COVID-19 in Pediatric Populations & Vaccines: Science Vs Antiscience

@PeterHotez

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NATIONAL SCHOOL OF TROPICAL MEDICINE, BAYLOR COLLEGE OF MEDICINE

- Portfolio of Global Health & Neglected Disease Vaccines
- Schistosomiasis
- Hookworm
- Chagas Disease
- Leishmaniasis
- Coronavirus Infections
  - SARS CoV
  - SARS CoV2
  - MERS

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NATIONAL SCHOOL OF TROPICAL MEDICINE

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Developing Country Vaccine Manufacturers Network

- Bangladesh
- China
- India
- Indonesia
- Thailand
- Vietnam

- Argentina
- Brazil
- Cuba

https://www.sciencedirect.com/science/article/pii/S2590136220300139

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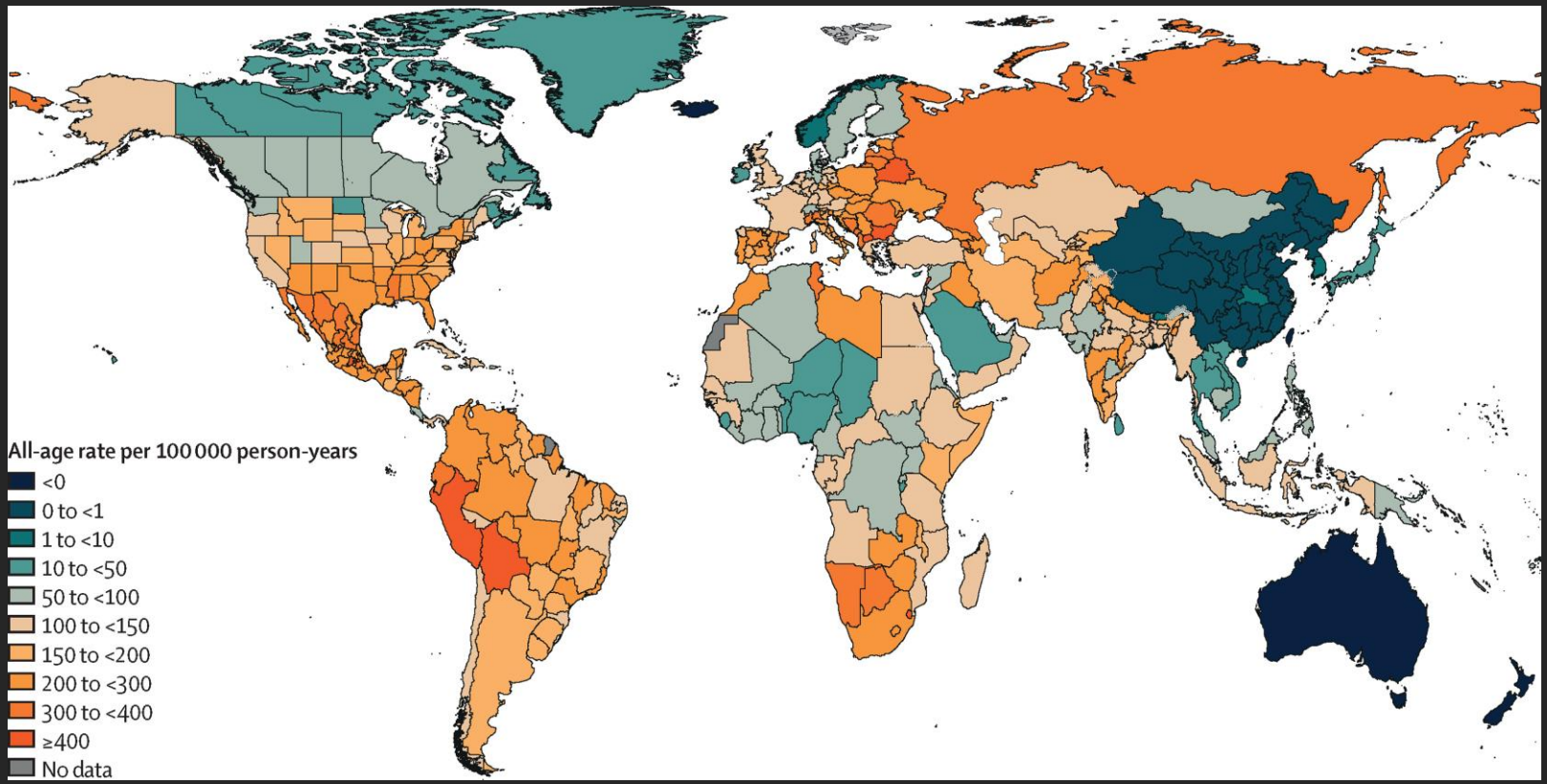
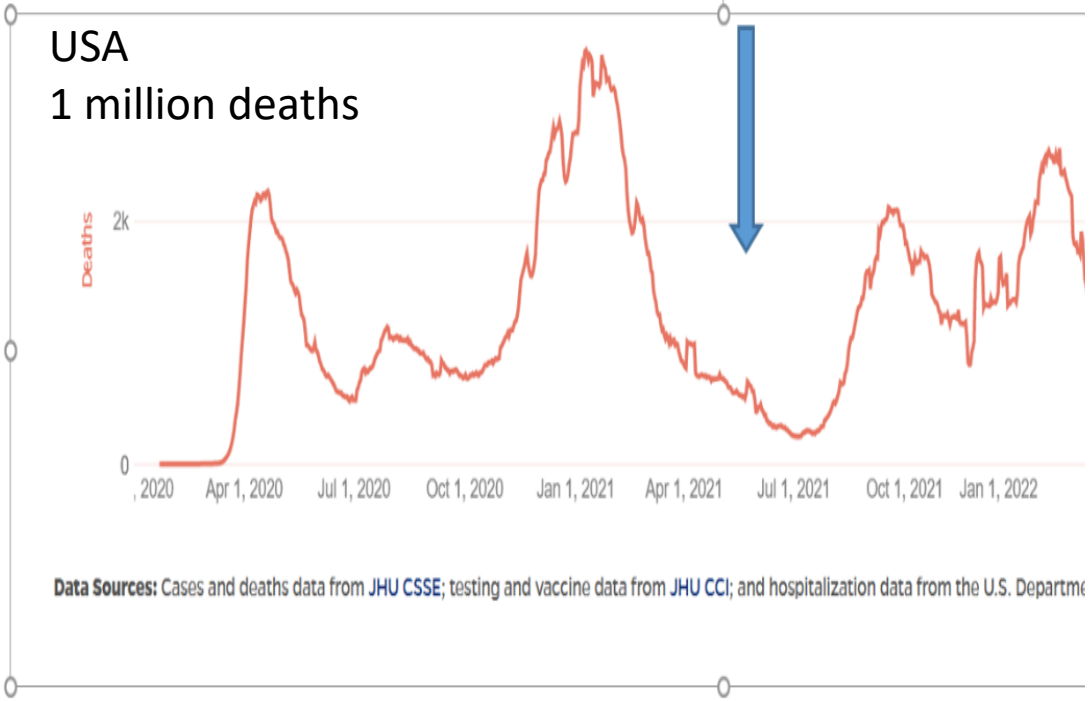
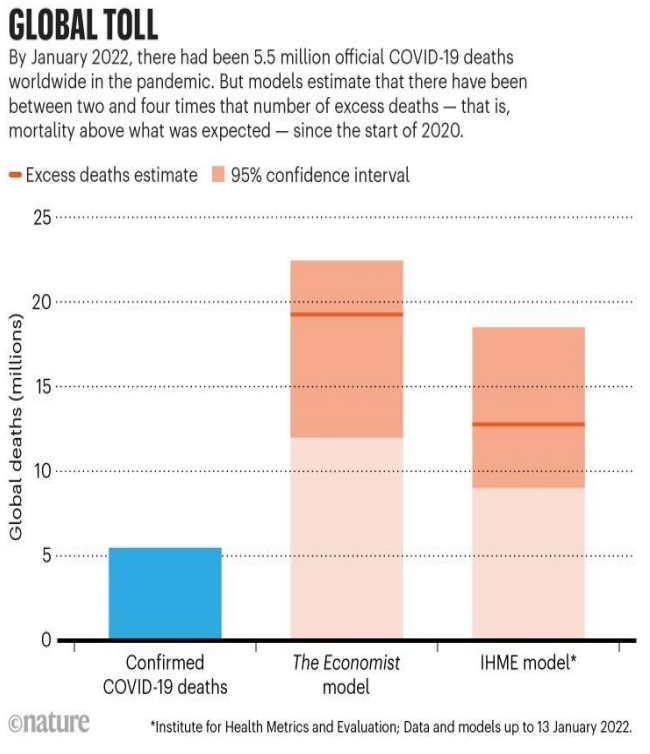
Cumulative excess deaths from COVID19



The Lancet 2022 3991513-1536DOI: (10.1016/S0140-6736(21)02796-3)

COVID-19 Deaths

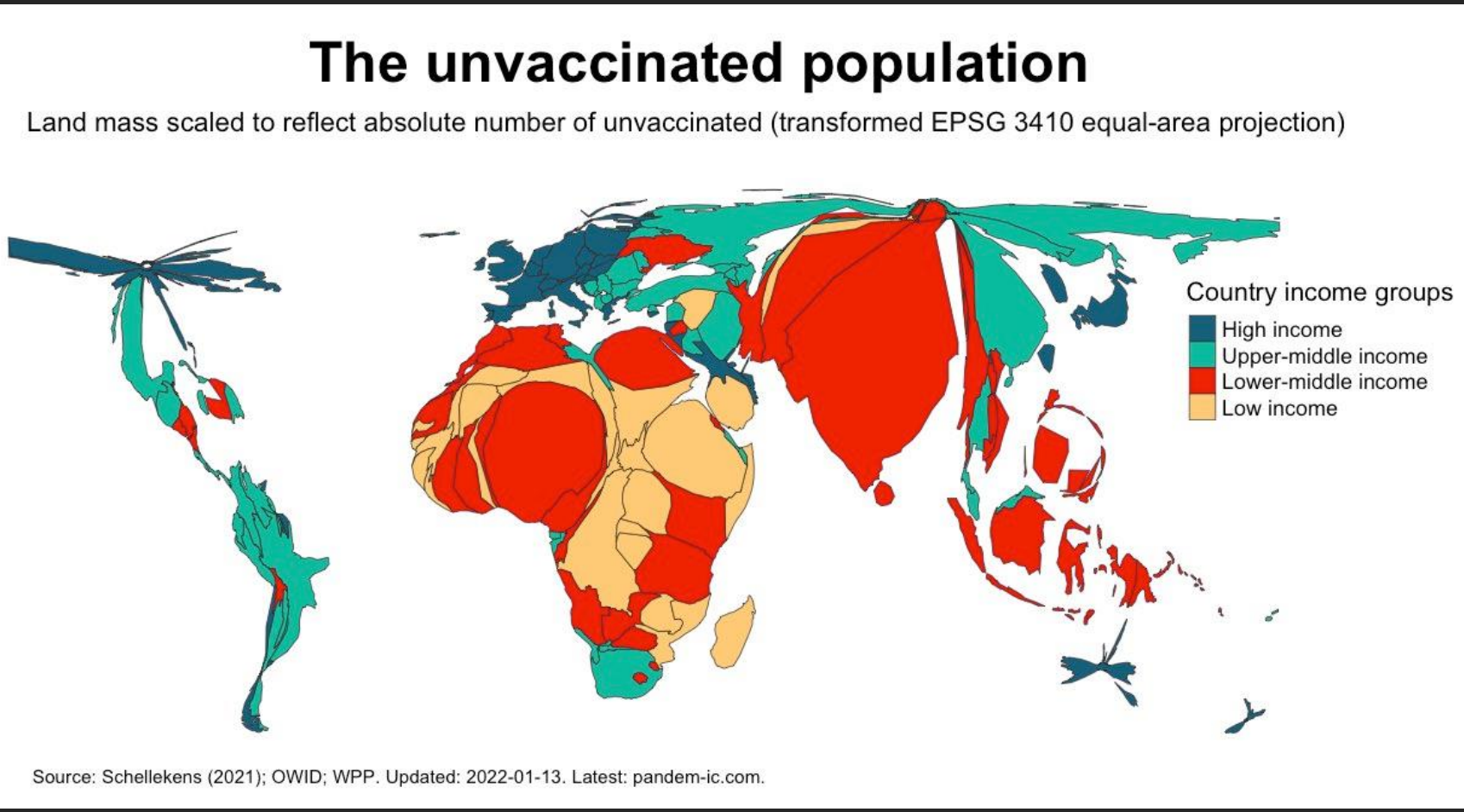




USA: Up to 40% of Deaths after COVID-19 Vaccines Widely Available After May 1, 2021

