Public Health
Seattle & King County

COVID-19 Clinical Update

I-TECH Videoconference September 14, 2020

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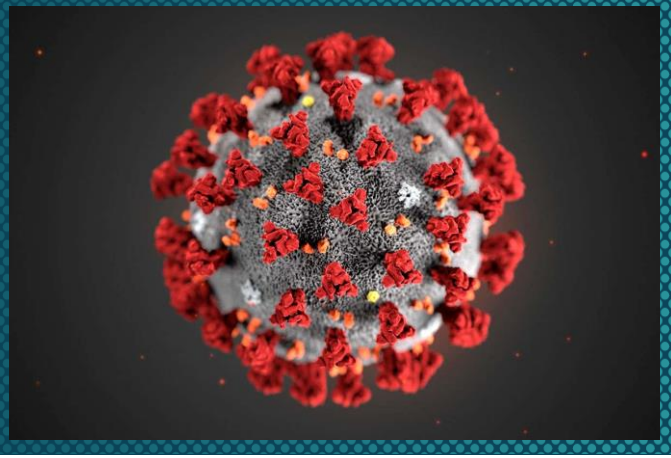


Last Updated: July 11, 2020

I-TECH
International Training and Education Center for Health

Overview

- Epidemiology & virology
- Laboratory testing
- Natural history - reinfection
- Treatment & vaccines
  - 3313 clinical trials as of September 14!

Impact of Social Distancing

- Population: 1030 Maryland residents enrolled in a data platform (Dynata)
- Survey about adoption of non-pharmaceutical protective interventions (NPIs)
- 55 (5.35) self reported having been diagnosed with SARS-CoV-2

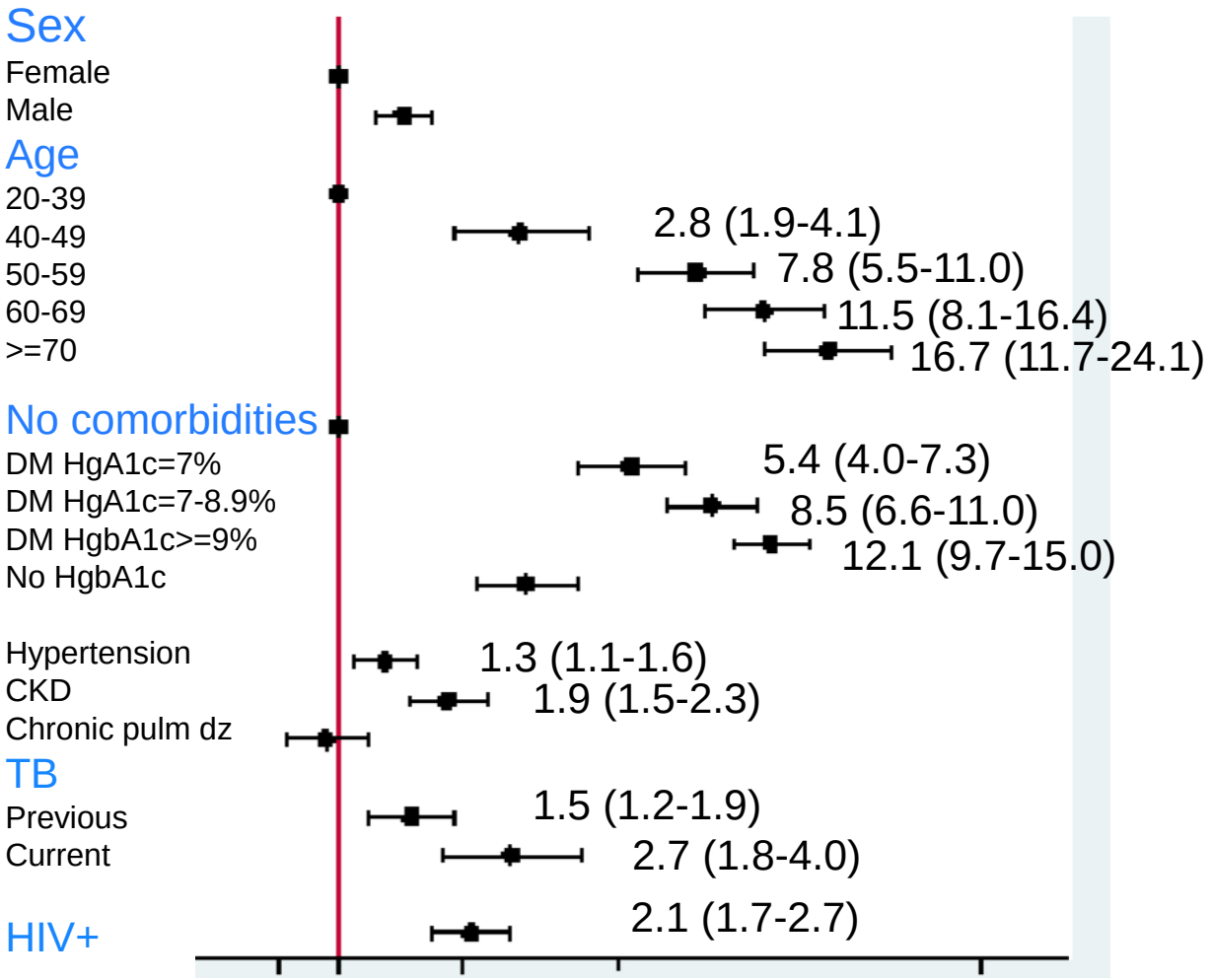
Variable	aOR SARS-CoV-2
Social distancing indoors	
Never	Ref
Sometimes	0.26 (0.08-0.9)
Always	0.32 (0.10-0.99)
Social distancing outdoors	
Never	Ref
Sometimes	0.34 (0.10-1.19)
Always	0.10 (0.03-0.33)
Use of public transport	
Never	Ref
1-2	6 (2.1-16.9)
3-7	3.8 (1.118-12.3)
>7 times	4.29 (1.12-16.5)
Visited place of worship	
Never	Ref
1-2	1.41 (0.38-5.31)
>=3 times	16 (5.97042.7)

