Welcome!

National Briefing on COVID-19 & Autoimmune Disease: *Research Insights, Treatment & Prevention*

Hosted by:

American Autoimmune Related Diseases Association, Inc.

Moderator

Dr. Betty Diamond
Chair, AARDA Scientific Advisory Board

American Autoimmune Related Diseases Association, Inc

Speakers

American Autoimmune Related Diseases Association, Inc.

Speaker

Zachary Wallace, MD, MSc
Assistant Professor of Medicine, Harvard Medical School

American Autoimmune Related Diseases Association, Inc

The Impact of COVID-19 on Patients with Autoimmune Disease

Zachary S. Wallace, MD, MSc
Clinical Epidemiology Program and Mongan Institute
Division of Rheumatology, Allergy, and Immunology
Massachusetts General Hospital and Harvard Medical School

What are the potential impacts of COVID-19?

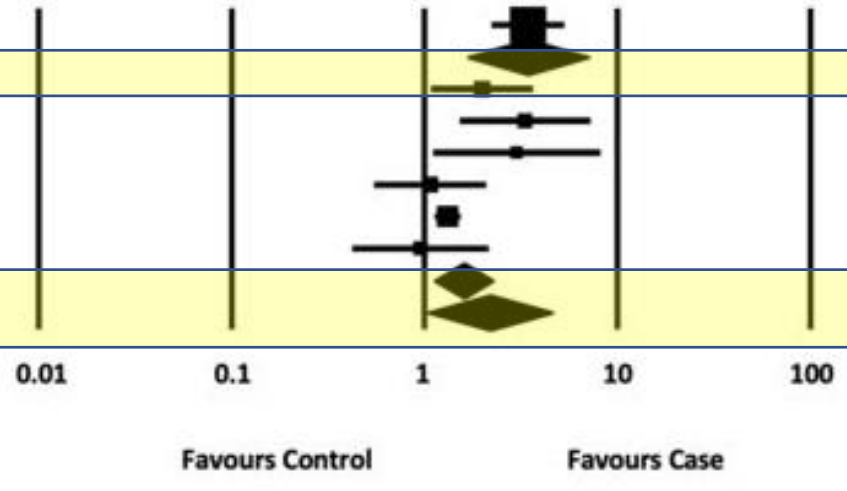
1. Increased risk of COVID-19 and worse outcomes?
   - Immunosuppression may increase risk of infection
   - But many of our treatments are being studied as effective therapies
2. Limited access to care because of changes in care delivery (e.g., telemedicine)?
3. Unable to get medications because of drug shortages, especially hydroxychloroquine, and self-discontinuation of treatments?
4. De novo manifestations of and/or exacerbations of autoimmunity due to COVID-19?
5. Loss of health insurance coverage for millions in the US because of the economic recession?

Outline

1. Risk of COVID-19 in patients with autoimmune diseases
2. Outcomes of COVID-19 infection in patients with autoimmune diseases from various large registries.
   - Rheumatic Disease
   - Inflammatory Bowel Disease
   - Psoriasis
3. Racial and ethnic differences in outcomes
4. Healthcare access

Risk of COVID-19 in Autoimmune Diseases

Study name	Subgroup within study	Odds ratio	Lower limit	Upper limit	COVID-19 / Total Case	Control	Relative weight
Damiani et al	Psoriasis	3.430	2.250	5.230	22 / 1193	54801 / 10060574	100.00
Subtotal		3.430	1.679	7.009	22 / 1193	54801 / 10060574	100.00
Michelena et al	RD	1.987	1.096	3.603	11 / 959	3903 / 672278	17.17
Zhong et al	RD	3.315	1.538	7.143	27 / 43	28 / 83	12.79
Benucci et al	RD	3.000	1.118	8.049	4 / 295	7393 / 1620952	9.03
Salvarani et al	RD	1.070	0.555	2.063	9 / 1195	3746 / 531891	15.45
Pablos et al_2	RD	1.315	1.143	1.513	199 / 26131	16820 / 2899935	33.48
Favalli et al_3	RD	0.952	0.426	2.124	6 / 955	57592 / 8726060	12.08
Subtotal		1.595	1.131	2.248	256 / 29578	89482 / 14451199	100.00
Overall		2.188	1.045	4.582	278 / 30771	144283 / 24511773	

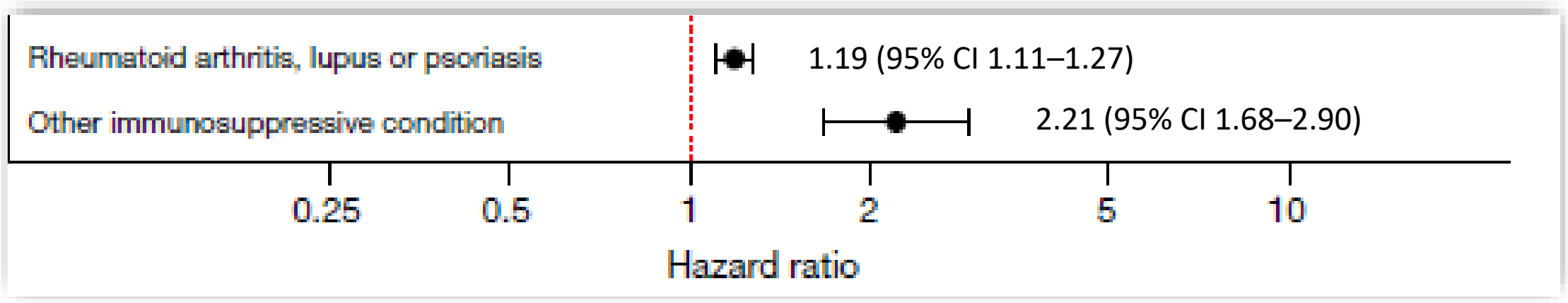


Psoriasis; $P = 0.001$, Heterogeneity: $I^2 = 0\%$, $Q = 0.00$, $P = 1.00$
RD: $P = 0.008$, Heterogeneity: $I^2 = 53.1\%$, $Q = 10.7$, $P = 0.058$
Overall: $P = 0.038$, Heterogeneity: $I^2 = 78.0\%$, $Q = 27.2$, $P < 0.001$

- Majority of patients had rheumatic disease
- Strongly driven by glucocorticoid use
- No seroprevalence studies and limited by many potential biases (e.g., testing practices) so interpret with caution.

Ann Rheum Dis 2020 (ePub)

Factors Associated with COVID-19 Related Death in the General Population in Open SAFELY



Nature 2020; 584:430

Outcomes in Patients with Rheumatic Diseases Compared to the General Population

Outcomes	RMD (N=143)	No RMD (N=688)
Hospitalization (N, %)	58 (41)	295 (43)
Unadjusted HR (95% CI)	0.95 (0.75, 1.21)	Ref
Adjusted HR (95% CI)*	0.87 (0.68, 1.11)	Ref
Intensive care admission (N, %)	28 (20)	96 (14)
Unadjusted HR (95% CI)	1.38 (0.95, 2.00)	Ref
Adjusted HR (95% CI)*	1.27 (0.86, 1.86)	Ref
Mechanical ventilation (N, %)	22 (15)	63 (9)
Unadjusted HR (95% CI)	**1.75 (1.12, 2.74)**	Ref
Adjusted HR (95% CI)*	1.51 (0.93, 2.44)	Ref
Death (N, %)†	12 (8)	48 (7)
Unadjusted HR (95% CI)	1.16 (0.63, 2.13)	Ref
Adjusted HR (95% CI)*	1.02 (0.53, 1.95)	Ref

Ann Rheum Dis 2020;79:1156
Under Review

Factors Associated with Hospitalization in Rheumatic Diseases (N=600)

Characteristic	OR (95% CI)*	P-value
Female	0.83 (0.54,1.28)	0.39
Age	**2.56 (1.62, 4.04)**	**<0.01**
Common diagnoses:		
RA	Ref	--
SLE	1.80 (0.99, 3.29)	0.06
SpA -PsA	0.94 (0.48, 1.83)	0.85
SpA – AS or other	1.11 (0.50, 2.42)	0.80
Vasculitis	1.56 (0.66, 3.68)	0.31
Other	0.94 (0.55, 1.62)	0.82
Common comorbidities		
HTN or CVD	**1.86 (1.23, 2.81)**	**<0.01**
Lung Disease	**2.48 (1.55, 3.98)**	**<0.01**
Diabetes	**2.61 (1.39, 4.88)**	**<0.01**
CKD/ESRD	**3.02 (1.21, 7.54)**	**0.02**

Characteristic	OR (95% CI)	P-value
Medications		
No DMARD	Ref	--
csDMARD only	1.23 (0.70, 2.16)	0.48
b/tsDMARD only	**0.46 (0.22, 0.93)**	**0.03**
csDMARD + b/tsDMARD	0.74 (0.37, 1.46)	0.38
Prednisone-Equivalent		
None	Ref	--
1-9 mg/day	1.03 (0.64, 1.66)	0.91
≥10 mg/day	**2.05 (1.06, 3.96)**	**0.03**

All reported OR are multi-variable adjusted

Ann Rheum Dis 2020;79:859

Selected Factors Associated with Death in Rheumatic Disease (N=3,729)

Medication	OR (95% CI)		
Methotrexate or Leflunomide	1	[Reference]	
No DMARD therapy	1.94	1.39	2.72
Antimalarials	0.92	0.63	1.33
Sulfasalazine	**3.28**	**1.63**	**6.60**
Immunosuppressants	**2.04**	**1.37**	**3.04**
TNF inhibitors	0.78	0.50	1.20
Abatacept	1.12	0.59	2.13
Rituximab	**3.68**	**2.09**	**6.47**
Belimumab	0.66	0.19	2.31
IL-6 inhibitors	0.74	0.35	1.56
IL-17/IL-23/IL-12+23 inhibitors	0.23	0.03	1.91
tsDMARDs	1.49	0.90	2.45

Medication	OR (95% CI)		
No Glucocorticoids	1	[Reference]	
GC 1-10mg/day	1.44	0.99	2.10
GC > 10mg/day	**1.67**	**1.17**	**2.37**

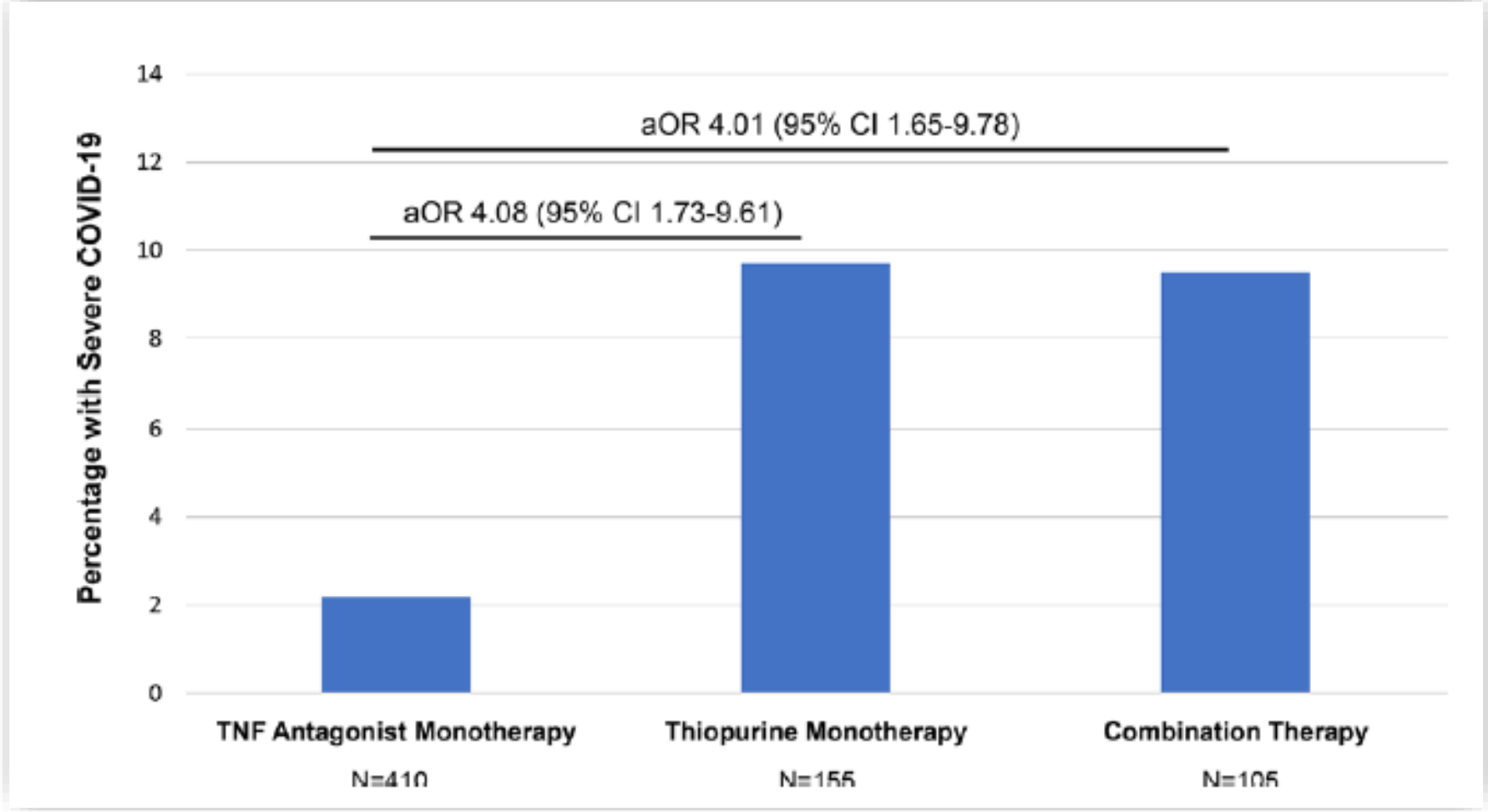
Submitted

Factors Associated with Poor Outcomes in Inflammatory Bowel Disease (N=525)

