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

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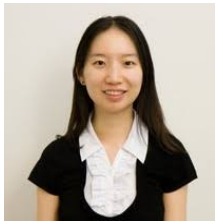
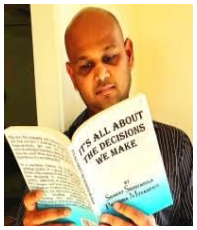

Jing Wang



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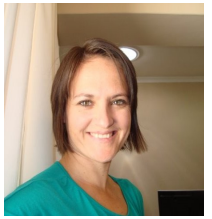
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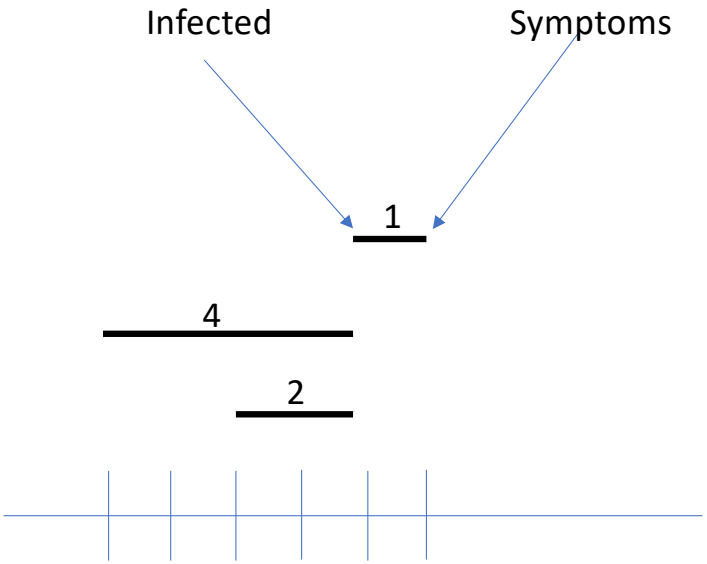
Topics

- Describe
  - Time from infection to symptoms (incubation)
  - Exploit a natural experiment
- Treatment
  - Adaptive Treatment Trial
  - Incredible pace, intense scrutiny
- Vaccines
  - Endpoint selection
  - Assessing disease severity --- only seen in the infecteds
  - Antibodies and disease acquisition/severity

Describe: Incubation Distribution

True Incubation Distribution

I	P(I)
1	Θ_1
2	Θ_2
3	Θ_3
4	Θ_4



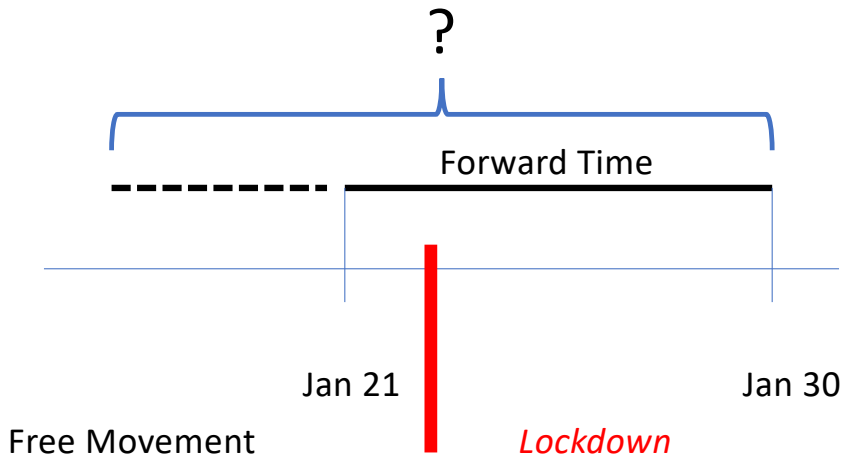
$P(I = 2) = \Theta_2$ = #(I =2) / Total = 1/3

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

A natural experiment

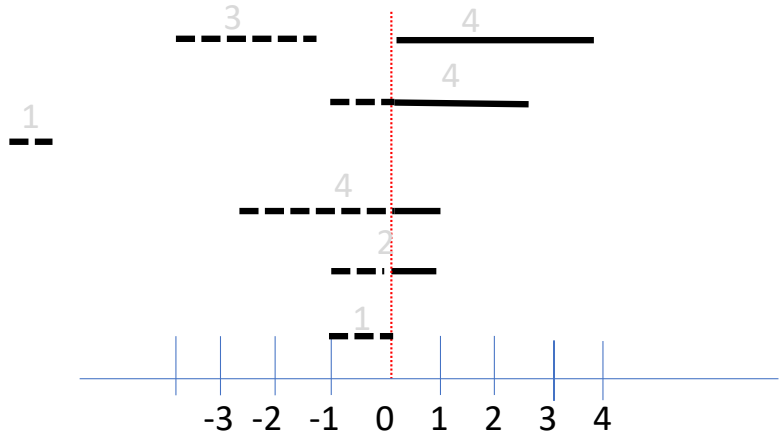
Jing Qin

- 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 longer than 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) $\propto$ P(I=4 | Infected on Day 0) P(Infected on Day 0)
$\propto$ Θ_4 (1/4)

P(Symptoms day 3) $\propto$ P(I=4 | Infected on Day -1) P(Infected on Day 0) + P(I=3 | Infected on Day 0) P(Infected on Day 0)
$\propto$ Θ_4 (1/4) + Θ_3 (1/4)

Weibull model for incubation distribution

Percentile	Steady State	20% infected at departure	100% infected at departure
50%	8.1 days	7.0 days	5.0 days
90%	14.7 days	13.3 days	11.0 days

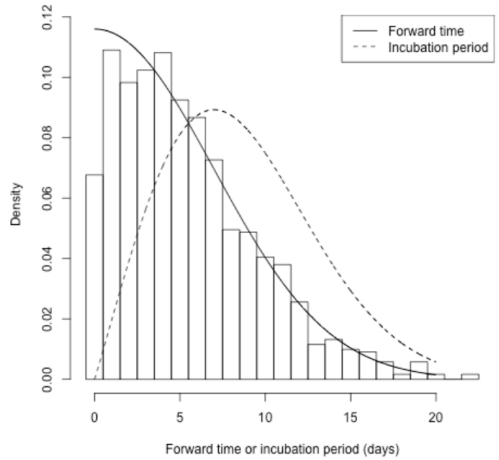
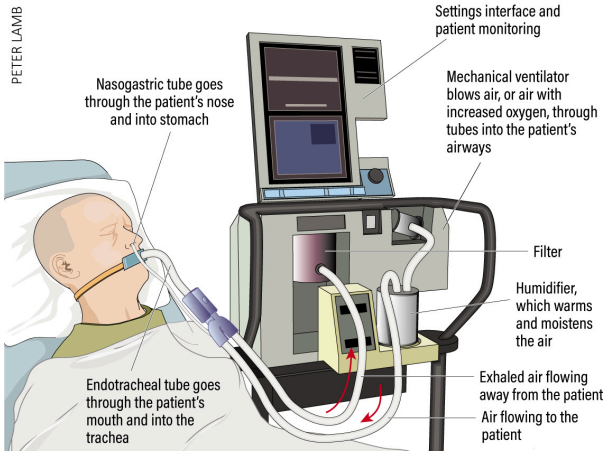


Figure 2. Histogram and estimated probability density functions for the time from Wuhan departure to symptoms onset, i.e.,

