Quantifying the breadth of vaccine response with antigenic distance

W. Zane Billings

Amanda Skarlupka, Ted Ross, Andreas Handel

Acknowledgements

- Ted Ross for sharing data
- CEIRR (CIDER), CIVIC (CIVR-HRP), and UGA Graduate School for funding
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- UGA Infectious Disease Interest Group
- Figures created with biorender.com
- R, RStudio, and Quarto development teams; countless package authors.

How do we compare universal vaccine candidates?

- **We need to somehow manage to measure individual responses to many strains.**

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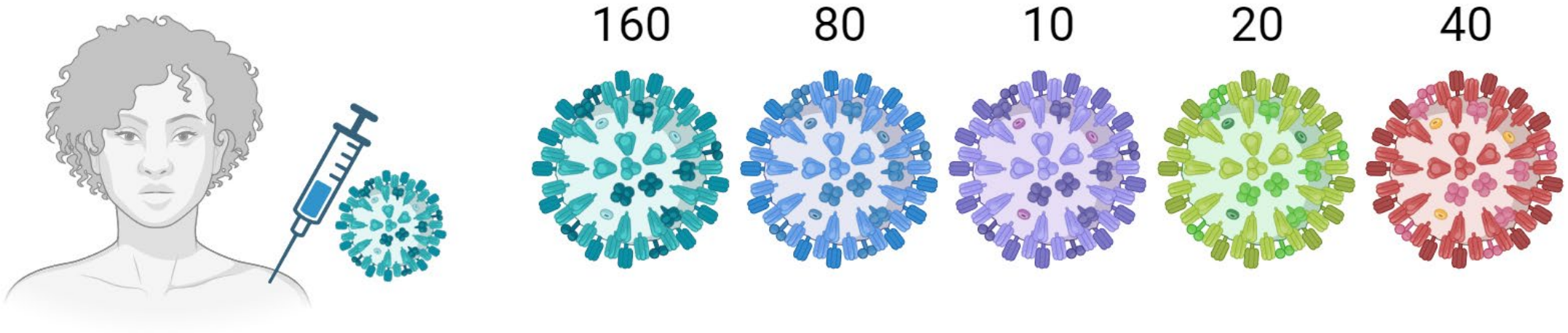
- We need to somehow manage to measure individual responses to many strains.
- Not feasible (or even possible) to do huge challenge studies.
- So we recruit a cohort and take a panel of immunological measurements (correlates of protection) from each individual.
- **For flu, most common measurement is HAI.**

What do we do with the titers we collect?



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3. **Overall strength:** can we combine magnitude and breadth into one measurement of vaccine “strength” or “goodness”?

Current methods

How do we measure the response?

- **Magnitude**: geometric mean titer of homologous responses.

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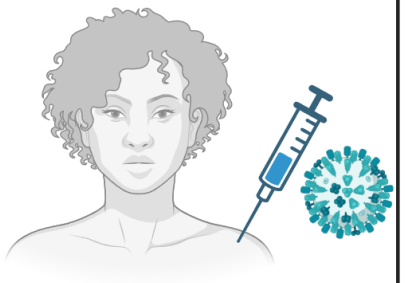
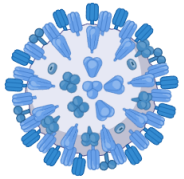
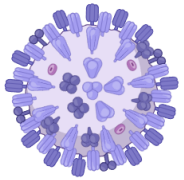
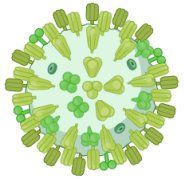
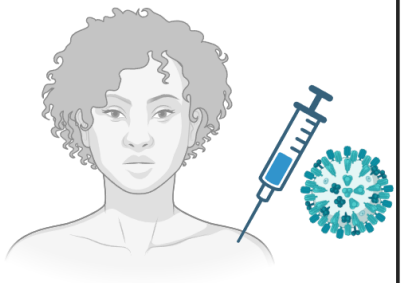
- Overall **strength**: GMT across all strains.

$$\exp\left(\frac{1}{n}\sum_{i=1}^{n}\sum_{j=0}^{k}\ln \text{titer}_{i,j}\right)$$

	Titer D0	Titer D28	Fold change	Seroprotection	Seroconversion
	10	160	16	✓	✓
	40	80	2	✓	✗
	10	10	1	✗	✗
	20	20	1	✗	✗
	10	40	4	✓	✓
Overall	15	40	2.6	60%	40%