Clipman SJ. CID 2020

Risks for COVID-19 Death in South Africa

- Population: 3,460,932 patients attending public clinics in Western Cape, SA (16%HIV+), 22,308 with COVID-19
- Design: Population-based cohort study to assess factors associated with mortality in people with COVID-19, focusing on association with HIV

- **HIV & TB are risks for COVID-19 associated mortality**
- **Conventional risk factors are still dominant**
  - **Uncontrolled diabetes more common among those who died than HIV**



Boulle A. CID 2020

SARS-CoV-2 Virology: G614 vs. D614 Variants Role in Transmissibility

- Background:
  - SARS-CoV-2 sequence diversity is low due to virally
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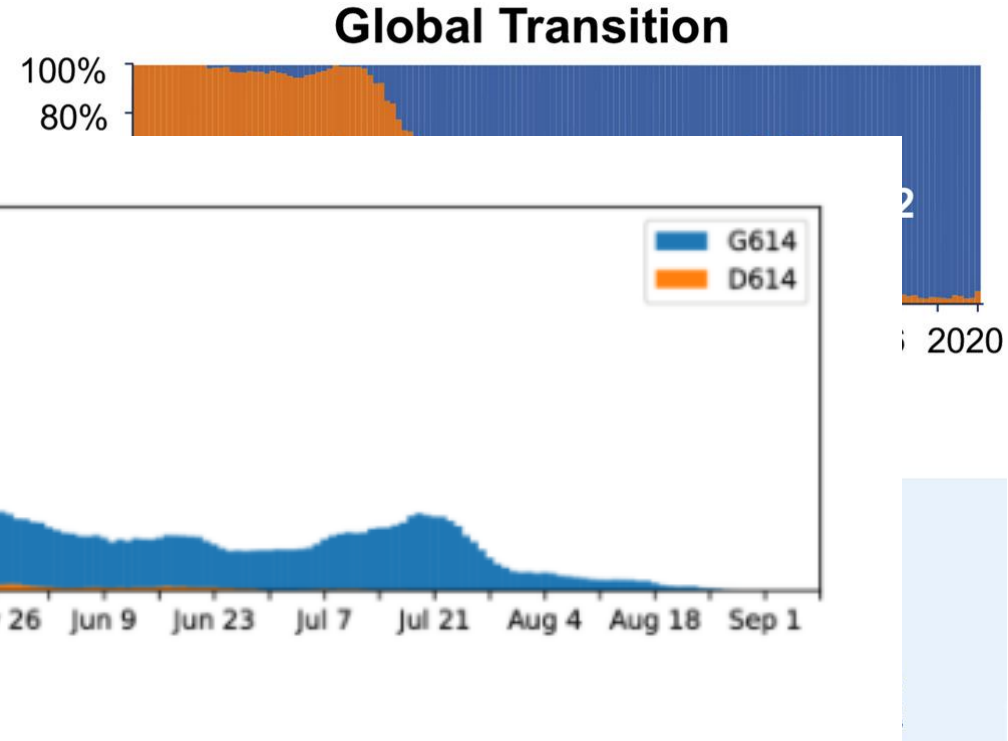
  Sequences in 999 patients hospitalized with COVID-19
- Spike G614 replaced D614 as dominant form worldwide
- G614 had lower RT PCR Cts – ↑ viral load



Korber B. Cell 2020

SARS-CoV-2 Virology: Delta 382 Variant Role in Severity

- Population: 131 hospitalized patients in Singapore 1/20-3/20 enrolled in a prospective study
- Design: retrospective analysis comparing association of viral variants in ORF8 with hypoxemia
- Results:
  - 70% wild type, 22% 382-nucleotide deletion, 8% Mixed infection
  - Δ382 less severe
  - Similar quantities of virus - No difference in replication capacity

