Statistical Methods and Modeling In Response to COVID-19 at NIAID

Dean Follmann

National Institute of Allergy and Infectious Diseases

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NIAID Biostatistics Research Branch


Dean Follmann


Erica Brittain


Sally Hunsberger


Michael Fay


Lori Dodd


Micheal Proschan


Jing Qin


Bruce Swihart


Misrak Gezmu


Zonghui Hu

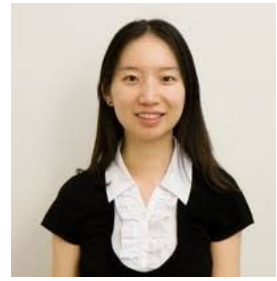

Jonathan Fintzi


Ana Villa -Ortega


Michele Di Mascio


Martha Nason


C. Jason Liang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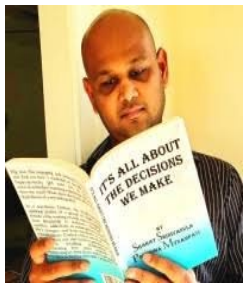

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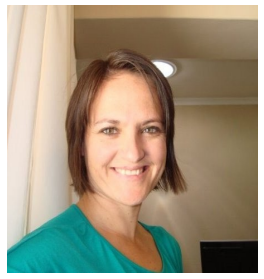
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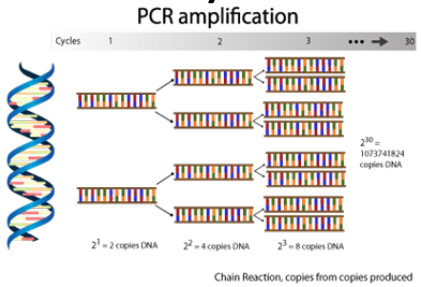
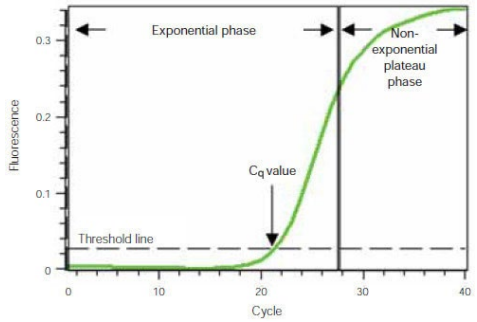
How we fight Infectious Diseases

- Identify
  - Diagnostic Tests
- Describe
  - Time from infection to symptoms (incubation)
  - Who has been infected (sero-prevalence)
  - Within household transmission
- Treatment
  - Adaptive Treatment Trial
- Prevention
  - Vaccines
  - Antibodies

Identify: Diagnostics

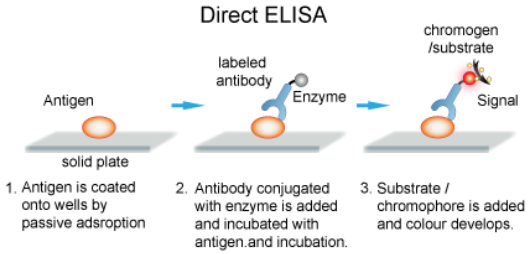
- Are you infected? (PCR tests)

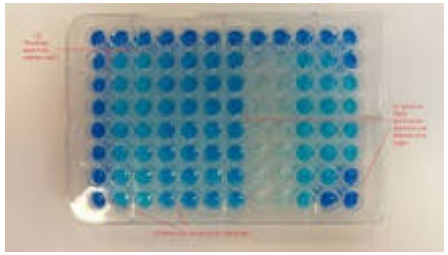




Y = abundance of SARS-CoV2 RNA

- Were you infected? (Serology)





Y = abundance of antibodies that fought SARS-CoV2

Exponential growth of testing?

- Ten Samples, Ten individual tests, Ten hours of work.

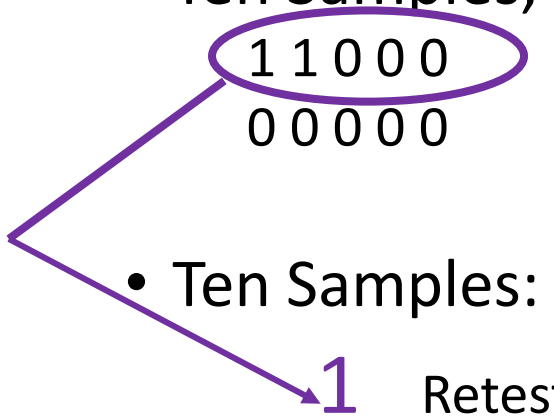
  1 1 0 0 0

  0 0 0 0 0

- 10, 20, 40, 80, 160, 320 test, 320 hours of work…

Exponential growth of testing?

- Ten Samples, Ten individual tests, Ten hours of work.