Variable (Referent group)[a]	ICU/Vent/Death Odds Ratio (95% CI) (n = 517)	P	Hospitalization or death Odds Ratio (95% CI) (n =517)	P	Death Odds Ratio (95% CI) (n = 513)	P
Age	1.04 (1.01–1.06)	.002	1.03 (1.01–1.04)	<.001	1.07 (1.03–1.11)	<.001
Male (Female[b])	1.20 (0.55–2.60)	.65	1.38 (0.89–2.15)	.15	2.78 (0.76–10.14)	.12
Diagnosis						
Crohn's disease (ulcerative colitis/IBD unspecified)	0.76 (0.31–1.85)	.54	0.84 (0.51–1.38)	.49	1.64 (0.42–6.43)	.48
Disease severity[c] (remission)						
Active disease	1.14 (0.49–2.66)	.76	1.96 (1.23–3.11)	.005	0.97 (0.26–3.62)	.96
Systemic corticosteroid (none)	6.87 (2.30–20.51)	<.001	6.46 (2.74–15.23)	<.001	11.62 (2.09–64.74)	.005
TNF antagonist (none)	0.90 (0.37–2.17)	.81	0.60 (0.38–0.96)	.03	0.99 (0.23–4.23)	.99
Current smoker	0.55 (0.06–4.94)	.59	2.38 (0.92–6.16)	.07	1.47 (0.12–17.53)	.76
BMI ≥ 30	2.00 (0.72–5.51)	.18	1.18 (0.61–2.31)	.63	1.58 (0.28–8.80)	.60
Comorbidities (none)						
1	1.22 (0.45–3.26)	.70	1.29 (0.76–2.20)	.34	1.64 (0.35–7.67)	.53
≥2	2.87 (1.05–7.85)	.04	4.42 (2.16–9.06)	<.001	2.51 (0.56–11.24)	.23
5-ASA/sulfasalazine (none)	3.14 (1.28–7.71)	.01	1.77 (1.00–3.12)	.05	1.71 (0.46–6.38)	.43

Gastroenterology 2020;159:481

Factors Associated with Severe COVID-19 Outcomes in Inflammatory Bowel Disease (N=1,439)



Severe Outcome: ICU, Ventilator, and/or Death

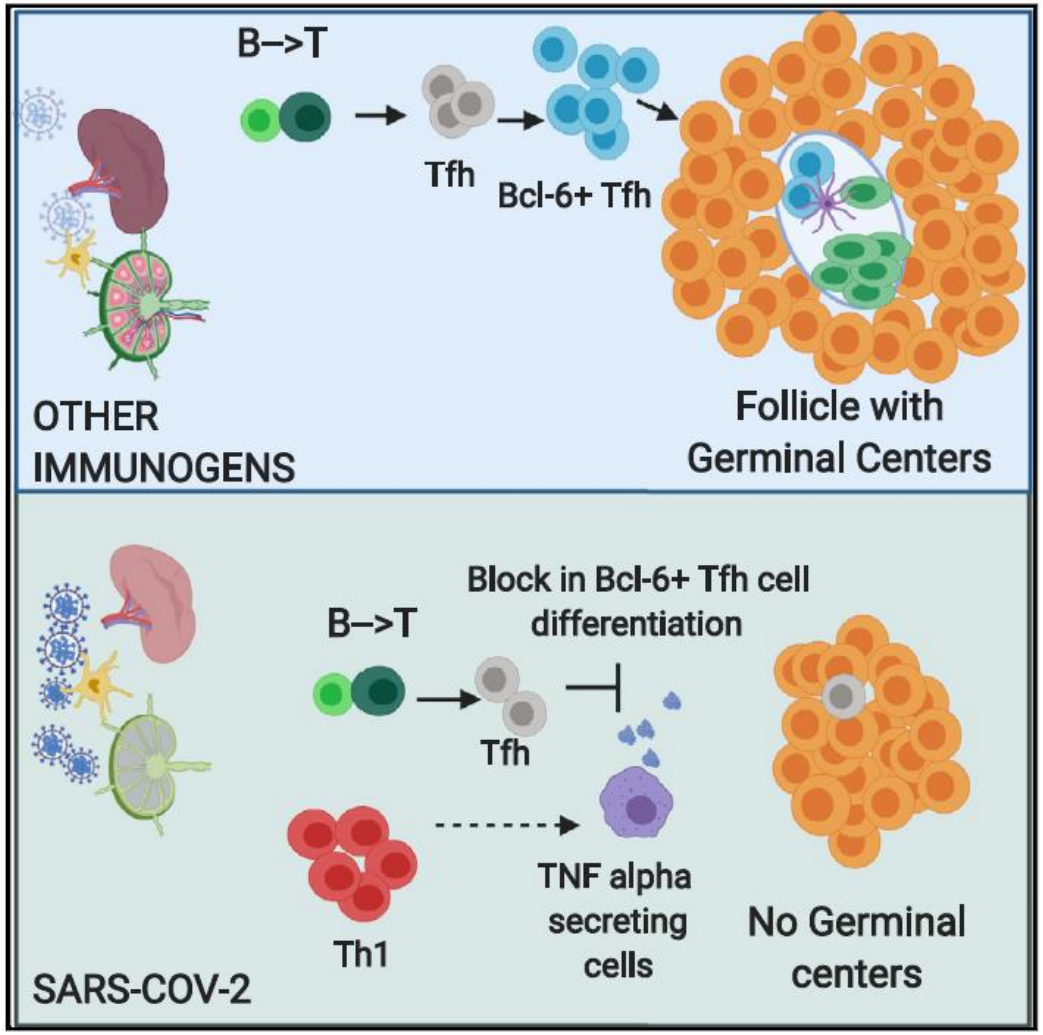
Gut 2020 (ePub)

Factors Associated with Hospitalization for COVID-19 in Psoriasis (N=374)

Characteristic	OR (95% CI)
Male	**2.51 (1.23-5.12)**
Age (/10 years)	**1.59 (1.19-2.13)**
Non-White Ethnicity	**3.15 (1.24-8.03)**
Ever Smoked	1.16 (0.54-2.49)
Comorbidities	
Lung Disease	**3.87 (1.52-9.83)**
Hypertension	2.03 (0.99-4.16)
CVD	2.01 (0.74-5.46)
Treatments	
Non-biologic systemic (vs biologic)	**2.84 (1.31-6.18)**
No treatment	2.35 (0.82-6.72)

JACI 2020 (ePub)

Why might TNF inhibitors be associated with better outcomes?



Cell 2020;183:143

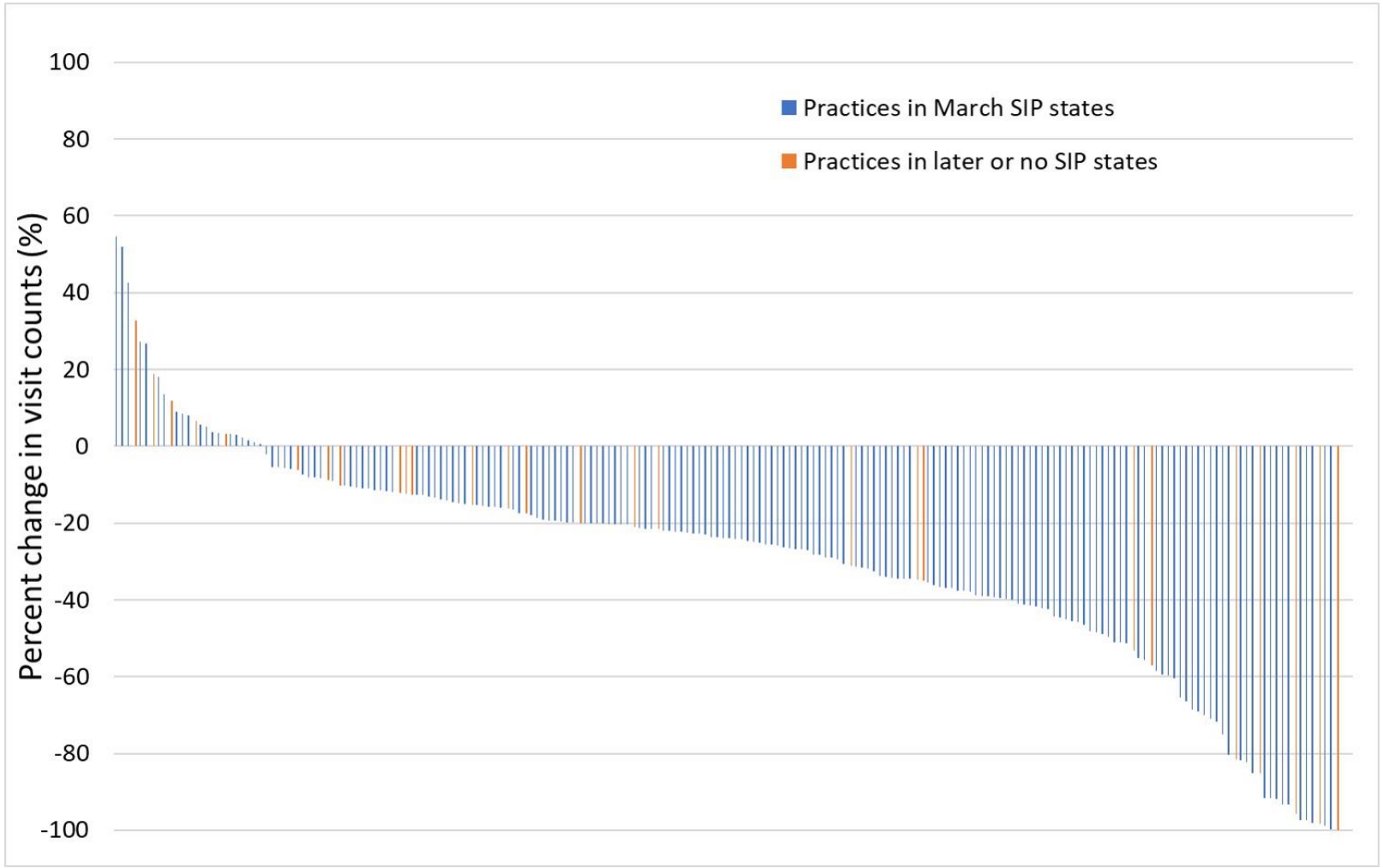
Racial Disparities in COVID-19 in Patients with Rheumatic Diseases in the USA

Race/Ethnicity	Hospitalization N=599	Ventilation N=540	Death N=681
White	Ref	Ref	Ref
Black	**2.70 (1.66, 4.42)**	**3.10 (1.77, 5.41)**	1.10 (0.49, 2.50)
Latinx	**1.98 (1.17, 3.33)**	**2.97 (1.63, 5.41)**	1.78 (0.84, 3.78)
Other/Mixed Race	1.79 (0.93, 3.44)	**2.34 (1.11, 4.95)**	1.22 (0.35, 4.26)

Estimates are OR (95% CI)

Arthritis Rheum 2020 (In Press)

Changes in Care Delivery During the Pandemic March 2020 vs March 2019



Arthritis Rheumatol. 2020; 72 (suppl 10).

