Causal inference in a time of coronavirus

Tenofovir, Tocilizumab, and Hydroxychloroquine

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Causal inference in a time of coronavirus

- To manage the pandemic, we need to make decisions
- To make decisions, we need to know what works
- Causal inference is what we do to learn what works
- Hence we need good causal inference for good decision-making

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COVID-19: Causal inference about what?

- Public health interventions
  - Lockdowns
  - Face masks
  - Surface cleaning
  - Limit size of gatherings
  - School closures
  - Restaurant closures
  - Contact tracing
  - …
- Clinical interventions
  - Antivirals
    - remdesivir, antiretrovirals, hydroxychloroquine, monoclonal antibodies, convalescent plasma…
  - Anti-inflammatory drugs
    - nospecific (dexamethasone), specific (tocilizumab…)
  - Critical care management
    - proning, ECMO
  - …

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COVID-19: a disease with 2 phases

1. Viral infection
   - moderate to mild or no symptoms
   - when viral replication declines, symptoms subside
   - Potential benefit of antivirals that block viral replication
2. Inflammatory response
   - in a subset of patients, even after viral replication declines
   - severe symptoms, including acute respiratory distress
   - Potential benefit of anti-inflammatory drugs
     - RECOVERY trial more benefit of dexamethasone in severe patients

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Three stories about causal inference in a time of coronavirus

1. The Tenofovir story
   - an antiviral to prevent hospitalizations among infected individuals?
2. The Tocilizumab story
   - an anti-inflammatory drug to prevent ICU admission and mortality among hospitalized individuals?
3. The Hydroxychloroquine story
   - an antiviral to prevent infections among exposed individuals?

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How do we learn what works?
(How do we estimate causal effects?)

- We carry out randomized trials
  - Method of choice to answer causal questions about comparative effectiveness and safety
- If randomized trials are not available, we carry out analyses of observational data
  - that emulate a (hypothetical) target trial as closely as possible

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How do we decide which existing drugs will be studied in randomized trials?

- We build evidence from different sources
  - Typical progression of evidence:
    - In vitro studies, in silico studies
    - Animal studies
    - Observational studies
- If evidence looks promising, we launch a trial

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The Tenofovir Story Background

- COVID-19 might be expected to be more severe in HIV-positive persons
  - immunosuppression
  - risk factors: older age, male, hypertension, diabetes, COPD, kidney disease…
- But HIV-positive individuals with suppressed viral load don't seems to have a greater risk of serious COVID-19
  - ?

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The Tenofovir Story
Background

- Two possibilities
  1. HIV infection prevents the intense immunologic response that often complicates COVID-19
  2. Antiretrovirals for treatment of HIV infection reduce the risk of serious COVID-19

- What antiretrovirals?
  - Nucleos(t)ide reverse transcriptase inhibitors (NRTIs)
    - **tenofovir**, abacavir, lamivudine

The Tenofovir Story
In vitro studies

- Tenofovir may
  - terminate extension of nascent RNA by RNA-dependent RNA polymerase of SARS-CoV-2 (RdRp-CoV-2)
    - Jockusch et al. *J Proteome Research* 2020 (first posted April)
    - Clososki et al. *J Braz Chem Soc* 2020 (May)
    - Sun. bioRxiv 2020 (November)
  - have an immunomodulating effect independent of its antiviral effect
- Tenofovir was already proposed as treatment for SARS-CoV-1 infection

The Tenofovir Story
In silico studies

- Tenofovir may
  - terminate extension of RNA
    - Molecular docking studies: Elfiky. *Life Sciences* 2020; Elfiky. J *Biomol Structure Dynamics* 2020.
  - but only if sufficient intracellular availability
    - Ensemble docking: De Salazar et al. *Authorea* 2020 (September)
- Interesting, because there are 2 prodrugs of tenofovir
  - Tenofovir disoproxil fumarate (TDF)
    - greater intracellular availability in most tissues
  - Tenofovir alafenamide fumarate (TAF)
    - preferential distribution in lymphoid tissues

The Tenofovir Story
Animal studies

- Ferrets were treated with antivirals
  - TDF/emtricitabine (FTC), lopinavir/ritonavir, HCQ
  - Park et al. *mBio* 2020 (May)
- The TDF/FTC group showed a reduction in overall clinical scores and a shorter duration of clinical symptoms
- "These results suggest that [TDF/FTC] may be the most likely candidate to reduce clinical symptoms, of SARS-CoV-2-infected hosts"