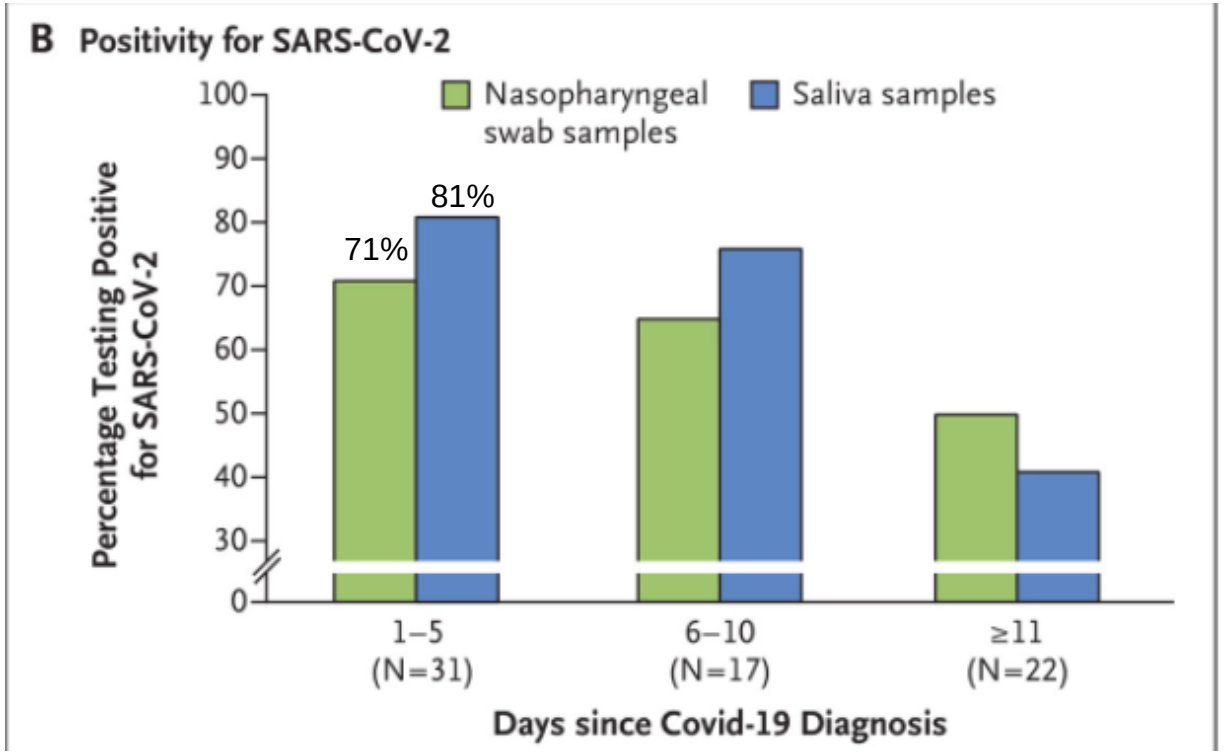
	Hypoxemia	aOR (95% CI)
Wild type (n=92)	26 (28%)	1 (ref)
Mixed (n=10)	3 (30%)	1.78 (0.22-11.02)
Δ382 (n=29)	0 (0%)	.07 (0.00-0.48)

Young BE Lancet 2020

- ORF8 could be a target for drug development
- Uncertain if ORF8 mutants are more or less transmissible and impact on longer-term viral evolution

SARS-CoV-2 in Salvia vs. Nasopharyngeal Swabs

- Population: 70 in-patients with COVID-19 at Yale hospital
- Design: Comparison of saliva and nasopharyngeal swab specimens
- Results:
  - Larger proportion of saliva specimens positive up to 10 days
  - Quantity of SARS-CoV-2 higher in saliva than NP specimens