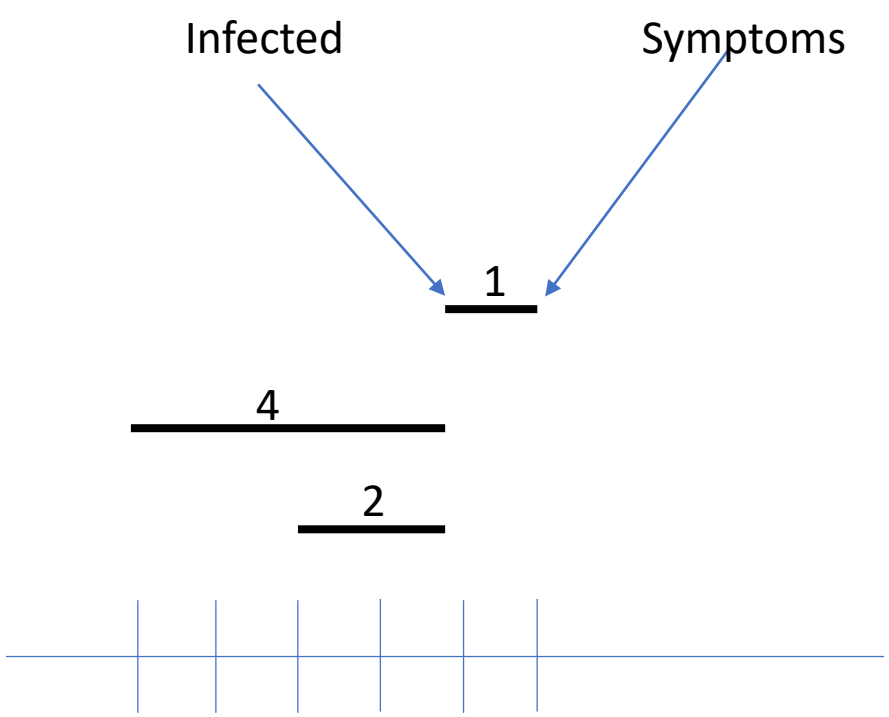


- Ten Samples: Two **pooled** tests. 5 individual tests. 7 hours of work.
  - 1 Retest individual samples 1 1 0 0 0
  - 0 *Infer individual samples* 0 0 0 0 0
- Concern
  - 1 positive in a big pool of negatives may be ‘drowned’ out
- Remedy
  - Do experiments

Current Work

- Collaborating with Asian Researchers to pool PCR tests
- Collaborating within NIAID to pool serologies
- Determine the pool size that still identifies one positive in the pool
- Labs choose number based on their current positivity rate
  - If rare maybe pool 10 or 20
  - If common don’t pool