Take Home Messages

1. Most available data is in rheumatic disease, psoriasis, and IBD.
2. Patients with autoimmune diseases may be at higher risk for COVID-19 but the data on this topic is limited.
3. Patients with autoimmune diseases may have worse outcomes compared to the general population, perhaps because of comorbidity burden.
4. Among patients with autoimmune diseases, certain disease-specific factors are associated with worse outcomes (glucocorticoids, sulfasalazine).
5. But certain factors may be associated with better outcomes (e.g., biologic DMARDs, especially TNF inhibitors).
6. Racial disparities in COVID-19 outcomes are observed in patients with rheumatic diseases.

Unanswered Questions

1. What is the incidence of COVID-19 in patients with autoimmune diseases?
2. What is the impact of autoimmune diseases and immunosuppression on the durability of the antibody response to COVID-19?
3. What are long-term outcomes of patients with autoimmune disease who had COVID-19?
4. Does COVID-19 lead to *de novo* autoimmunity or exacerbate pre-existing autoimmune disease?
5. Will vaccine efficacy be affected by autoimmune disease or immunosuppression?

Speaker

Arturo Casadevall, MD, MSc
Chair, Department of Molecular Microbiology and Immunology, Johns Hopkins Bloomberg School of Public Health
Alfred & Jill Sommer Professor and Chair
Bloomberg Distinguished Professor

American Autoimmune Related Diseases Association, Inc

Convalescent Plasma for COVID-19

Arturo Casadevall MD, PhD
Johns Hopkins School of Public Health

Some Background

- In early 2020, there was no effective therapy for COVID-19
- Convalescent Plasma (serum) had been used in past epidemics since 1918 and there was considerable human experience that it was relatively safe and possibly effective.
- Plasma is widely used throughout the world and its risks and benefits are known to physicians and regulators.
- COVID-19 convalescent plasma differs from regular plasma only in that came from COVID-19 survivors.
- The use of convalescent plasma is supported by > 130 years of immunological studies of antibody function, which showed that certain antibodies can neutralize virus (mechanistic causality).

Early Days – Plasma not in radar screen

- **January 2020 – Increasing concerns that it is not containable**
- **History of antibody-based therapies not well known**
- **Public response does not mention plasma therapy**
- **How do I get the word out?**
- **Early February Decide to try OpEd.**
- **NYT, WAPO, Bloomberg News, do not want it..but WSJ takes it…**

OPINION | COMMENTARY

How a Boy's Blood Stopped an Outbreak

A school physician's approach to measles in 1934 has lessons for the coronavirus.

By *Arturo Casadevall*
Feb. 27, 2020 6:48 pm ET

March 2020…Things now move fast

Feb 27

WSJ Editorial and JCI paper

Mid-March 2020

General Media Covers Plasma

FDA Receives overwhelming number of Requests for Plasma Use

April 4

FDA issues single Extended Access Protocol and contracts
Mayo Clinic to run it (Joyner is PI)

The ‘EAP’

April-May 2020

- **The Unexpected Happened**
- Thousands of individuals with COVID-19 treated in USA
- 80% of usage occurs in hospitals with no access to RCTs
- Most usage occurred outside Randomized Clinical Trials
- Donation campaigns insured a steady supply of convalescent plasma
- Usage is driven by physicians who have embraced
- Criticism mounts of large scale use without safety and efficacy data

Convalescent Plasma and COVID-19: The two questions everyone wants answered

- **Is it Safe?**
- **Does it work?**

Is it safe?...Yes, as safe as Plasma

Early Safety Indicators of COVID-19 Convalescent Plasma in 5,000 Patients

Michael J. Joyner[1], DeLisa Fairweather[2], Jonathon W. Senefeld[1], Katelyn A. Bruno[2], Stephen A. Klassen[1], Rickey E. Carter[3], R. Scott Wright[4,5], Allan M. Klompas[1], Chad C. Wiggins[1], John R.A. Shepherd[1], Robert F. Rea[4], Emily R. Whelan[3], Andrew J. Clayburn[1], Matthew R. Spiegel[3], Patrick W. Johnson[3], Elizabeth R. Lesser[3], Sarah E. Baker[1], Kathryn F. Larson[1], Juan G. Ripoll[1], Kylie J. Andersen[1], David O. Hodge[3], Katie L. Kunze[6], Matthew R. Buras[6], Matthew N.P. Vogt[1], Vitaly Herasevich[1], Joshua J. Dennis[1], Riley J. Regimbal[1], Philippe R. Bauer[7], Janis E. Blair[8], Camille M. Van Buskirk[9], Jeffrey L. Winters[9], James R. Stubbs[9], Nigel S. Paneth[10,11], Arturo Casadevall[12]

J. Clin. Invest. 2020

Concerns about antibody-dependent immunity cytokine storms and worsening of disease with specific antibody administration have not materialized!

Mayo Clinic Proceedings
COVID-19 Convalescent Plasma in 20,000 Patients

Safety Update: COVID-19 Convalescent Plasma in 20,000 Hospitalized Patients

Michael J. Joyner[1#*], MD, Katelyn A. Bruno[2#], PhD, Stephen A. Klassen[1#], PhD, Katie L. Kunze[3#], PhD, Patrick W. Johnson[4#], BS, Elizabeth R. Lesser[4#], MS, Chad C. Wiggins[1#], PhD, Jonathon W. Senefeld[1#], PhD, Allan M. Klompas[1#], MB, BCh, BAO, David O. Hodge[4], MS, John R.A. Shepherd[1], MD, Robert F. Rea[5], MD, Emily R. Whelan[2], BS, Andrew J. Clayburn[1], BS, Matthew R. Spiegel[4], BS, Sarah E. Baker[1], PhD, Kathryn F. Larson[1], MD, Juan G. Ripoll[1], MD, Kylie J. Andersen[1], BS, Matthew R. Buras[3], MS, Matthew N.P. Vogt[1], MD, Vitaly Herasevich[1], MD, PhD, Joshua J. Dennis[1], BS, Riley J. Regimbal[1], BS, Philippe R. Bauer[6], MD, PhD, Janis E. Blair[7], MD, Camille M. Van Buskirk[8], MD, Jeffrey L. Winters[8], MD, James R. Stubbs[8], MD, Noud van Helmond[9], MD, Brian P. Butterfield[1], BS, Matthew A. Sexton[1], MD, Juan C. Diaz Soto[1], MD, Nigel S. Paneth[10,11†], MD, MPH, Nicole C. Verdun[12†], MD, Peter Marks[12†], MD, PhD, Arturo Casadevall[13†], MD, PhD, DeLisa Fairweather[2†], PhD, Rickey E. Carter[4†], PhD, R. Scott Wright[5,14†], MD

Table 2. SAE Characteristics in Patients Transfused with COVID-19 Convalescent Plasma. (*n* = 20,000)

Serious Adverse Events (SAE): Transfusion Reactions	Reported	Related	Estimate[a] (95% CI)
Mortality within four hours of transfusion	63	13	0.06% (0.04%, 0.11%)
Transfusion-Associated Circulatory Overload (TACO)	37	37	0.18% (0.13%, 0.25%)
Transfusion-Related Acute Lung Injury (TRALI)	20	20	0.10% (0.06%, 0.15%)
Severe allergic transfusion reaction	26	26	0.13% (0.09%, 0.19%)

Mayo Clinic Proceedings 2020

Is it working? Many Encouraging Reports…The major lines of evidence

1. EAP Data Analysis – suggests lower mortality with early use of high titer plasma (used by FDA in EUA recommendation)

2. > 10 Observational studies: Mt. Sinai NYC, Methodist Houston, Hackensack NJ, Italy, Iran, etc. report large reductions in mortality if given early – before ICU.

3. Five Randomized controlled trials – all suboptimal in some way but all provide some encouragement.

4. Experiments of nature. Convalescent plasma has dramatic effects patients with congenital immune suppression (X-linked agammaglobulimia)

Let's take a look at some of these reports…

Analysis of the Extended Access Protocol Data

Effect of Convalescent Plasma on Mortality among Hospitalized Patients with COVID-19: Initial Three-Month Experience

Michael J. Joyner[1*], M.D., Jonathon W. Senefeld[1], Ph.D., Stephen A. Klassen[1], Ph.D., John R. Mills[2], Ph.D., Patrick W. Johnson[3], Elitza S. Theel[2], Ph.D., Chad C. Wiggins[1], Ph.D., Katelyn A. Bruno[4], Ph.D., Allan M. Klompas[1], M.B., B.Ch., B.A.O., Elizabeth R. Lesser[3], Katie L. Kunze[5], Ph.D., Matthew A. Sexton[1], M.D., Juan C. Diaz Soto[1], M.D., Sarah E. Baker[1], Ph.D., John R.A. Shepherd[1], M.D., Noud van Helmond[6], M.D., Nigel S. Paneth[7,8#], M.D., M.P.H., Ph.D., DeLisa Fairweather[4#], Ph.D., R. Scott Wright[9,10#], M.D., Rickey E. Carter[3#], Ph.D., Arturo Casadevall[11#], M.D., Ph.D., *the US EAP COVID-19 Plasma Consortium,*

US EAP COVID-19 Plasma Consortium: Camille M. van Buskirk[2], M.D., Jeffrey L. Winters[2], M.D., James R. Stubbs[2], M.D., Robert F. Rea[9], M.D, David O. Hodge[3], Vitaly Herasevich[1], M.D., Ph.D., Emily R. Whelan[4], Andrew J. Clayburn[1], Kathryn F. Larson[9], M.D., Juan G. Ripoll[1], M.D., Kylie J. Andersen[1], Matthew R. Buras[5], Matthew N.P. Vogt[1], M.D., Joshua J. Dennis[1], Riley J. Regimbal[1], Philippe R. Bauer[12], M.D., Ph.D., and Janis E. Blair[13], M.D.

Compassionate use of convalescent plasma for treatment of moderate and severe pneumonia in COVID-19 patients and association with IgG antibody levels in donated plasma

Yasmin Maor[a,b], Daniel Cohen[c], Nir Paran[d], Tomer Israely[d], Vered Ezra[e], Ofra Axelrod[f], Eilat Shinar[g], Marina Izak[g], Galia Rahav[h,b], Naomi Rahimi-Levene[i,b], Baruch M Bazofin[j], Ram Gelman[k,l], Dror Dicker[h,m], Tal Brosh-Nissimov[n,o], Orli Megged[p], David Dahan[q], Avi Benov[l,r], Alona Paz[s], Kaykov Edward[t], Amit Moran[u], Ori Rogowski[v,b], Patrick Sorkine[w], Ami Mayo[x], Oren Zimhony[y,*], Jacob Chen[e,l,**]

- > 35,000 patients analyzed
- If plasma is given in first 3 days mortality is 27% lower than if given after day 4 ($p < 0.001$)
- Dose Response with IgG to SARS-Cov-2

Dose IgG	Mortality
High	8.9
Medium	11.6
Low	13.7

(35% reduction in mortality high vs low)

Overall Mortality in this group lower than reported From many institutions.