The Tenofovir story
Human studies

- Observational studies have been conducted in individuals already receiving antiretrovirals for
  - treatment of HIV-positive individuals
  - prophylaxis of HIV infection (PrEP)
- Let's review them

The Tenofovir story
Spanish HIV/COVID-19 Collaboration

- Observational study of 77,590 HIV-positive persons receiving antiretrovirals
  - >100 investigators, HIV clinics in 60 Spanish hospitals
    - del Amo et al. *Ann Int Med* 2020 and *Epidemiology* 2020

ORIGINAL RESEARCH

Annals of Internal Medicine

Incidence and Severity of COVID-19 in HIV-Positive Persons Receiving Antiretroviral Therapy

A Cohort Study

Julia del Amo, MD, PhD; Rosa Polo, MD, PhD; Santiago Moreno, MD, PhD; Asunción Díaz, MD, PhD; Esteban Martínez, MD, PhD; José Ramón Arribas, MD, PhD; Inma Jarrín, PhD; and Miguel A. Hernán, MD, DrPH; for The Spanish HIV/COVID-19 Collaboration*

The Tenofovir story
Spanish HIV/COVID-19 Collaboration

- Lower risk of hospitalization in TDF/FTC users

NRTI Backbone	Estimated Persons at Risk[a]	COVID-19 Hospital Admission N	COVID-19 Hospital Admission Rate Ratio (95% CI)
TAF/FTC	25,571	52	1 (ref.)
TDF/FTC	12,395	13	0.53 (0.29–0.97)
ABC/3TC	20,105	47	1.0 (0.69–1.5)
Other regimes[b]	19,520	39	0.89 (0.59–1.4)

- Age- and sex-adjusted

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The Tenofovir story
Spanish HIV/COVID-19 Collaboration

- Perhaps TDF/FTC are healthier than others?
  - Confounding by comorbidity?
  - No data on comorbidity so adjustment not possible
- Sensitivity Analysis 1: Younger than 60 years
  - low prevalence of comorbidities, little confounding
  - Rate ratio of COVID-19 hospitalization
    - 0.55 (95% CI 0.29–1.04)
    - for TDF/FTC compared with TAF/FTC

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The Tenofovir story
Spanish HIV/COVID-19 Collaboration

- Sensitivity Analysis 2: Compare risk of COVID-19 hospitalization between hospitals which used
  - >70% of tenofovir as TDF/FTC vs.
  - >70% of tenofovir as TAF/FTC
- Distribution of comorbidities across hospitals is similar
  - differences in risk between hospitals not explained by individual-level differences in comorbidities
  - little confounding, huge misclassification
- Rate ratio: 0.80 (95% CI: 0.41–1.56)

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The Tenofovir story
Western Cape Province, South Africa

- Observational study of 3978 HIV-positive individuals with COVID-19
  - medRxiv 2020 (first reported July)
- Lower risk of death in TDF/FTC users
  - among those on antiretroviral therapy
- Mortality hazard ratio
  - 0.42 (95% CI 0.22, 0.78)
  - for TDF vs. abacavir/zidovudine
  - Adjusted for sex, age, **comorbidities** (including kidney disease) and viral suppression

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The Tenofovir story
PrEP users in Madrid

- Observational study in HIV/STI clinic for PrEP
  - Ayerdi et al. *Open Forum Infectious Diseases* 2020
- 60 individuals on TDF/FTC and 15 on TAF/FTC with positive IgG serology
- Risk of COVID-19 symptoms
  - Risk ratio 0.73 (95% CI: 0.49, 1.07)
  - for TDF/FTC vs. TAF/FTC

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The Tenofovir story
A nice progression for causal inference

- In vitro studies
- In silico studies
- Animal experiments
- Observational studies
- Next step: Randomized trials
  - A strong case has been built for TDF/FTC
  - Stronger than for, say, hydroxychloroquine or remdesivir
  - There must have been many trials of TDF/FTC to prevent serious COVID-19, right?

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Number of randomized trials of PrEP with TDF/FTC: 1 (one)

- EPICOS, Spain and Latin America
  - 4 arms: TDF/FTC, HCQ, TDF/FTC+HCQ, placebo
    - PIs: Julia del Amo, Rosa Polo (Plan del Sida, Ministerio Sanidad)
  - TDF/FTC
    - Prophylaxis: trial designed but not launched in Colombia
    - Treatment of high-risk patients: PANCOVID trial in Spain
  - TAF/FTC
    - Prophylaxis: CoviPreP trial in Argentina
    - Treatment: Sichuan, China

So… how do we decide which existing drugs will be studied in randomized trials?