  - 495 healthcare workers tested – 13 SARS-CoV-2 + in saliva
  - 9 tested by NP and 7 were negative
    - All had subsequent positive NP tests



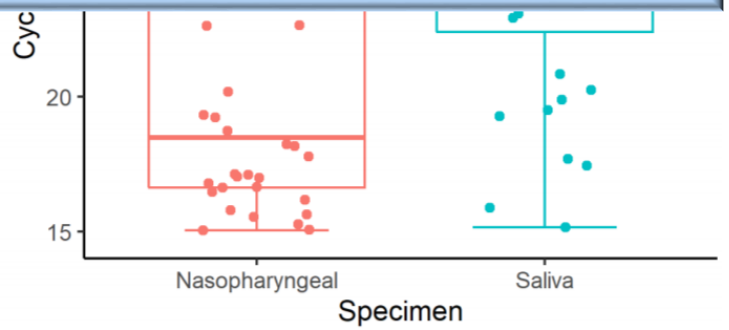
Morawska L. CID 2020

SARS-CoV-2 in Salvia vs. Nasopharyngeal Swabs

- Population: 224 patients with symptoms consis
- Design "enhar NP sw
- Result
  - High
  - 1 po
  - Mea swabs, suggestive of more RNA

		NP Swab	
		+	-

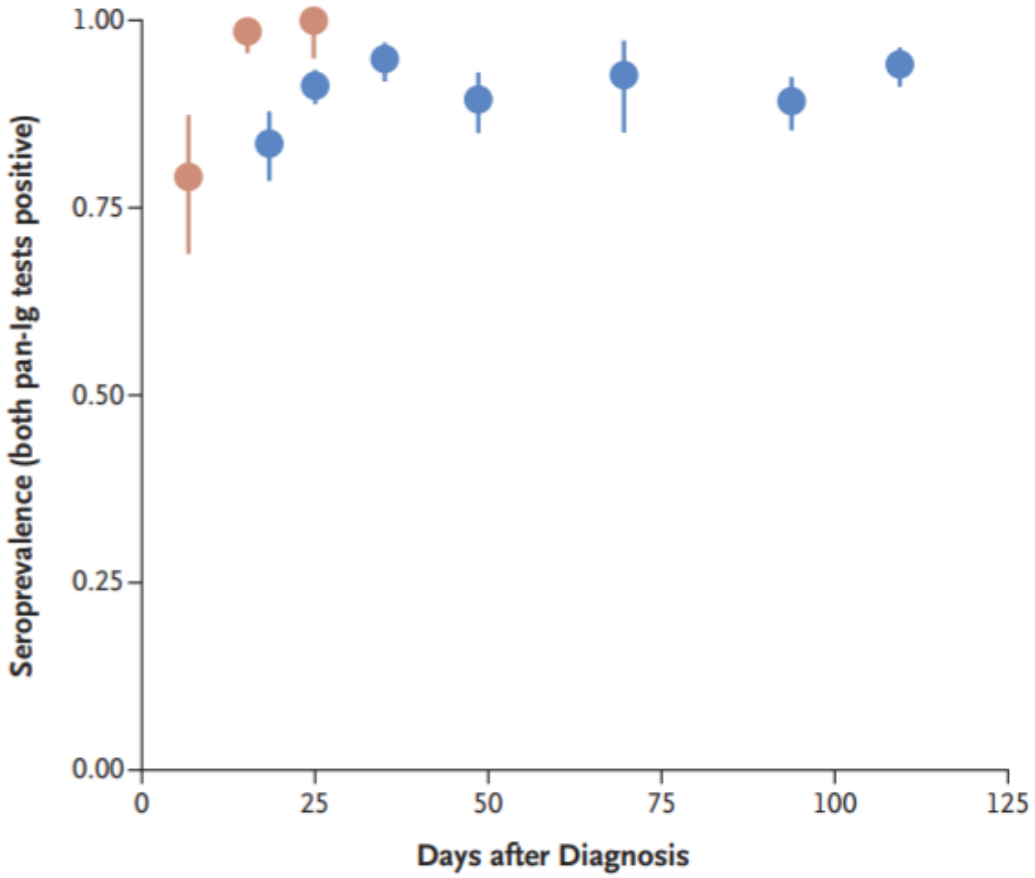
- Two studies both support the use of salvia for PCR diagnostics
  - Saves PPE
  - Simplifies procedures
  - More acceptable to patients
- Contradictory data on quantity of virus – uncertain how much that matters