Observational Studies with Propensity Controls show large decrease in mortality if plasma used early

Mount Sinai Hospital, NYC

DispatchDate: 05.09.2020 · ProofNo: 1088, p.1

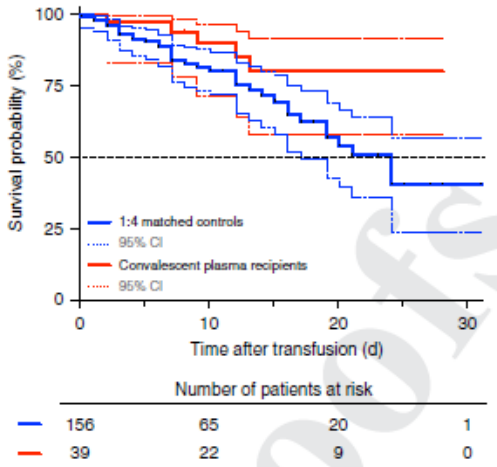
nature medicine

LETTERS

https://doi.org/10.1038/s41591-020-1088-9

Convalescent plasma treatment of severe COVID-19: a propensity score–matched control study

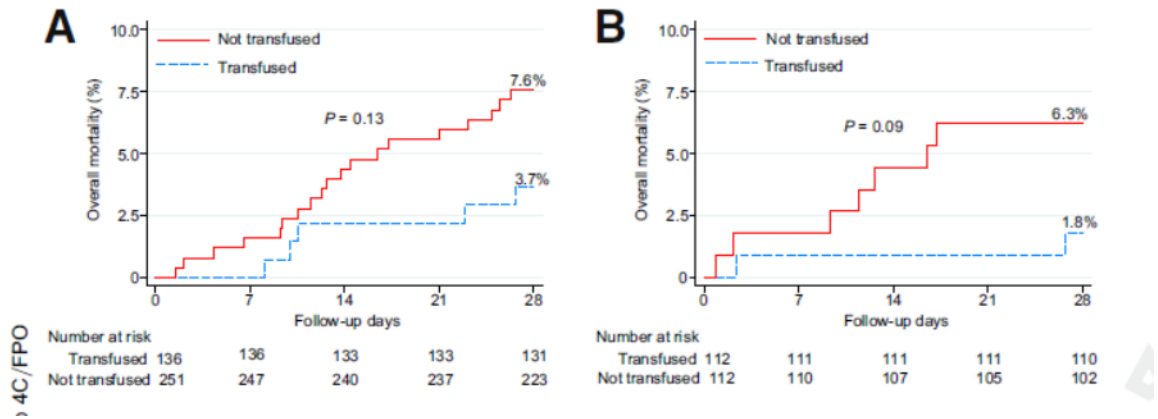
Sean T. H. Liu[1,2], Hung-Mo Lin[3], Ian Baine[4], Ania Wajnberg[5], Jeffrey P. Gumprecht[1], Farah Rahman[1], Denise Rodriguez[6], Pranai Tandon[7], Adel Bassily-Marcus[8], Jeffrey Bander[9], Charles Sanky[10], Amy Dupper[1], Allen Zheng[2], Freddy Nguyen[4], Fatima Amanat[2,11], Daniel Stadlbauer[2], Deena R. Altman[1], Benjamin K. Chen[1], Florian Krammer[2], Damodara Rao Mendu[4], Adolfo Firpo-Betancourt[4], Matthew A. Levin[12], Emilia Bagiella[3], Arturo Casadevall[13], Carlos Cordon-Cardo[4], Jeffrey S. Jhang[4], Suzanne A. Arinsburg[4], David L. Reich[12], Judith A. Aberg[1,14] and Nicole M. Bouvier[1,2,14]



Methodist Hospital, Houston Texas

Treatment of Coronavirus Disease 2019 Patients with Convalescent Plasma Reveals a Signal of Significantly Decreased Mortality

Eric Salazar,*† Paul A. Christensen,* Edward A. Graviss,*‡ Duc T. Nguyen,‡ Brian Castillo,* Jian Chen,* Bevin V. Lopez,§ Todd N. Eagar,*† Xin Yi,*† Picheng Zhao,* John Rogers,* Ahmed Shehabeldin,* David Joseph,* Christopher Leveque,* Randall J. Olsen,*†‡ David W. Bernard,*† Jimmy Gollihar,¶ and James M. Musser*†‡



First Randomized Clinical Trial done Wuhan: Prematurely Stopped

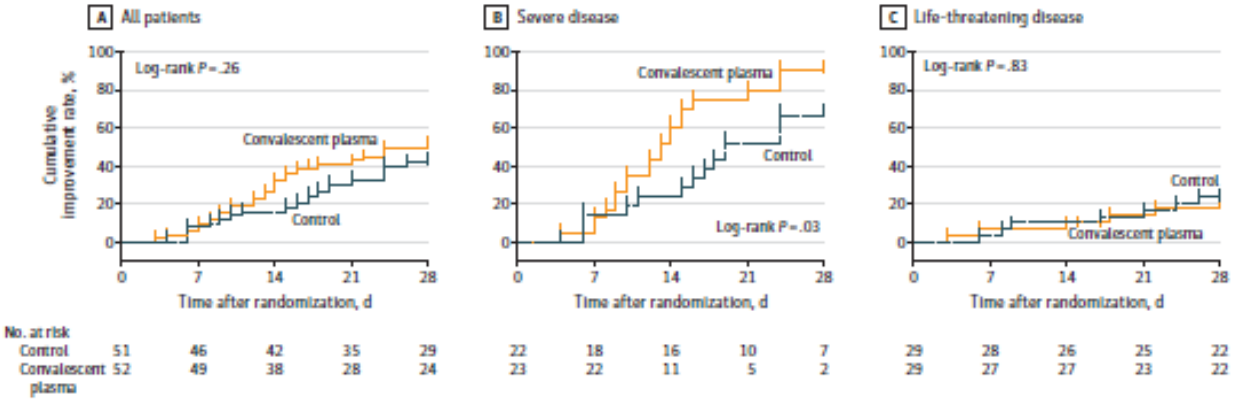
Research

JAMA | Original Investigation

Effect of Convalescent Plasma Therapy on Time to Clinical Improvement in Patients With Severe and Life-threatening COVID-19
A Randomized Clinical Trial

Ling Li, MD, PhD; Wei Zhang, MD; Yu Hu, MD, PhD; Xunliang Tong, MD, PhD; Shangen Zhang, MD; Juntao Yang, PhD; Yujie Kong, MD; Lili Ren, PhD; Qing Wei, MD; Hang Mei, MD, PhD; Caiying Hu, MD; Cuihua Tao, MD; Ru Yang, MD; Jue Wang, MD; Yonggui Yu, PhD; Yong Guo, PhD; Xiaodong Wu, MD; Zhihua Xu, MD; Li Zeng, MD; Nian Xiong, MD; Lifeng Chen, MD; Juan Wang, MD; Ning Man, MD; Yu Liu, PhD; Haixia Xu, MD; F. Deng, MS; Xuejun Zhang, MS; Chenyuan Li, MD; Conghui Wang, PhD; Shisheng Su, PhD; Linqi Zhang, PhD; Jianwei Wang, PhD; Yanyun Wu, MD, PhD; Zhong Liu, MD, PhD

Figure 2. Time to Clinical Improvement in Patients With COVID-19



EDITORIAL

A Randomized Trial of Convalescent Plasma for COVID-19—Potentially Hopeful Signals

Arturo Casadevall, MD, PhD; Michael J. Joyner, MD; Liise-Anne Pirofski, MD

Editorial notes:

- **Plasma effect comparable to Remdisevir**

They got significance with a fraction of what Was needed for the antiviral study

- **Antiviral effect even when late**

A Closer Look at the Five Randomized Controlled trials

Trial	Location	Mortality	Other Variables	Status	Comment
Li et al (JAMA)	China	26% → 16% NS	↓Viral Load ↓Recovery time	Premature termination	Late usage
Gharbahan (Preprint)	Netherlands	24% → 14% NS		Premature termination	Late usage
Avendano-Sola (Preprint)	Spain	9% → 0 % **(p = 0.055)**	↓Progression to ICU	Premature Termination	
Agarwal et al. (BMJ)	India	14% → 14% NS	↓Viral Load ↓FiO2 ↓Fever	Completed	Late usage; 27% unit low antibody
Rasheed et al. (published)	Iraq	40% → 5% **(p < 0.05)**	↓Recovery time	Completed	Small, not blinded, quirky randomization

The 5 RCTs:

- **illustrate difficulties of doing RCTs in the midst of a pandemic**
- **all provide some nugget of encouragement and efficacy**
- **none provide definitive evidence for convalescent plasma efficacy**

Meta-Analysis of Publicly Available Studies

Table 1 | Mortality Rates in Hospitalized COVID-19 Patients

		Convalescent Plasma			Control			Statistics		
Study	**Location**	**Survivor**	**Non-Survivor**	**Mortality**	**Survivor**	**Non-Survivor**	**Mortality**	***OR***	***P***	***95% CI***
Randomized Clinical Trials										
Avendano-Sola et al.	ESP	38	0	0%	39	4	9%	0.11	0.15	0.01, 2.19
Rasheed et al.	IRQ	20	1	5%	20	8	29%	0.13	0.06	0.01, 1.09
Gharbharan et al.	NLD	37	6	14%	32	11	26%	0.47	0.18	0.16, 1.42
Li et al.	CHN	43	8	16%	38	12	24%	0.59	0.30	0.22, 1.59
Agarwal et al.	IND	201	34	14%	198	31	14%	1.08	0.77	0.64, 1.83
Random Effects Model		339	49	13%	327	66	17%	0.58	0.12	0.29, 1.15
Random Effects Model excluding Agarwal et al.		138	15	10%	129	35	21%	0.43	0.01	0.22, 0.84
Matched-Control Studies										
Duan et al.	CHN	10	0	0%	7	3	30%	0.10	0.15	0.01, 2.28
Perotti et al.	ITA	43	3	7%	16	7	30%	0.16	0.01	0.04, 0.69
Hegerova et al.	Washington, USA	18	2	10%	14	6	30%	0.26	0.13	0.05, 1.49
Zeng et al.	CHN	1	5	83%	1	14	93%	0.36	0.49	0.02, 6.85
Donato et al.	New York, USA	36	11	23%	775	565	42%	0.42	0.01	0.21, 0.83
Liu et al.	New York, USA	34	5	13%	118	38	24%	0.46	0.13	0.17, 1.25
Abolghasemi et al.	IRN	98	17	15%	56	18	24%	0.54	0.10	0.26, 1.13
Salazar et al.	Texas, USA	137	6	4%	159	14	8%	0.50	0.16	0.19, 1.33
Xia et al.	CHN	135	3	2%	1371	59	4%	0.52	0.27	0.16, 1.67
Rogers et al.	Rhode Island, USA	56	8	13%	149	28	16%	0.76	0.52	0.33, 1.77
Random Effects Model		568	60	10%	2666	752	22%	0.47	<0.001	0.33, 0.65
Overall Random Effects Model [a]		706	75	10%	2795	787	22%	0.54	<0.001	0.41, 0.72
Case Series or Reports										
Martinez-Resendez et al.	MEX	8	0	0%						
Jin et al.	CHN	6	0	0%						
Ye et al.	CHN	6	0	0%						
Shen et al.	CHN	5	0	0%						
Zhang et al.	CHN	4	0	0%						
Ahn et al.	KOR	2	0	0%						
Bobek et al.	HUN	2	0	0%						
Jin et al.	New York, USA	3	0	0%						
Im et al.	KOR	1	0	0%						
Peng et al.	CHN	1	0	0%						
Xu et al.	CHN	1	0	0%						
Anderson et al.	Tennessee, USA	1	0	0%						
Bao et al.	CHN	1	0	0%						
Cinar et al.	TUR	1	0	0%						
Kong et al.	CHN	1	0	0%						
Hueso et al.	FRA	16	1	6%						
Hartman et al.	Wisconsin, USA	27	4	13%						
Olivares-Gazca et al.	MEX	8	2	20%						
Tremblay et al.	New York, USA	14	10	42%						
Case Series or Reports Total		108	17	14%						

57% Reduction in Mortality p < 0.01

August 23, 2020 FDA issues Emergency Use Authorization for Convalescent Plasma…controversy immediately ensues

The New York Times

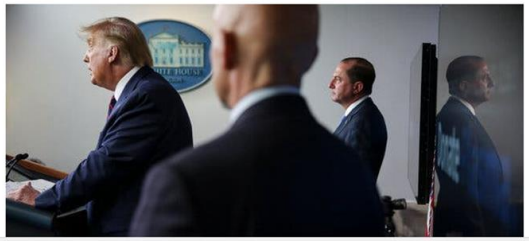
F.D.A.'s Emergency Approval of Blood Plasma Is Now on Hold

Government health leaders including Dr. Francis S. Collins and Dr. Anthony S. Fauci urged caution last week, citing weak data from the country's largest plasma study.

Javier Alvarez donating his plasma at Houston Methodist Hospital in July after his grandmother died from the virus. Erin Schaff/The New York Times

Trump Pressed for Plasma Therapy. Officials Worry, Is an Unvetted Vaccine Next?

New details of how the president has demanded faster action from health agencies help explain the intensifying concern that he could demand pre-Election Day approval of a vaccine.



Business

Blood plasma looked like a promising covid-19 treatment. Then Trump got involved.

The president's politicized rollout of a plasma authorization triggered a backlash, disrupting a business coalition's carefully honed message.