Incubation period longer than 2 weeks for 5% - 10% of the cases

Most studies estimate P(I > 2weeks) quite small

Figure I. Mechanical ventilator for positive pressure ventilation



Invasive Mechanical Ventilation
Intubated & Sedated

High Flow Oxygen

Low flow oxygen

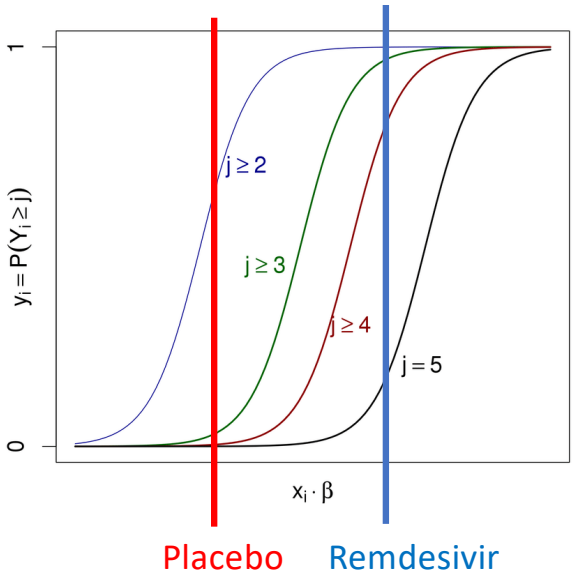
Treatment: ACTT-1



- 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

Proportional Odds Model

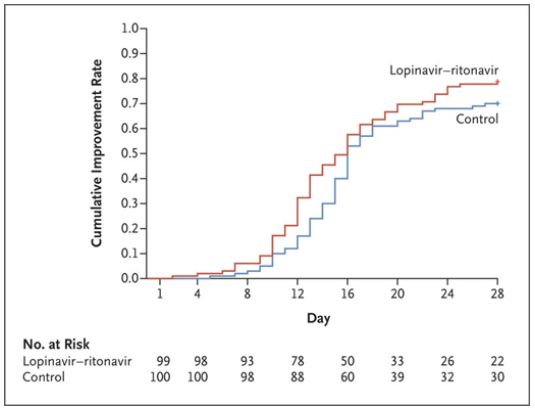
- Logit{ $P(Y \leq j)$ } = α_j - Z β
  - Z = I(treatment)
- Can be derived by assuming a latent U
  - U = Z β + e
  - e ~ standard Logistic
  - we see Y = interval censored U
- Can estimate by maximum likelihood and test H_0: β =0
- Asymptotically very similar to doing a Wilcoxon test
- Hard for me to explain to clinicians



Think and Act

- Hard to get the day right for ordinal score analysis
- Use average ordinal score (OS) over follow-up?
  - Hard to interpret.
- Three endpoints Day 14 OS, Day 21 OS, Day 28 OS
  - Different days for different baseline strata?
  - Little too awkward.
- Mortality
  - Much bigger study
- Time to recovery
  - Avoids timing issue, meaningful

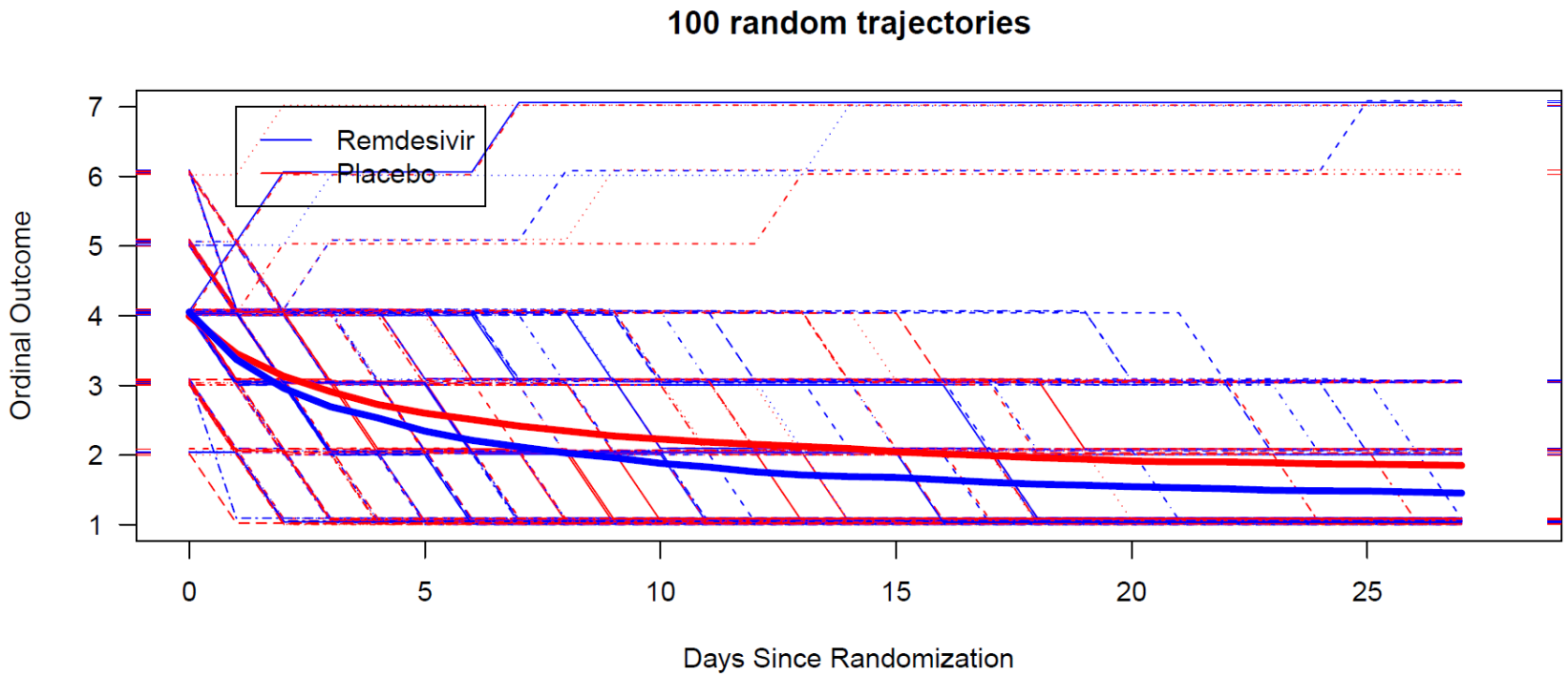
Cao 2020 study of Kaletra



Simulations

- Draw a 'line of destiny' to define score over day 0,28
  - $U_{id} = B0 + B1\ log(d) + B2\ Z\ log(d) + b_{0i} + b_{1i} log(d)$
  - $b_{0i} \sim N(0, 1.5^2)$
  - $b_{1i} \sim I \times N(4, .3^2) + (1-I) \times N(-7, s^2)$ $I \sim Be(p)$
  - $Z \sim$ Treatment indicator
- Integer part of U_{id} is ordinal score for day d.
- Fun Fact:
  - Can transform so every day is [U]|Z follows proportional odds model
  - Transform Y from normal to uniform to logistic, each day is a shift of size B2

Simulate trajectories, determine power



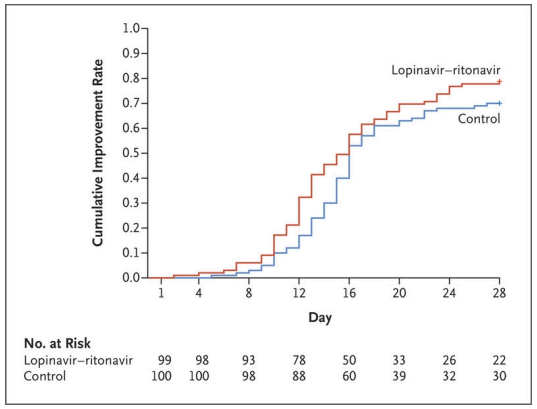
Test	P-Odds Day 1	P-Odds Day 7	P-Odds Day 14	P-Odds Day 28	Mean Score	Cox on 2 point	Cox on Recovery	Cox on Death	28 Day Mortality
Simple	.046	.755	.851	**.877**	.800	.808	.818	.626	.579
Adjusted					**.917**	.834	**.909**		