Describe Incubation Distribution



$P(I = 2) = \Theta_2 = \#(I = 2) / \text{Total} = 1/3$

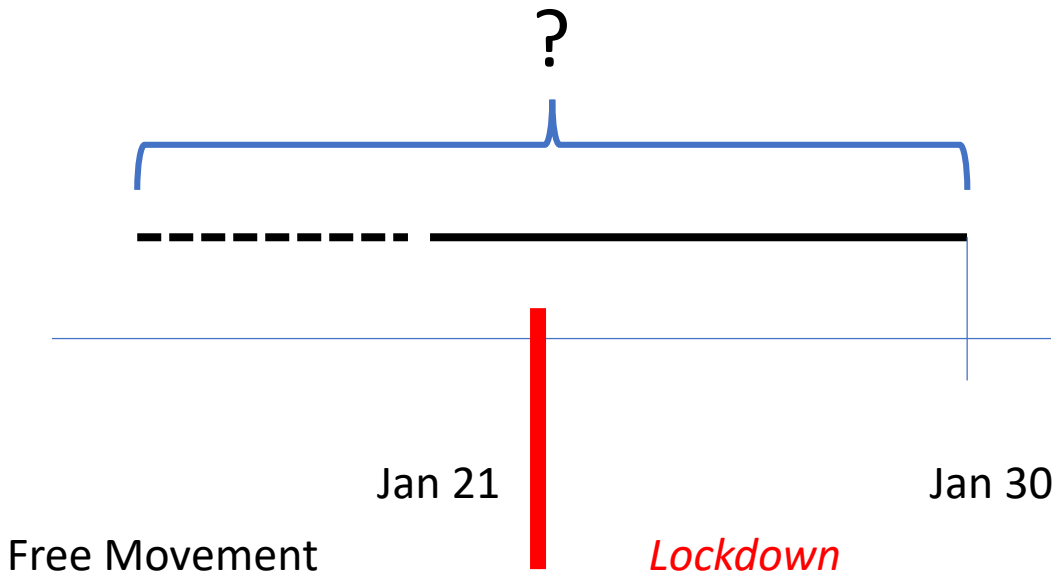
True Incubation Distribution

I	P(I)
1	Θ_1
2	Θ_2
3	Θ_3
4	Θ_4

If always $I < 14$ days, then quarantine for 14 days

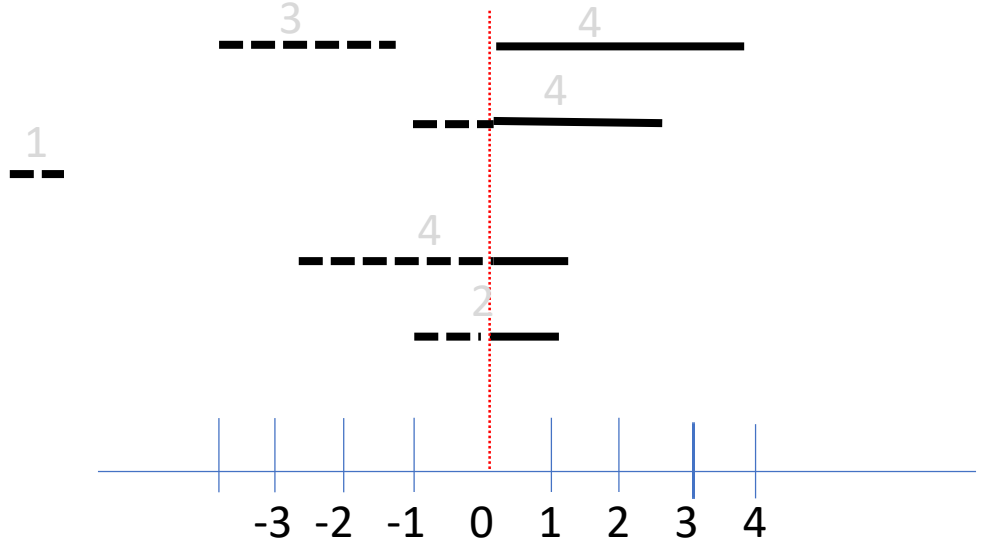
A natural experiment

- In January, Epidemic was mostly in Wuhan
- On Jan 23, China imposed a countrywide lockdown
- Suppose Zonghui leaves Wuhan on Jan 21 goes to Beijing. On Jan 23 she is stuck in her apartment
- Zonghui tests positive on Jan 30
  - Must’ve got it in Wuhan
  - Incubation must be at least 9 days
  - Can we do better?



Two issues, but a solution

- Incubation period as least what we see
- Wuhan emigres tend to nave longer incubations



True Incubation Distribution

I	P(I)
1	Θ_1
2	Θ_2
3	Θ_3
4	Θ_4

P(Symptoms day 4) = P(I=4 | Infected on Day 0) P(Infected on Day 0)/C
= Θ_4 (1/4)/C

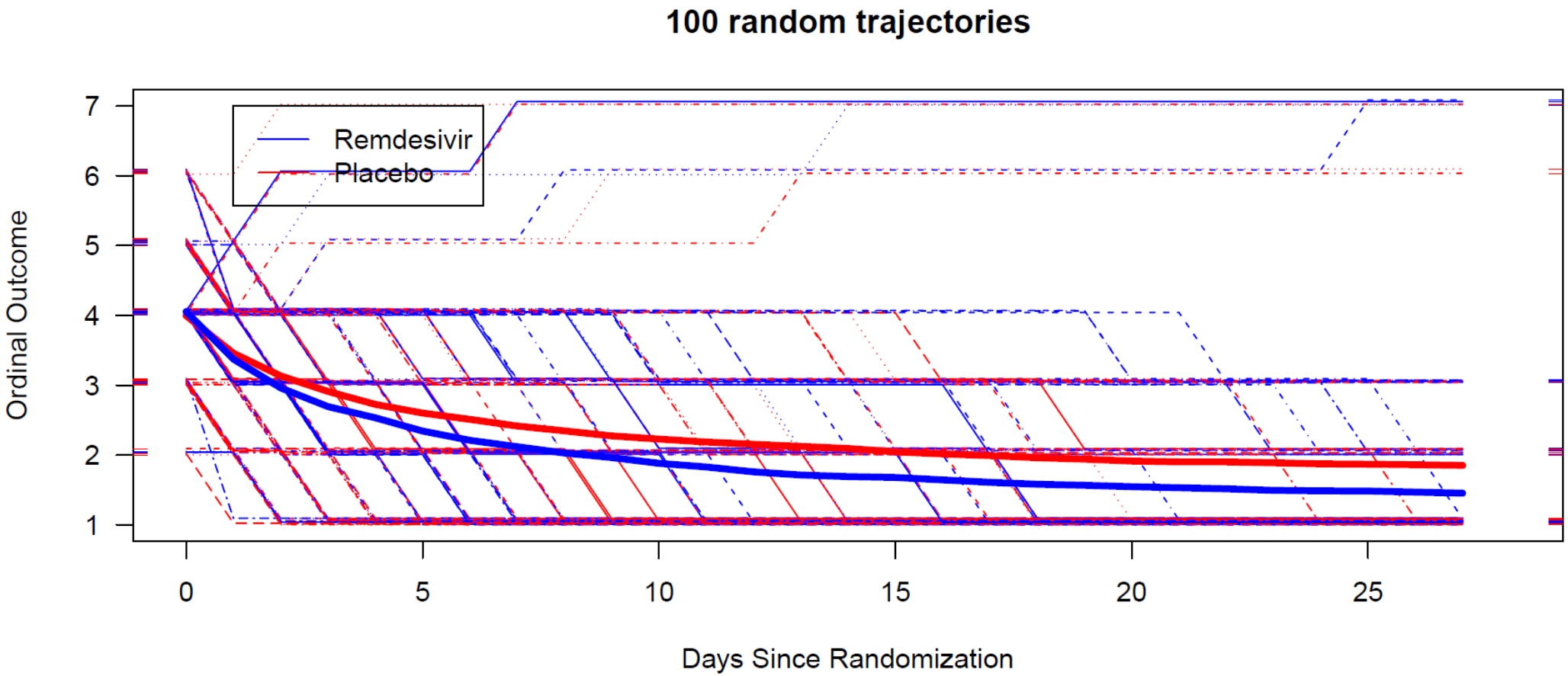
P(Symptoms day 3) = P(I=4 | Infected on Day -1) P(Infected on Day 0) + P(I=3 | Infected on Day 0) P(Infected on Day 0)
= {Θ_4 (1/4) + Θ_3 (1/4)}/C