	Titer D0	Titer D28	Fold change	Seroprotection	Seroconversion
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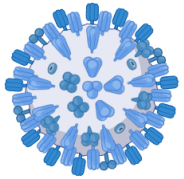
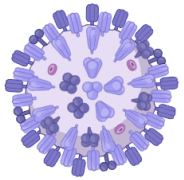
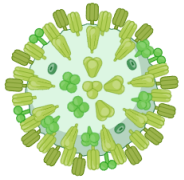
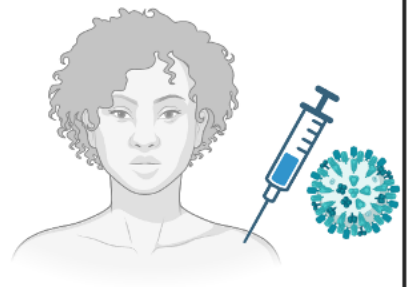
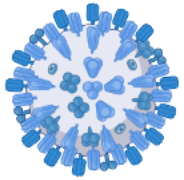
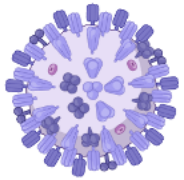
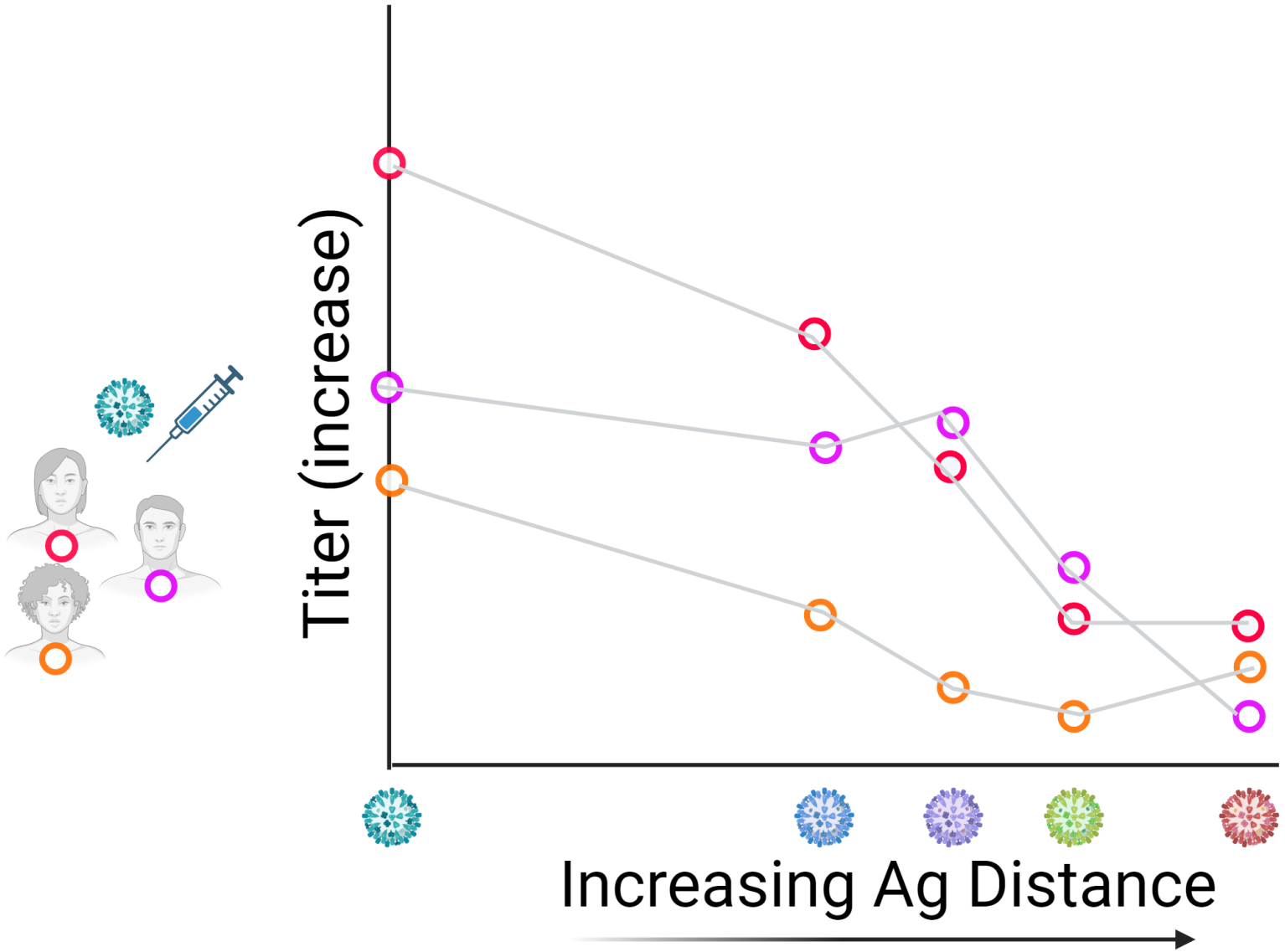
	40	80	2	✓	✗
	10	10	1	✗	✗
	20	20	1	✗	✗
	10	40	4	✓	✓
Overall	15	40	2.6	60%	40%

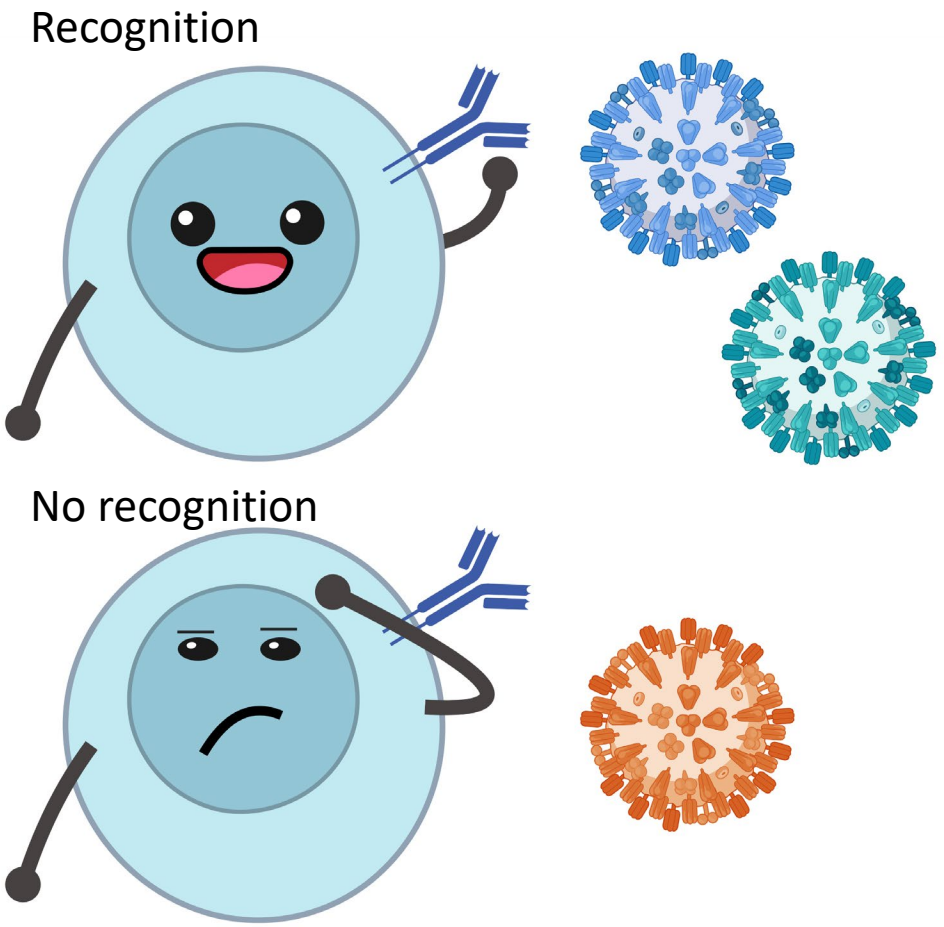
	Titer D0	Titer D28	Fold change	Seroprotection	Seroconversion
	10	160	16	✓	✓
	5	80	16	✓	✓
	5	40	8	✓	✓
	40	80	2	✓	✗
	10	10	1	✗	✗
Overall	10	53	8.6	80%	60%