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 Cox PH 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
  - With no administrative censoring.
- Designed to achieve 400 recoveries

Cao 2020 study of Kaletra



Fine-Grey with administrative censoring

- Fine-Grey PH removes the deaths at their censoring time.
  - Joe dies on day 3, but would've been censored at day 14. Censor at day 14.
- Cox PH keeps deaths in risk set throughout follow-up

- Fine-Grey estimates exp(β) with complete follow-up or administrative censoring
- Cox PH estimates exp(β) with complete follow-up

- Simulations rho=0.99 FG-PH = 1.294 Cox-PH = 1.287

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 11.6% Placebo

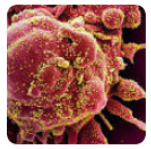
"Although a 31% improvement doesn't seem like a knockout 100%, it is a very important proof of concept," Fauci said. "Because what it has proven is that a drug can block this virus."

pharmaceutical-technology.com

Gilead secures FDA's EUA for remdesivir to treat Covid-19

Credit: NIAID. Gilead Sciences has secured emergency use authorisation (EUA) from the US Food and Drug Administration (FDA) for remdesivir ...

8 hours ago



Intense interest

The Washington Post
Democracy Dies in Darkness

"NIAID statisticians performed modeling of what happens if the right day is not picked for assessment, which revealed that meaningful treatment effects could be missed with that primary endpoint," NIAID said. "Time to recovery avoids this issue, and the change in primary endpoint seemed appropriate given the evolving clinical data."

Government researchers who decided to make the switch in outcome measure did not have access to clinical data, NIAID added.

STAT

BIOTECH

Were researchers wrong to move the goalposts on remdesivir? In the end, it may not have mattered

By MATTHEW HERPER @matthewherper / MAY 5, 2020

EXCLUSIVE

Inside the NIH's controversial decision to stop its big remdesivir study

By MATTHEW HERPER @matthewherper / MAY 11, 2020

The Washington Post
Democracy Dies in Darkness

Business

Government researchers changed metric to measure coronavirus drug remdesivir during clinical trial

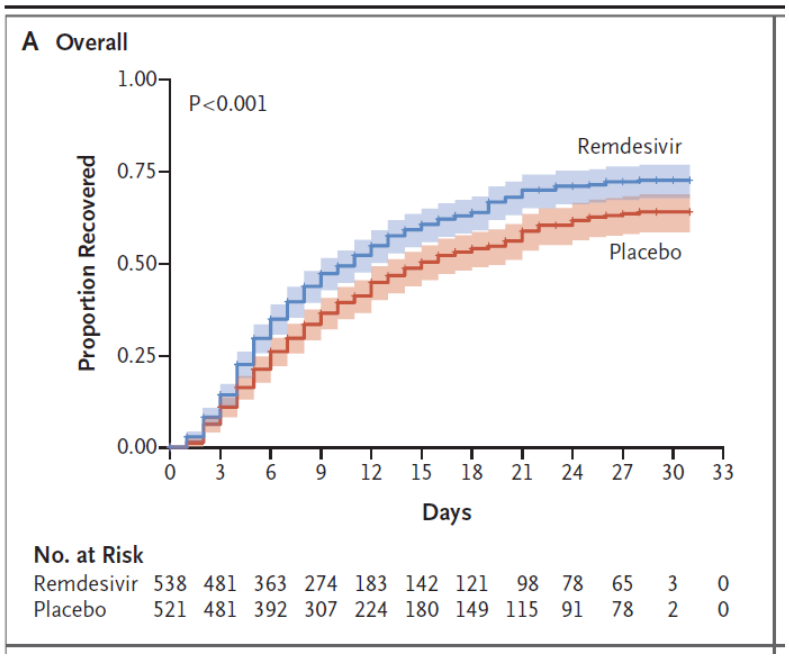
Death rate was eliminated as a primary outcome measure, replaced with the time it took patients to recover.

The NEW ENGLAND JOURNAL of MEDICINE

Remdesivir for the Treatment of Covid-19 — Preliminary Report

John H. Beigel, M.D., Kay M. Tomashek, M.D., M.P.H., Lori E. Dodd, Ph.D., Aneesh K. Mehta, M.D., Barry S. Zingman, M.D., Andre C. Kalil, M.D., M.P.H., Elizabeth Hohmann, M.D., Helen Y. Chu, M.D., M.P.H., Annie Luetkemeyer, M.D., Susan Kline, M.D., M.P.H., Diego Lopez de Castilla, M.D., M.P.H., Robert W. Finberg, M.D., et al., for the ACTT-1 Study Group Members*

May 22, 2020
DOI: 10.1056/NEJMoa2007764



Concept development started Feb 6

106 days later:

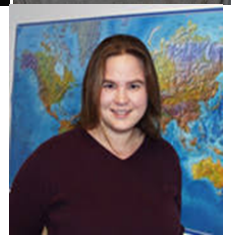
- 1063 participants enrolled
- 73 sites in 10 countries
- Over 16000 study visit/days
- One new drug
- One NEJM paper

ACTT-2

- Currently enrolling into a trial of
  - Baricitinib + remdeisivir
  - Placebo + remdesivir
- Hope for an answer in a couple months . . .

Prevention: Planning for Vaccines





- Possible Endpoints
  - Infection - PCR+ for virus or sero-conversion
  - 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"

Prevention: Planning for Vaccines

- Possible Endpoints
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Vaccine "lift"

Burden of Disease

- Disease yes/no doesn't care about severity.
- Severity of disease among those with disease is messy
  - Conditions on having disease

Outcome	Score	Placebo Overall At 2 years	Placebo Diseased	Vaccine Overall At 2 years	Vaccine Diseased
No disease	0	95.0%	---	98.0%	---
Disease	1	4.0%	80%	1.6%	80%
Hospitalized	2	0.8%	16%	0.3%	15%
Dead	3	0.2%	**4%**	0.1%	**5%**

- ITT type measures appealing
  - Difference in mean score
  - Or . . . . ratio of mean scores?

Batter-up

- In baseball a common metric is the batting average
  - Batting Average = # hits/# at bats
- Another metric is slugging percentage
  - Slugging % = # bases/# at bats
- Want to compare teams by slugging %
  - Take difference or ratio
- For ratio of slugging %s don't need at bats!
  - $\frac{\text{\# bases Pilots}}{\text{\#at bats Pilots}} / \frac{\text{\# bases Sox}}{\text{\#at bats Sox}} \sim \frac{\text{\# bases Pilots}}{\text{\# bases Sox}}$
- at bats = SARS-CoV-2 exposures

Burden of Disease

- *Per-exposure distribution*

Outcome	X	Per-exposure distribution	Distribution Given Diseased
No disease	0	Θ_0	---
Disease	1	Θ_1	$\Theta_1/(1-\Theta_0)$
Hospitalized	2	Θ_2	$\Theta_2/(1-\Theta_0)$
Dead	3	Θ_3	$\Theta_3/(1-\Theta_0)$

- Mean Severity = E(X) = $E(X)\frac{P(X>0)}{P(X>0)} = \frac{E(X)}{P(X>0)}(1-\Theta_0)$

- Truncated mean x Disease Probability

Will Assume
$1-\Theta_0^{Vaccine} = \exp(\beta)(1-\Theta_0^{Placebo})$

Proportional Means Model – ITT analysis of BOD

- $\frac{E(X|Z=1)}{E(X|Z=0)} = \frac{P(X>0|Z=1)}{P(X>0|Z=0)} \; \frac{\frac{E(X|Z=1)}{P(X>0|Z=1)}}{\frac{E(X|Z=0)}{P(X>0|Z=0)}}$ = exp(β) $\frac{E(X|X>0,vaccine)}{E(X|X>0,placebo)}$

