Mucosal Correlates of Protection after Influenza Viral Challenge of Vaccinated and Unvaccinated Healthy Volunteers

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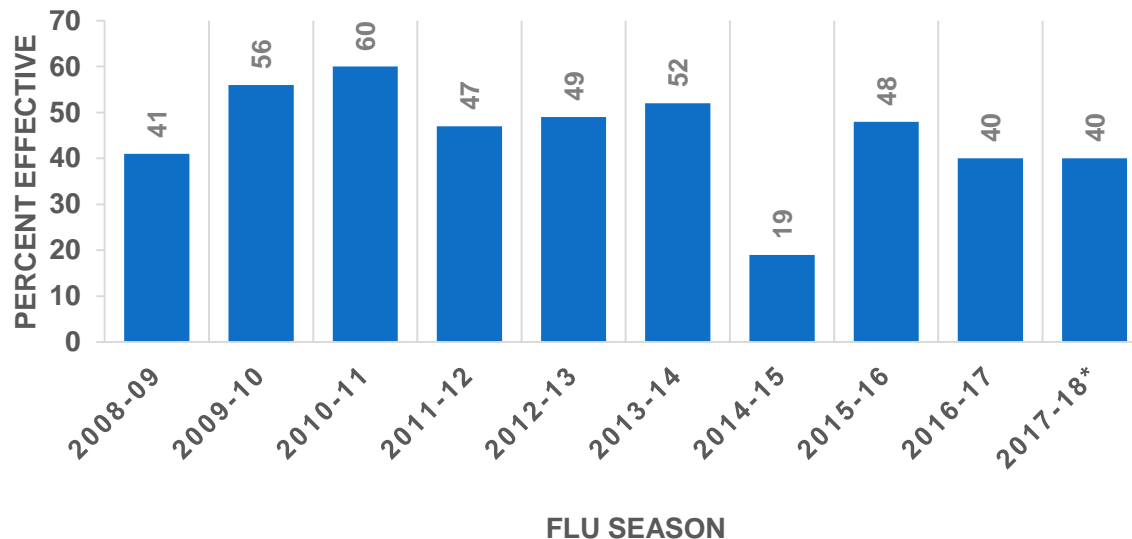**AAAAI Faculty Development Program**

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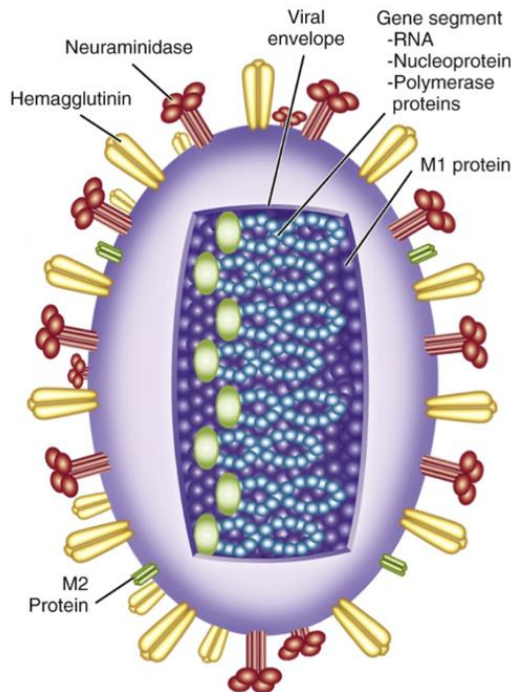National Institute of Allergy and Infectious Diseases

Background: Are we missing the mark?

- Influenza is a major public health burden
  - Seasonal influenza causes up to 36,000 deaths/year in the USA

- Vaccination is the cornerstone of prophylaxis
  - Effectiveness ranges from 10-56% in select populations
  - Better vaccines are urgently needed
  - How to design and evaluate them?