Treatment: ACTT-1



- Double blind, adaptive, randomized trial of remdesivir vs placebo in mild-severe COVID-19 disease
- Measure ordinal scale every day. *Feels, functions, survives, … & logistics*
  - 8 Death;
  - 7 Hospitalized, on invasive mechanical ventilation or ECMO;
  - 6 Hospitalized, on non-invasive ventilation or high flow oxygen devices;
  - 5 Hospitalized, requiring supplemental oxygen;
  - 4 Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care
  - 3 Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care;
  - 2 Not hospitalized, limitation on activities and/or requiring home oxygen;
  - 1 Not hospitalized, no limitations on activities.
- Primary endpoint ordinal outcome at day 14, . . . But
  - How firm are the categories?
  - What if treatment effects show up later.
  - Blinded adaptation after pilot of 100 doesn't help much

Simulate trajectories, determine power



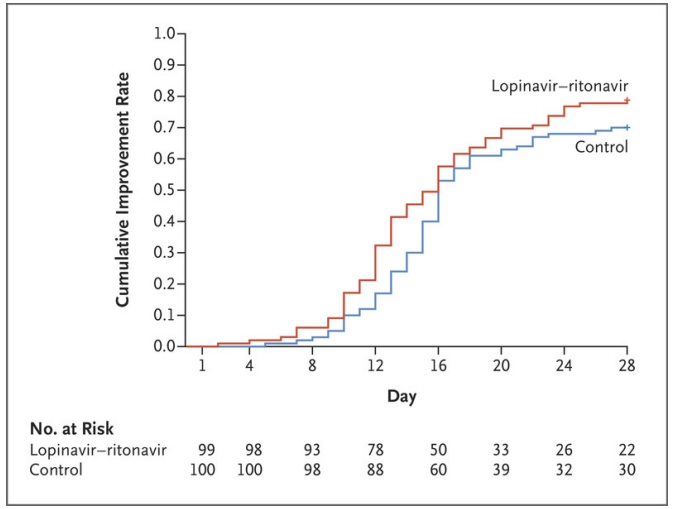
Test	P-Odds Day 1	P-Odds Day 7	P-Odds Day 14	P-Odds Day 28	Mean Score	Cox on 2 point	Cox on Recovery	Cox on Death	28 Day Mortality
Simple	.046	.755	.851	**.877**	.800	.808	.818	.626	.579
Adjusted					**.917**	.834	**.909**		

Power:
Proportion of times we conclude Remdesivir works for different tests

Endpoint: Time to Recovery

- How to treat deaths? People who die can never recover. Set their recovery times to infinity.
- Use log-rank test with time to recovery over day [0,28]
- Kaplan-Meier curve estimates the *cumulative incidence* of recoveries.
- Corresponds to Fine-Grey method for competing risks
- Designed to achieve 400 recoveries

Cao 2020 study of Kaletra



ACTT-1

- Study accrued extremely rapidly as epidemic exploded
  - Required quick flexible thinking/action
- First interim look = final look had more than 400 recoveries
- Study well powered and well run
  - 31% faster recovery p-value = 0.001
  - Median recovery 11 days Remdesivir vs 15 days Placebo
  - Mortality 8% Remdesivir 11% Placebo
- ACTT --- a powerful collaboration poised to keep getting answers
  - ACTT-2 being finalized given ACTT-1 results

Prevention: Planning for Vaccines

- Many vaccine candidates to be evaluated
- Possible Endpoints
  - Infection - PCR+ for virus
  - Disease - PCR+ for virus & symptomatic disease
- Which will be sensitive to vaccine effects? Help patient health?
- What if major effect of vaccine is to lessen disease severity?