- Use Cox Regression to estimate exp(β)
- Use arithmetic to estimate mean severity among the diseased
- $VE_S = 1 - \frac{E(X|Z=1)}{E(X|Z=0)}$ = the proportion reduction in mean severity score

- Note: exposure *undefined* yet mean BOD ratio recovered

Ten Thousand Simulations

- Pure staggered entry trial—keep enrolling until approximately 100 cases
- Exponential failure times with VE on any disease = 45%
- Power for H_0: No effect of vaccine

Power

Test	Big Lift	Small Lift	All-or-None
Prop Hazard	0.808	0.808	0.808
Prop Mean	0.910	0.871	0.770
BOI mean diff	0.715	0.756	0.806

Disease Rates *among diseased*

Outcome	Placebo	Vaccine	Placebo	Vaccine	Placebo	Vaccine
Mild	80%	95%	80%	90%	80%	80%
Hospital	15%	5%	15%	7.5%	15%	15%
Death	5%	0%	5%	2.5%	5%	5%
	Big Lift		Small Lift		All-or-None	

Comments

- Can be estimated with weighted Cox regression
  - Count symptomatic infections once, hospitalized twice, death three times
- With ACTT-1 ordinal score, 1 vaccine death = 8 mild placebo cases
  - Very fragile!
- Prop Mean BOD more powerful than mean difference BOD why?
  - With scores of 0,1,2,3, can't really do a location shift…

- Mean difference BOD estimand depends on censoring dbn, attack rate

Immune Correlates of Enhancement

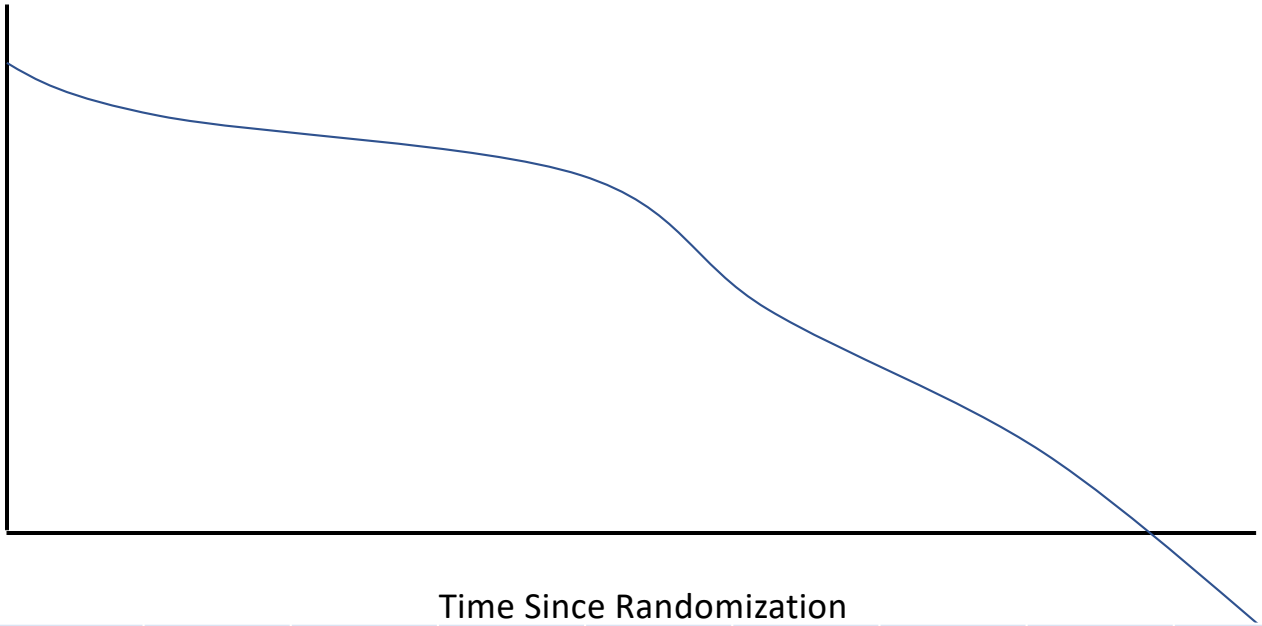
- Theoretical concern that vaccination might *enhance* disease
  - Might it coincide with waning immunity/ antibodies
- How to address?
- Monitor the V:P split in disease and severe disease cases
  - Stratified by age other factors
- Connection with waning antibodies difficult.
  - Poorer power for a subgroup
  - Know antibody trajectory in vaccinees, not placebos.

Ecological analysis

Vaccine Efficacy = 1- exp(β(t))

Ecological analysis

Vaccine Efficacy = 1- exp(β(t))



Time Since Randomization

Mean Ab	**8.7**	**7.3**	**6.8**	**5.3**	**4.7**	**3.1**	**2.1**	**1.0**	**0.3**

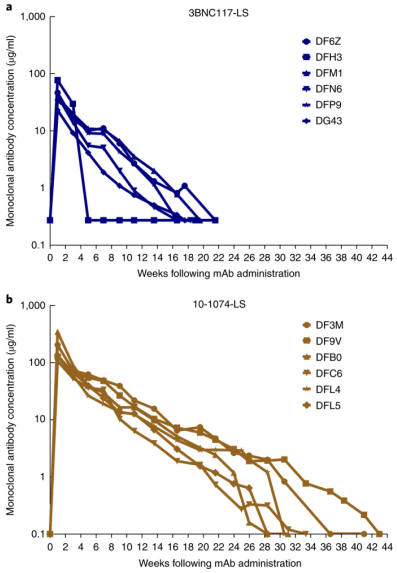
Experiment Ab Injection followed by
Weekly low-dose challenge
Some weeks Ab not measured

ARTICLES
https://doi.org/10.1038/s41591-018-0001-2
nature medicine
OPEN

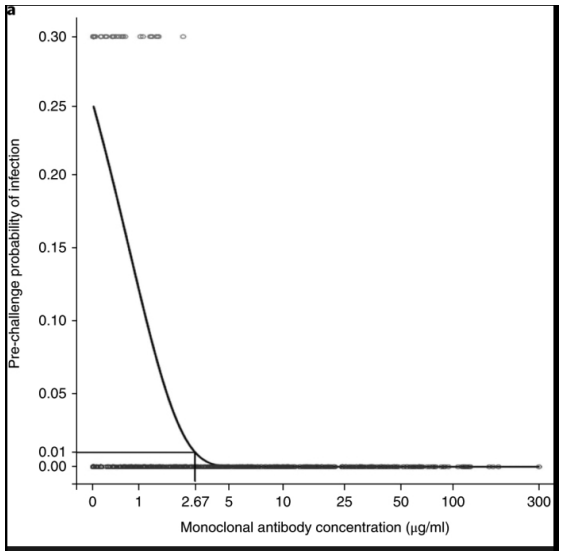
A single injection of crystallizable fragment domain-modified antibodies elicits durable protection from SHIV infection

Rajeev Gautam[1], Yoshiaki Nishimura[1], Natalie Gaughan[1], Anna Gazumyan[2], Till Schoofs[2], Alicia Buckler-White[1], Michael S. Seaman[3], Bruce J. Swihart[4], Dean A. Follmann[4], Michel C. Nussenzweig[2,5*] and Malcolm A. Martin[1*]