Globally 5-20 million Deaths

COVID-19 Vaccinations



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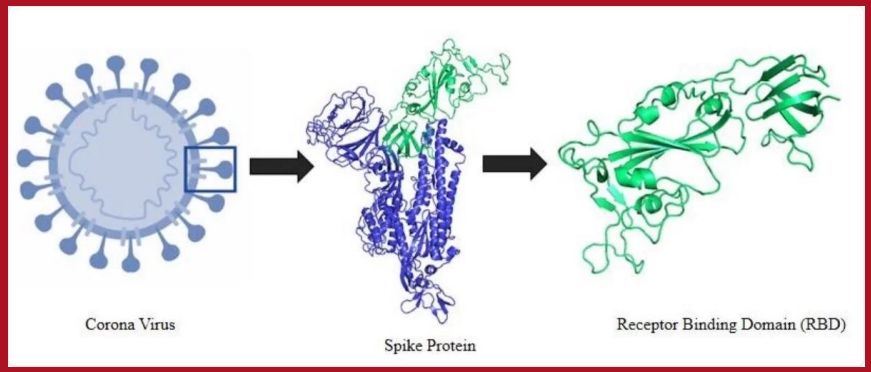
Texas Children's CVD Recombinant Protein COVID-19 Vaccine

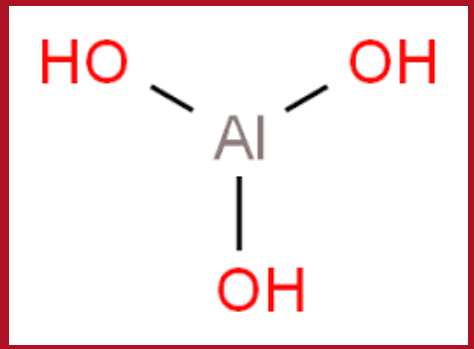
Vaccine

- Receptor binding domain
- RBD- SARS CoV2
- Aluminum hydroxide
- CpG ODN TLR9-Agonist



Advantages

- Highly effective NHPs
- High levels neutralizing antibodies in Phase 1-3
- Low cost, ease of production, tech transfer
- EUL in India
- Plans for Indonesia, Bangladesh, African Continent
- Designed for LMICs



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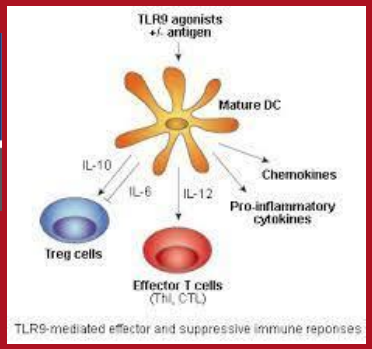