Outcome	Placebo	Vaccine
Infection	1.0%	1.5%
Mild Disease	0.6%	0.4%
Hospitalized	0.3%	0.1%
Death	0.1%	0.0%

Vaccine "lift"

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Potential Analyses

- Time to disease
  - Use proportional hazards model
  - % Reduction in the instantaneous of probability of disease
- Time to weighted disease: mild=1, hosp=2, death=3
  - Proportional means model
  - % Reduction in the mean severity of disease
- Simulations being conducted to inform choice
  - Usual Wilcoxon 66% power
  - Proportional Hazards 81% power
  - Proportional Means 93% power

Outcome	Placebo	Vaccine
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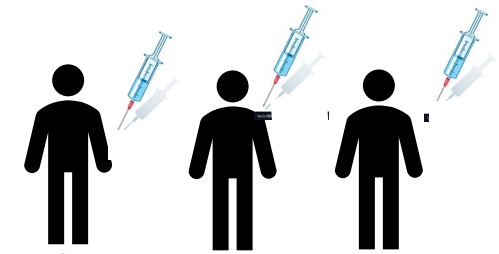
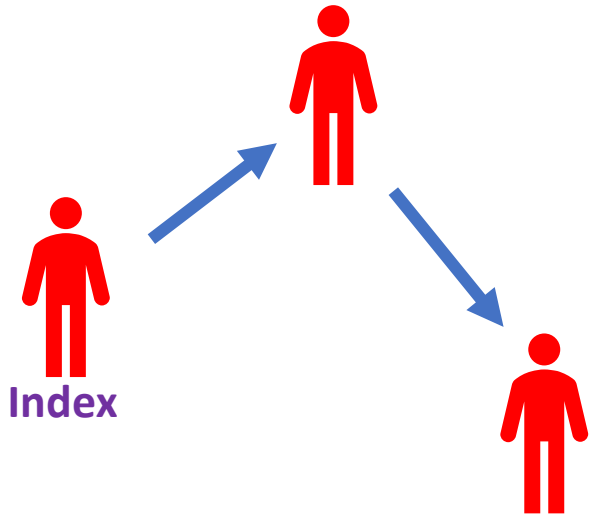
Prevention: Antibodies

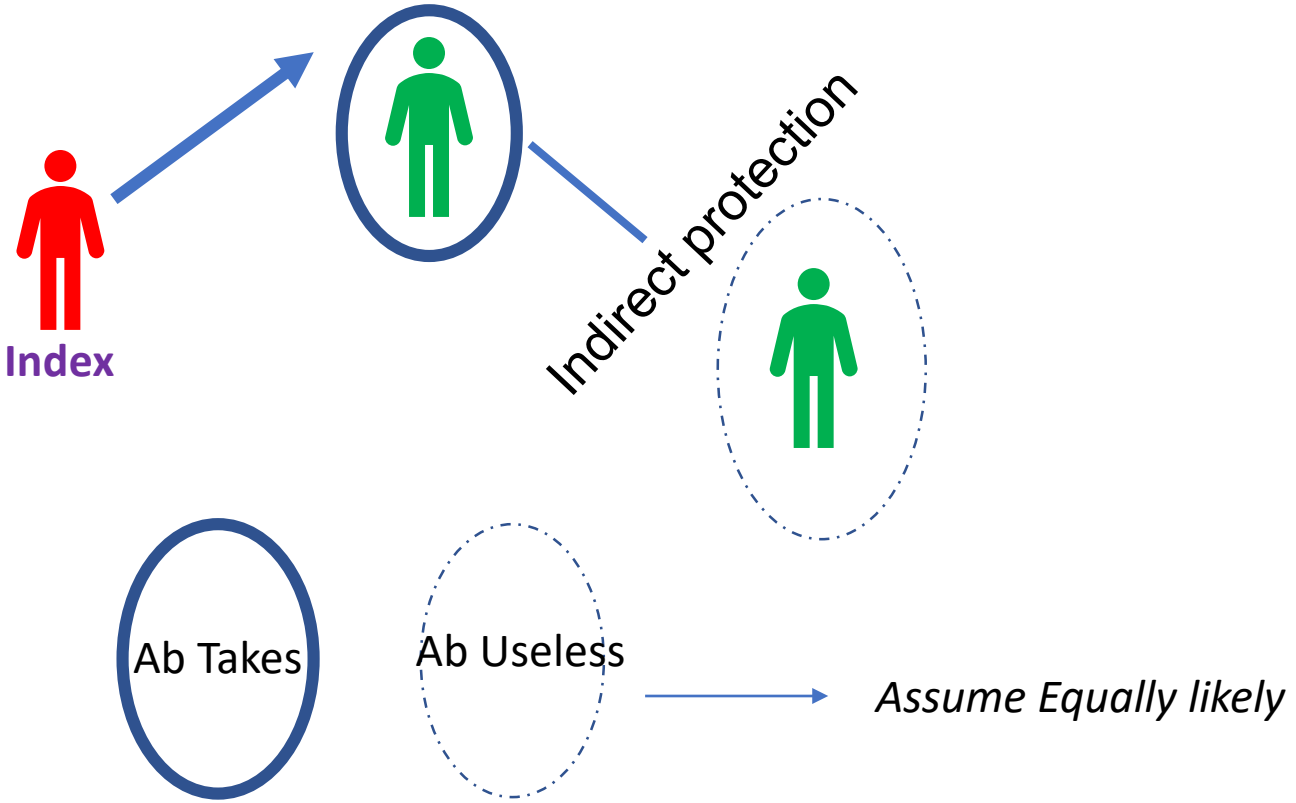
- Injected SARS-CoV2 antibodies might prevent infection
- Identify **someone** with COVID-19
- Enroll them and their family members
- Randomize the *entire family* to
  - Anti-CoV2 antibodies
  - Placebo
- Treatment trial for index case
- Prevention trial for family members
  - Abs reduce individual risk AND cuts down on the within family attack rate