- **Tempest in a teapot**: USA was already operating under EUA conditions
- EUA addresses issue of equity
- Bar for issuance of EUA is relatively low: **reasonable safety** and **probable efficacy**
- Differences between NIH and FDA reflects differences between degree of certainty
- Mechanism for conflict resolution: get more data; do RTCs
- Good outcome – NIH moved to support RTCs

Proving That It Works

BLOOMBERG PHILANTHROPIES SUPPORT SERVED AS THE CATALYST FOR THE DEFINITIVE STUDY

Outpatient Prophylaxis Protocol (150 Participants)

- Phase 2 trial to evaluate COVID-19 plasma for prophylaxis
- Randomized, double-blind, controlled, multicenter study
- Participants:
  - Healthcare workers with high-risk exposure
  - Individuals with high-risk exposure **(Examples?)**
  - Both groups tested negative and no symptoms

Ambulatory Protocol (1,344 Participants)

- Phase 2 trial to evaluate COVID-19 plasma for treatment in mild COVID-19
- Randomized, double-blind, controlled, multicenter study
- Participants:
  - Adults, who are positive with COVID-19 with mild symptoms

PRINCIPLE INVESTIGATORS

JOHNS HOPKINS SCHOOL of MEDICINE

Dr. Shmuel Shoham

Dr. Dan Hanley

JOHNS HOPKINS BLOOMBERG SCHOOL of PUBLIC HEALTH

Dr. David Sullivan

The Situation Today

- **Convalescent plasma is available throughout the United States for the treatment of COVID-19**
- **Plasma use in USA is under 'Emergency Use Authorization', which was granted 8/21/20, five months after first use in 3/27/20 (Texas). Available data strongly supports EAP criteria of 'may be effective' and 'safety'.**
- **Definitive data on efficacy from RCTs is not available.**
- **Convalescent plasma use has cleared the way for mAbs and vaccines…no major ADE concerns.**
- **Supplies are plentiful as a result of recruitment campaigns '*The fight is in us*'**
- **Deployment of plasma has been driven by physicians, scientists, etc…there is no pharmaceutical company involved or supporting this…no one will make money!**
- **Numerous randomized clinical trials underway. More certainty as to efficacy can be expected over the next few months.**
- **However, epidemic has show limitations of RCT as a epistemic instrument: changing epidemic, rigidity of RCT cannot accommodate new information, etc.**
- **If (and I stress if) 100,000+ patients have been treated, in hospital mortality is ~20%, plasma reduces mortality by 50% when used early and with sufficient antibody amount...then ~10,000 lives have been saved in the USA alone.**

Speaker

Daniel Rotrosen, MD
Director of the Division of Allergy, Immunology, and Transplantation (DAIT)

American Autoimmune Related Diseases Association, Inc

AARDA National Briefing on COVID-19 and Autoimmune Disease

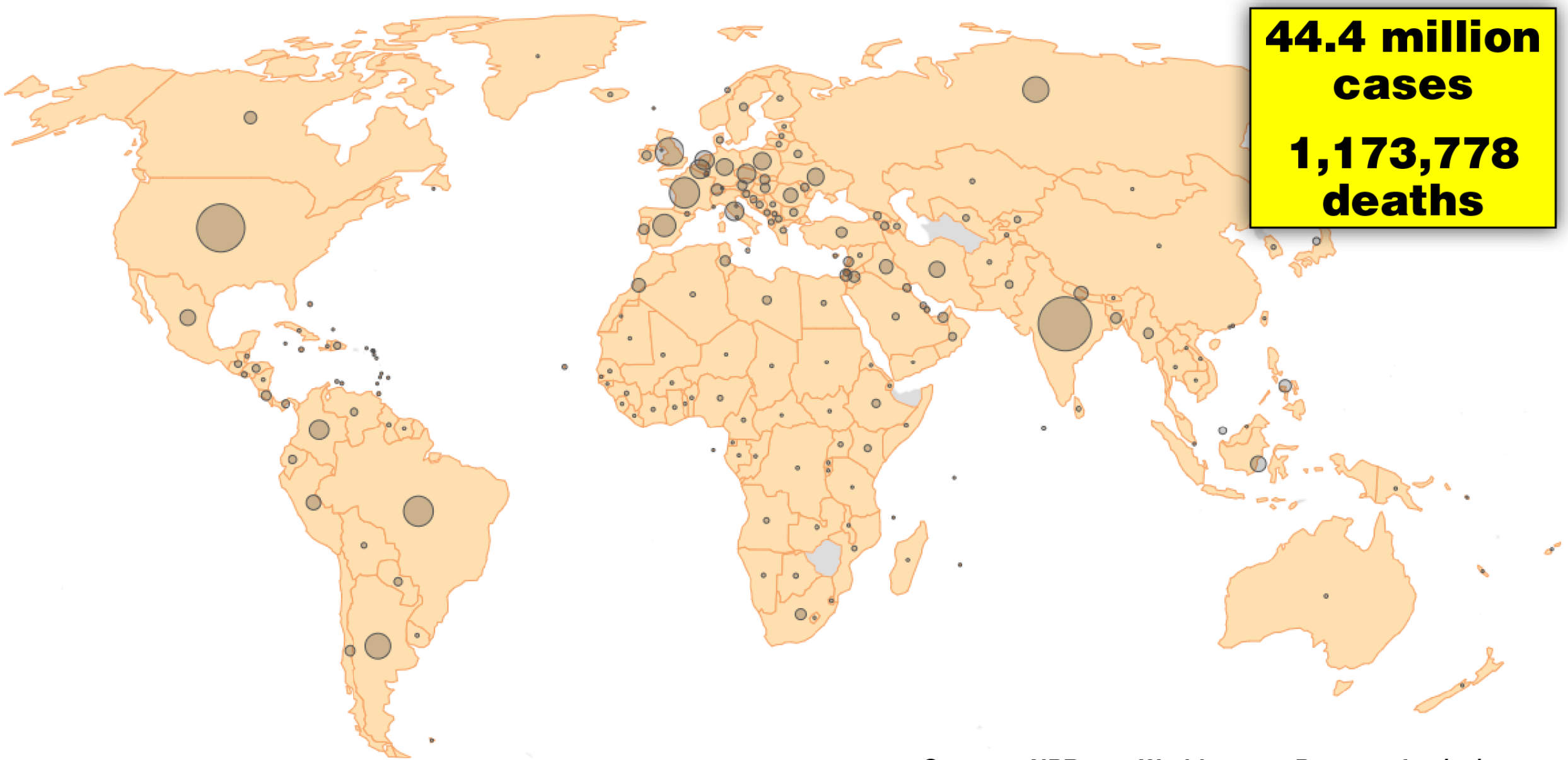
COVID-19 Vaccine Development: Public Health Challenges and The Role of the NIH

Daniel Rotrosen, M.D.
Director
Division of Allergy, Immunology and Transplantation
National Institute of Allergy and Infectious Diseases
National Institutes of Health

October 30, 2020

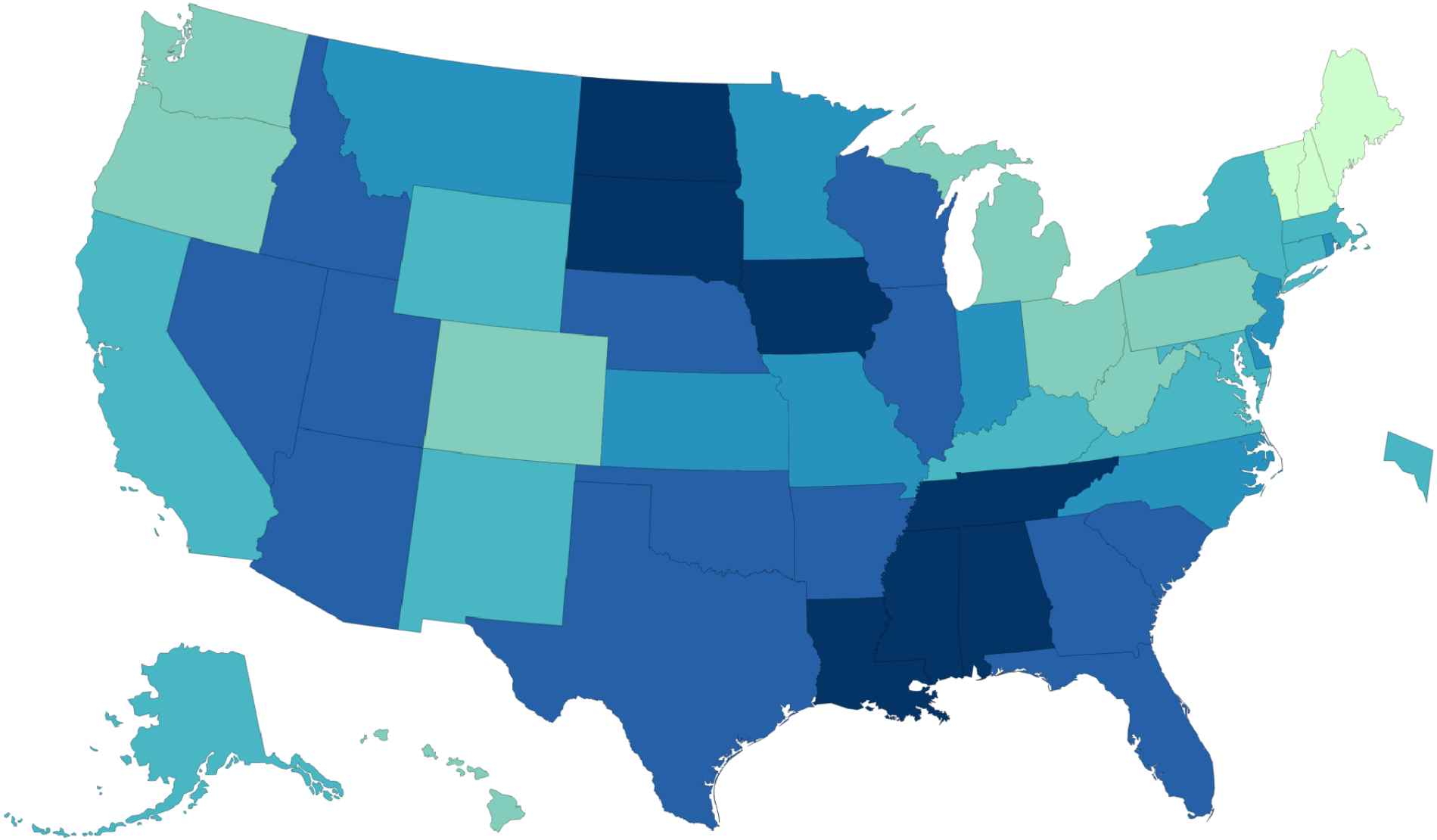
National Institute of Allergy and Infectious Diseases

COVID-19 Globally



Sources: NPR.org; Worldometer. Data as of 10/28/2020

COVID-19 in the United States



8.7 million cases

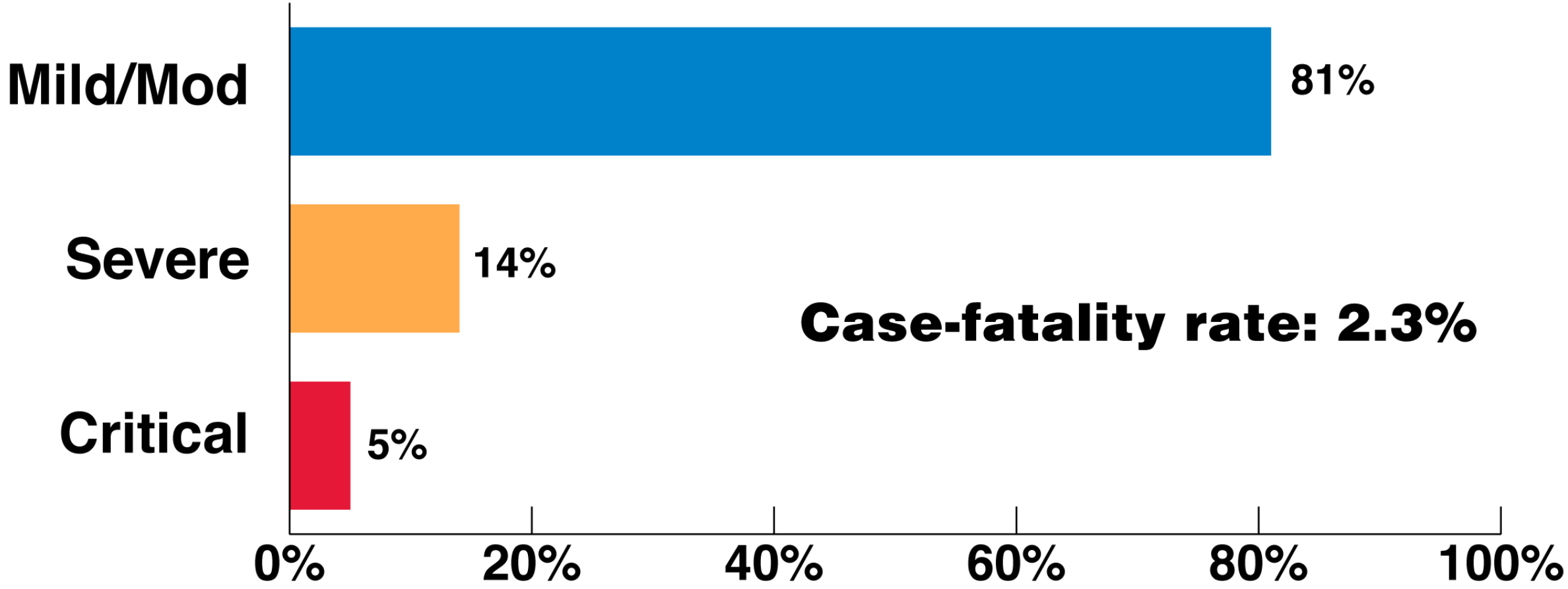
225,084 deaths

Cases/100,000

- 0-766
- 1,013-1,799
- 1,812-2,393
- 2,412-2,934
- 3,012-3,645
- 3,691-5,148

Source: CDC. Data as of 10/28/2020.