Random Effects Model to get Empirical Bayes $\hat{A}\ (t)$



Logistic regression of Infection on $\hat{A}\ (t)$

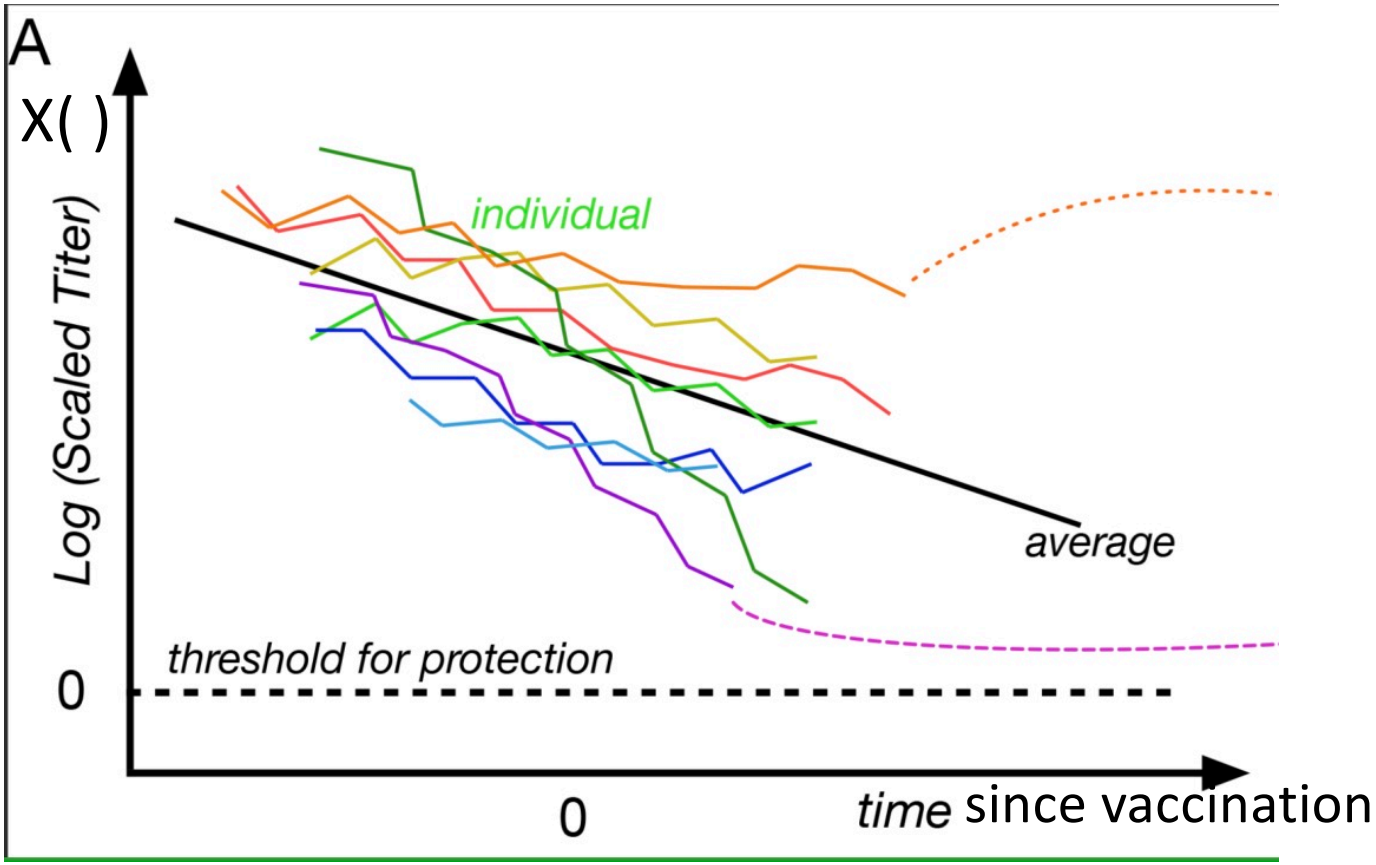


Challenge Study in NHP vs Phase III in human

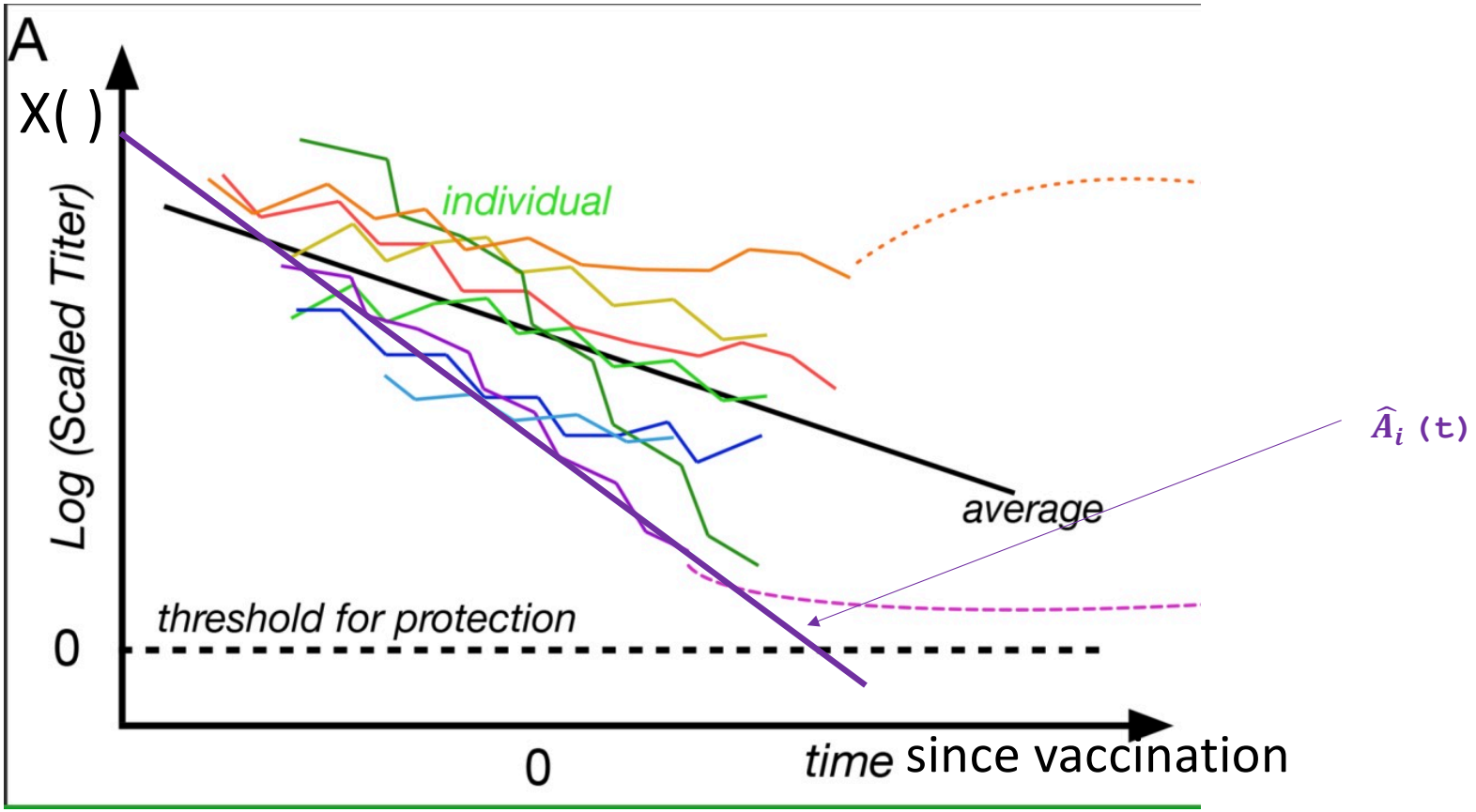
- In NHP Challenge Study
  - NHPs are homogenous
  - Injected antibody levels have similar curves
  - Weekly exposures with amount of virus
- In human Phase III trial
  - Humans are heterogeneous: age, risk of severe disease, response to vaccine
  - Vaccine induced antibodies variable in initial magnitude, decay
  - Exposures extremely variable by behavior, site, time, etc

