What Research is Critical to Prepare and Respond to H5N1 outbreaks

Critical research needs on Assays

1. Rafael Medina, Emory Vaccine Center, Emory University – "Correlates of improved outcome revealed by Omics analyses"
2. Surender Khurana, Center for Biologics Evaluation and Research, U.S. Food and Drug Administration (FDA)-"Neutralizing antibodies generated by U.S. licensed H5N1 vaccines against highly pathogenic H5N1 clade 2.3.4.4b influenza virus."
3. Malik Peiris, School of Public Health, The University of Hong Kong – "Sero epidemiology: Knowledge gaps for pandemic preparedness and risk assessment"

Virtual discussion on Sept 3rd 2024

Correlates of disease severity with seasonal influenza: Omics cohort study – Rafael Medina

Cohort of mild and severe influenza. Conventional and multi-Omics Systems biology in Chile

- Higher HI and stalk antibody titres early or late in disease were NOT correlated with reduced severity
- Cytokine, cellular, metabolomic and lipidomic signatures are early markers of mild (higher CD4/8 responses, higher fumarate) vs. severe disease (CD8 exhaustion)
- Some markers of severe disease (IL1β, IL8 signalling) are also seen in non-infected individuals with co-morbidities (obesity, hypertension) without infection

Neutralizing antibodies generated by U.S. licensed H5N1 vaccines against highly pathogenic H5N1 clade 2.3.4.4b influenza virus.
- Surender Khurana

- Compared antibody responses in humans to non-adjuvanted and adjuvanted (AS03, MF59) vaccines based on clade 1 (A/Vietnam/04), clade 2.1 (A/Indonesia/05), clade 2.2 (A/Turkey) vaccines vs homologous and heterologous H5N1 viruses including A/Astrakhan/2020 clade 2.3.4.4b (Khurana et al Mat Med 2024).
- Developed genome fragment phage display antibody assay to assay to map genome-wide epitope mapping of antibody response.
- AS03 and MF59 adjuvented vaccines generated
  - Broad antibody diversity and high affinity against HA1 domain
  - Cross-neutralizing antibody to heterologous (clade 2.3.4.4b) H5N1 was modest (60-63% seroconversion) and lower GMT
  - Correlation between high antibody affinity and cross neutralization of recent H5N1

Knowledge gaps in sero-epidemiology of H5N1 – Malik Peiris

Neuramindase inhibiting antibody (known to be an independent correlate of protection vs influenza)

- While human population has little of no HI or MN antibody vs H5N1, there is very high prevalence and GMT titers of neuramindase inhibiting antibody to N1 of H5N1 clade 2.3.4.4b
- Such cross-reactive NI antibody is elicited by the N1 of pdmH1N12009 (which was also of avian origin). Population cross-reactivity extends to other avian N1 but not to other avian subtypes e.g. N4 (Daulagala P et al Emerg Infect Dis 2024)
- Similar cross reactivity in older humans to N2 of avian H9N2 (Liang et al Nat Comm 2024)

Gaps in knowledge and Future work

- **Correlates of protection:**
  - While HI antibody is clearly a correlate of protection in influenza, it is not the sole correlate of protection and not equally so for all types of vaccines. Need to further explore role of antibody binding and functional assays (FcR binding, ADCC,ADCP), antibody affinity, neuramindase inhibition, T cell immunity (e.g. CD8)?
  - What contribution does prior influenza infection (cross-reactive anti N1 antibody, T cells) provide against H5N1 infection / disease? What is mechanisms of ferrets previously infected with pdmH1N12009 being protected from H5N1 (Le Sage et al bioRxiv 2024)
  - Correlates of protection may differ with age group and co-morbidity groups?
  - Systems serology, systems biology (Omics) assays may provide novel biomarkers of protection from severe disease (antibody not the key factor)
  - **Mucosal immunity** – very little is known: need to standardize sample collection, storage, assay methods and correlation with protection
- **Assay reproducibility:**
  - Qualification, validation, standardization, use of “open-use” (e.g. BEI resources) standards for cross-lab comparability