Procop GW. JCM 2020

Antibody Response

- Population-based study Iceland
- Among 1215 recovered cases, 25 days after diagnoses, 91-95% of people had antibodies based on 2 pan-IgG tests
- Estimated 26.6% of household exposed and 5% of nonexposed with SARS-CoV-2 positive (PCR or Ab positive)
  - 2.3% of quarantined persons with negative PCR developed antibody
- 0.6% of PCR+ cases and 0.3% of infected persons died (based on 10 deaths)



Gudbjartsson DF NEJM 2020

Antibody Response

- Population: 37 symptomatic and 37 asymptomatic persons with postivei SARS-CoV-2 PCR tests in Wuhan, China
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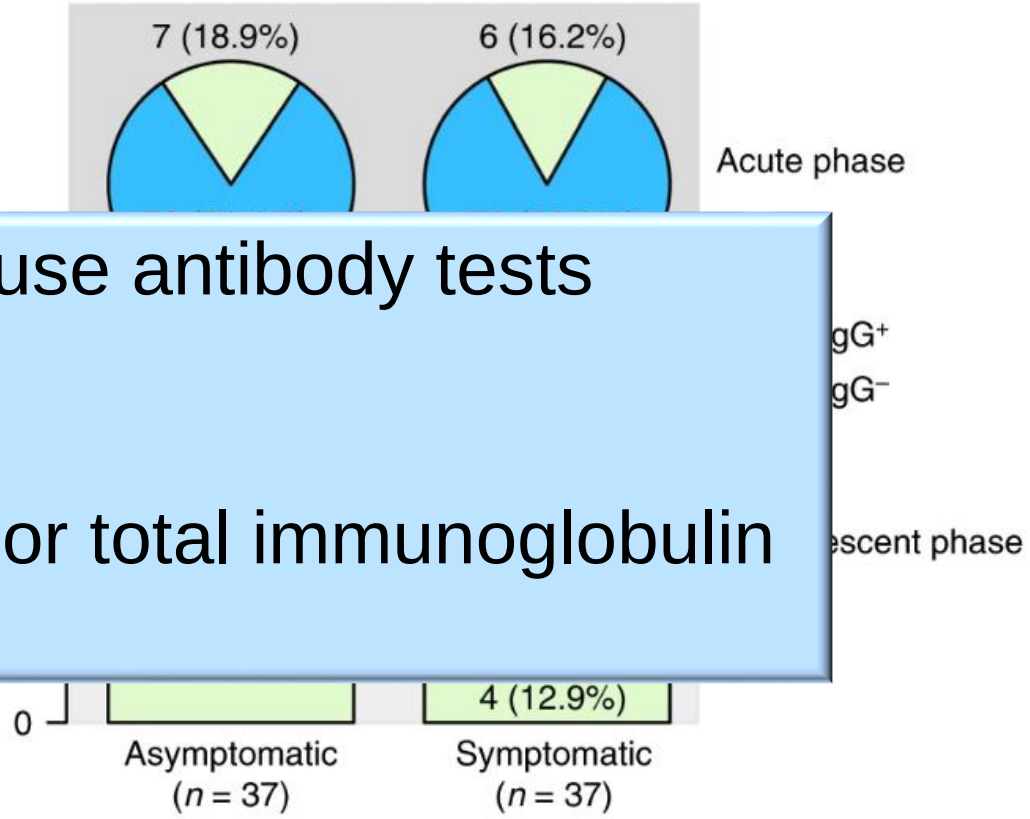
- Controversy about if and how to use antibody tests persists
- Probably lots of variable of tests
- IDSA recommends using an IgG or total immunoglobulin tests (not IgM or IgG/IgM)



Long QX Nature Med 2020

SARS-CoV-2 Reinfection

- Patient experiences symptomatic COVID-19 in March, then tests positive on a screening test in an airport in Hong Kong 142 after the first positive test.
- CRP elevated at second test, IgG negative at time of second positive test, but positive 5 days later
- Whole genome sequencing demonstrate that the infecting viruses were from different clades/lineages
  - 1st US/UK lineage March/April
  - 2nd Switzerland/UK July/August

Kai-Wang To K.. CID 2020

SARS-CoV-2 Reinfection #2

- 2nd Case in U.S.
- Sequences supposedly different

Case History

- March 25: Onset of sore throat, cough, headache, nausea, diarrhea.
- April 18: Tested positive for SARS-CoV-2 by PCR.
- April 27: Symptoms resolved.
- May 9 and 26: Tested negative for virus by two methods.
- May 28: Onset of fevers, headache, dizziness, cough, nausea, and diarrhea. Chest x-ray negative.
- June 5: Symptoms worsened -> hypoxia, new infiltrates on CXR – admitted - RT-PCR positive for SARS-CoV-2.
- June 6: SARS-CoV-2 IgM and IgG antibody positive.