Engineering and Cloning Strategy

Selection of SARS CoV-2 RBD 219-N1C1 Construct (residues 331–549)

```
RBD219-WT    NITNLCPFGEVFNATRFASVYAWNRKRISNCVADYSVLYNSASFSTFKCYGVSPTKLNDL 60
RBD219-N1    -ITNLCPFGEVFNATRFASVYAWNRKRISNCVADYSVLYNSASFSTFKCYGVSPTKLNDL 59
RBD219-N1C1  -ITNLCPFGEVFNATRFASVYAWNRKRISNCVADYSVLYNSASFSTFKCYGVSPTKLNDL 59
             ************************************************************

RBD219-WT    CFTNVYADSFVIRGDEVRQIAPGQTGKIADYNYKLPDDFTGCVIAWNSNNLDSKVGGNYN 120
RBD219-N1    CFTNVYADSFVIRGDEVRQIAPGQTGKIADYNYKLPDDFTGCVIAWNSNNLDSKVGGNYN 119
RBD219-N1C1  CFTNVYADSFVIRGDEVRQIAPGQTGKIADYNYKLPDDFTGCVIAWNSNNLDSKVGGNYN 119
             ************************************************************

RBD219-WT    YLYRLFRKSNLKPFERDISTEIYQAGSTPCNGVEGFNCYFPLQSYGFQPTNGVGYQPYRV 180
RBD219-N1    YLYRLFRKSNLKPFERDISTEIYQAGSTPCNGVEGFNCYFPLQSYGFQPTNGVGYQPYRV 179
RBD219-N1C1  YLYRLFRKSNLKPFERDISTEIYQAGSTPCNGVEGFNCYFPLQSYGFQPTNGVGYQPYRV 179
             ************************************************************

RBD219-WT    VVLSFELLHAPATVCGPKKSTNLVKNKCVNFNFNGLTGT 219
RBD219-N1    VVLSFELLHAPATVCGPKKSTNLVKNKCVNFNFNGLTGT 218
RBD219-N1C1  VVLSFELLHAPATVCGPKKSTNLVKNKAVNFNFNGLTGT 218
             ***************************  ***********
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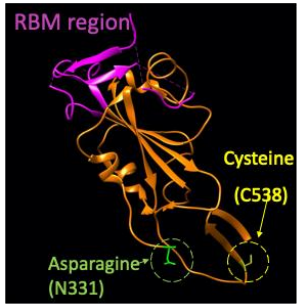


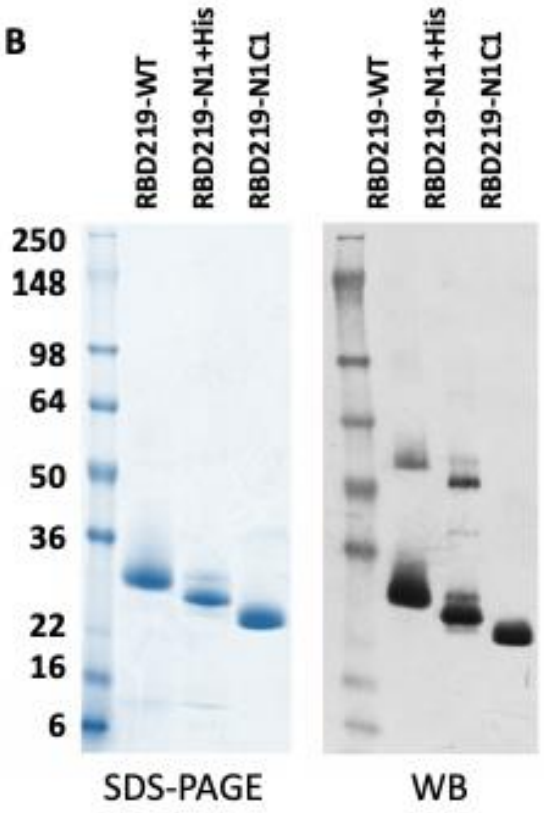
Contents lists available at ScienceDirect

BBA - General Subjects

journal homepage: www.elsevier.com/locate/bbagen

Genetic modification to design a stable yeast-expressed recombinant SARS-CoV-2 receptor binding domain as a COVID-19 vaccine candidate

Wen-Hsiang Chen[a,b], Junfei Wei[a], Rakhi Tyagi Kundu[a], Rakesh Adhikari[a], Zhuyun Liu[a], Jungsoon Lee[a], Leroy Versteeg[a], Cristina Poveda[a], Brian Keegan[a], Maria Jose Villar[a], Ana C. de Araujo Leao[a], Joanne Altieri Rivera[a], Portia M. Gillespie[a], Jeroen Pollet[a,b], Ulrich Strych[a,b], Bin Zhan[a,b], Peter J. Hotez[a,b,c,d,*], Maria Elena Bottazzi[a,b,c,d,*]



https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7955913/

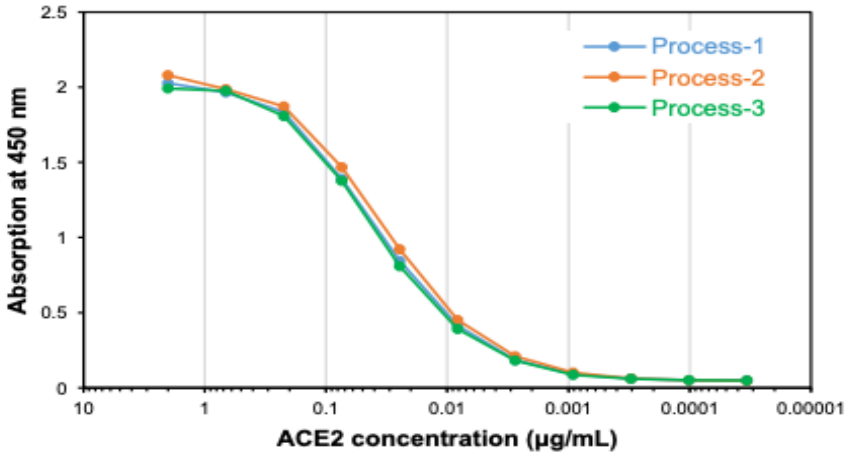
Process Development and Scale-up Strategy

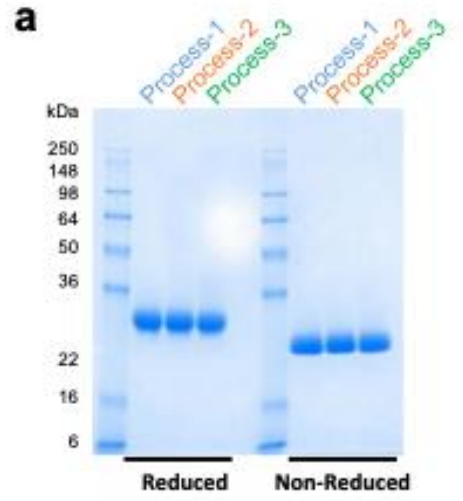
Applied Microbiology and Biotechnology (2021) 105:4153–4165
https://doi.org/10.1007/s00253-021-11281-3

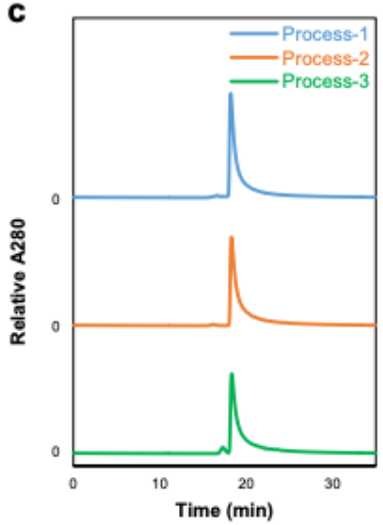
BIOTECHNOLOGICAL PRODUCTS AND PROCESS ENGINEERING

Process development and scale-up optimization of the SARS-CoV-2 receptor binding domain–based vaccine candidate, RBD219-N1C1