- We build evidence from different sources
  - Typical progression of evidence:
    - In vitro studies, in silico studies
    - Animal studies
    - Observational studies
- If evidence looks promising, we launch a trial
- Ahem
  - What else is needed to start randomized trials of TDF/FTC?

Something didn't quite work here

- TDF/FTC is a cheap generic drug
  - with excellent safety profile for use over several months
- Evidence is compatible with effectiveness of TDF/FTC similar to one-dose vaccination
  - for prevention of hospitalization
- Yet no randomized trials
  - and observational results were not trusted
- Did we miss a chance to make a difference?
  - We may never know… because we didn't do the trials
- Who decides these things anyway?

Three stories about causal inference in a time of coronavirus

1. The Tenofovir story
   - an antiviral to prevent hospitalizations among infected individuals?
2. The Tocilizumab story
   - an anti-inflammatory drug to prevent ICU admission and mortality among hospitalized individuals?
3. The Hydroxychloroquine story
   - an antiviral to prevent infections among exposed individuals?

The Tocilizumab story
Background

- Tocilizumab is a humanized monoclonal antibody against the interleukin 6 (IL-6) receptor
  - Used in inflammatory arthritis, giant cell arteritis, and cytokine release syndrome after chimeric antigen receptor T-cell therapy
- Early observation from China
  - Increased death risk in COVID-19 patients with elevated IL-6 levels

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The Tocilizumab story
Background

- Off-label use is common in many hospitals for COVID-19 patients with evidence of hyperinflammation
- But guidelines recommend against it use
  - National Institutes of Health
  - Infectious Disease Society of America
- What did observational studies find?
  - In critical patients
  - In noncritical patients

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The Tocilizumab story
STOP-COVID Observational Study

- 3924 individuals with COVID-19 admitted to ICU
  - 68 U.S. hospitals
  - Gupta et al. *JAMA Internal Medicine* 2020

JAMA Internal Medicine | Original Investigation

Association Between Early Treatment With Tocilizumab and Mortality Among Critically Ill Patients With COVID-19

Shruti Gupta, MD, MPH; Wei Wang, PhD; Salim S. Hayek, MD; Lili Chan, MD, MSCR; Kusum S. Mathews, MD, MPH, MSCR; Michal L. Melamed, MD, MHS; Samantha K. Brenner, MD, MPH; Amanda Leonberg-Yoo, MD, MS; Edward J. Schenck, MD, MS; Jared Radbel, MD; Jochen Reiser, MD, PhD; Anip Bansal, MD; Anand Srivastava, MD, MPH; Yan Zhou, MD; Diana Finkel, DO; Adam Green, MD, MBA; Mary Mallappallil, MD; Anthony J. Faugno, MD; Jingjing Zhang, MD, PhD; Juan Carlos Q. Velez, MD; Shahzad Shaefi, MD, MPH; Chirag R. Parikh, MD, PhD; David M. Charytan, MD, MSc; Ambarish M. Athavale, MBBS, MD; Allon N. Friedman, MD; Roberta E. Redfern, PhD; Samuel A. P. Short, BA; Simon Correa, MD, MMSc; Kapil K. Pokharel, MBBS; Andrew J. Admon, MD, MPH, MSc; John P. Donnelly, PhD; Hayley B. Gershengorn, MD; David J. Douin, MD; Matthew W. Semler, MD; Miguel A. Hernán, MD, DrPH; David E. Leaf, MD, MMSc; for the STOP-COVID Investigators

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The Tocilizumab story
STOP-COVID Observational Study

- Patients treated with tocilizumab in the first 2 days of ICU admission
  - younger, fewer comorbidities
  - higher prevalence of hypoxemia and levels of inflammatory markers
- Statistical adjustment balanced these characteristics between toci and not toci groups
  - Inverse probability weighting

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The Tocilizumab story
STOP-COVID Observational Study

- 30-day mortality
  - 27.5% in the tocilizumab group
  - 37.1% in the non-tocilizumab group
  - Risk difference: 9.6% (95% CI 3.1%-16.0%)
- Hazard ratio: 0.71 (95% CI 0.56-0.92)
  - If admitted to the ICU within 3 days of symptom onset: 0.41 (95% CI: 0.23-0.74)
  - If admitted to the ICU after 3 days of symptom onset: 0.85 (95% CI: 0.65-1.11)

The Tocilizumab story
Observational studies in non-critical patients

- Better outcome for individuals treated with tocilizumab
  - lower risk of death and intubation
- But not in pre-inflammatory stage of COVID-19
- What about the randomized trials?