Proposed method

Antibody landscape: titer vs. antigenic distance for all participants.

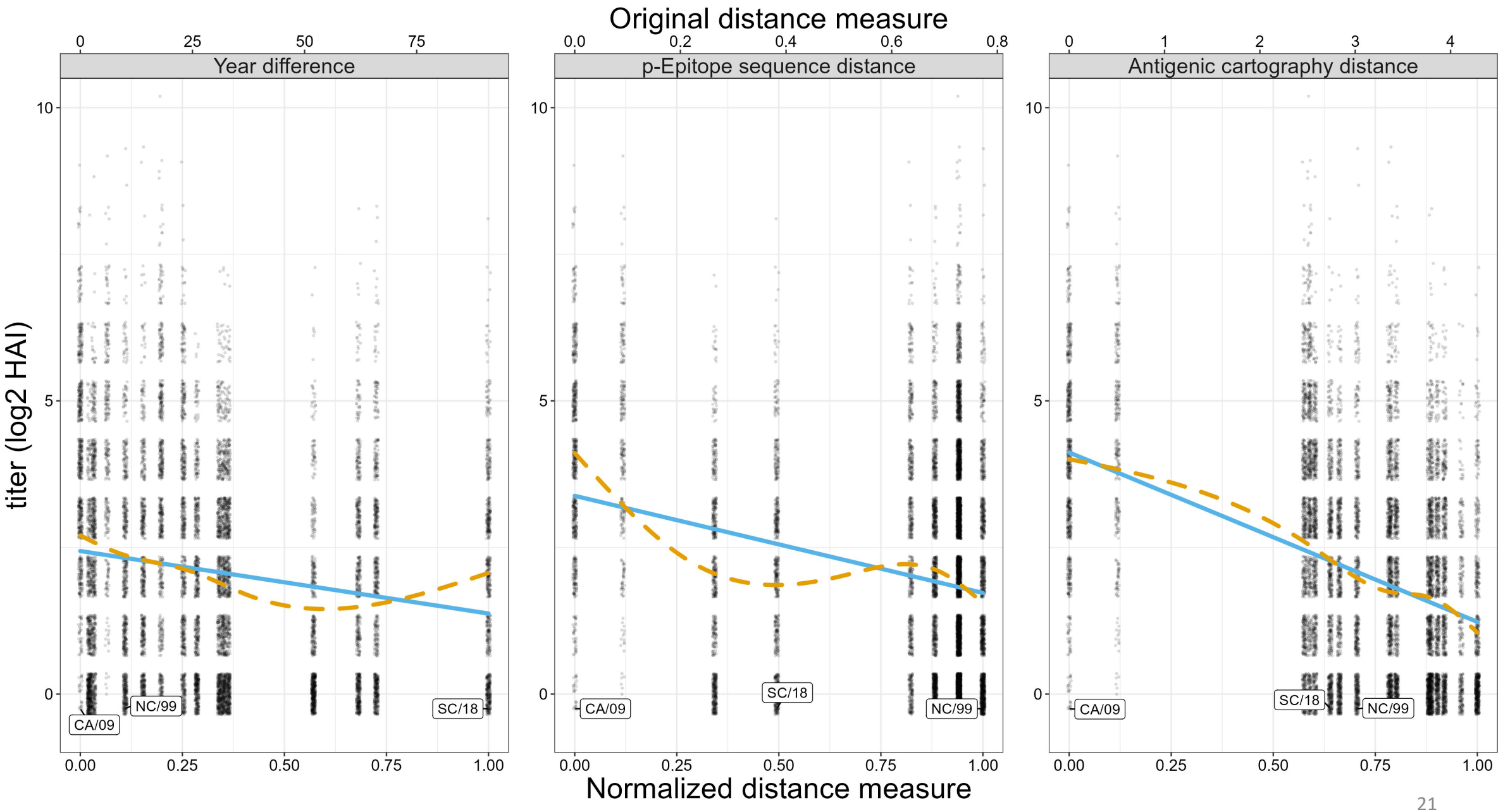


Antigenic distance: how different are two strains?