Placebo Family



Counterfactual Antibody Family



Randomize families: 75% of the family members are protected
Randomize individuals: 50% of the family members are protected.

Effective family-ring interventions will help to control the virus

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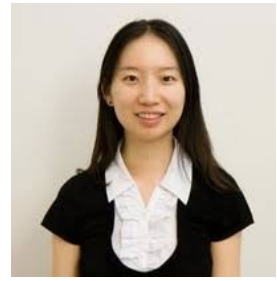
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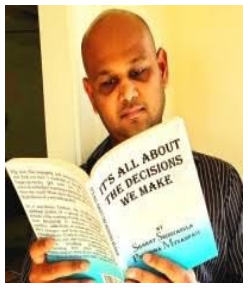

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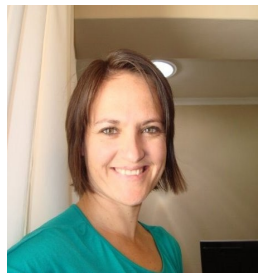
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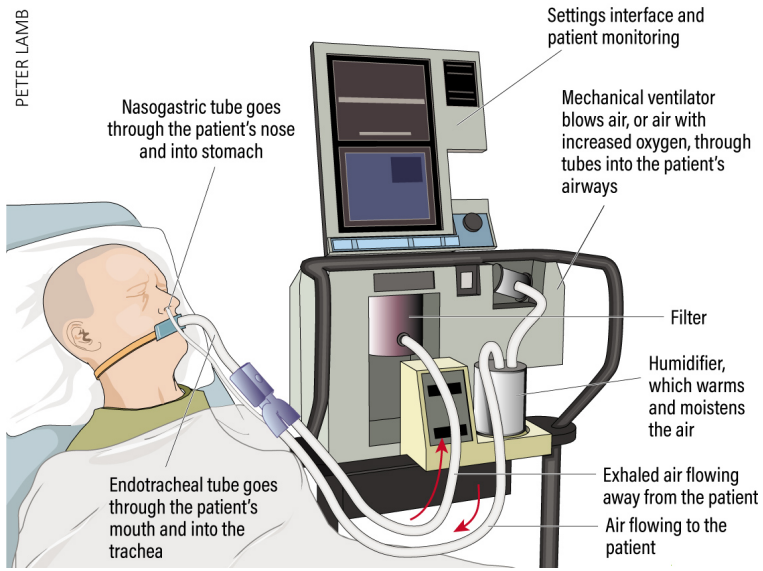
Thanks

- NIAID BRB
- NIH Statisticians
- Emmes Corporation
- Fred Hutch Statisticians

Treatment & Prevention

- Plasma from COVID-19 survivors is rich in SARS-CoV2 antibodies
- Extract it, check it, pool it, test it in clinical trials
- Huge logistical issues with tracking, cataloging, verifying etc.
- BRB-CTRS is essential in ensuring that survivor's donated antibodies can be rigorously evaluation for treatment and prevention