Jungsoon Lee[1,2] · Zhuyun Liu[1,2] · Wen-Hsiang Chen[1,2] · Junfei Wei[1,2] · Rakhi Kundu[1,2] · Rakesh Adhikari[1,2] · Joanne Altieri Rivera[1,2] · Portia M. Gillespie[1,2] · Ulrich Strych[1,2] · Bin Zhan[1,2] · Peter J. Hotez[1,2,3,4,5] · Maria Elena Bottazzi[1,2,3,4]

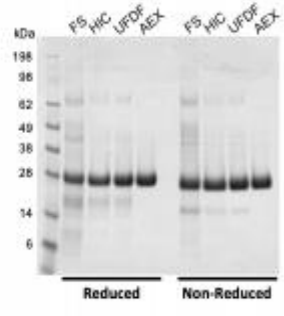






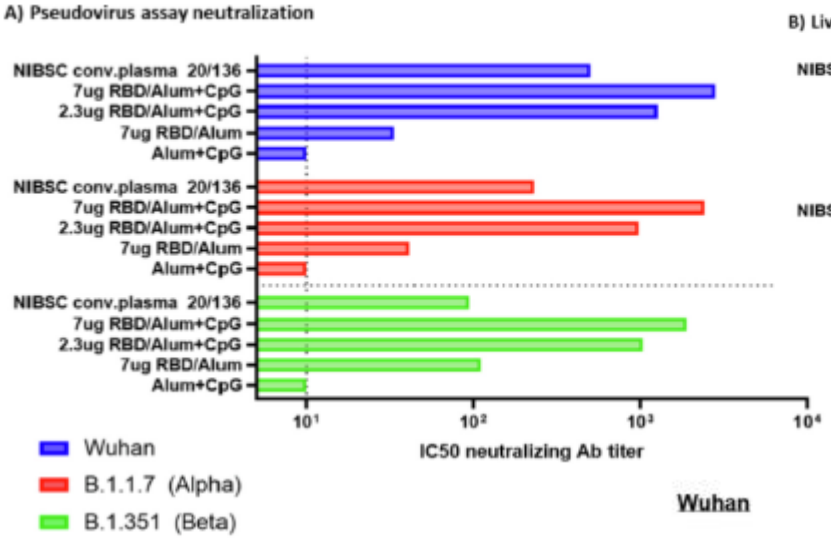
b **Process-2**

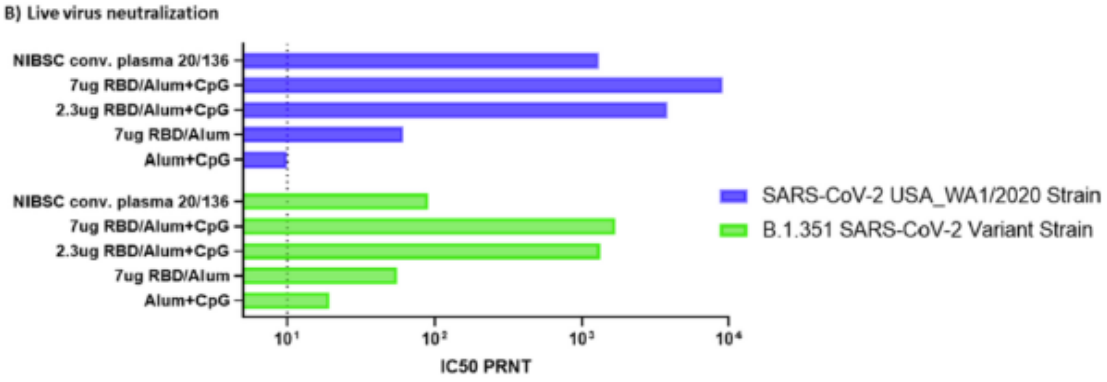
	Yield (mg)	Step Recovery (%)	Overall Recovery (%)	Purity, Non-Reduced (%)
FS	345.0 ± 7.1			77.0 ± 0.4
HIC	154.4 ± 0.0	45 ± 1	45 ± 1	95.2 ± 0.9
UFDF	173.6 ± 5.7	113 ± 4	50 ± 3	94.6 ± 1.2
AEX	134.9 ± 1.8	78 ± 4	39 ± 0	95.1 ± 0.4

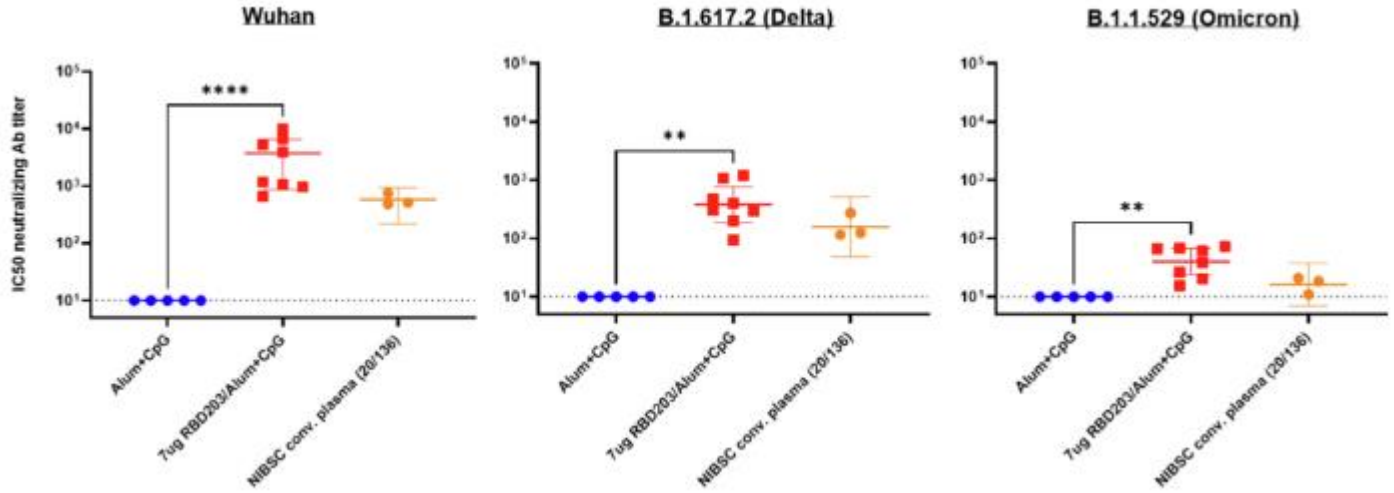


https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8102132/

The RBD219-N1C1/alum + CpG1826 elicits robust neutralizing antibodies effective against variants





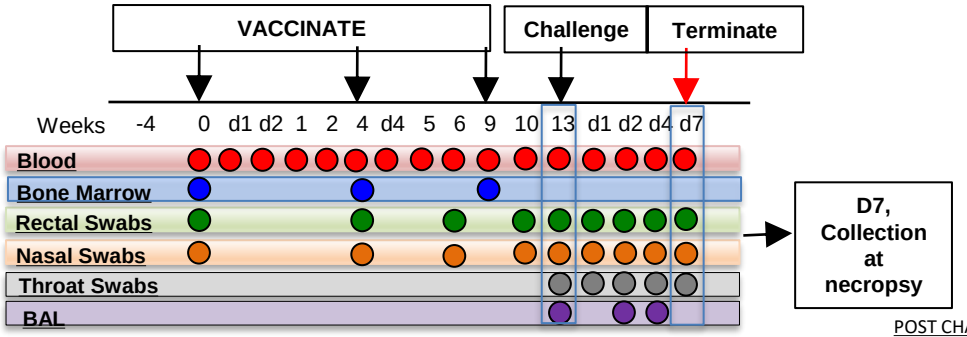


https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9080055/

Efficacy and Safety in a NHP Model

EMORY UNIVERSITY

Dr. Sudhir Kasturi



Blood

- Innate responses by Flow, transcriptomics
- CD4+ and CD8+ T cell responses
- Serology (binding, neutralization, ADCC)
- Plasmablast analysis by ELISPOT and FACS

Bone Marrow

- Plasma cell analysis by ELISPOT

Mucosal assays

- IgG and IgA binding antibody
- BAL collections for immune phenotyping

POST CHALLENGE
Frequency of collections TBD

- Nasal swabs (PCR)
- Throat swabs (PCR)
- Serum/plasma (SEROLOGY)
- PBMCs
- BAL (Immune cell phenotyping)
- H&E (Immunepathology at necropsy)

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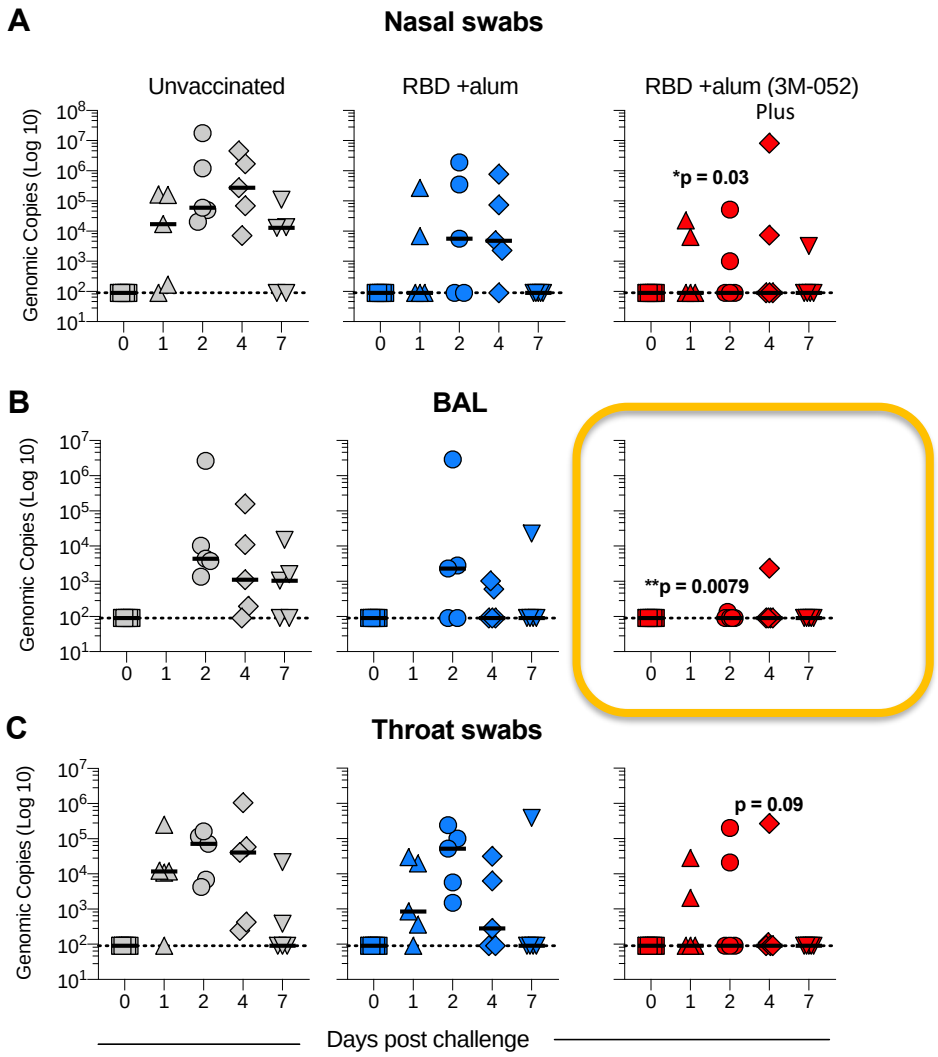
http://immunology.sciencemag.org/lookup/doi/10.1126/sciimmunol.abj1031

RBD + Alum-Plus vaccine promotes striking reduction of replicating SARS-CoV-2 in rhesus macaque BAL post challenge



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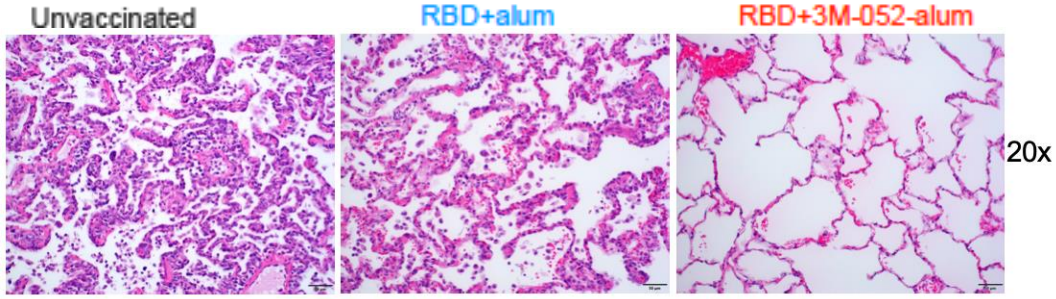
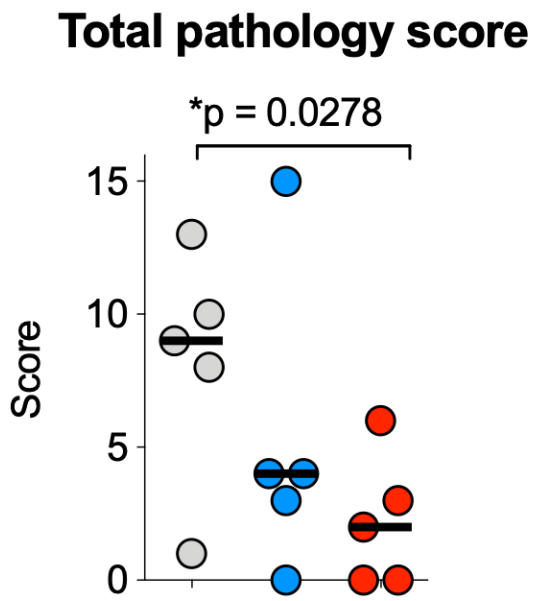
http://immunology.sciencemag.org/lookup/doi/10.1126/sciimmunol.abj1031

Safety in a NHP Model

RBD formulated with 3M-052+alum promotes significant reduced lung pathology after respiratory challenge with SARS CoV-2



Hematoxylin and eosin-stained sections of lung lobes from representative animals in the study at (20x) magnifications. Scale bars = 50µM.



Total and average pathology scores quantified as explained in methods.

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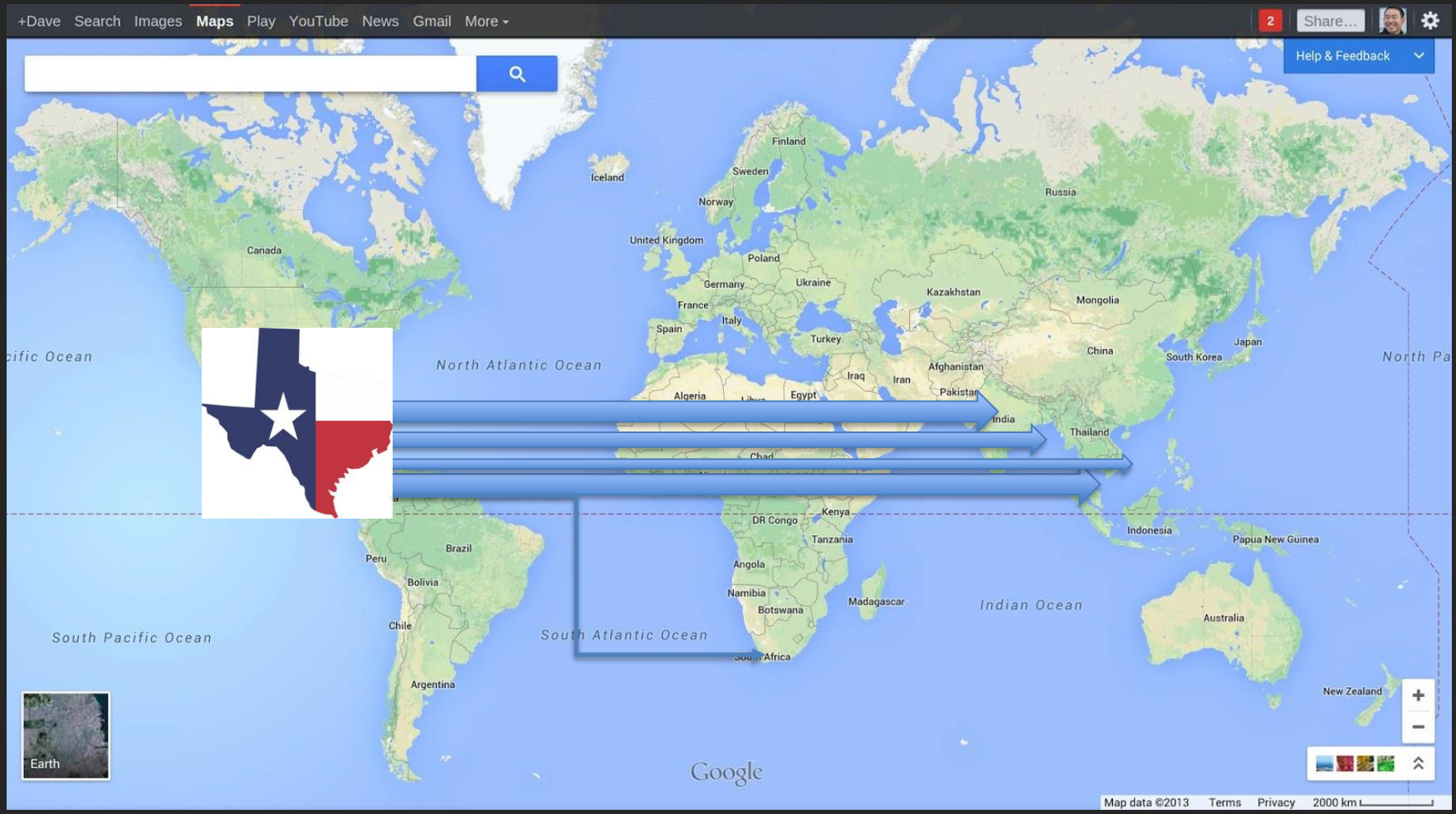
http://immunology.sciencemag.org/lookup/doi/10.1126/sciimmunol.abj1031