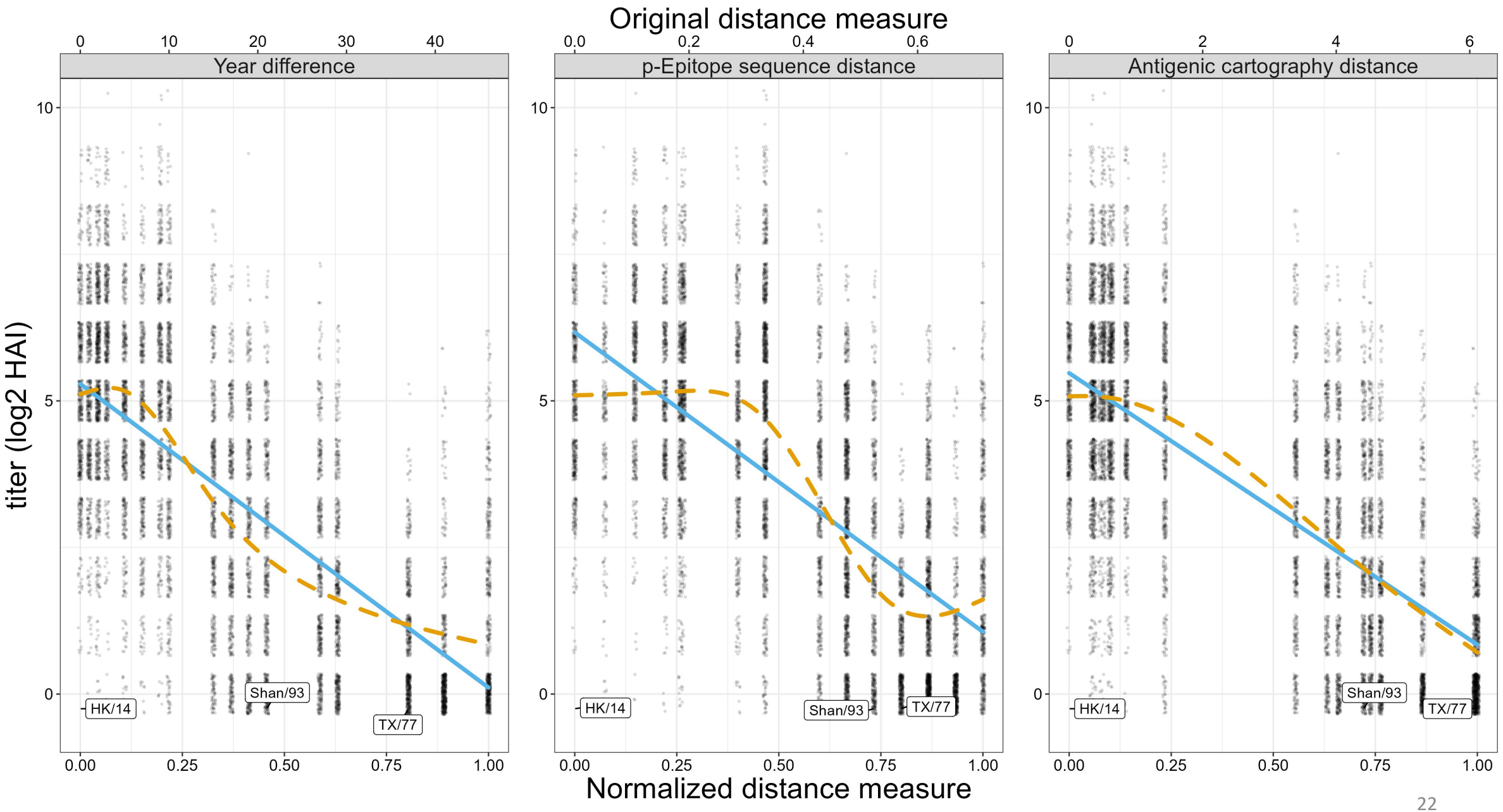


- **Temporal** method: absolute difference in years of strain isolation.
- **Sequence** method: based on genetic or protein sequence comparison. We use the dominant *p*-epitope distance, which is the maximum Hamming distance across all HA epitope regions.
- **Antigenic** method: based on maps created with antigenic cartography.

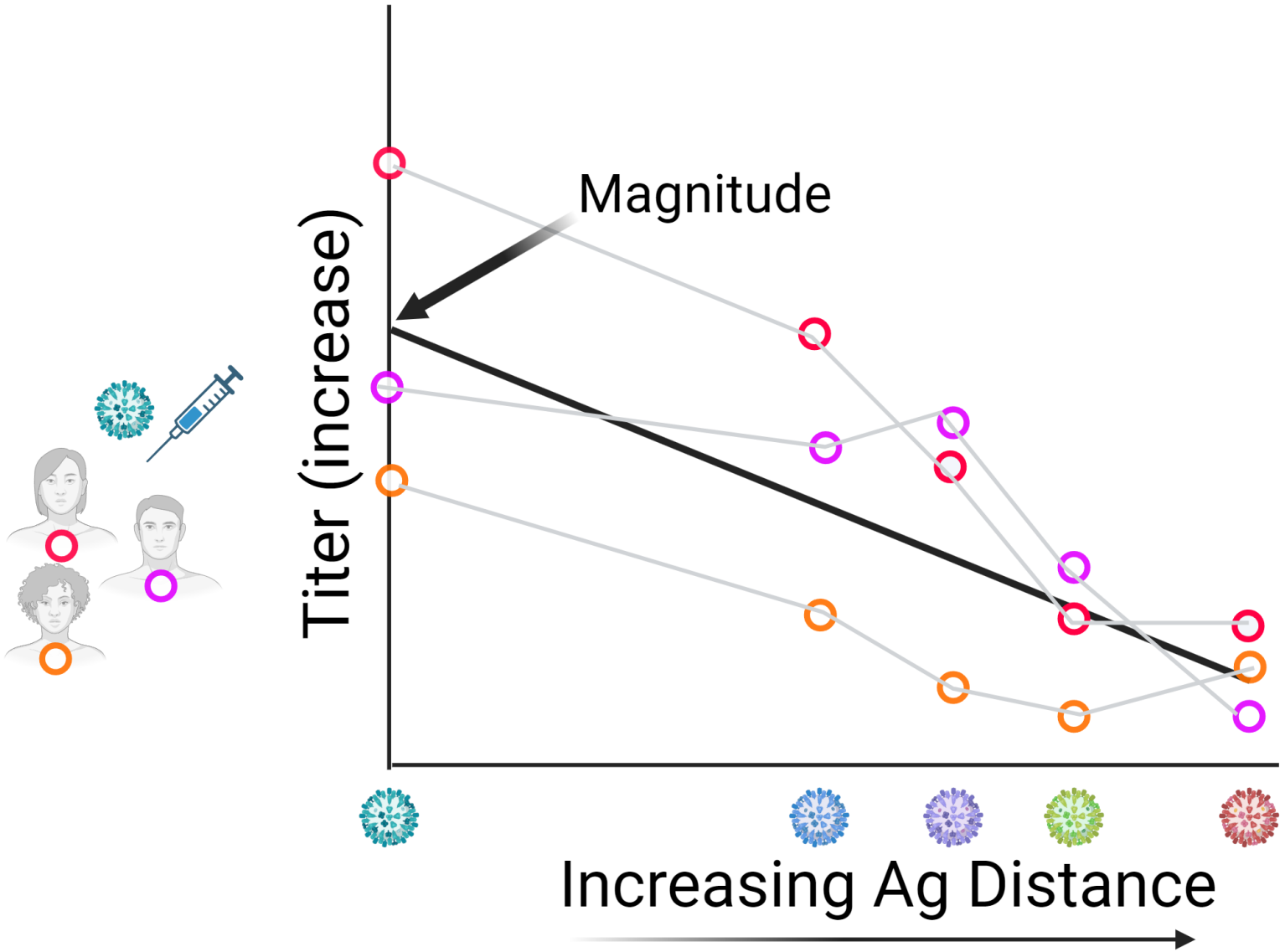
H1N1-California-2009 (n = 773)