Sax P. NEJM Blog 2020

SARS-CoV-2 Reinfection #3

- Case in Belgium
- Sequences different – 11point mutations

Case History

- March: 51 y/o woman develops mild COVID-19 – HA, fever, myalgia, coughing, HA – Positive NP swab
- June – HA, cough, fatigue, rhinitis – 2nd positive NP swab

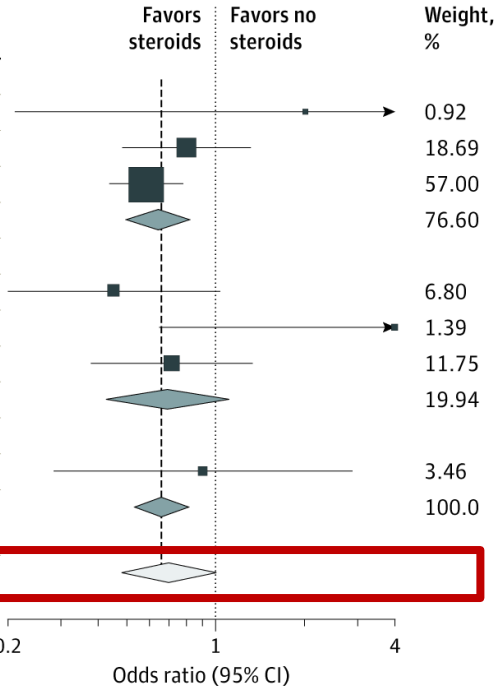
- Reinfections happen
- Sometimes these reinfections can be more clinically severe
- Retesting people make sense in at least some patients – particularly if we can save sequences – hard to interpret
- **No immunity passport!**

Van Elslande. CID 2020

Corticosteroids

- Background: Recovery trial demonstrated the methylprednisolone decreased mortality in patients with COVID-19 on supplemental 02 or mechanical ventilation
- Meta-analysis of 7 trials among critically ill patients
- 30% reduction in mortality

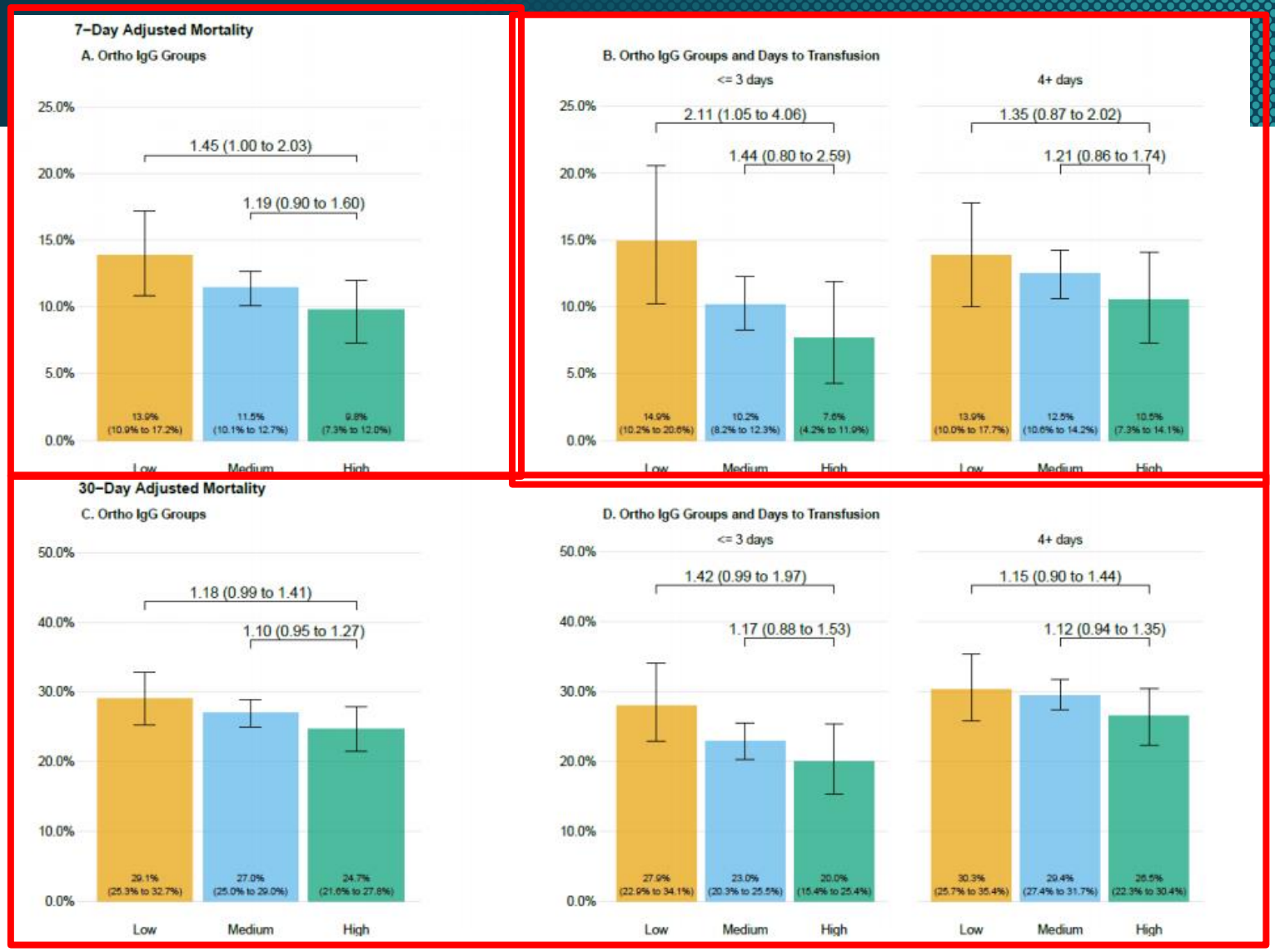
Drug and trial	ClinicalTrials.gov identifier	Initial dose and administration	No. of deaths/total No. of patients: Steroids	No steroids	Odds ratio (95% CI)	Weight, %
Dexamethasone						
DEXA-COVID 19	NCT04325061	High: 20 mg/d intravenously	2/7	2/12	2.00 (0.21-18.69)	0.92
CoDEX	NCT04327401	High: 20 mg/d intravenously	69/128	76/128	0.80 (0.49-1.31)	18.69
RECOVERY	NCT04381936	Low: 6 mg/d orally or intravenously	95/324	283/683	0.59 (0.44-0.78)	57.00
Subgroup fixed effect			166/459	361/823	0.64 (0.50-0.82)	76.60
Hydrocortisone						
CAPE COVID	NCT02517489	Low: 200 mg/d intravenously	11/75	20/73	0.46 (0.20-1.04)	6.80
COVID STEROID	NCT04348305	Low: 200 mg/d intravenously	6/15	2/14	4.00 (0.65-24.66)	1.39
REMAP-CAP	NCT02735707	Low: 50 mg every 6 h intravenously	26/105	29/92	0.71 (0.38-1.33)	11.75
Subgroup fixed effect			43/195	51/179	0.69 (0.43-1.12)	19.94
Methylprednisolone						
Steroids-SARI	NCT04244591	High: 40 mg every 12 h intravenously	13/24	13/23	0.91 (0.29-2.87)	3.46
Overall (fixed effect)			222/678	425/1025	0.66 (0.53-0.82)	100.0
$P = .31$ for heterogeneity; $I^2 = 15.6\%$						
Overall (random effects[a])			222/678	425/1025	0.70 (0.48-1.01)	