Figure I. Mechanical ventilator for positive pressure ventilation



Invasive Mechanical Ventilation
Intubated & Sedated

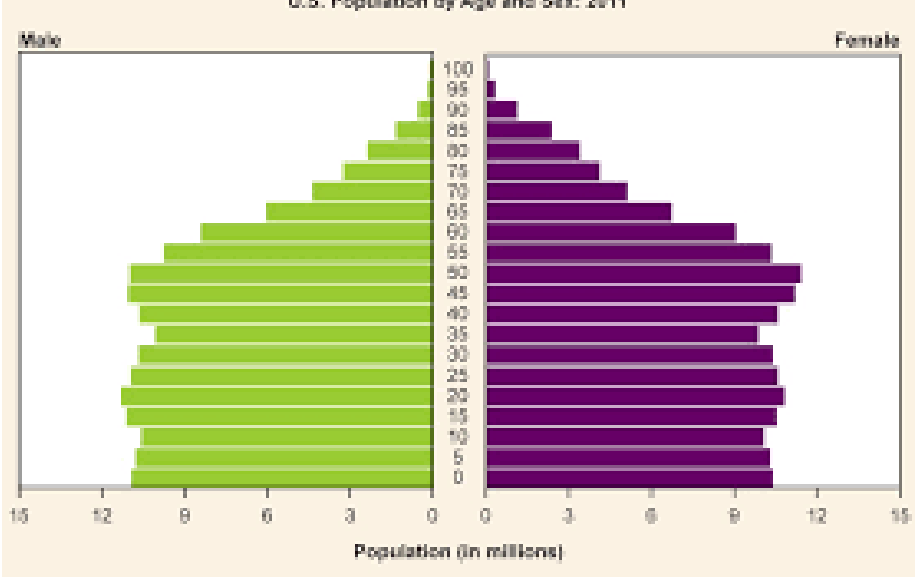
High Flow Oxygen

Low flow oxygen

Describe: Sero-prevalence

- Ideally, do a random sample of the US population
  - That would take a while, especially for us
- Encourage people to volunteer throughout the country
  - d
- Fix up this convenience sample so it represents the US population of sero-prevalence volunteers
  - Can’t really make it random

Sero-prevalence fixup



10 Male 30-40 y.o. donors in Elgin
3 seropositive

$$\text{Estimate} = \frac{3/10 \times w_{\_Elgin} + \ldots}{w_{\_Elgin} + \ldots}$$

$w_{\_Elgin} = 1/28$

Generalization

- Can correct for geographical location, age, gender, etc. Estimate of seroprevalence in Illinois

$$\frac{\sum_{i\ in\ Illinois}\ w_i\ Y_i}{\sum_{i\ in\ Illinois}\ w_i}$$

$w_i = \Pr(\text{ person } i\ \ would\ be\ \ selected\ in\ a\ random\ sample)$

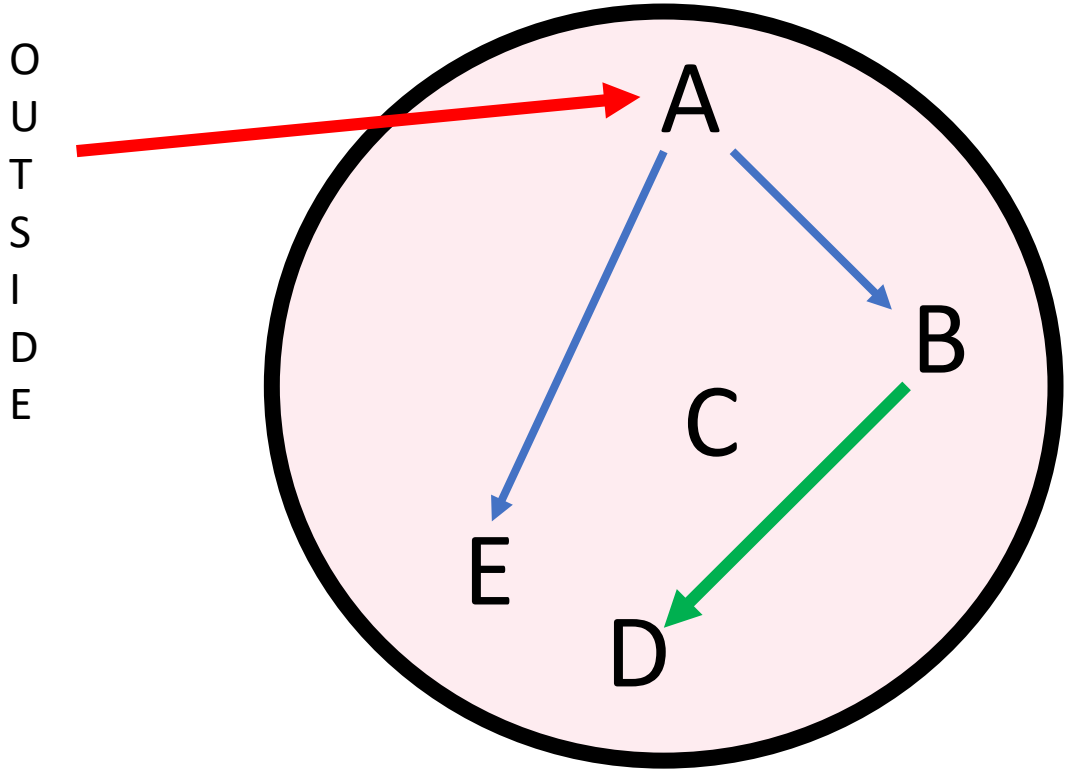
Y_i = 1 if person is is seropositive

Transmission

- NIH employees are getting COVID-19. Designed a protocol
- Identify contacts and family members for onward transmission.