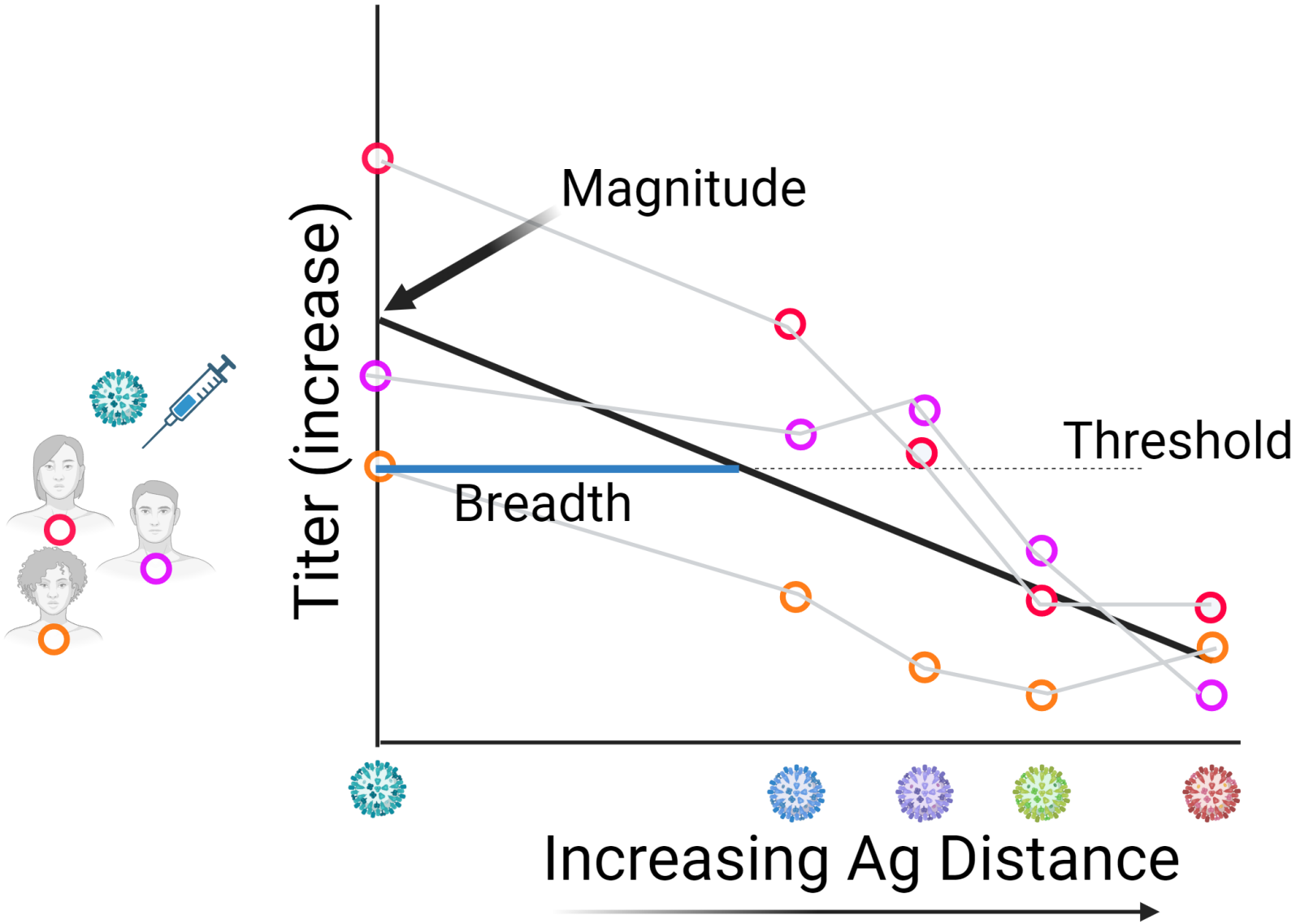
H3N2-Hong Kong-2014 (n = 583)