Spectrum of Disease Among 44,672 Individuals with Confirmed COVID-19, China

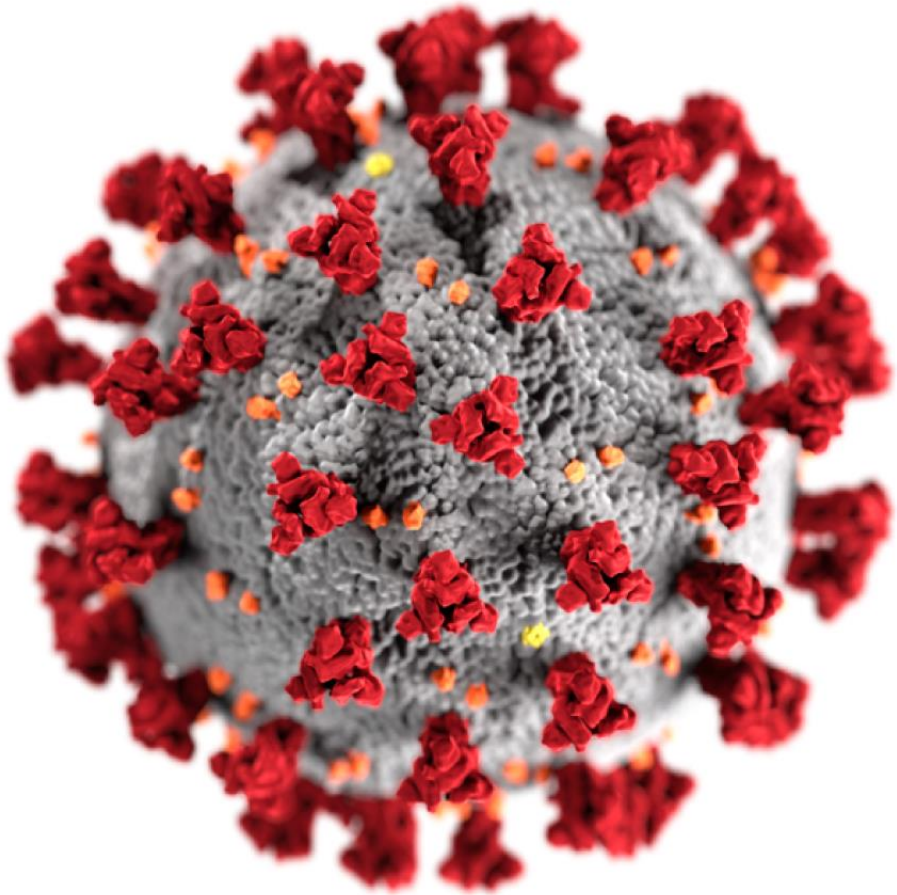


Source: Z Wu & JM McGoogan, *JAMA* 323:1239, 2020.

People at Increased Risk for Severe COVID-19 Illness

- Older adults

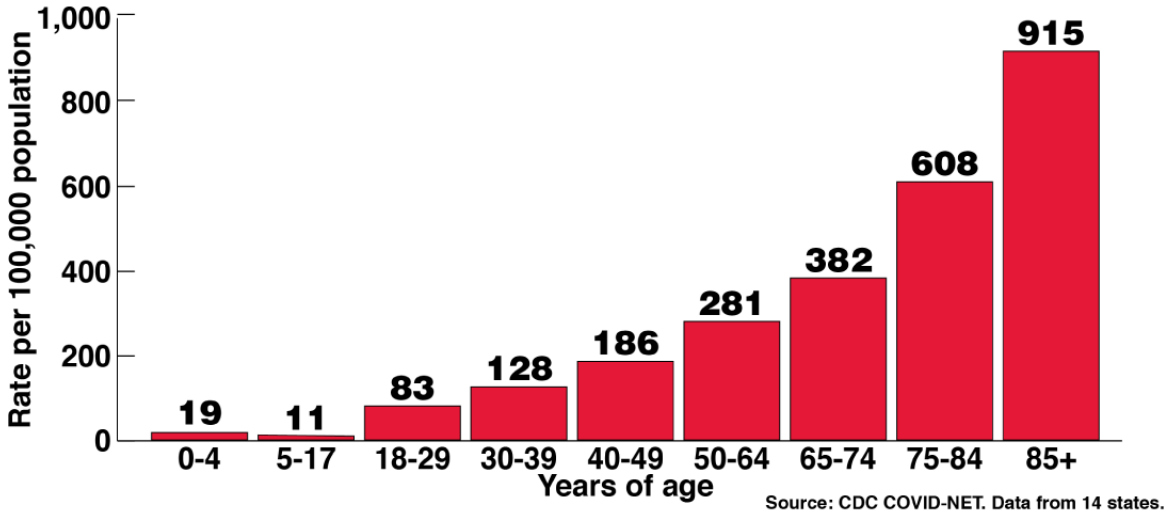
- People of any age with certain underlying medical conditions



Source: CDC, 6/25/2020

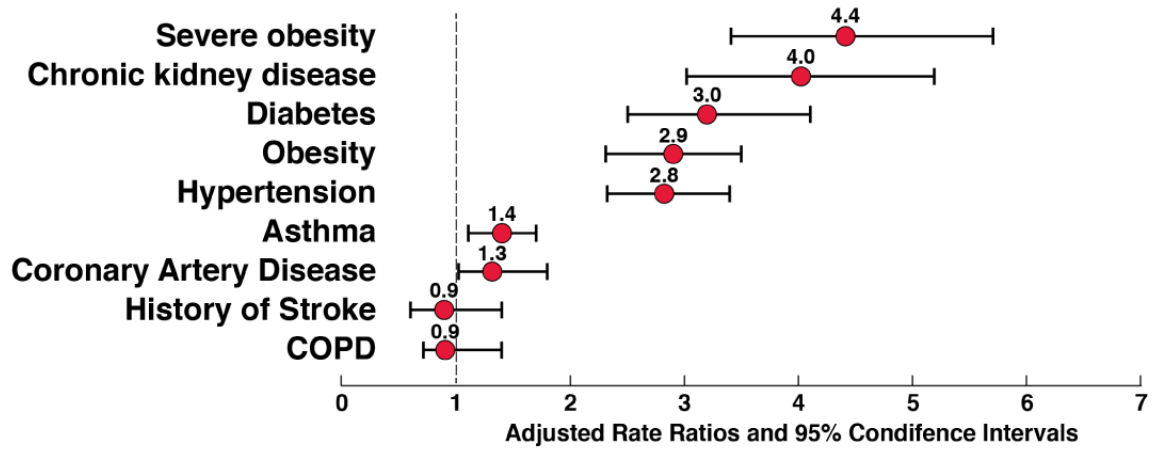
Risk Factors for COVID-19 Severity: Age and Underlying Medical Conditions

Cumulative Rates of Laboratory-Confirmed COVID-19-Associated Hospitalizations by Age, United States, March 1 – October 10, 2020



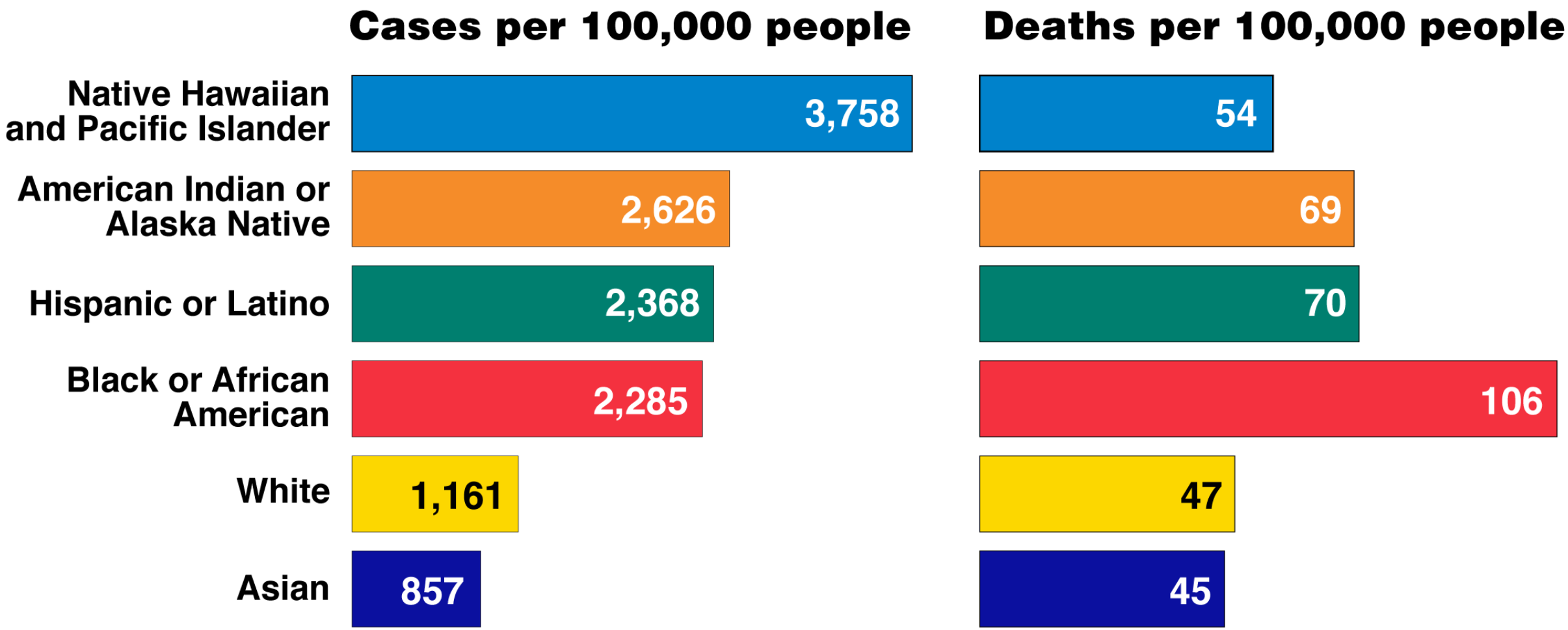
Source: CDC COVID-NET. Data from 14 states.

Individuals with Underlying Medical Conditions Are at Increased Risk for Severe COVID-19



Source: COVID-net ACIP Presentation 8-26-20

COVID-19 Cases and Deaths by Race/Ethnicity, United States, 2020



Source: COVID Tracking Project. Data through 10/28/2020.

A Strategic Approach to COVID-19 Vaccine R&D

L Corey, JR Mascola, AS Fauci & FS Collins

- Unprecedented collaboration and resources will be required to research and develop safe and effective vaccines for COVID-19 that can be manufactured and delivered in the scale of billions of doses to people globally.