  => Potential for confounding of vaccine induced Abs with risk in humans

Measured Antibodies Over Time



Predicted $\widehat{A}_i$ (t) levels over time



Apples to Apples

- Can build a random effects prediction model for antibody decay in vaccinees

$$A_i(t) = B_0 + B_1 t + b_{0i} + b_{1i} t + B_2 age_i + e_i(t)$$

- Use $\widehat{A}_i(t) = E\{A_i(t) = age_i, t, A_i(t_1), \ldots A_i(t_{(i)})\}$
  - Prediction only uses time and age…

- Fit Cox model with $\widehat{A}_i(t)$ a time-varying covariate

$$h(t) = h_0(t) \exp(Z \beta_1 + \widehat{A}_i(t) \beta_2 + Z \widehat{A}_i(t) \beta_3)$$

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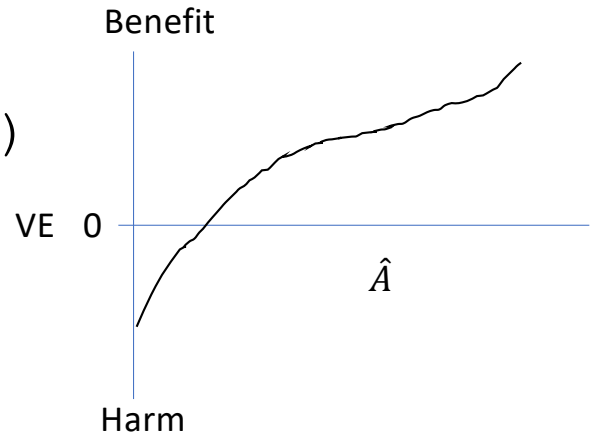

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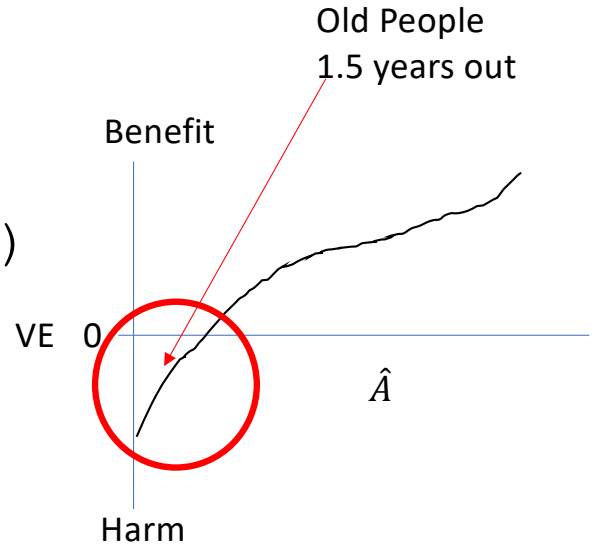
- Fit Cox model with $\widehat{A}_i(t)$ a time-varying covariate

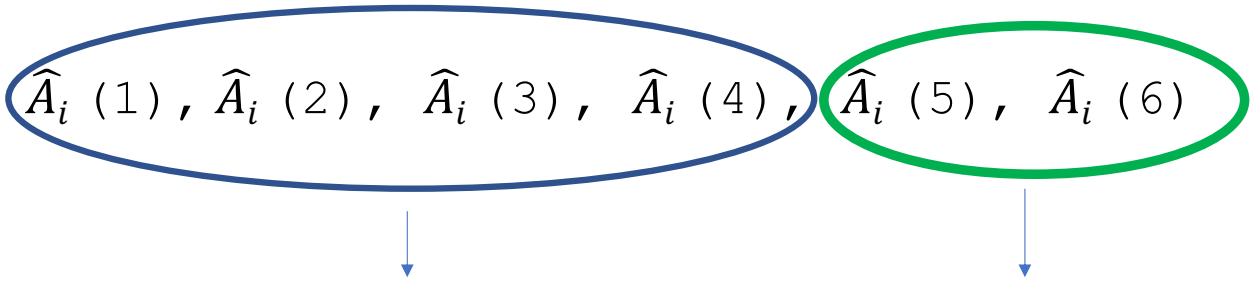
$$h(t) = h_0(t) \exp(Z \beta_1 + \widehat{A}_i(t) \beta_2 + Z \widehat{A}_i(t) \beta_3)$$



Communicate

- $h(t) = h_0(t) \exp(Z \beta_1 + \widehat{A}_i (t) \beta_2 + Z \widehat{A}_i (t) \beta_3)$?

- For each person, determine $\widehat{A}_i (t)$ for t = each month of follow-up
  - 6 months FU, make $\widehat{A}_i (1), \widehat{A}_i (2), \widehat{A}_i (3), \widehat{A}_i (4), \widehat{A}_i (5), \widehat{A}_i (6)$
- Put them into bins



Communicate Apples to Apples

Quartile	Average($\widehat{A}_i$ (t))	Typical Person	Placebo Attack rate	Vaccine Attack Rate	Vaccine Efficacy
1	1.2	Age=65 1.5 years FU	8.0	10.0	-25%
2	3.2	Age=40 1.0 years FU	7.1	6.9	3%
3	4.1	Age=38 0.5 years FU	12.1	7.4	39%
4	5.7	Age=23 0.2 years FU	8.4	3.4	59%

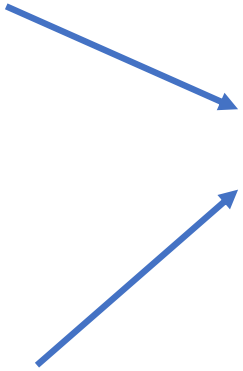
If antibodies wane, time since randomization might predict well

Better than ecological analysis

Communicate Apples to Oranges Analysis

Quartile $\widehat{A}_i$ (t))	Avg($\widehat{A}_i$ (t))	Typical Person	Placebo Attack rate
1	1.2	Age=65 1.5 years FU	8.0
2	3.2	Age=40 1.0 years FU	7.1
3	4.1	Age=38 0.5 years FU	12.1
4	5.7	Age=23 0.2 years FU	8.4

Quartile A_i(t)	Avg(A_i(t))	Typical Person	Vaccine Attack rate
1	0.2	Age=60 2.0 year FU	11.1
2	2.2	Age=37 1.1 years FU	6.9
3	7.1	Age =36 0.9 year FU	7.4
4	12.7	Age =18 0.1 years FU	1.0



Avg(A_i(t))	VE
0.2	-37.5%
2.2	2.8%
7.1	38.8%
12.7	88.0%

Meta-analysis of immune correlates

Vaccine #1

Benchmark Interval $A_i(t)$	VE
0.0-1.0	-37.5%
1.0-3.4	2.8%
3.4-7.1	38.8%
7.1-12.4	88.0%

Vaccine #2

Benchmark Interval $A_i(t)$	VE
0.0-1.0	0.0%
1.0-3.4	1.8%
3.4-7.1	48.0%
7.1-12.4	94.0%

Vaccine # 1 alone shows
Disease Enhancement for those
With poor antibodies

Antibody level of 7.1 protective
License new vaccines that achieve 7.1

Full Blown Principal Stratification

- Can also do a full blown principal stratification type analysis
- Model the hazard of disease

$$h(t) = h_0(t) \exp(Z \beta_1 + A_i(t) \beta_2 + Z A_i(t) \beta_3)$$

- Model the antibody decay
- Derive the proper likelihood
- Missing $A_i(t)$ integrated out in placebos, $A_i(t)$ used directly in vaccinees
- More efficient, but more demanding of correct specification than apples to apples

Communicate Full Blown Principal Stratification

Quartile	Avg ($A_i(t)$)	Model Based Placebo Attack rate	Model Based Vaccine Attack Rate	Vaccine Efficacy
1	0.2	8.0	10.0	-25%
2	2.2	7.1	6.9	3%
3	7.1	12.1	7.4	39%
4	12.7	8.4	3.4	59%