Technology Transer:

India (Corbevax), Indonesia, Bangladesh, S Africa



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CORBEVAX™

- Recombinant protein sub-unit vaccine, developed from the (RBD) of the spike protein combined with Dynavax's CpG 1018 adjuvant with alum
- Developed by Biological E. Ltd in collaboration with Texas Children's Hospital Center for Vaccine Development (Texas Children's CVD) and Baylor College of Medicine in Houston, Texas.
- EUL India Dec 2021

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Phase 1-2
25 ug Antigen + 750 ug CpG

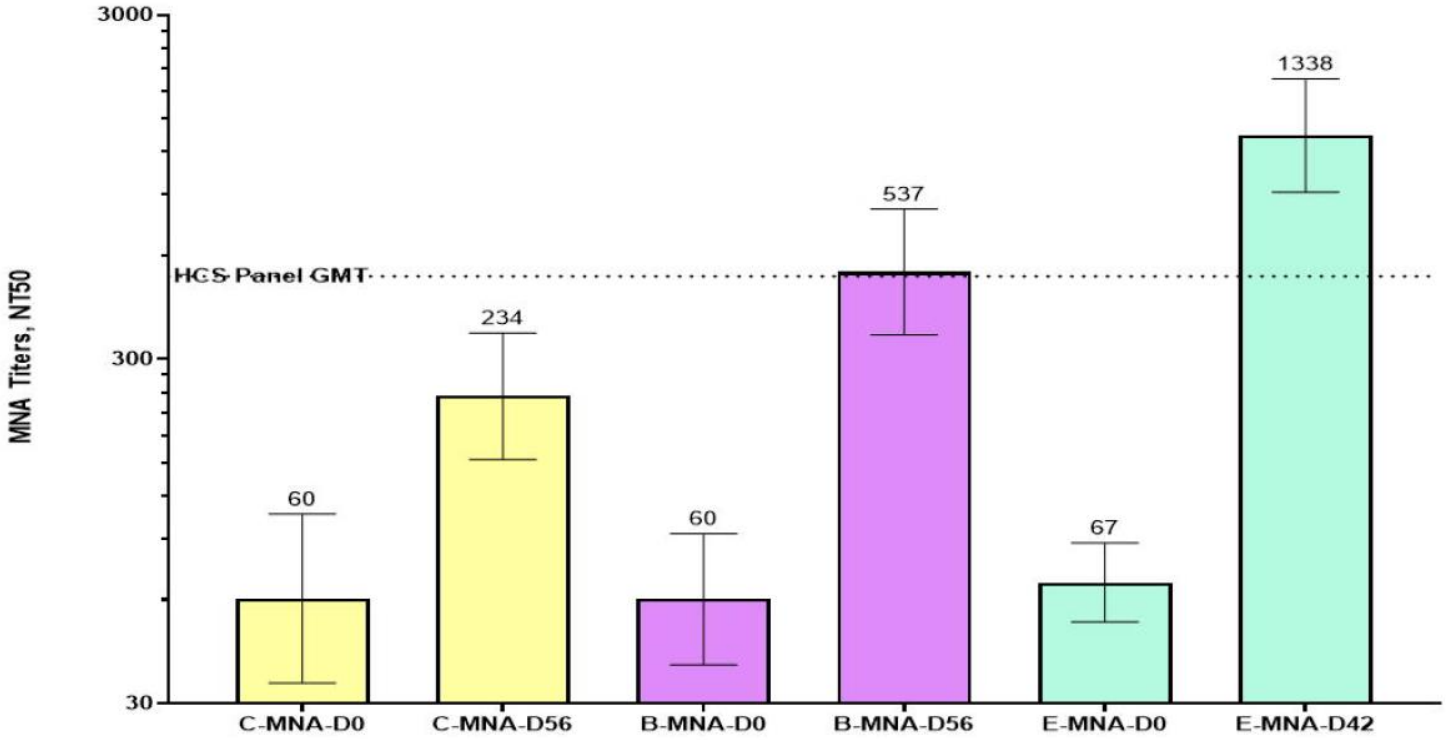

Figure 9 : Comparison of nAb titers by MNA method against the Ancestral-Wuhan strain of SARS-COV-2 for Formulations C & B from Phase I/II study vs. Formulation E in Phase II study. GMT's are shown at the top of the respective columns and the 95% Confidence interval is shown as two-sided bars. GMT's for Day-0 (pre-vaccination) and Day-56 or Day-42 time-point (post two-dose vaccination) are shown in the figure.

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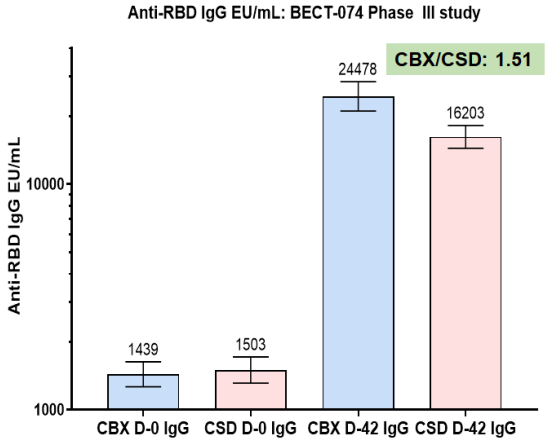
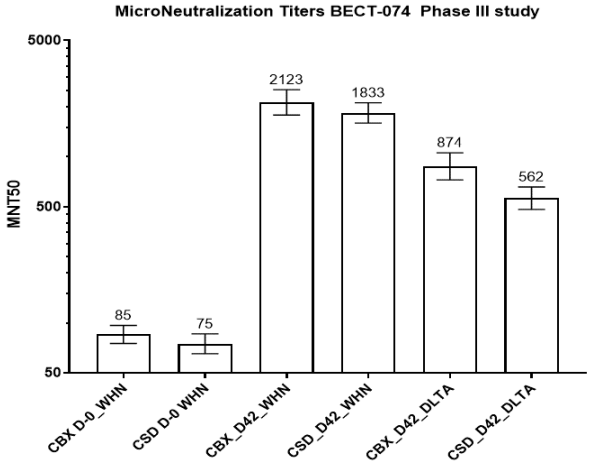
Immunogenic superiority and safety of Biological E's CORBEVAX™ vaccine compared to COVISHIELD™ (ChAdOx1 nCoV-19) vaccine studied in a phase III, single blind, multicenter, randomized clinical trial

Anti-RBD IgG concentration



Vaccine Arm & Number of subjects	Day-0 Testing		Day-42 testing		Ratio of Corbevax to Covishield	% SCR
	GMC ; EU/mL	95% CI	GMC, EU/mL	95% CI		
Corbevax N=304	1439	1268 -1633	24478	21075 -28431	1.51	91%
Covishield N=307	1503	1316 – 1716	16203	14428 – 18196		88%

nAb titers against Wuhan and Delta strains



	# of Subjects	MNT Titres GMT (95% CI)
CX-day-0	303	**85** (75 – 96)
D-day-0	307	**75** (65 - 86)
Corbevax-day-42	301-Wuhan 95% SCR	**2123** (1801 – 2514)
	301-Delta	**874** (724 – 1055)
Covishield - day-42	304-Wuhan 94% SCR	**1833** (1632 - 2089)
	304-Delta	**562** (482 – 657)

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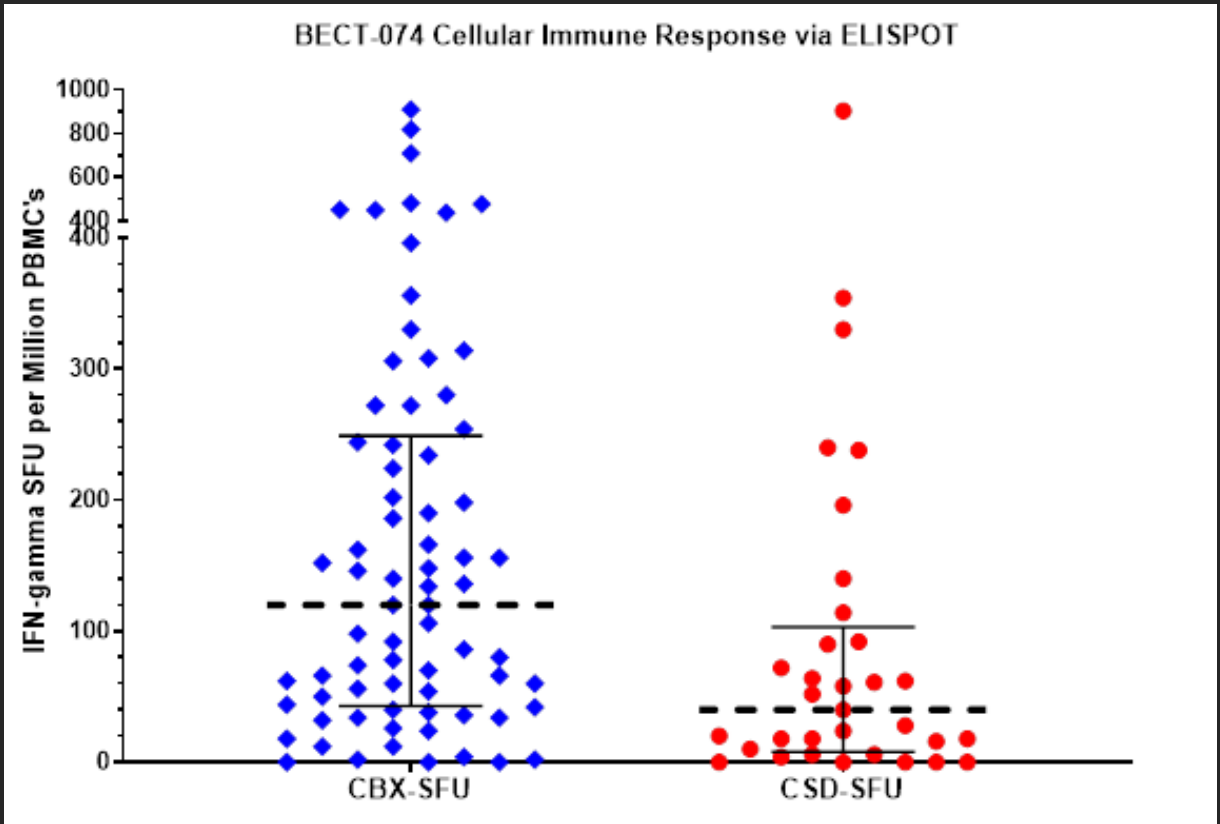
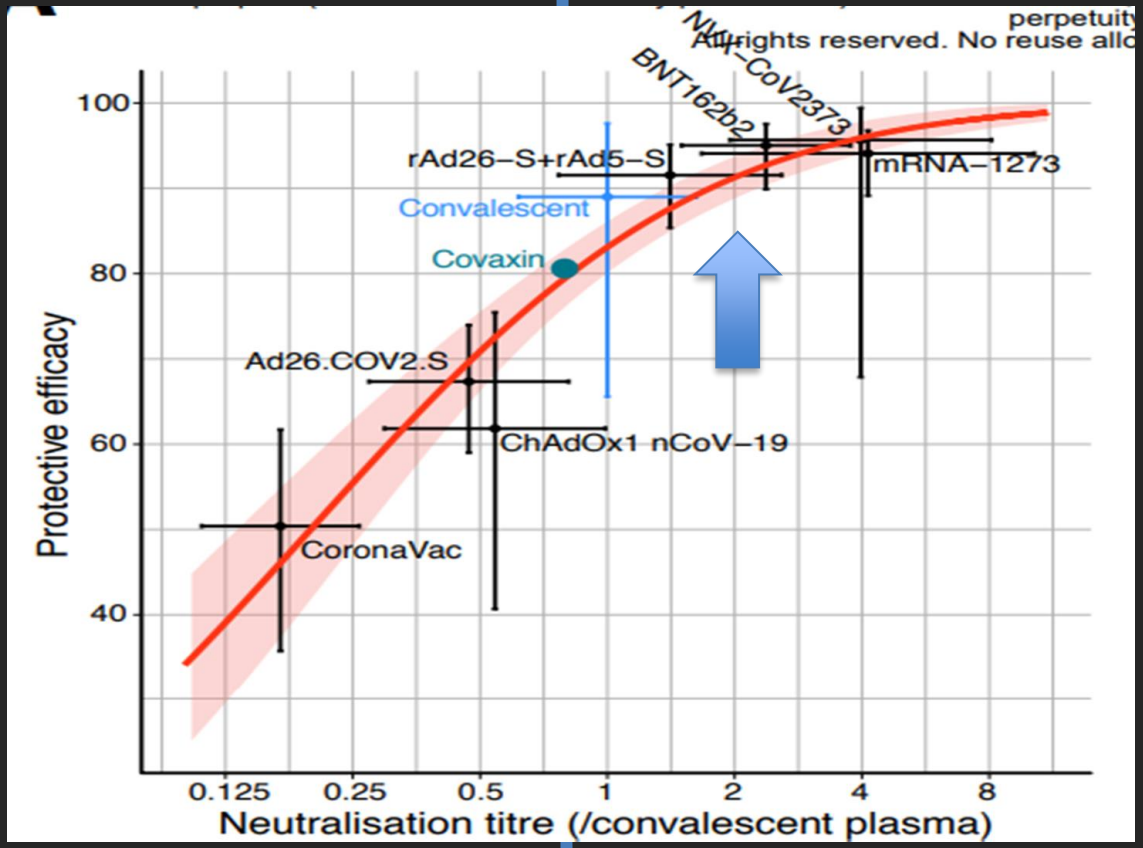
https://www.medrxiv.org/content/10.1101/2022.03.20.22271891v1?rss=1

Phase 3

Cellular responses in terms of ELISPOT data observed in a randomly selected sub-set of subjects in Corbevax and Covishield cohorts



Corbevax (Bio E) Immunogenicity



Times of India
March 15, 2022

https://timesofindia.indiatimes.com/city/mumbai/in-photos-covid-vaccination-for-12-14-years-of-age-group-begins-in-mumbai-and-thane/photostory/90263346.cms