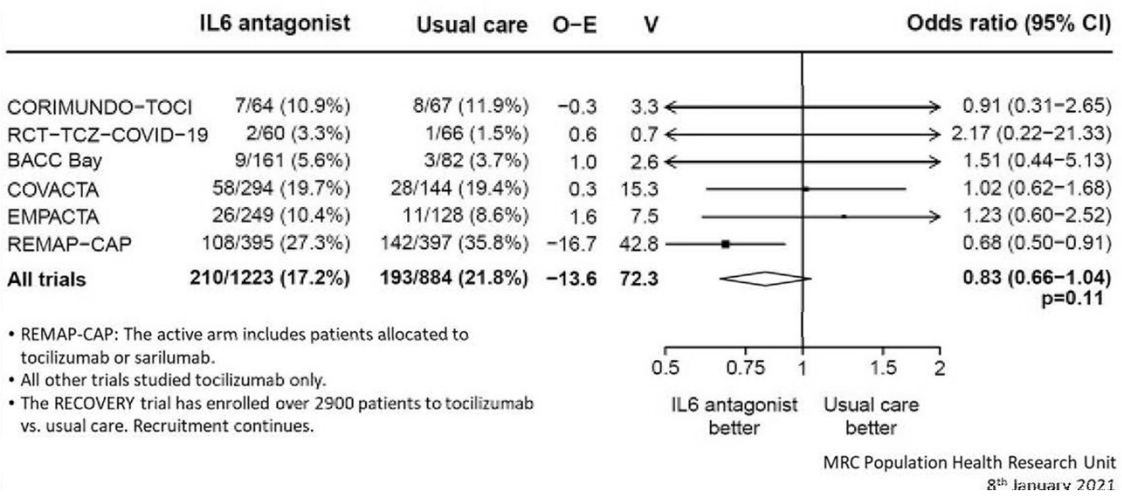
The Tocilizumab story
Randomized trials

- No double-blind, no placebo
  - CORIMUNDO-TOCI (France)
    - Hermine et al. *JAMA Int Med* 2020
  - RCT-TCZ-COVID-19 Study Group (Italy)
    - Salvarani et al. *JAMA Int Med* 2020
- Double-blind, placebo
  - BACC Bay Tocilizumab Trial, noncritical patients
  - COVACTA, mixed of critical and noncritical patients
  - EMPACTA, noncritical patients
- Platform trials with a master protocol, open label
  - REMAP-CAP, critical patients
  - RECOVERY, critical and noncritical patients

One possible summary of findings from trials

- Meta-analysis of mortality results
  - Just pool all trials, regardless of design features
  - Estimate pooled relative risk of 28-day mortality for tocilizumab vs. no tocilizumab
- Approach followed by MRC Population Health Research Unit
  - In Letter to RECOVERY Investigators, 8 Jan 21
    - https://www.recoverytrial.net/files/recovery_lettertoinvestigators_tocilizumab_2021-01-08.pdf

Effect of interleukin-6 antagonists on 28-day mortality among patients hospitalised with COVID-19



- REMAP-CAP: The active arm includes patients allocated to tocilizumab or sarilumab.
- All other trials studied tocilizumab only.
- The RECOVERY trial has enrolled over 2900 patients to tocilizumab vs. usual care. Recruitment continues.

MRC Population Health Research Unit
8th January 2021

The Tocilizumab story
BACC-Bay Tocilizumab Trial (Stone et al. *NEJM* 2020)

- 243 Covid-19 noncritical inpatients from Boston
- 28-day risk of death or intubation
  - 10.6% in the tocilizumab group
  - 12.5% in the placebo group
  - Risk difference: -2.1%
- Unadjusted hazard ratio: 0.83 (95% CI: 0.38-1.81)
- Adjusted hazard ratio: 0.66 (95% CI: 0.28, 1.52)
  - older patients in tocilizumab group

The Tocilizumab story
BACC-Bay Tocilizumab Trial

- Adjusted hazard ratio: 0.66 (95% CI 0.28, 1.52)

> **CONCLUSIONS**
> Tocilizumab was not effective for preventing intubation or death in moderately ill hospitalized patients with Covid-19. Some benefit or harm cannot be ruled out, however, because the confidence intervals for efficacy comparisons were wide. (Funded by Genentech; ClinicalTrials.gov number, NCT04356937.)