Source: https://www.cdc.gov/flu/professionals/vaccination/effectiveness-studies.htm

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Figure: CDC.gov

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Background: Current vaccine targets

- Immune correlates of protection against influenza are imperfect
  - Serum antibodies to hemagglutinin (HA) are measured by hemagglutination inhibition (HAI) assay
  - FDA defines "protective" vaccine by HAI titer $\geq$1:40

Neuraminidase

Hemagglutinin

Viral envelope

Gene segment
-RNA
-Nucleoprotein
-Polymerase proteins

M1 protein

M2 Protein

The role of serum haemagglutination-inhibiting antibody in protection against challenge infection with influenza A2 and B viruses

By D. HOBSON AND R. L. CURRY

Department of Medical Microbiology, University of Liverpool

A. S. BEARE

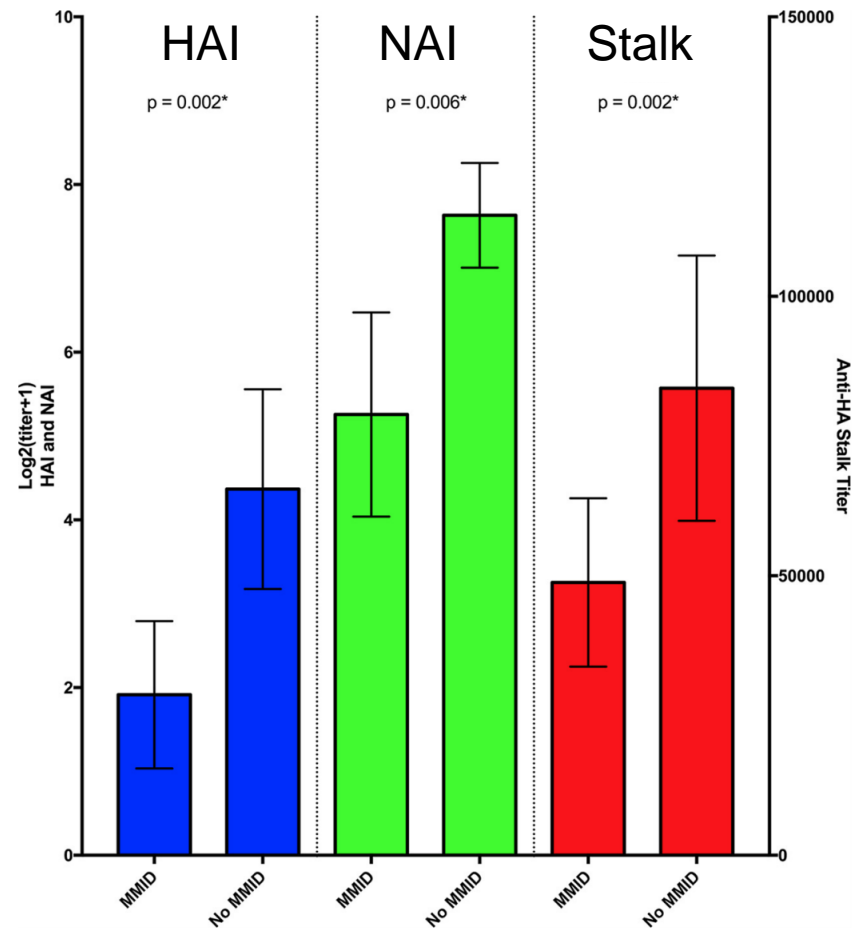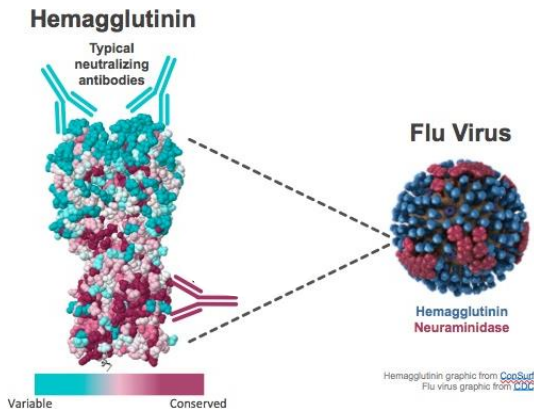*M.R.C. Common Cold Research Unit, Salisbury*

AND A. WARD-GARDNER

Medical Department, Esso Refinery, Fawley

(Received 17 May 1972)

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Background: Correlates of protection

- Our group has studied antibodies to HA, stalk and neuraminidase (NA) as predictors of outcomes
    - HA and stalk predict viral shedding
    - NA predicts symptom severity