The safety profile of CORBEVAX™ vaccine was comparable to the placebo control group with mild AEs. No medically attended AEs (MAAEs) or AEs of special interest (AESI) reported

Subjects showed significant improvement in anti-RBD-IgG concentrations, anti-RBD-IgG1 titers, neutralizing antibody (nAb)-titers against Ancestral Wuhan and Delta strains. Significantly high interferon gamma immune response (cellular) elicited with minimal effect on IL-4 cytokine secretion.

Figure 3. Anti-RBD IgG1 and IgG4 sub class titers in the two age-groups, pre (day-0) and post-vaccination (day-42)

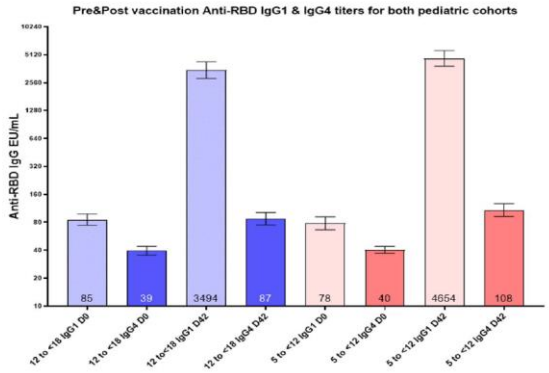


Figure 3: Summary of anti-RBD IgG sub class titers in both pediatric age sub groups: A) Anti-RBD IgG1 and IgG4 geometric mean concentrations were measured at day0 and day 42 post vaccination. In both age sub groups, IgG1 subclass titers predominantly increased after vaccination with CORBEVAX™ whereas IgG4 levels were comparable at day 0 and day 42 time points, indicating that CORBEVAX™ vaccine induces Th1 skewed immune responses. GMCT's with 95% Confidence Interval (two-sided bars) are included in the figure.

Figure 4. Neutralizing antibody titers against Ancestral and Delta strains of SARS-COV-2

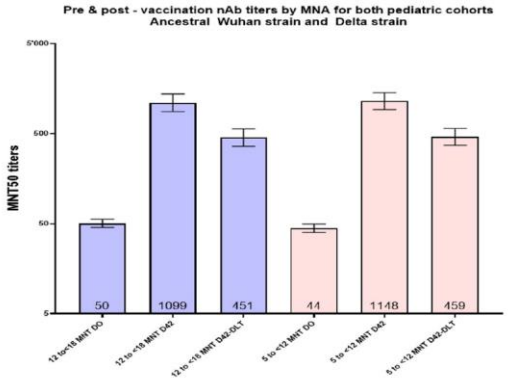


Figure 4: nAb titers measured against ancestral and Delta strains of SARS-COV-2: Neutralizing Antibody titers were tested in the subject sera samples collected prior to vaccination (Day-0) and fourteen days after two doses of vaccination (Day-42). The testing was conducted against Wild-Type SARS-COV-2 strain and Delta strain in a Micro Neutralization Assay (MNA). The observed nAb GMT's in both age groups that received CORBEVAX™ vaccine are much higher than the thresholds induced by other COVID-19 vaccines, which is indicative of >90% vaccine effectiveness of CORBEVAX™ vaccine. GMCT's with 95% Confidence Interval (two-sided bars) are included in the figure.

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https://www.medrxiv.org/content/10.1101/2022.04.20.22274076v1

Botswana Innovation Hub
Pula-Corbevax

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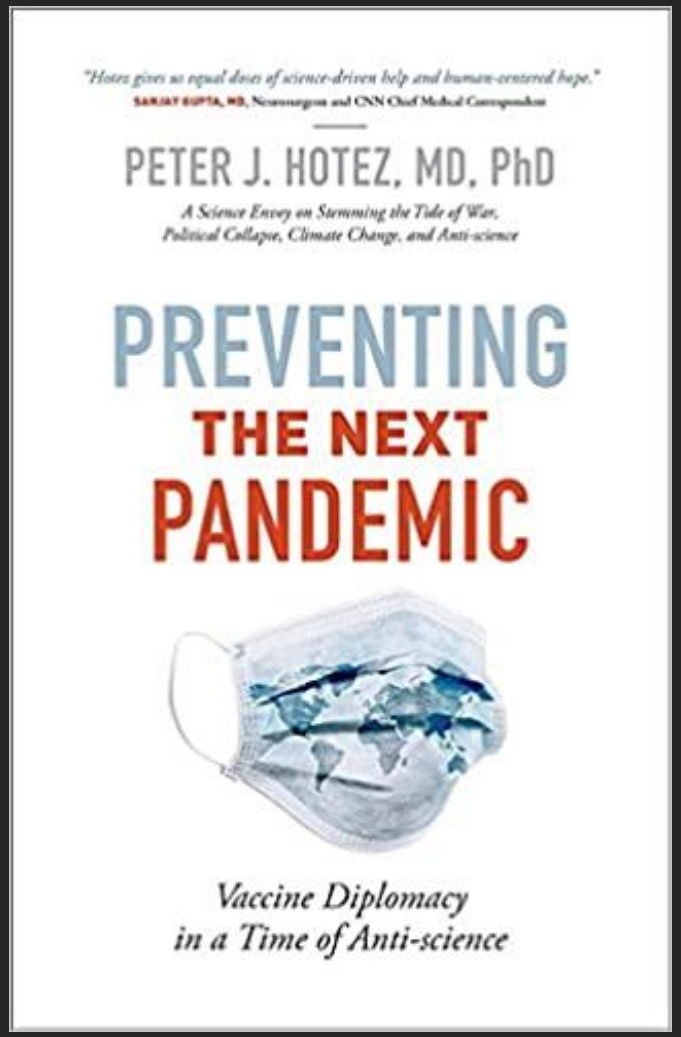
New 21st Century Drivers

- Poverty
- War
- Political Instability
- Urbanization
- Deforestation
- Climate Change
- Anti-Science

JOHNS HOPKINS
UNIVERSITY PRESS



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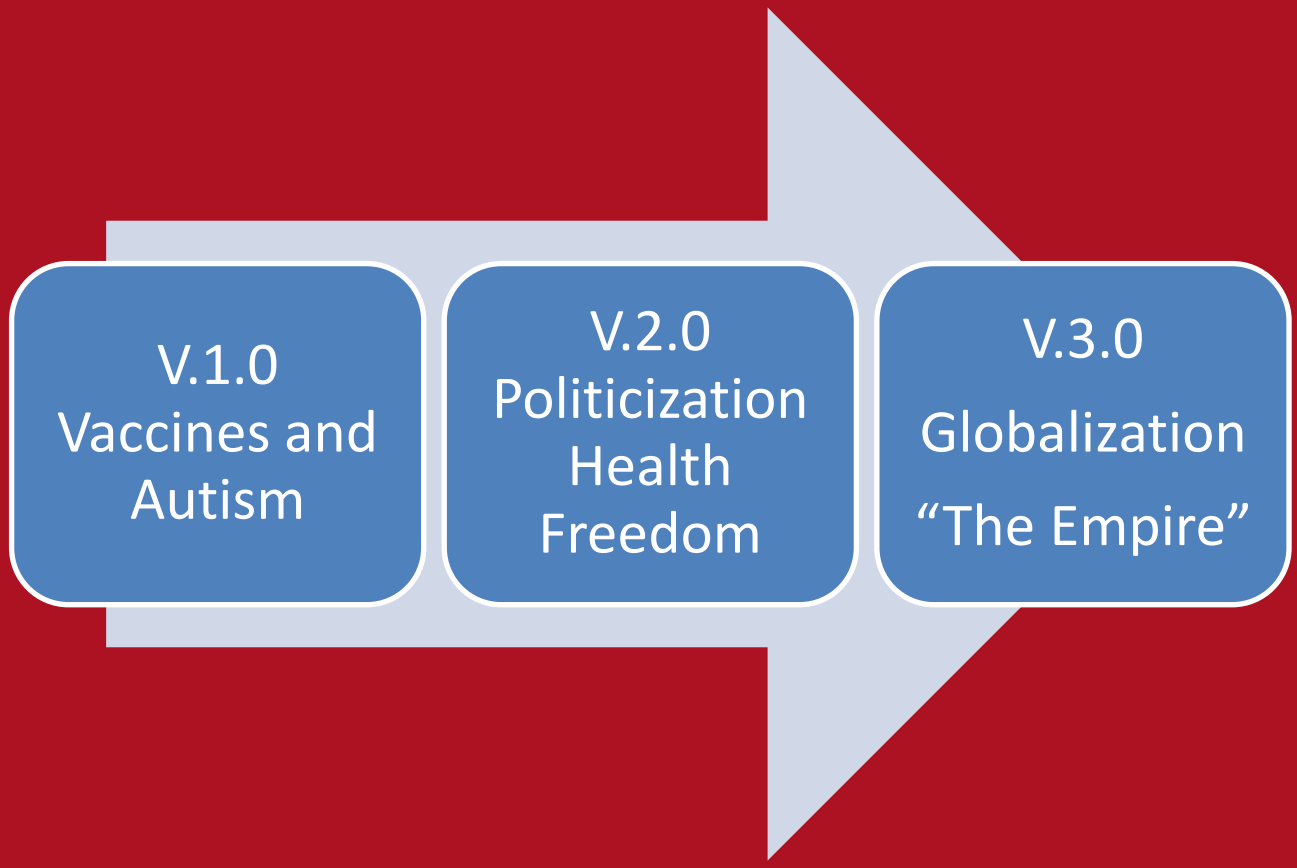
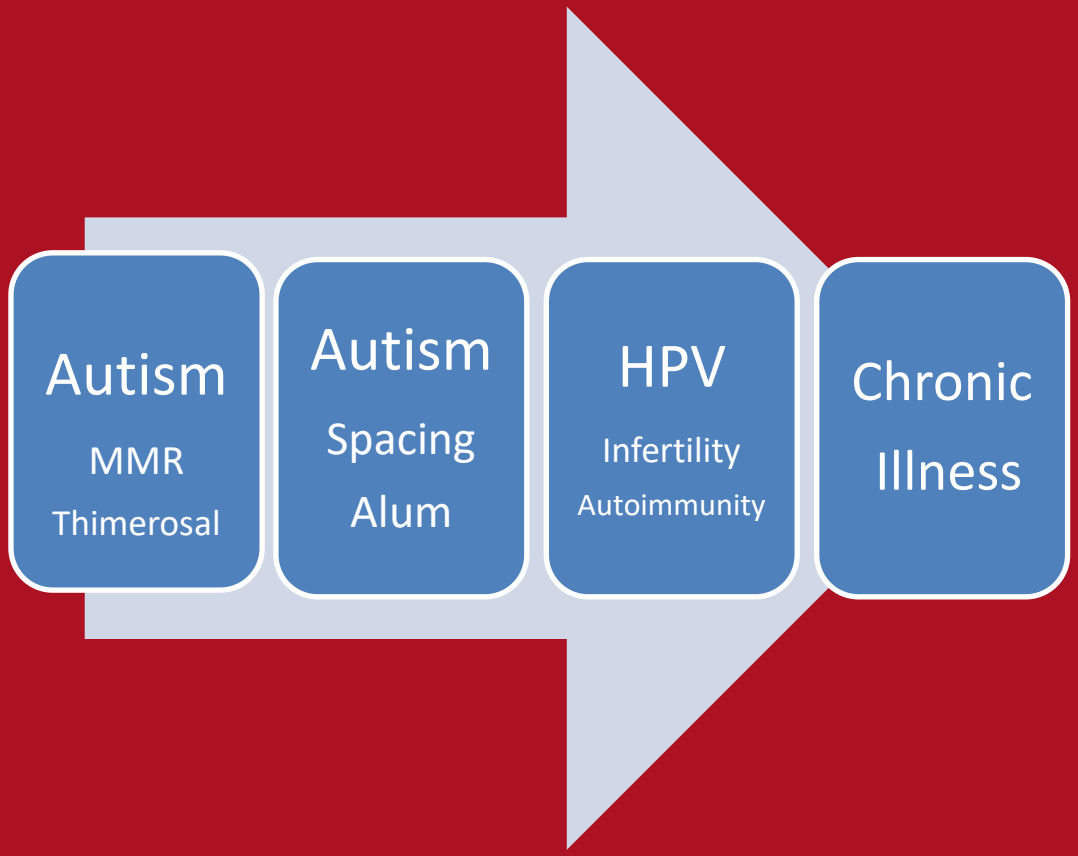
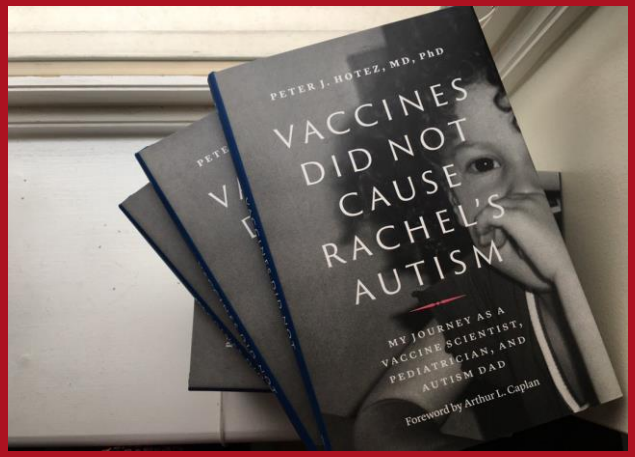