  - Note the two sentences of the "Conclusions" are contradictory

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Adjusted hazard ratio:
0.66 (95% CI 0.28, 1.52)

- Podcast from the Journal Editors
  - https://www.nejm.org/doi/full/10.1056/NEJMe2032051
- Deputy Editor, says
  - there was a "failure to show a benefit"
  - "these data are pretty clear there is no big effect, no obvious effect, of toci in patients who are progressing with severe COVID"
  - (Editor-in-Chief says there may be effect, more data needed)
- Not surprisingly, these findings were reported by the media as evidence **against** the efficacy of tocilizumab!

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The Tocilizumab story
EMPACTA Trial (Salama et al. *NEJM* 2021)

- 389 COVID-19 noncritical patients from 6 countries
- 28-day risk of death or intubation
  - 12.0% in the tocilizumab group
  - 19.3% in the placebo group
  - Risk difference: -7.3%
- Hazard ratio: 0.56 (95% CI: 0.33, 0.97)

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The Tocilizumab story
COVACTA (medRxiv 2020)

- 452 COVID-19 patients (~35% intubated) from 9 countries
- Risk of ICU admission
  - 24% in the tocilizumab group
  - 41% in the placebo group
  - Risk difference: -17.2% (95% CI -31.3 to -3.0)
- In non-ventilated patients
  - HR 0.61 (0.40, 0.94) for death, withdrawal during hospitalization, mechanical ventilation, or ICU admission
- No differences in mortality but
  - More patients in placebo arm than tocilizumab arm received
    - steroids (55% vs 36%) and antivirals (35% vs 30%)

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The Tocilizumab story
REMAP CAP (medRxiv 2021)

- ~800 critical patients within 24 h of ICU admission
  - sample size approx equal to all previous trials combined
- Risk of hospital mortality
  - 28.0% in the tocilizumab group
  - 35.8% in the placebo group
  - Risk difference: -7.8%
- Odds ratio: 0.60 (95% CrI: 0.46, 0.79)
  - UK immediately approved toci for critically ill COVID-19 patients

Randomized trials with >70 patients per arm found a benefit of tocilizumab

- For intubation+death (noncritical patients)
- For death (critical patients)
- Interpretation of individual trials was often incorrect
  - No "statistical significance" was equated with no effect
- Meta-analyses concluded no effect
  - focused on mortality – odd choice given ICU crisis
  - mixed up critical and noncritical patients

How do we learn what works?

- We treat observational studies cautiously
- We don't rely on a single randomized trial
- We meta-analyze trials

- Meta-analyses of trials with different design features may be too simplistic
  - But let's say that we accept this simplification
  - Will we always accept whatever the meta-analysis says?

Three stories about causal inference in a time of coronavirus

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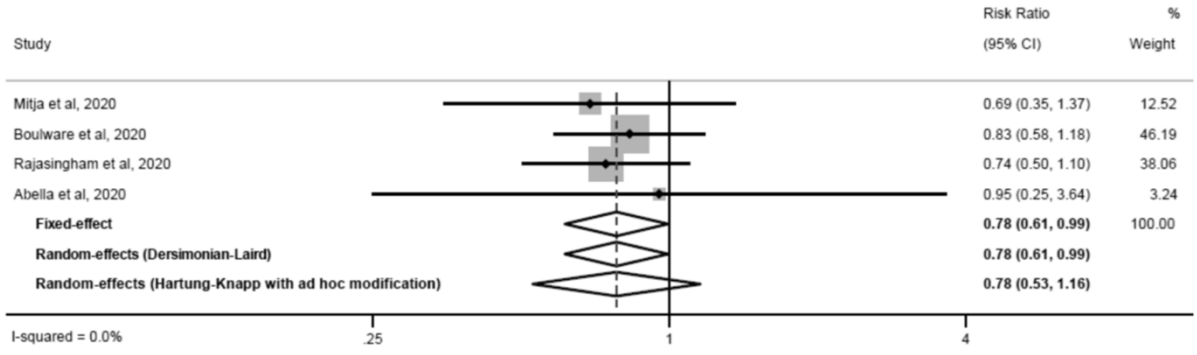
   - an antiviral to prevent infections among exposed individuals?