Cluster	Members	Times of Detection	Covariates
1	A, B, C, D, E	0, 3, 7, --, 2, 4	X_A X_B X_C X_D X_E
2	A, B	0, ---	X_A X_B
3	A, B, C	0, 4, ---	X_A X_B X_C

Transmission Sequence Known

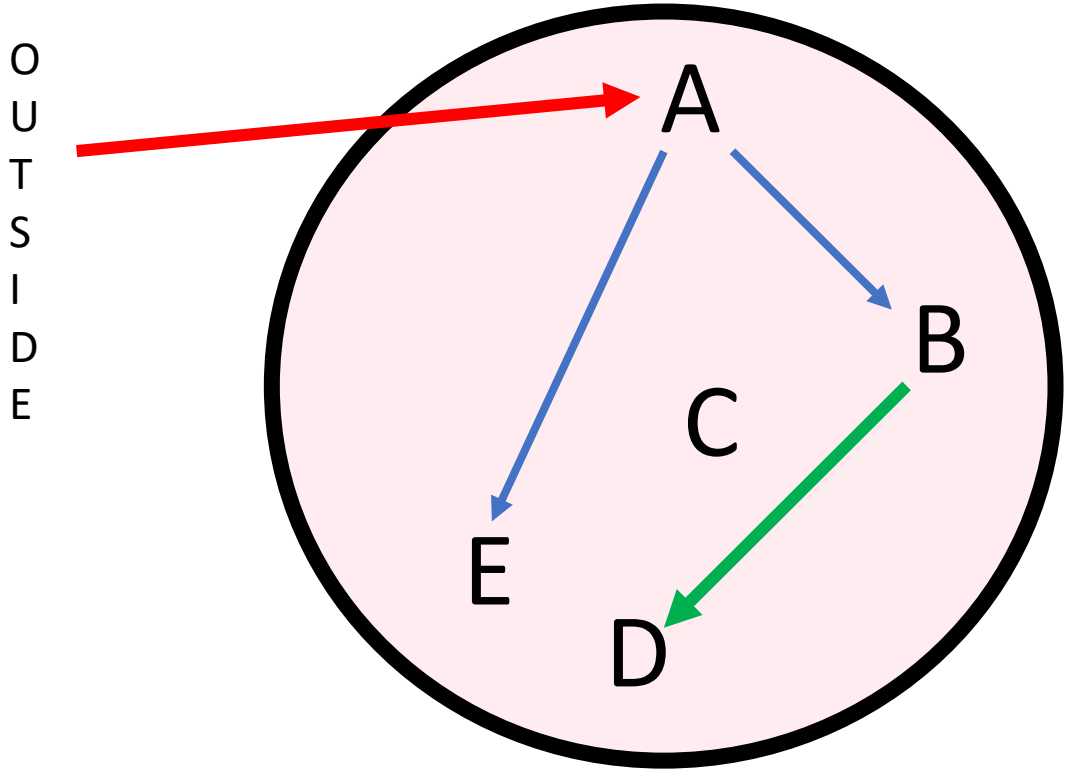


Logit

- Each person A, . . . , E flips a coin to see if they're infected
  - logit{P(Out->A)} = $\boldsymbol{\alpha}_0$+ $\boldsymbol{\alpha}_1$ $\mathbb{I}$(A works outside)

- Say A and B are infected from outside. A and B draw *avoidance scores* for everyone else.
  - If *S*(AC) < 1 then A infects C
  - *S*(AC) ~ Exponential{ exp($\boldsymbol{\beta}_0$ + $\boldsymbol{\beta}_1\mathbb{I}$(A,C share room) }
- Repeat with the newly infected.

Transmission Sequence Known



Outside: P(Out->A) (1-P(Out->B)) (1-P(Out->C)) (1-P(Out->D)) (1-P(Out->E))

1 – P(no one is infected)

Likelihood equals Product of :

Inside Gen 1: P(*S*(AB)<1) P(*S*(AE)<1) P(*S*(AC)>1) P(*S*(AD)>1)

Inside Gen 2: P(*S*(BD)<1 & *S*(BD) < *S*(ED)) P(*S*(BC)>1) P(*S*(EC)>1)

But we don’t know the sequence

- Missing data Likelihood contribution sums over possibilities
  - Suppose A,B infected, C not. Three possibilities
    - Out-> A,B {2}
    - Out-> A, A->B {1,1}
    - Out-> B, B->A {1,1}
- With bigger clusters # of possibilities explodes. Cluster of size 9 has many *partitions*
  - {9}
  - {8,1}, {7,2}, …. {1,8}
  - {1,1,7}, {1,2,6}, …. {7,1,1}
  - {1,1,1,6}, . . .
  - . . .

Evaluate

Agree Run 1 vs Run 2	Run 1 Individual	Run 2 Individual	Pool	Depooled	Agree Run 2 vs Pool
Yes	0 0 0 0 0	0 0 0 0 0	0		Yes
Yes	0 0 0 0 0	0 0 0 0 0	0		Yes
No	1 0 0 0 0	0 0 0 0 0	0		Yes
Yes	1 0 0 0 0	1 0 0 0 0	0		No
Yes	1 0 0 0 0	1 0 0 0 0	1	1 0 0 0 0	Yes
Yes	0 0 0 0 0	0 0 0 0 0	0		Yes

5/6 Pooling and re-running have similar reproducibility