Antivaccine-Antiscience Ecosystems and Empires

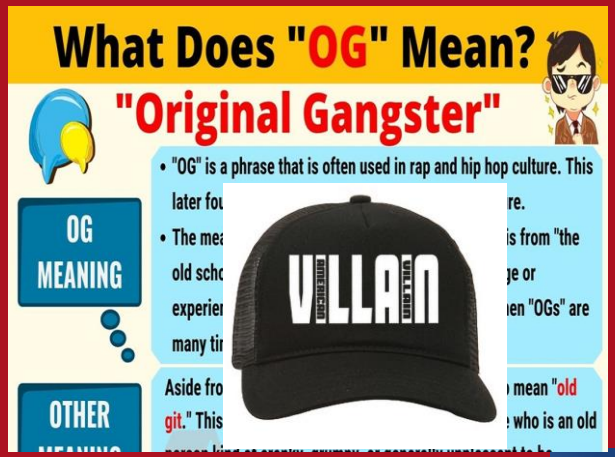


V.1.0: Vaccines and Autism
"Moving Goalposts"



Vaccine Scientist, Pediatrician, Parent of Adult Daughter with Autism, and the "OG Villain"





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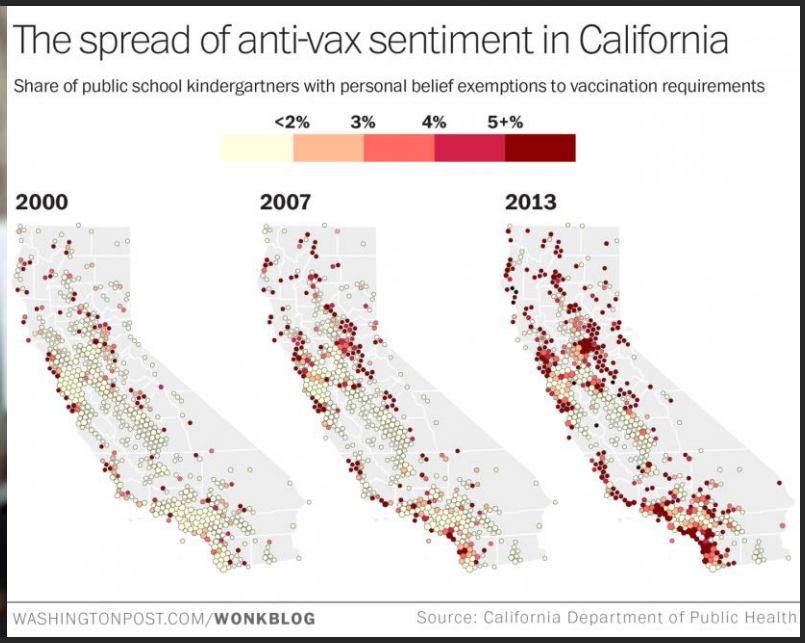
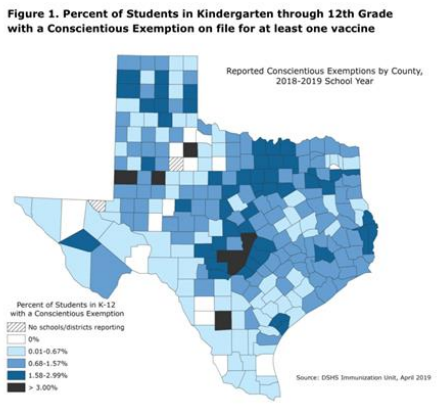
V.2.0: Origins of the Health Freedom Movement in Orange CA



Expansion of “Health Freedom” to Texas

TEXAS NON-MEDICAL EXEMPTIONS (2003-2020)



Source: Tex. Dep't St. Health Serv., *Vaccination Coverage Levels in Texas Schools* (May 4, 2020), https://www.dshs.texas.gov/immunize/coverage/schools/.

Texas COVID-19 Vaccinations Or “Not Vaccinations”

959d3578-42ba-46e6-99e1-a0222be33e77-election_results1-1.webp

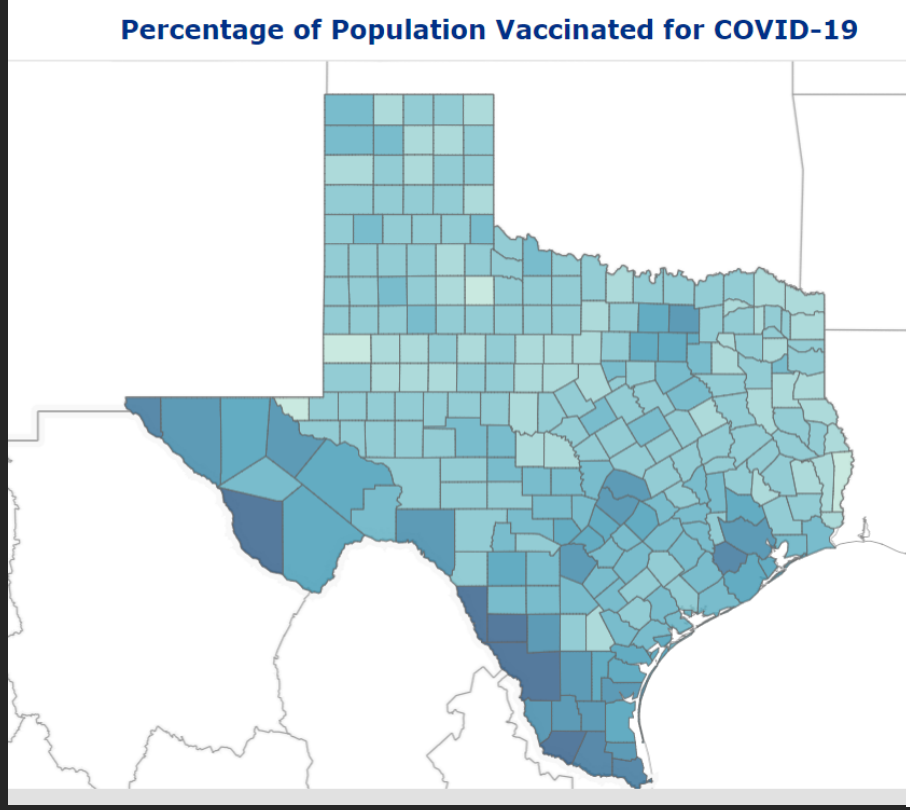
ated
with At Least One Dose
ated

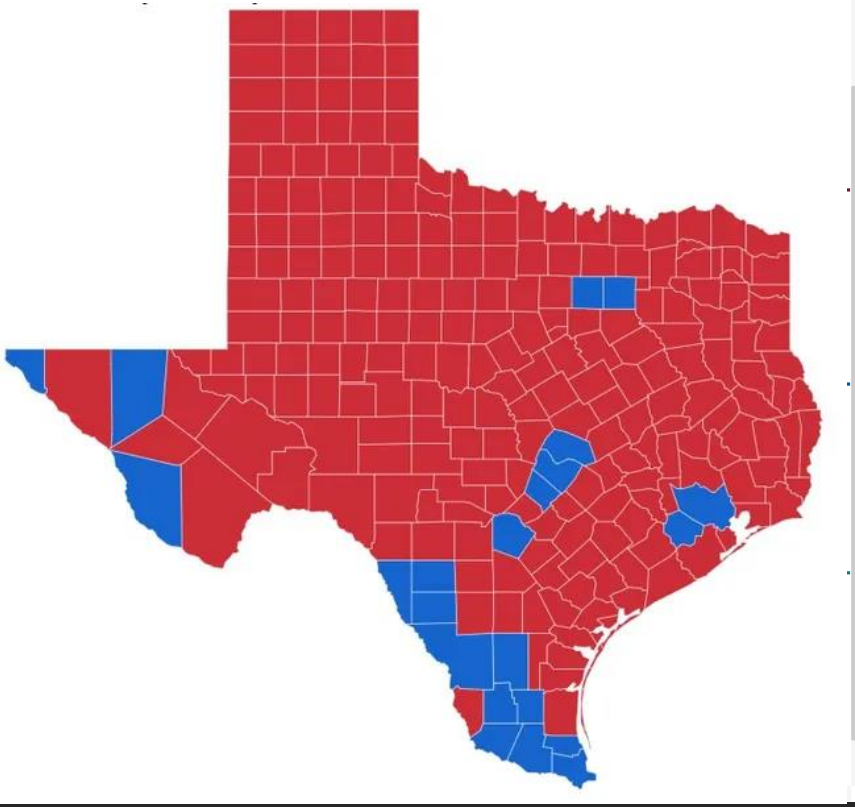
Percentage of County Population Vaccinated

21.86% 99.99%

day with data as of 11:59 pm the previous night. See the About the Data tab for mor information on data sources.

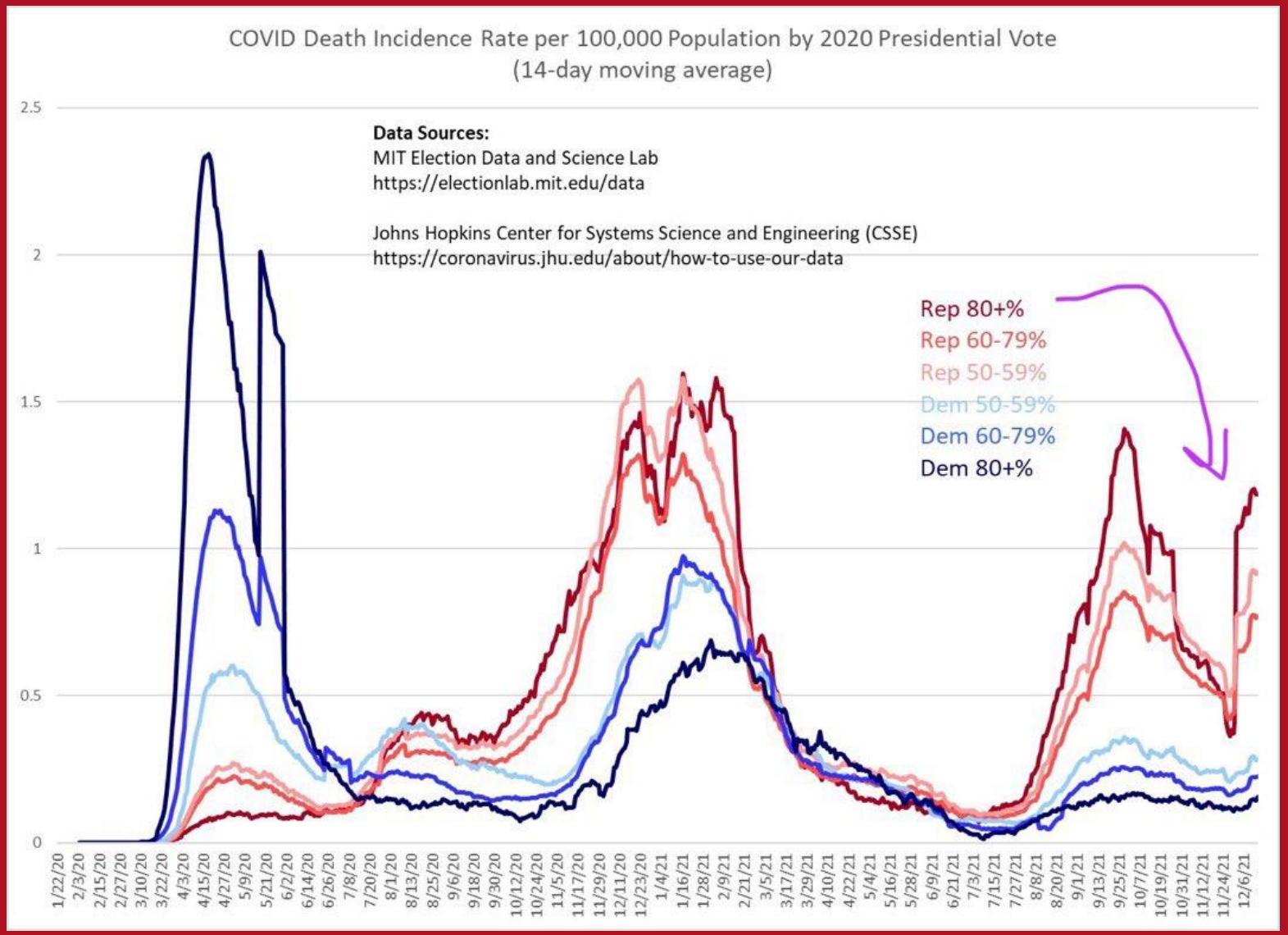
Percentage of Population Vaccinated for COVID-19

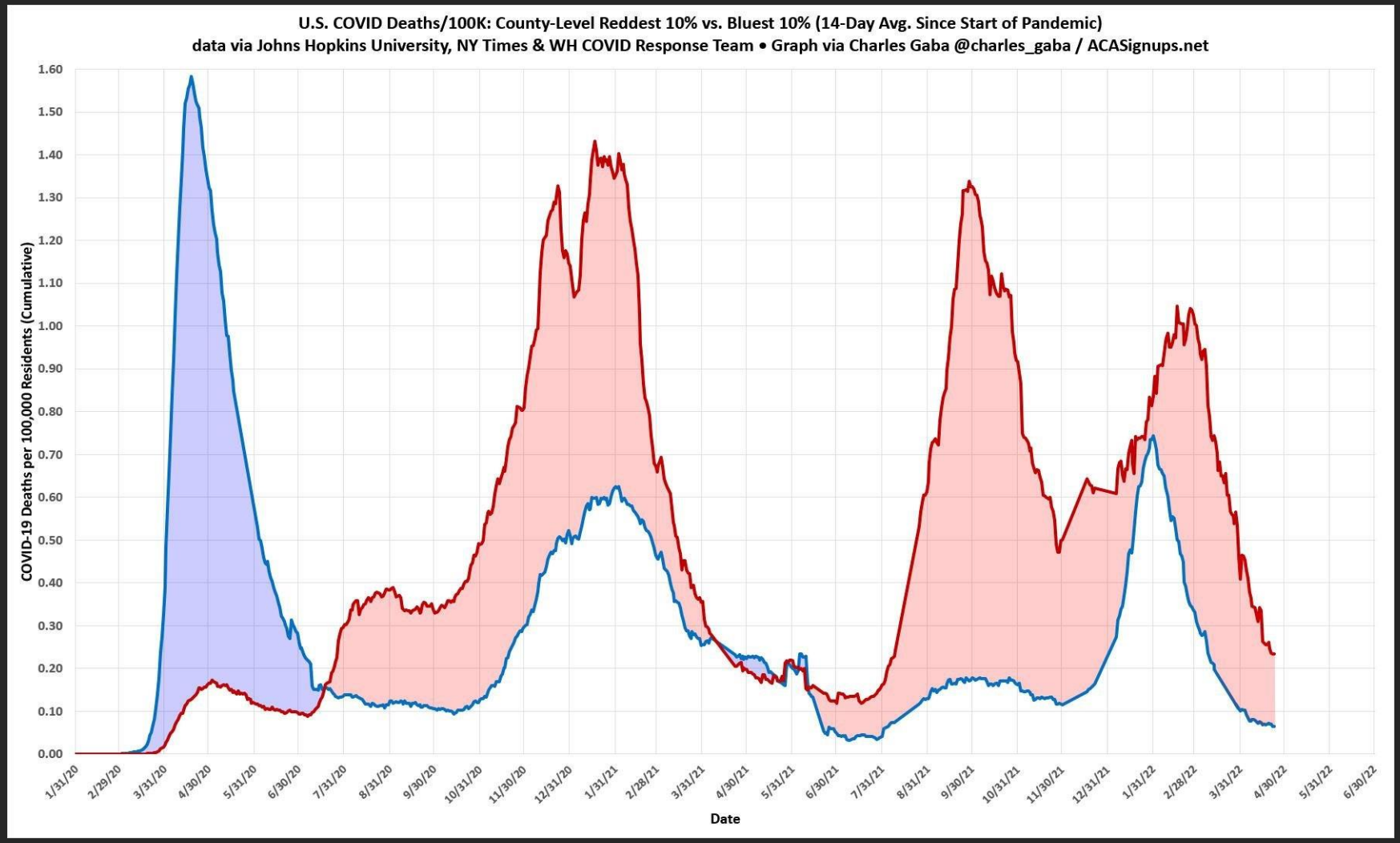




https://tabexternal.dshs.texas.gov/t/THD/views/COVID-19VaccineinTexasDashboard/Summary

Red COVID Deaths





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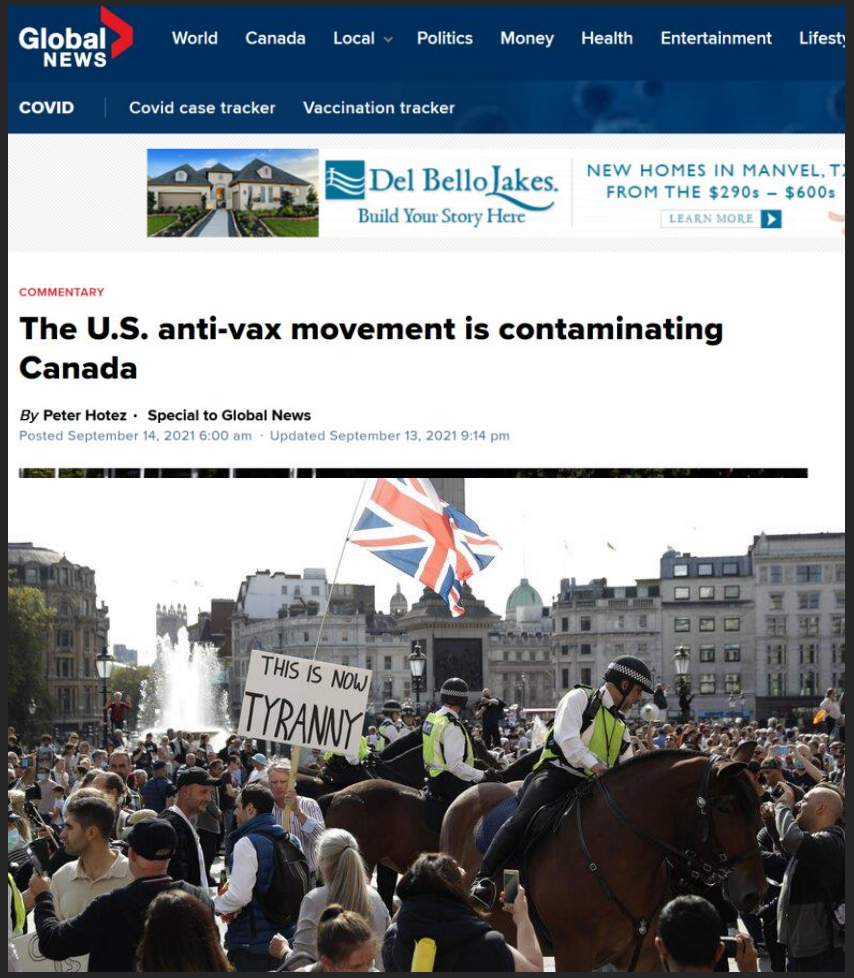
V.3.0: Globalization of American Anti-Science Western Europe, Canada

Hotez PJ (2021) *PLOS Biology*

- Globalization of US Health Freedom
- 2020-2 Antimask Antivaccine rallies in Western Europe and Canada
- QAnon and Political Extremism Far Right



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BEHAVIOR & SOCIETY | OPINION

The Antiscience Movement Is Escalating, Going Global and Killing Thousands

Rejection of mainstream science and medicine has become a key feature of the political right in the U.S. and increasingly around the world

By Peter J. Hotez on March 29, 2021

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ESSAY

Anti-science kills: From Soviet embrace of pseudoscience to accelerated attacks on US biomedicine

Peter J. Hotez

Published: January 28, 2021 • https://doi.org/10.1371/journal.pbio.3001068

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Abstract

An anti-science legacy through vaccines

Convergence and expansion: Exploiting the

Abstract