Hydroxychloroquine (HCQ) doesn't work for treatment of hospitalized COVID-19 patients

- Multiple randomized trials
  - Case closed
- But does it work for the prevention of COVID-19 as pre-exposure or post-exposure prophylaxis?
  - Several randomized trials
  - Let's do a simplistic meta-analysis

The Hydroxychloroquine story
4 randomized trials of HCQ for prophylaxis

- Garcia-Albeniz et al. medRxiv 2020 (November version)



The Hydroxychloroquine story Again…

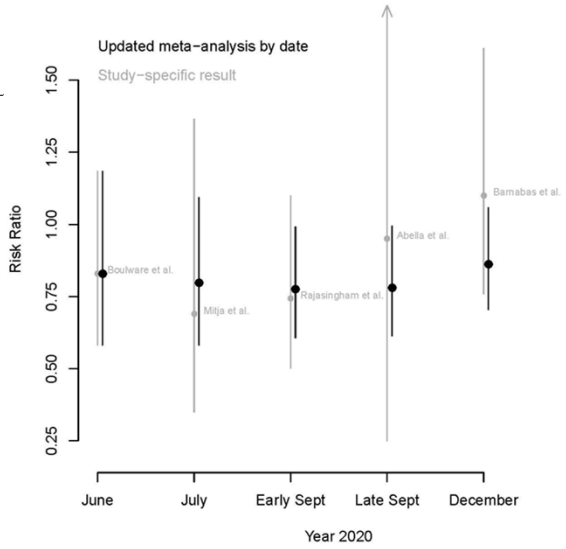
- Interpretation of individual trials was often incorrect
  - No "statistical significance" was equated with no effect by researchers and media
- Abella et al. (September)
  - "no significant difference [for] hydroxychloroquine compared with placebo (4 of 64 [6.3%] vs 4 of 61 [6.6%]; P > .99)"
  - Risk ratio: 0.95 (95% CI: 0.24, 3.64)

The Hydroxychloroquine story But this time…

- Meta-analyses of trials with different design features were considered too simplistic
  - Mixing pre-exposure and post-exposure studies?
  - Garcia-Albeniz et al; Lewis et al. *PLoS ONE* 2021
- So the meta-analysis was questioned
  - The appropriate thing to do
  - Except that the conclusion was "no effect"
    - Risk ratio: 0.78 or less through November

The Hydroxychloroquine story

- Risk ratio of COVID-19:
  - 0.78 or less through November
    - 95% CI: 0.61, 0.99
    - 95% CI: 0.53, 1.16
  - 0.89 through December
    - 95% CI: 0.73, 1.08
    - 95% CI: 0.58, 1.37



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Our causal inference framework didn't work perfectly

- The selection of drugs for randomized trials was sometimes idiosyncratic
  - lots of trials for remdesivir, almost none for tenofovir
- The interpretation of available evidence was sometimes flawed
  - large observational studies of tocilizumab were dismissed
  - small randomized trials of tocilizumab were overinterpreted
- Consensus emerged quickly in the absence of supporting evidence
  - hydroxychloroquine was "determined" to be ineffective for prophylaxis in the Summer of 2020
- Problems
  - We miss the benefits of timely implementation of these interventions
  - We interfere with the generation of additional evidence

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What did these three case studies have in common?

- Lack of coordinated leadership
  - No global governance systems to prioritize and harmonize lines of research
    - WHO, Gates tried
  - Not even national systems, even though that many national regulators must approve every study in their country
- Lack of cooperation among investigators
  - Multiple uninformative trials with small sample sizes
  - Different protocols make hard to combine the evidence
- Lack of technical sophistication
  - We need to be skeptical of observational analyses
    - But skeptical doesn't mean dismissive
  - We need to learn to communicate uncertainty
    - The scourge of statistical significance

Lessons for next pandemic… or this one

- Use observational data faster and better
  - Use sound methodology to emulate target trials
  - Use findings to prioritize compounds and design better trials
- COLLABORATE
  - Most effective causal inference came from collaborative work
  - Observational studies
    - STOP-COVID, Spanish HIV/COVID-19 Collaboration
  - Platform randomized trials, Master protocols
    - RECOVERY, REMAP-CAP
  - Requires generosity