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A mixture model to estimate SARS-CoV-2 seroprevalence in Chennai, India

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BACKGROUND

- **Serological assays** used to determine SARS-CoV-2 seropositivity often rely on **cut-offs** established based on early COVID-19 cases who tended to be more severe.
- **Many authorized COVID-19 vaccines target the spike** (S) protein of SARS-CoV-2 promoting the production of anti-Spike immunoglobulin-G (anti-S IgG); the role of anti-S IgG assays to determine prior infection is now limited.
- Quantifying antibody response targeting **other regions** such as the nucleocapsid (N) protein is therefore critical to understanding the **burden of infection**, and factors associated with infection and re-infection.

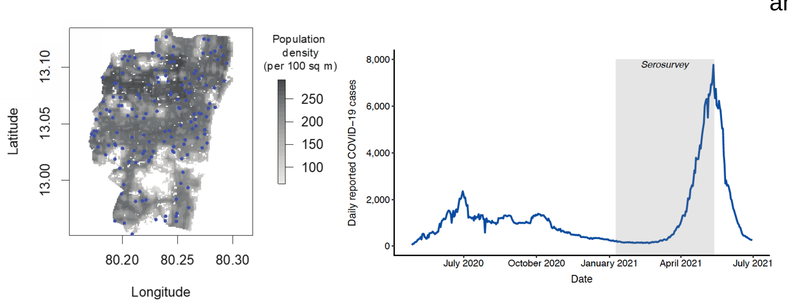
METHODS

- We conducted a **household-based serosurvey** of 4,677 individuals from 2,619 households in Chennai, India from Jan-May, 2021.
- We tested serum samples for anti-SARS-CoV-2 IgG to two proteins: **Spike** (S) and **Nucelocapsid** (N)
- **Mixture model**: Assume study population was divided into two (unobserved) groups: those with no exposure to SARS-CoV-2/vaccination (**seronegative**) and those who have been infected/vaccinated (**seropositive**).
- **Objectives**: estimate seroprevalence and predictors of infection.

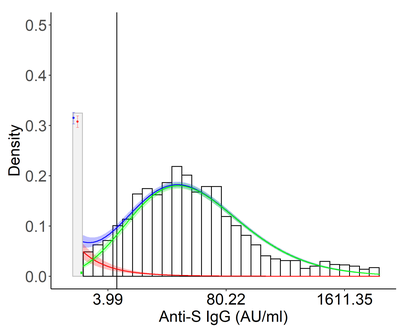
In Chennai, we found a 5-fold difference in seroprevalence of anti-SARS-CoV-2 IgG using two assays (62% vs 14%). A mixture model reconciled these differences.

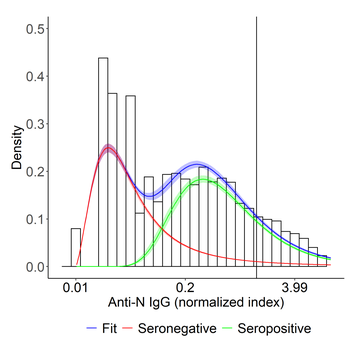
RESULTS

- Figure 1 shows distribution of **anti-S IgG** (left) and **anti-N IgG** (right) among participants in the serosurvey, with the inferred IgG distribution among seropositive (green) and seronegative (red) and overall fit of the mixture model to the data (blue). Vertical lines show the manufacturer's cut-offs.
- Anti-N IgG seroprevalence is underestimated using manufacturer's cut-off (Table)
- **Correlates of infection**: being a man (↓ seropositivity vs. women); improved household ventilation (↓ seropositivity); # regular visitors to the home (↑ seropositivity); COVID-19 vaccine (↑ seropositivity, anti-S only); sampling time (↓ seropositivity, waning).



Quantity	Manufacturer's cut-off	Mixture model
Anti-S IgG seroprevalence	62.0% (60.6-63.4)	64.9% (63.8-66.0)
Anti-N IgG seroprevalence	**13.5%** (12.6-14.5)	**51.5%** (50.2-52.9)
Agreement (Cohen's kappa)	0.15	0.66





CONCLUSIONS

- We observed strikingly **disparate prevalence of SARS-CoV-2 antibodies** using two assays according to manufacturer's cut-offs, which was largely corrected using a mixture model fit to the continuous IgG.
- Previous studies have shown **faster waning of anti-N IgG** over time compared to anti-S, but the widespread use of COVID-19 vaccines generating an anti-S IgG response makes assays targeting other regions critically important for estimating cumulative incidence.
- Mixture models can address limitations of assays using a single cut-off to define seropositivity, but further work should focus on making such methods **accessible** to a wide array of researchers.
- In this study, markers of low SES were associated with higher odds of seropositivity (i.e. prior infection), but there was **no strong association with age**. Such conclusions could change in the context of the Omicron variant.

ADDITIONAL KEY INFORMATION

- Matt Hitchings (mhitchings@ufl.edu), Shruthi Mehta (smehta@jhu.edu), Derek Cummings (datc@ufl.edu), Sunil Solomon (sss@jhmi.edu).
- We thank the Chennai Municipal Corporation for their collaboration, the field teams and all of the study participants.

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