Can impose $\beta_2 = 0$

Placebo rates might still vary if $h_0(t)$ & $A_i(t)$ have similar shapes

Conclusions

- COVID-19 challenging for all of us
  - Incomplete knowledge of disease, intense scrutiny, incredible pace
- Treatment Trial
  - Pivoted to a more robust primary endpoint during trial
  - Rapid evaluation, decisions on principle/instinct
  - Intense interest
- Vaccine Trial
  - Different endpoints/methods of analysis evaluated
  - Proportional Means model gives nice ITT analysis of Burden of Disease
  - Disease enhancement especially re waning immunity is tricky

Thanks

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

Burden of Disease

- *Per-exposure distribution*

Outcome	X	Per-exposure distribution	Distribution Given Diseased
No disease	0	Θ_0	---
Disease	1	Θ_1	$\Theta_1/(1-\Theta_0)$
Hospitalized	2	Θ_2	$\Theta_2/(1-\Theta_0)$
Dead	3	Θ_3	$\Theta_3/(1-\Theta_0)$

- Thus $$\frac{E(Xv)}{E(Xp)} = \frac{\Theta_{1v}+\Theta_{2v}+\Theta_{3v}}{\Theta_{1P}+\Theta_{2P}+\Theta_{3P}} \frac{(1-\Theta_{0p})}{(1-\Theta_{0v})}$$

- Truncated mean x Disease Probability

Will Assume

$1-\Theta_0^{Vaccine} = \exp(\beta)\,(1-\Theta_0^{Placebo})$

Trial level causality of the hazard ratio

- Y(**0**) = # cases if all get placebo = 100
- Y(**1**) = # cases if all get vaccine = 20

Estimate hazard ratio VE as 1 - Y(**1**)/ Y(**0**) = .80[+]

We randomize and get randomization*

- Y*(**0**) = # cases with specific* half getting placebo = 54
- Y*(**1**) = # cases with remainder getting vaccine = 11

1- Y*(**1**)/ Y*(**0**) = 1 – 11/54 = .796

[+]Stuart Pocock's PH estimator. Also roughly the mle if we transform to exponential dbn i.e. PH model

Remdesivir for the Treatment of Covid-19 — Preliminary Report

J.H. Beigel, K.M. Tomashek, L.E. Dodd, A.K. Mehta, B.S. Zingman, A.C. Kalil, E. Hohmann, H.Y. Chu, A. Luetkemeyer, S. Kline, D. Lopez de Castilla, R.W. Finberg, K. Dierberg, V. Tapson, L. Hsieh, T.F. Patterson, R. Paredes, D.A. Sweeney, W.R. Short, G. Touloumi, D.C. Lye, N. Ohmagari, M. Oh, G.M. Ruiz-Palacios, T. Benfield, G. Fätkenheuer, M.G. Kortepeter, R.L. Atmar, C.B. Creech, J. Lundgren, A.G. Babiker, S. Pett, J.D. Neaton, T.H. Burgess, T. Bonnett, M. Green, M. Makowski, A. Osinusi, S. Nayak, and H.C. Lane, for the ACTT-1 Study Group Members*

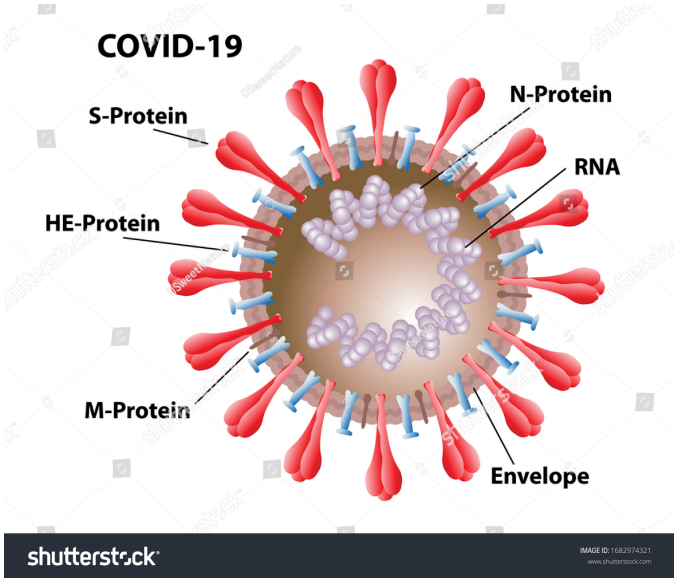
This article was published on May 22, 2020, at NEJM.org.

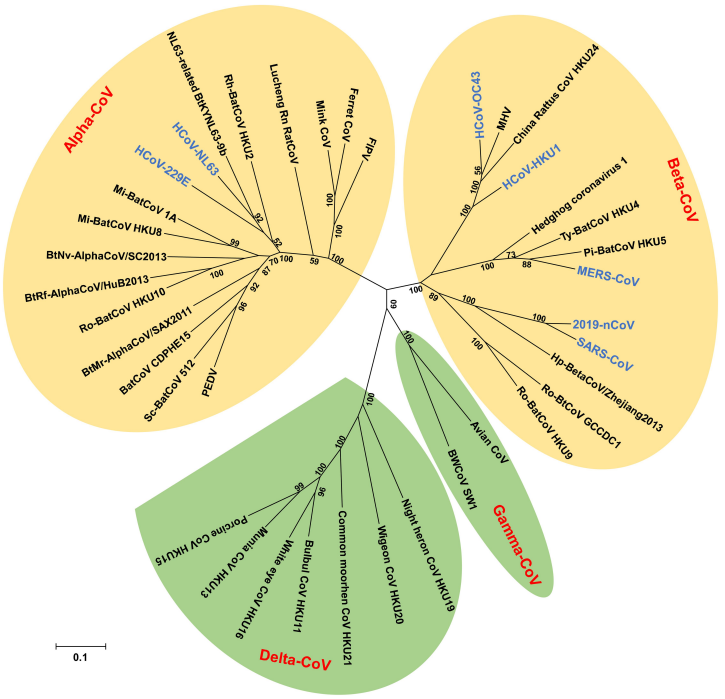
Endpoints for randomized controlled clinical trials for COVID-19 treatments

Lori E Dodd[1], Dean Follmann[1], Jing Wang[2] , Franz Koenig[3], France Mentre[4,5], Lisa L. Korn[6], Christian Schoergenhofer[7], Michael Proschan[1] , Sally Hunsberger[1] ,Yeming Wang[8,9], Bin Cao[8,9], Drifa Belhadi[4,5], Thomas Jaki[10,11] *under review Clinical Trials*

Estimation of incubation period distribution of COVID-19 using disease onset forward time: a novel cross-sectional and forward follow-up study Qin Jing, Chong You, Qiushi Lin, Taojun Hu, Shicheng Yu, Xiao-Hua Zhou
medRxiv 2020.03.06.20032417; doi: https://doi.org/10.1101/2020.03.06.20032417

Immune Correlates Analysis Using Vaccinees from Test Negative Designs
Dean A Follmann, Lori Dodd *under review Biostatistics*





Subunit Vaccines Against Emerging Pathogenic Human Coronaviruse: Frontiers in Microbiology 2020
Wang… Du