Vaccine Development Under Operation Warp Speed (OWS)

- Partnership and broad-based plan to accelerate development, manufacturing, and distribution of 300 million doses of safe and effective vaccines
  - HHS, CDC, NIH, BARDA, DoD, Industry partners
  - FDA consultation and interim review
  - Coordinated testing and evaluation of vaccine candidates under harmonized protocols, review by independent Data and Safety Monitoring Board
- Financial risks of accelerated timeline borne by manufacturers and governmental sponsors
- Not compromised
  - Scientific integrity, safety of clinical trial participants
  - FDA decision-making on vaccine licensure

SARS-CoV-2 Virus Structure: Importance of Basic Research and Implications for Infectivity and Vaccine Design

- Rapid determination of the SARS-CoV-2 genetic sequence and its spike structure accelerated vaccine design
  - Circulating strains show little variability in the spike ACE2 binding domain
  - Suggests the spike and ACE2 binding domain may be good vaccine immunogens with little potential for antibody escape
- Virion structural integrity contributes to high infectivity
  - Virus entry via ACE2 mainly in the airways, but ingested virus can survive the stomach to infect the intestinal epithelium
  - May also infect the lung via the circulation
- Multiple virus proteins involved in immune evasion

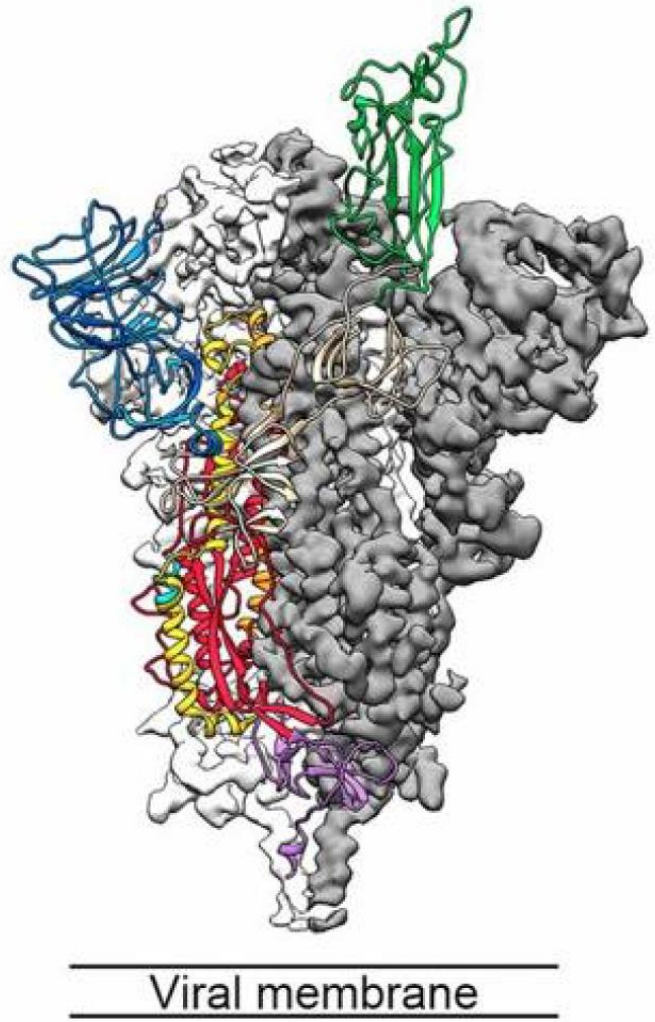
published online August 5, 2020

nature

International weekly journal of science

SARS-CoV-2 mRNA Vaccine Design Enabled by Prototype Pathogen Preparedness

KS Corbett, BS Graham et al.

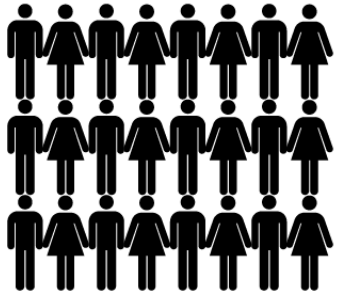


Atomic-level structure of SARS-CoV-2 spike protein. Receptor binding domain is colored green.

Image source: Wrapp et al., *Science* 2020.

Randomized, Placebo Controlled, Phase 3 COVID Vaccine Efficacy Trial Explained

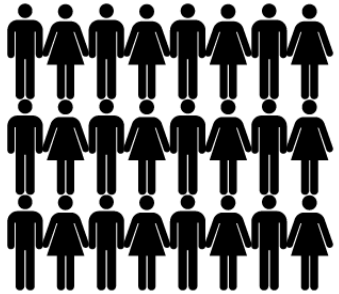
Vaccine Group



?

Volunteers don't know if they receive vaccine or placebo

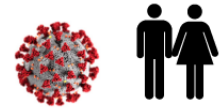
Placebo Group



Volunteers are closely monitored as they go about their lives

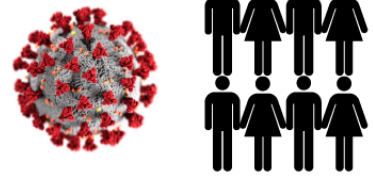
Symptomatic COVID-19 cases are diagnosed by study team (PCR+)

Vaccine Group



Vaccine Efficacy (VE) = %reduction disease incidence in vaccine group vs control group

Placebo Group



Total number of volunteers range from 30,000 to 60,000 per trial

Asymptomatic COVID cases will be defined by retrospective analysis.

Phase 3 Vaccine Trial Design - Overview

- Randomized, placebo-controlled, blinded design
  - Sample size – 30,000 – 60,000 participants
  - ≥18 years of age, at risk for acquisition, diverse populations
  - Targets a subset of participants at high risk of severe disease
  - One or two dose regimen, depending on the particular vaccine
- Primary efficacy endpoint
  - Prevention of symptomatic COVID-19 (PCR confirmed)
  - All confirmed cases assessed for severity and followed to resolution
  - Vaccine efficacy of ≥50% with a goal of substantially greater protection, including protection from severe disease
  - Duration of protection
- Emergency Use Authorization vs. licensure

COVID-19 Vaccines in Operation Warp Speed Development

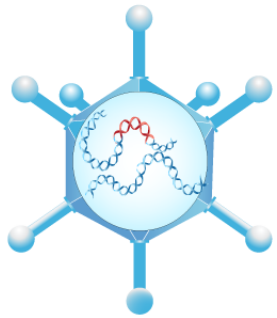
moderna — mRNA

BIONTECH Pfizer — mRNA

- **mRNA:** rapid manufacturing facilitating efficient move to clinic, highly immunogenic

AstraZeneca — Adenovirus vector

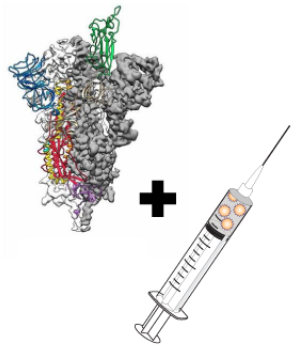
Janssen PHARMACEUTICAL COMPANIES OF Johnson & Johnson — Adenovirus vector



- **Adenovirus:** rapid manufacturing facilitating efficient move to clinic, vaccine using this platform is approved in Europe

NOVAVAX Creating Tomorrow's Vaccines Today — Recombinant protein + adjuvant

gsk SANOFI — Recombinant protein + adjuvant

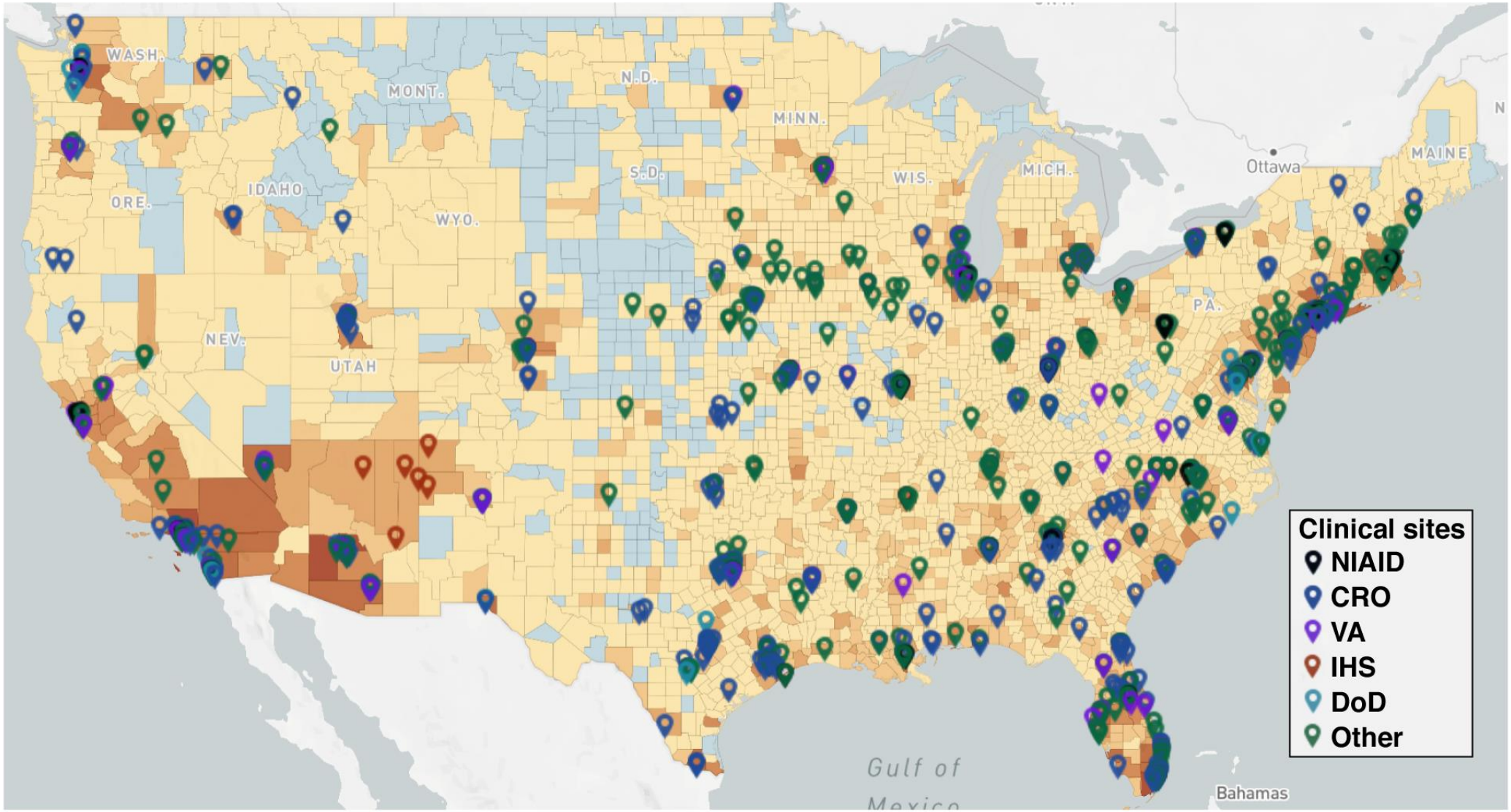


- **Adjuvanted recombinant protein:** not as fast to manufacture but scalable, several approved vaccines use this approach

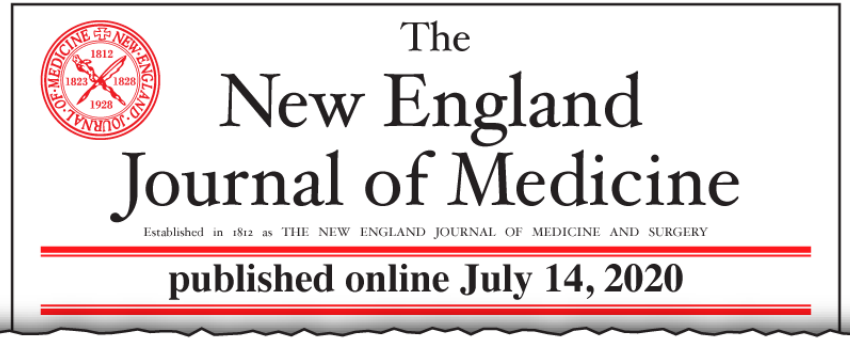
Selected COVID-19 Vaccine Candidates

Platform	Developer	Phase 1/2	Phase 2/3
Nucleic acid	moderna	Enrolled	Ongoing
	BIONTECH Pfizer	Enrolled	Ongoing
Viral vector	UNIVERSITY OF OXFORD AstraZeneca	Enrolled	Ongoing
	Janssen PHARMACEUTICAL COMPANIES OF Johnson & Johnson	Enrolled	Ongoing
	MERCK	Ongoing	--
Protein subunit	NOVAVAX Creating Tomorrow's Vaccines Today	Ongoing	Ongoing
	gsk SANOFI	Ongoing	--