Sources: WHO Rapid Evidence Appraisal for COVID-19 Therapies WG. JAMA 2020

Convalescent Plasma: Observational Data

- Background – Small Chinese RCT did not show CP was effective (underenrolled)
- Design – Analysis data open label expanded access program
- Population – 35,322 US patients 4/4-7/4/20
  - 52% in ICU
  - 8.7% 7 day mortality
- Outcome: 7 and 30-day mortality, outcomes stratified by timing of administration & quantity of SARS-CoV-2 IgG in plasma (subset receiving 1 unit)



Suggests that Convalescent Plasma is beneficial if given early and has a high titer of IgG – Not an RCT

Source: Joyner MJ. MedRxiv 2020

Convalescent Plasma: PLACID Trial

- Design – Open label RCT
- Population – 464 hypoxemic hospitalized patients in India with confirmed COVID-19
  - 68% of patients received hydroxychloroquine
  - ~50% received methylpred
  - ~65% eeceived AZM
- Intervention – 2 doses of convalescent vs. standard of care – only 24 patients received CP within 3 days of symptom onset
- Outcome: composite of progression or death at 28 days

Source: Agarway A. MedRxiv 2020

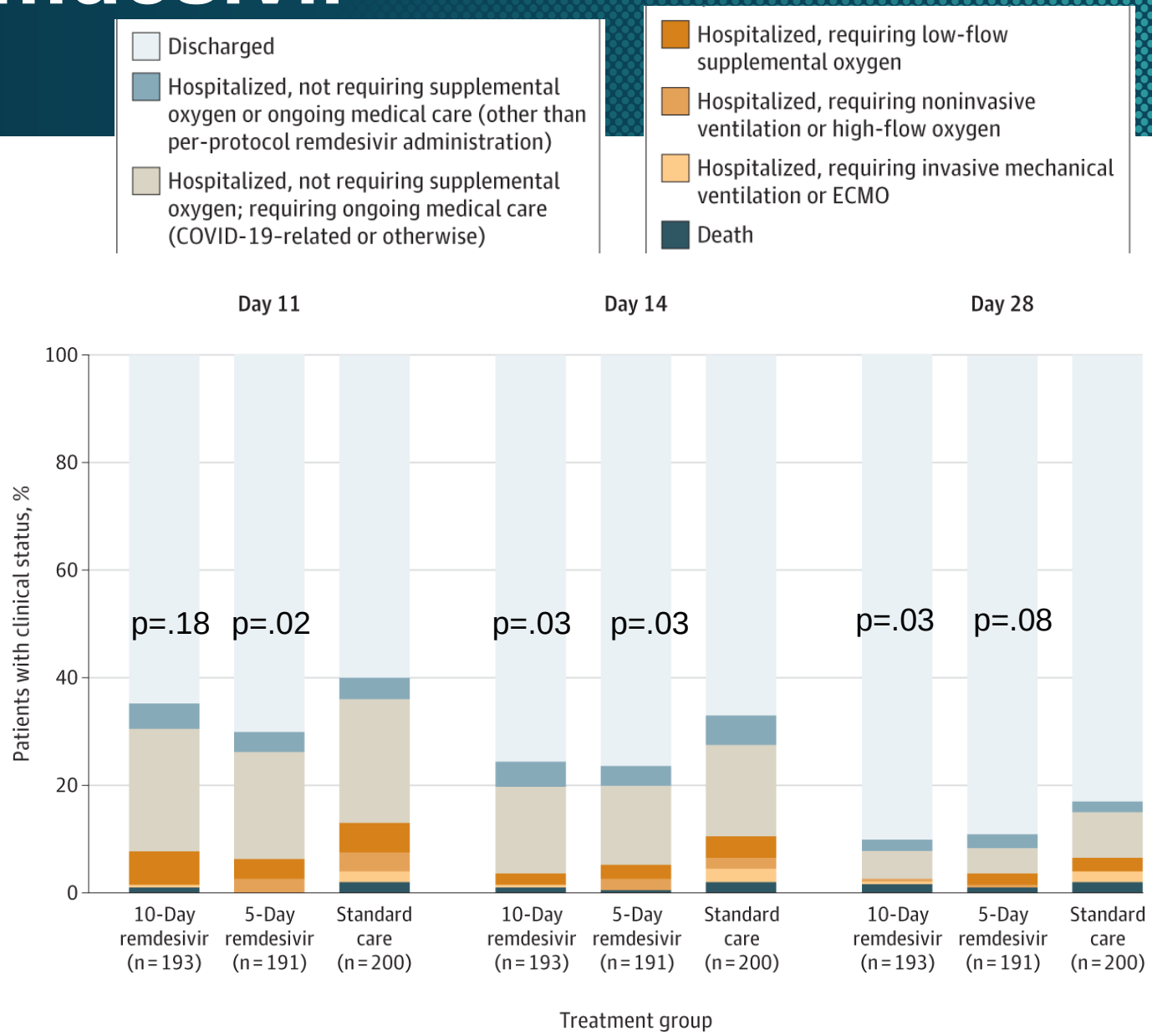
	Standard of Care N=229	CP N=235	CP (with detectable neutralizing antibody [NAbs])	CP (NAbs ≥1:80)	CP (NAbs undetectable)
All cause Mortality	13.5%	14.5%	13.8%	14.9%	18.7%
Profession to severe disease	7.4%	7.2%	6.8%	8.9%	9.4%
Composite outcome	17.9%	18.7%	16.9%	17.9%	20.3%

- CP arm had significantly greater resolution of SOB and fatigue at day 7, greater improvement in Fi02 and faster conversation to negative SARS-CoV-2 PCR
- Among 24 pts receiving CP within 3 days of symptom onset - aOR: 0.59 (95% CI: 0.28, 1.24)]

Convalescent Plasma did not improve clinical outcomes in people with moderate COVID-19 – Lots we don't know

Remdesivir

- Background
  - Small Chinese study – no benefit
  - ACTT-1 - Remdesivir decreased time to recovery by 4 days in hypoxemic patients with COVID-19 with a non-significant trend toward ↓ mortality -> FDA approval for severe disease
- Design – Open label RCT
- Population – COVID-19 pneumonia with 02 sat >94% (no supplemental 02)
- Intervention: SOC, 5-days or 10 days of remdesivir
- Outcome: Hospital discharge by day 14, 7-point ordinal scale at day 11 (higher score is better)



Spinner CD JAMA 2020

Remdesivir

- Trial "… suggests modest clinical benefit for a 5 day course compared to standard of care"
- Major questions
  - Who should get Remdesivir
    - Current practice at UW is to limit use to patients with a 02 sat <94%
  - Still some uncertainty about optimal duration
    - 5 days is best supported
  - Effect on discrete outcomes is not clear – ordinal scale as an outcome is hard to interpret
    - Duration of hospitalization, mechanical ventilation, and death are different
  - Role of drug in persons receiving dexamethasone is not clear
    - Dexamethasone is much less expensive and more widely available

McCreary EK JAMA 2020

Are Nonsteroidal Anti-Inflammatories Safe in COVID-19?

- Previously studies have raised concern that NSAIDS may be unsafe in COVID-19
- Design – Population-based cohort study using Danish health – NSAID users matched to 4 non-users based on propensity scoring
- Population – 9236 Danes with a positive SARS-CoV-2 test
- Exposure – Filled NSAID in 30 days prior to SARS-CoV-2 test
- Outcome: Mortality, hospitalization, ICU, mechanical ventilation