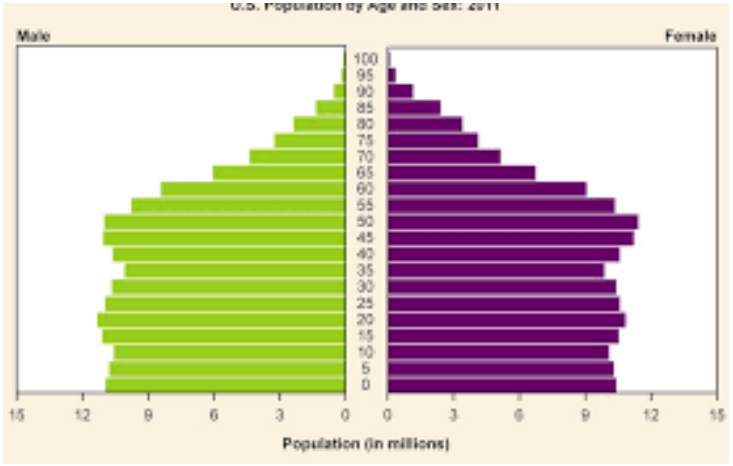
Treatment & Prevention

- 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

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

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

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

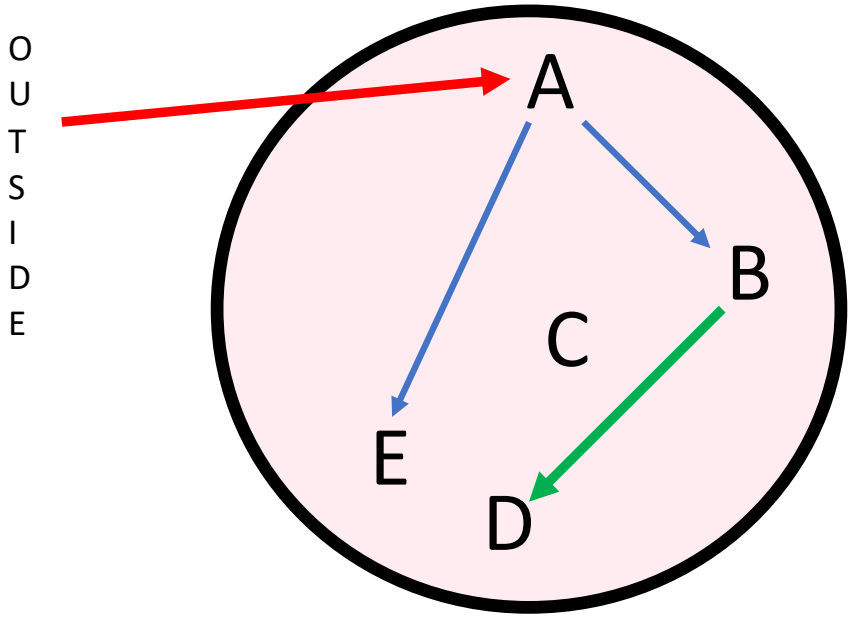
Y_i = 1 if person is is seropositive

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

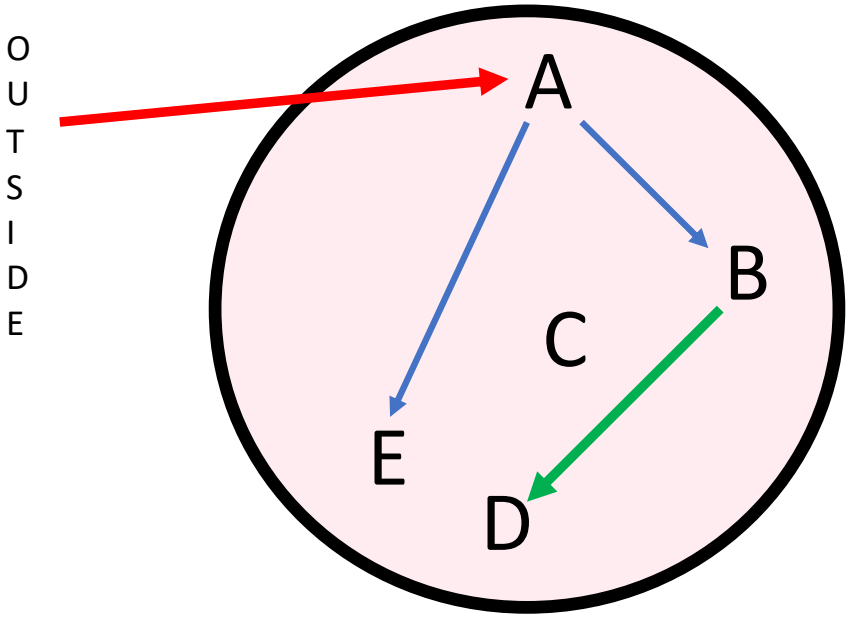


Logit

- Each person A, . . . , E flips a coin to see if they're infected
  - logit{P(Out->A)} = $\boldsymbol{\alpha}_0$+ $\boldsymbol{\alpha}_1$ 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($\boldsymbol{\beta}_0$ + $\boldsymbol{\beta}_1$I(A,C share room) }
- Repeat with the newly infected.

Transmission Sequence Known



Likelihood equals Product of :

Outside: $P(\text{Out}\to A)\,(1-P(\text{Out}\to B))\,(1-P(\text{Out}\to C))\,(1-P(\text{Out}\to D))\,(1-P(\text{Out}\to E))$ / $1 - P(\text{no one is infected})$

Inside Gen 1: $P(S(AB)<1)\;P(S(AE)<1)\quad P(S(AC)>1)\quad P(S(AD)>1)$

Inside Gen 2: $P(S(BD)<1 \;\&\; S(BD) < S(ED))\quad P(S(BC)>1)\quad P(S(EC)>1)$

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}, . . .
  - . . .

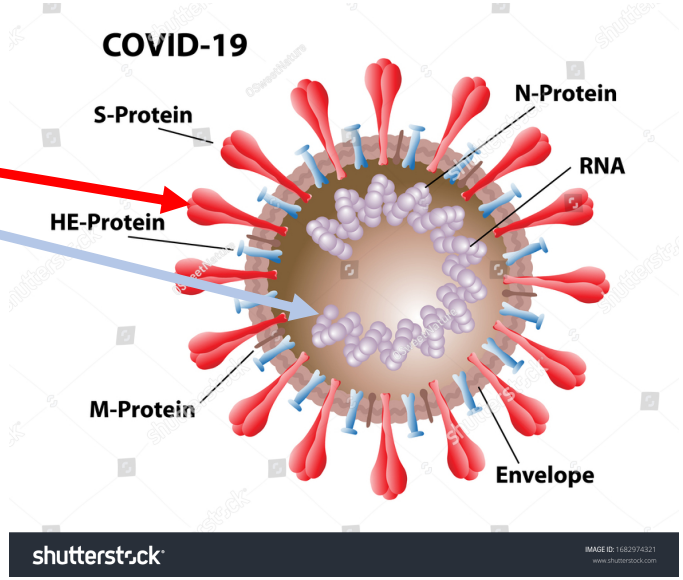
Evaluate

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

Vaccine Immunology Program

- Assay qualification of binding ELISA for different SARS-CoV-2 proteins
  - Spike, S1, RBD, NTD
- For SARS-CoV-2 vaccine, need to
  - Measure vaccine induced immune response
  - Measure natural infection immune response
- Assay needs to be reliable
  - Sensitive
  - Specific
  - Linear
  - Precise



Fine-Grey Proportional Subhazards

- Cox model assumes the hazards are proportional
  - $S_0(t) = \exp(-\int_0^t \lambda_0(s)ds\ )$
  - $S_1(t) = \exp(-\int_0^t \lambda_1(s)ds\ )$
  - Hey $\frac{\lambda_1(s)}{\lambda_0(s)}$ = exp(β)
- But not all recover
  - $S_0(t) = p_0 \exp(-\int_0^t \lambda_0(s)ds\ ) - p_0$ I(t=oo)
  - $S_1(t) = p_1 \exp(-\int_0^t \lambda_1(s)ds\ ) - p_1$ I(t=oo)
  - Hey $\frac{\log(p_1)\lambda_1(s)}{\log(p_0)\lambda_0(s)}$ = exp(β) <*not right. Something like this ?*>

p = Proportion recovered at day=28