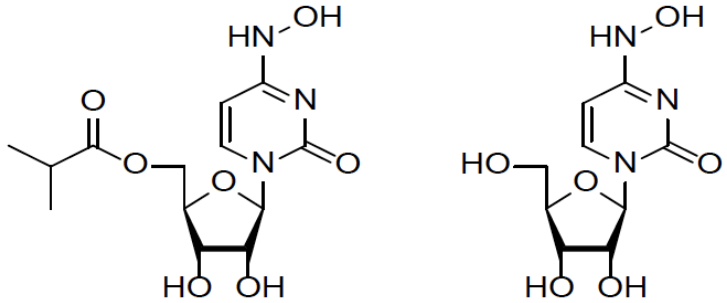
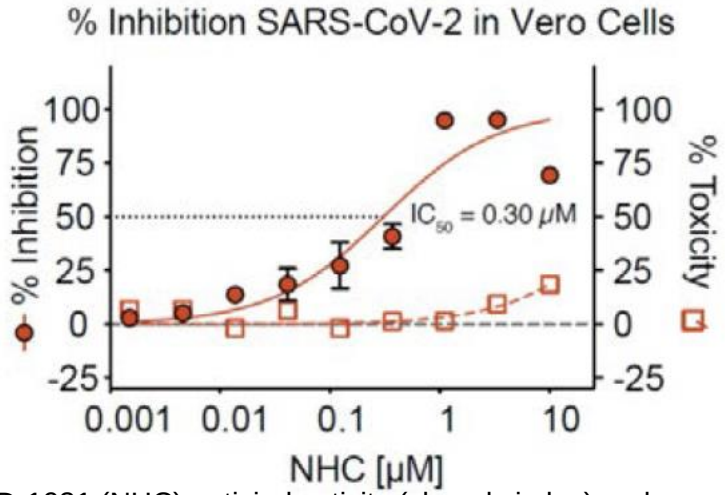
Molnupiravir: An Antiviral Agent for COVID-19

- A ribonucleoside analog that inhibits viral RNA replication by incorporation of the 5'-monophosphate metabolite (EIDD-1931) into the viral genome producing viral error catastrophe
- Active against SARS-CoV-2, SARS-CoV, MERS-CoV, and other human CoV (Also against influenza virus and others); EC50= 0.17 µM
- 800 mg MOVBID inhibits replication in vivo
- Phase 3 treatment study underway
- **Phase 3 TaSP study in protocol development**

Structure of EIDD-2801 and EIDD-1931





EIDD-1931 (NHC) antiviral activity (closed circles) and cytotoxicity (open squares) in Vero Cells infected with SARS-CoV-2.

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‘The Biggest Monster’ Is Spreading. And It’s Not the Coronavirus.

Apoorva Mandavilli | Aug. 3, 2020

www.nytimes.com › coronavirus-tuberculosis-aids-malaria

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Thank you!

- To all study participants
- To all investigators
- To All Funders at NIH, BMGF and many, many industry partners

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