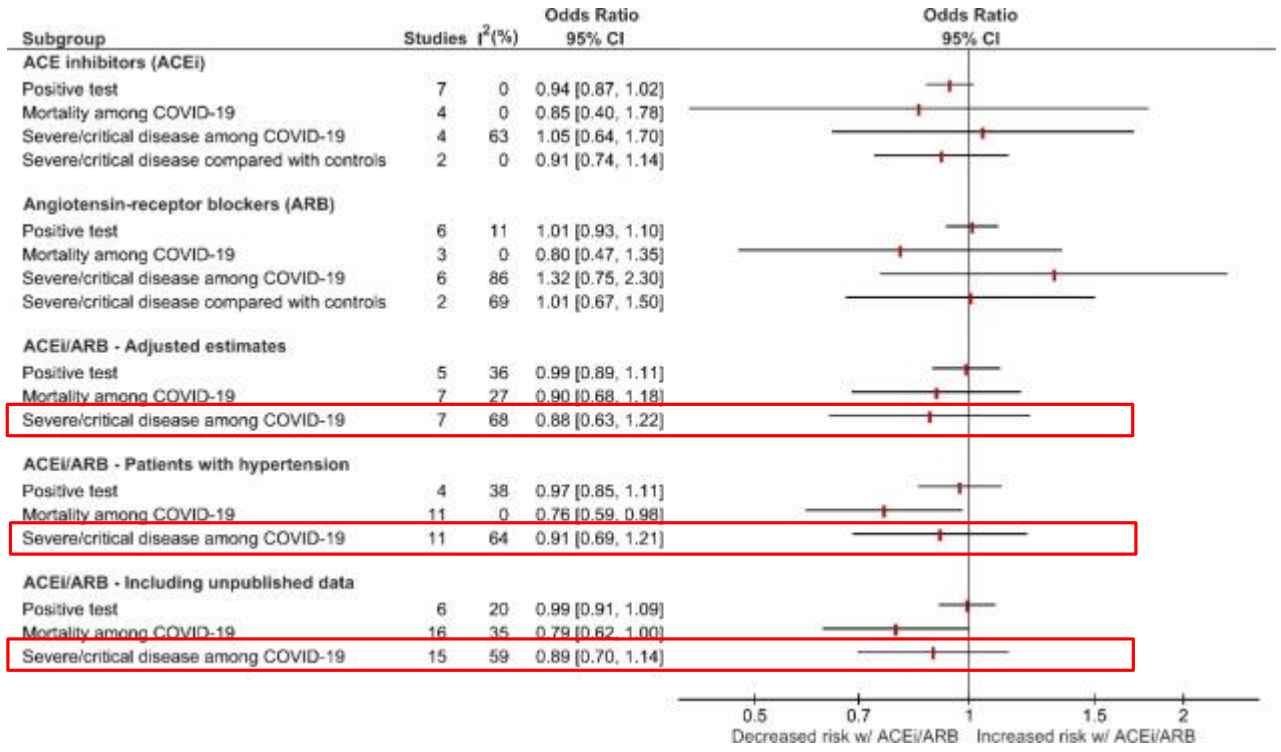
Outcome	NSAID users		Non-users		Comparison			
	Number of events/ sample size	Risk (%) (95% CI)	Number of events/ sample size	Risk (%) (95% CI)	Risk difference (%) (95% CI)	*p*-Value	Risk ratio (95% CI)	*p*-Value
Matched cohort								
Death	14/224	6.3 (3.1, 9.4)	55/896	6.1 (4.4, 7.8)	0.1 (−3.5, 3.7)	0.95	1.02 (0.57, 1.82)	0.95
Hospitalization*	50/204	24.5 (18.6, 30.4)	175/826	21.2 (18.1, 24.3)	3.3 (−3.4, 10.0)	0.33	1.16 (0.87, 1.53)	0.31
ICU admission*	11/223	4.9 (2.1, 7.8)	42/889	4.7 (3.2, 6.2)	0.2 (−3.0, 3.4)	0.90	1.04 (0.54, 2.02)	0.90
Mechanical ventilation*	10/224	4.5 (1.8, 7.2)	35/891	3.9 (2.5, 5.3)	0.5 (−2.5, 3.6)	0.73	1.14 (0.56, 2.30)	0.72
Renal replacement therapy*	$n < 5$/224	—**	—**	—**	−0.2 (−2.0, 1.6)	0.81	0.86 (0.24, 3.09)	0.81

Use of NSAIDs was not associated with 30-day mortality, hospitalization, ICU admission, mechanical ventilation, or renal replacement therapy.

Source: Lund LC PLOS Medicine 2020

Are ACE Inhibitors (ACEi) & ARBs Safe in COVID-19?

- SARS-CoV-2 enters cells via binding to ACE2. Animal studies suggest that ACE inhibitors & ARBs may increase ACE2 expression, potentially increasing COVID-19 risk.
- Design – Systemic review of studies investigating the association of ACEi and ARB use and COVID-19 disease, severity and mortality
- 27 studies included



Evidence does not suggest an association of ACEi or ARB use with SARS-CoV-2 infection or COVID-19 severity or mortality

Source: Caldeira D. IJC Heart & Vasculature 2020

Operation Warp Speed (OWS)

- US government initiative to develop a COVID-19 vaccine by the end of 2020 and have 300 million doses available and deployed by mid-2021
- 4 vaccine candidate selection criteria
  - Robust pre-clinical or early stage data on safety & potential efficacy
  - Potential to enter phase 3 trials by July-Nov 2020 - efficacy outcomes 1st half 2021
  - Platforms allow fast and effective manufacturing - capacity to produce >100 million doses by mid-2021
  - Use of one of 4 vaccine platforms thought most likely to be safe and effective – 6 of 8 planned partnerships announced

Operation Warp Speed (OWS)

Technology	Vaccine	Status
mRNA	Moderna	Immunogenic in phase I – phase 3 ongoing
	Pfizer/BioNTech	Immunogenic in phase I – phase 3 ongoing
Replication defective live vector	ChAdOx – AstraZeneca & Oxford*	Ongoing phase 3 in UK, Brazil and South Africa Phase 3 US trial started in August
	Janssen Ad26	Effective nonhuman primates, ongoing phase 1 with planned phase 3 in September
Recombinent subunit adjuvant protein	Novavax	Phase 1 done – phase 3 start in September
	Sanofi/GSK	Preclinical – phase 1 in Sept
Attenuated replicating live vector	Not yet chosen	

- Study on hold due to episode of transverse myelitis in a vaccinated study subject
- Development of manufacturing capacity ongoing in parallel with trials
- WHO website shows 9 vaccines in phase III trials (https://www-who-int.offcampus.lib.washington.edu/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines)

Questions and Discussion