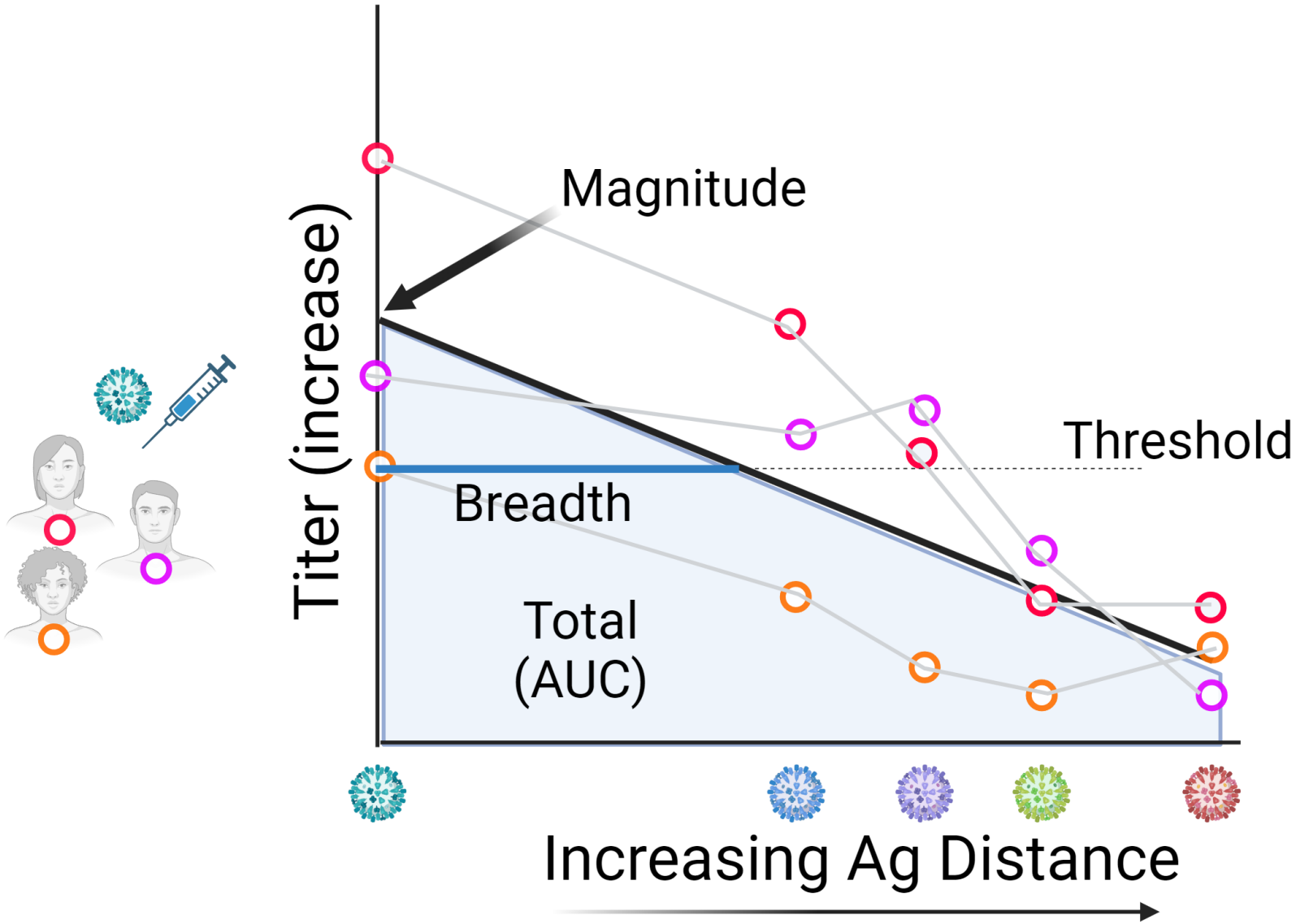
Magnitude: regression line intercept



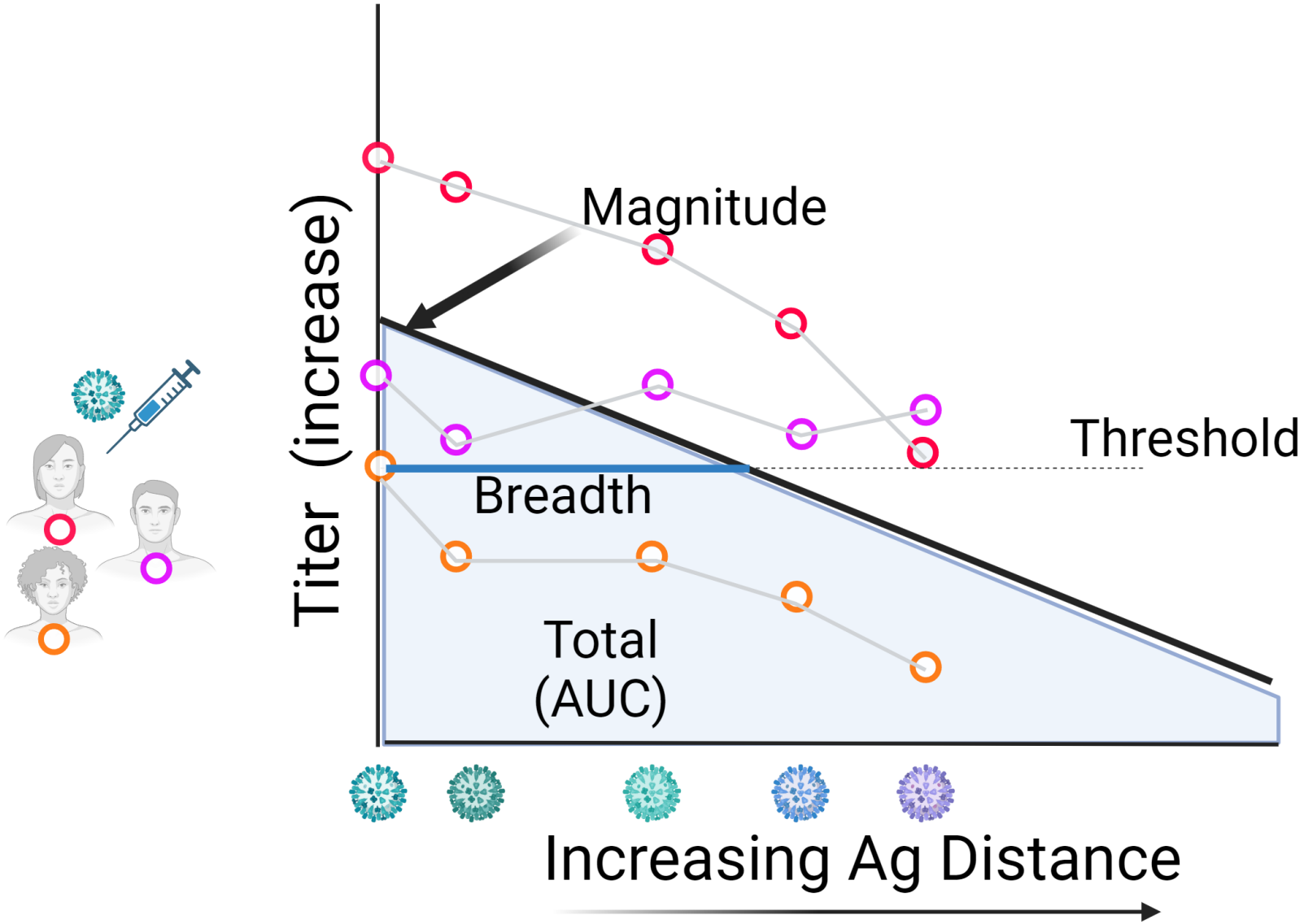
Breadth: prop. of line above threshold



Total strength: area under the curve



We predict this will be robust across multiple panels!



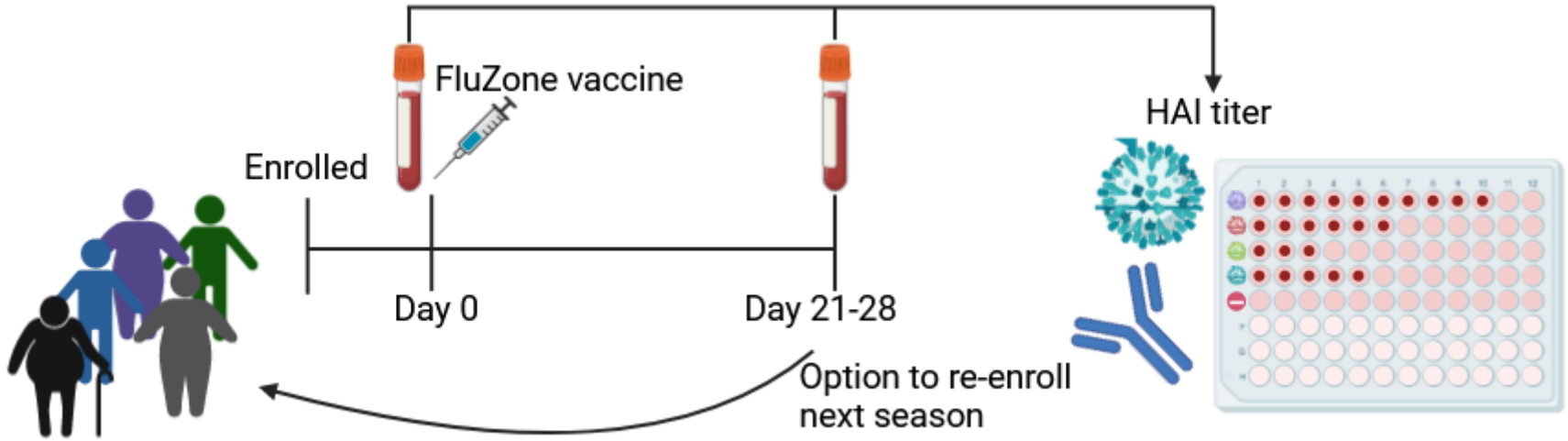
We expect our methods to be more robust across multiple labs.

	Current method	Proposed method
Magnitude	Homologous GMT	Intercept
Breadth	Overall SCR	Fraction above threshold
Overall strength	Overall GMT	AUC

Case study

UGAFluVac study

- Run by Ted Ross, currently housed at UGA
- 2013-2016 in Stuart, FL and Pittsburgh, PA
- January 2017 – Present in Athens, GA
- Prospective open cohort design with prevaccination and postvaccination HAI assays against a wide heterologous panel
- Participants received FluZone vaccine.



Case study methods

- We pooled together study years that used the same vaccine component (analysis was done separately for H1 and H3).
- For each vaccine, there is a panel of *K* heterologous strains (this number changes by season).
- We create a simulated “lab” by randomly sampling 9 strains. We also randomly sample individuals, so each lab only has 100.
- We create 10 of these labs. Each lab also gets the data for the homologous strain.
- For each lab, we evaluate the vaccine by calculating the current metrics and our new proposed metrics.

Our methods don’t look better!!
(Table shows coefficient of variation.)