Nationwide Collaborative Network of COVID-19 Vaccine Clinical Trial Sites



Safety and Immunogenicity of Lead Vaccine Candidates



An mRNA Vaccine against SARS-CoV-2 — Preliminary Report

LA Jackson, JH Beigel et al. for the mRNA-1273 Study Group

Safety and Immunogenicity of SARS-CoV-2 mRNA-1273 Vaccine in Older Adults

EJ Anderson, B Flach et al. for the mRNA-1273 Study Group

- **Vaccine candidates appear to be safe with minimal side effects in the majority of participants**
  - Some adverse events/reactogenicity are dose-related
  - Rare serious adverse events are being closely monitored – on temporary FDA holds or voluntarily paused by sponsors
- **Abundant evidence for immunogenicity**
  - Neutralizing antibody to spike domains
  - $CD4^+$ T cell responses to multiple epitopes
  - Protection in SARS-CoV-2 challenge studies including nonhuman primate models

NASEM Releases Final Framework for Distributing COVID-19 Vaccine

Phase 1

Phase 1a

- High-risk HCWs
- First responders

Phase 1b

- High-risk co-morbid conditions
- Older adults in congregate/ crowded residences

Phase 2

- K-12 teachers/ school staff, child care workers
- Critical risk workers (essential industry etc.)
- Moderate-risk co-morbid conditions
- Homeless shelters/group homes
- Jails/prisons
- Other older adults

Phase 3

- Young adults
- Children
- Workers of high importance not included in Phase 1 or 2

Phase 4

- All others

Source: NAM, Framework for Equitable Allocation of COVID-19 Vaccine, 2020

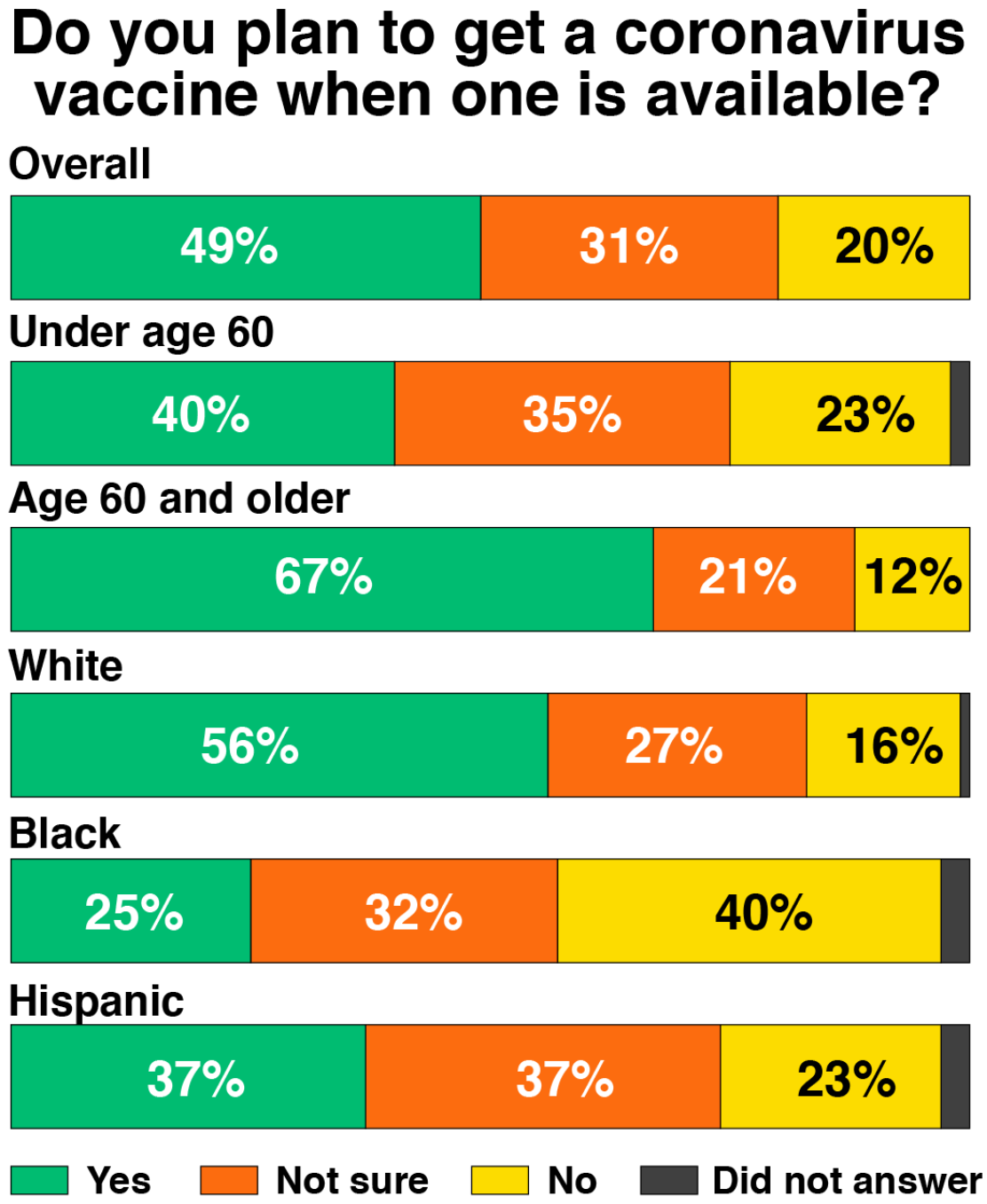
Vaccine Hesitancy

June 30, 2020

Science

Just 50% of Americans Plan to Get a COVID-19 Vaccine. Here's How to Win Over the Rest

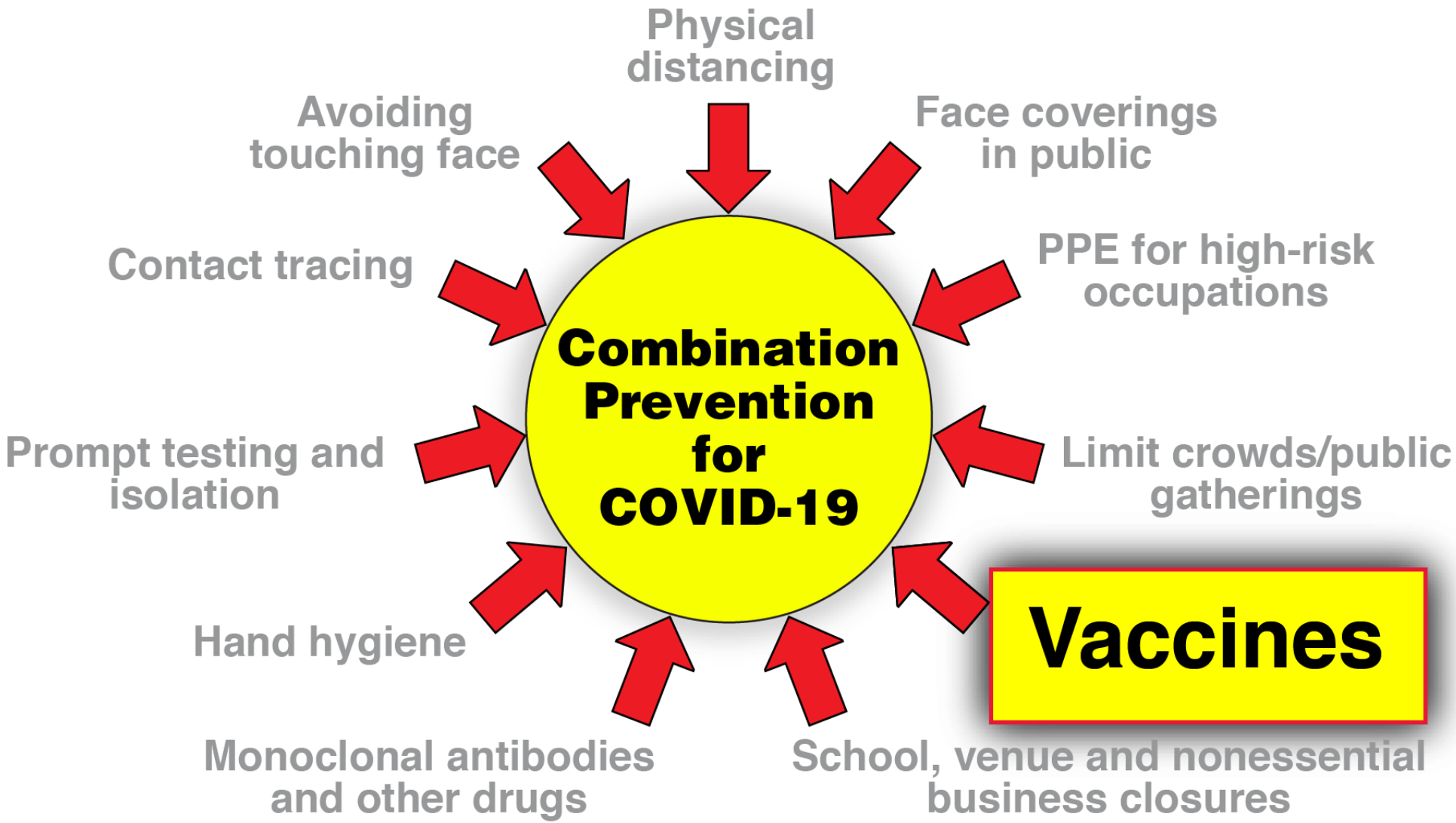
W Cornwall

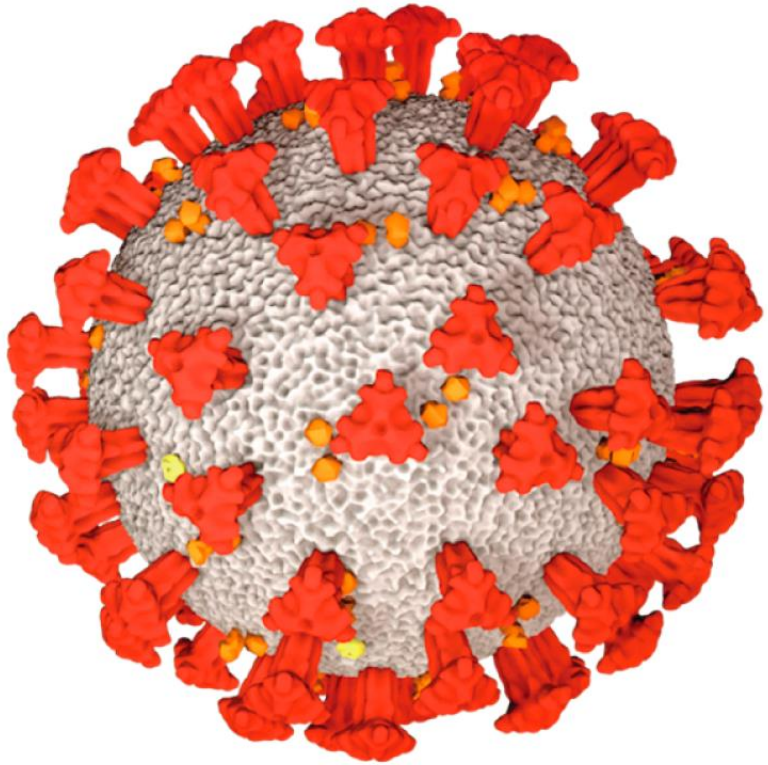


Specific Efforts to Increase Confidence in Vaccine Trials

- Maintaining safeguards for volunteers and study conduct
- Engaging directly with stakeholders including those from underserved minorities hardest hit by the pandemic
- Communicating the roles that entities like the NIH, oversight bodies, and regulatory groups play and their independence from vaccine manufacturers
- Committing to transparency
  - FDA guidance to industry
  - Vaccine manufacturers have posted final protocols and enrollment data, including by race/ethnicity
  - Prompt sharing of results and public deliberations of FDA advisory committees

Prevention of COVID-19 with a Highly Effective Vaccine and Widespread Uptake





COVID-19

Prevention Network

www.preventcovid.org

Selected Questions

When will people with pre-existing conditions get the vaccine?

Are all monoclonal anti-Covid antibodies the same? How do I choose one?

Are people with autoimmune disease more likely to get Covid a second time?

Do people on immunosuppressive therapy shed virus longer?

Is there a preferable vaccine for people with autoimmune disease? Not adenovirus?

Does famotidine work to prevent disease?

Will vaccines be free?

Are people with autoimmune disease more likely to get Covid?

American Autoimmune Related Diseases Association, Inc.

Thank you for attending!

For a recording of this presentation, slides, and more resources regarding autoimmune disease, please visit:

www.aarda.org

American Autoimmune Related Diseases Association, Inc.

/autoimmunity

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