The United States witnessed an unprecedented politicization of biomedical science starting in 2015 that has exploded into a complex, multimodal anti-science empire operating through mass media, political elections, legislation, and even health systems. Anti-science activities now pervade the daily lives of many Americans, and threaten to infect other parts of the world. We

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Vol 592 | 29 April 2021 | **661**

A personal take on science and society

World view

By Peter Hotez

COVID vaccines: time to confront anti-vax aggression

Defeating the coronavirus will need high-level action against new destructive forces.

Nearly one billion COVID-19 vaccine doses have been delivered in less than six months, but anti-vaccine disinformation and targeted attacks on scientists are undermining progress. These threats must be confronted directly, and the authority and expertise of the health community alone aren't enough to do this.

Even before the pandemic, I had a front-row seat to all of this. I have co-led efforts to develop vaccines in programmes, including a COVID-19 vaccine currently being tested in India. I also have an adult daughter with autism; my 2018 book, *Vaccines Did Not Cause Rachel's Autism*, became a dog whistle for anti-vaccine activists.

The World Health Organization recognized vaccine hesitancy as a top threat to global health before the pandemic. As COVID-19 vaccines moved through devel-

> "Accurate, targeted counter-messaging from the global health community is important but insufficient."

to destabilize the United States and other democratic countries. The administration of US President Joe Biden has warned Russian media groups to halt their anti-vaccine aggression, and announced sanctions tied to disinformation and other behaviour, but we need much more.

The United States hosts the world's largest and best-organized anti-vaccine groups. According to the London-based Center for Countering Digital Hate, these are influential groups, not a spontaneous grass-roots movement. Many far-right extremist groups that spread false information about last year's US presidential election are doing the same about vaccines. Anti-vaccine groups also target Black communities; an anti-vaccine documentary released in March vilifies COVID-19 vaccine testing among African Americans, calling it "medical racism".

Global anti-vaccine messaging around the adenovirus vaccines means that more people will die and the pandemic will be prolonged. Extremely rare but life-threatening blood clots caused the United States to pause roll-out of the Johnson & Johnson vaccine, and many European nations