	Current method	Proposed method
Magnitude	0.088	0.103
Breadth	0.059	0.431
Overall strength	0.083	0.081

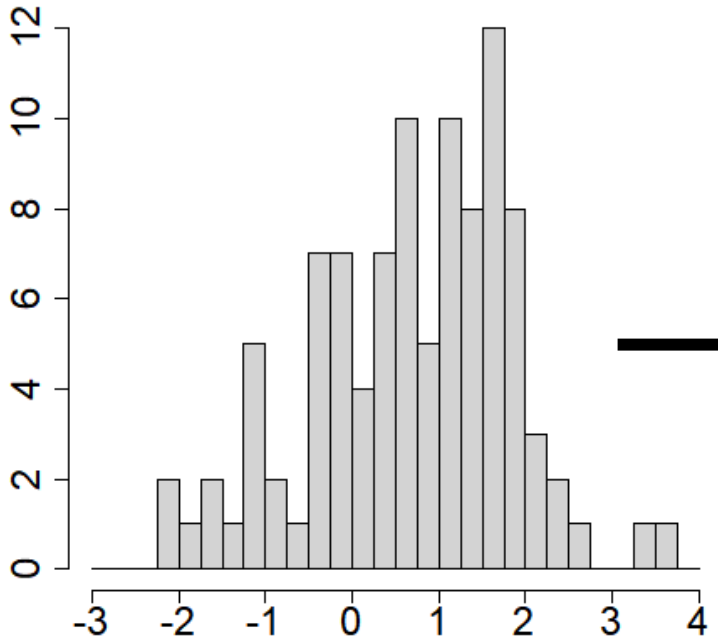
Simulation study

Simulation study methods

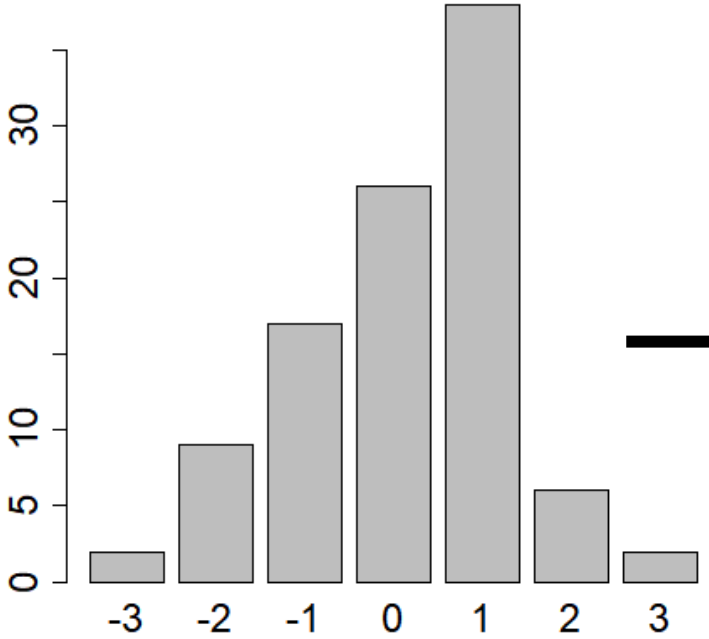
- Create a universe of 50 possible heterologous strains. These have antigenic distances 0.02, 0.04, and so on up to 1.00.
- Create 10 lab panels by randomly sampling 9 strains from the universe and adding the homologous strain (distance of 0).
- For each lab, generate 100 random individuals by simulating titers to the entire panel from a linear model.
- I.e. $\text{titer}_{\text{individual, strain}} \sim \text{Normal}(\alpha + \beta \cdot \text{distance}_{\text{strain}}, \sigma)$.
- From the simulated data, compute metrics.

In this simulation, our metrics are less variable. What's going on?

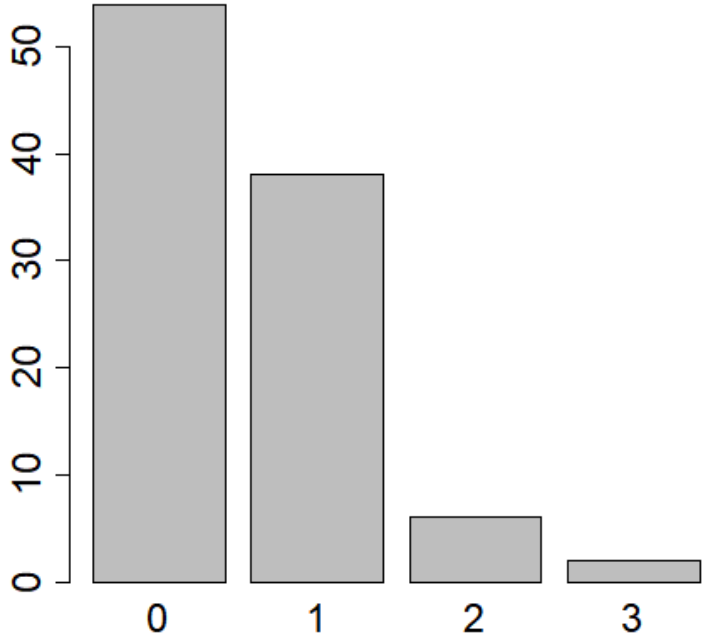
	Current method	Proposed method
Magnitude	0.025	0.008
Breadth	0.199	0.020
Overall strength	0.155	0.007



Continuous “underlying” titer



Floored titer (round down)



Floored titer with LoD

But the variation increases when we have similar percent at LoD to real data!

≈30% at LoD	Current method	Proposed method
Magnitude	0.028	0.033
Breadth	0.290	0.316
Overall strength	0.137	0.071

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≈30% at LoD	Current method	Proposed method
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Overall strength	0.137	0.071

Ignoring LoD	Current method	Proposed method
Magnitude	0.002	0.001
Breadth	0.290	0.000
Overall strength	0.172	0.001

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- If we correctly order strains by antigenic distance, we can find a linear pattern between distance and response.
- Our proposed method is generally more robust.
- If many data points are below LoD, the current approach has artificially low uncertainty.
- **Our method is also better at capturing the uncertainty in values below the LoD, but is still not completely correct.**

Future work

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- We need to use a method that accounts for values below LoD correctly.
- We need to compare our proposed methods to current methods after accounting for LoD.
- **We are currently implementing models in a Bayesian hierarchical framework that can take the LoD and discretization into account.**

Thank you!

Contact info: https://wzbillings.com/