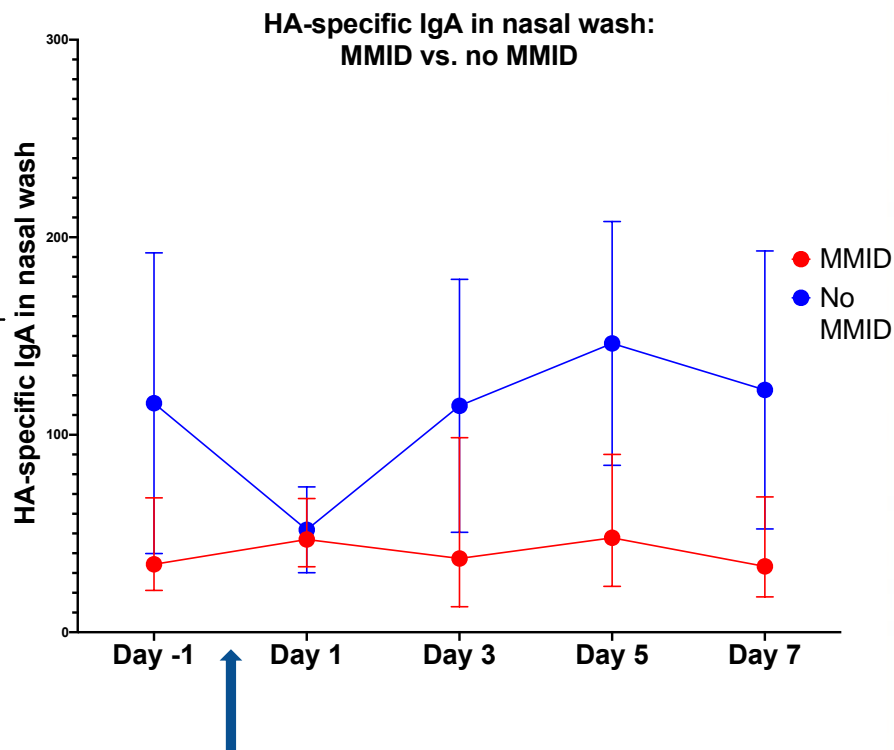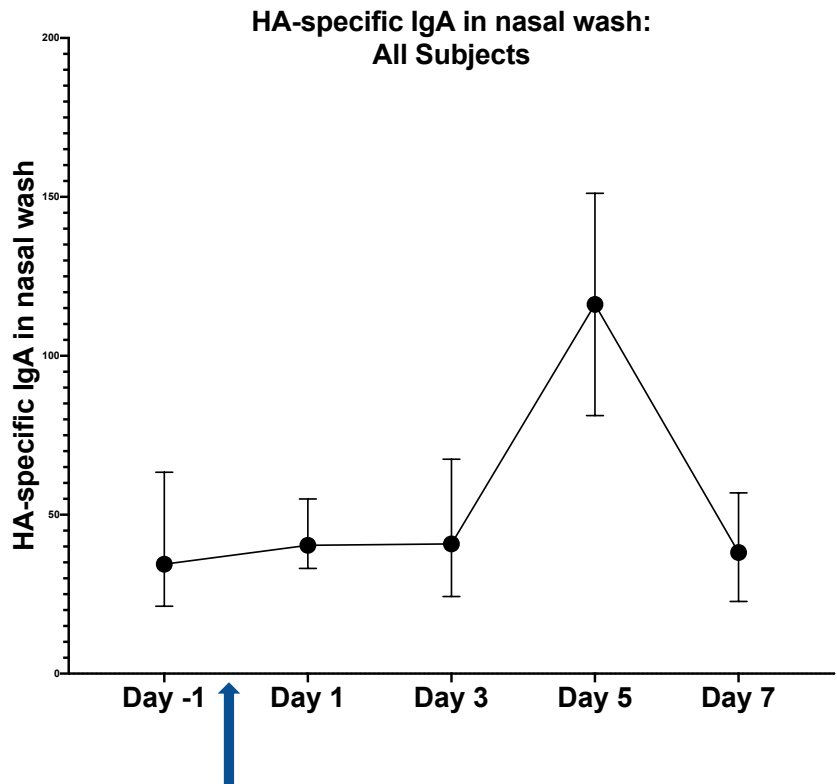- These are broad trends with limitations

Lab Project:
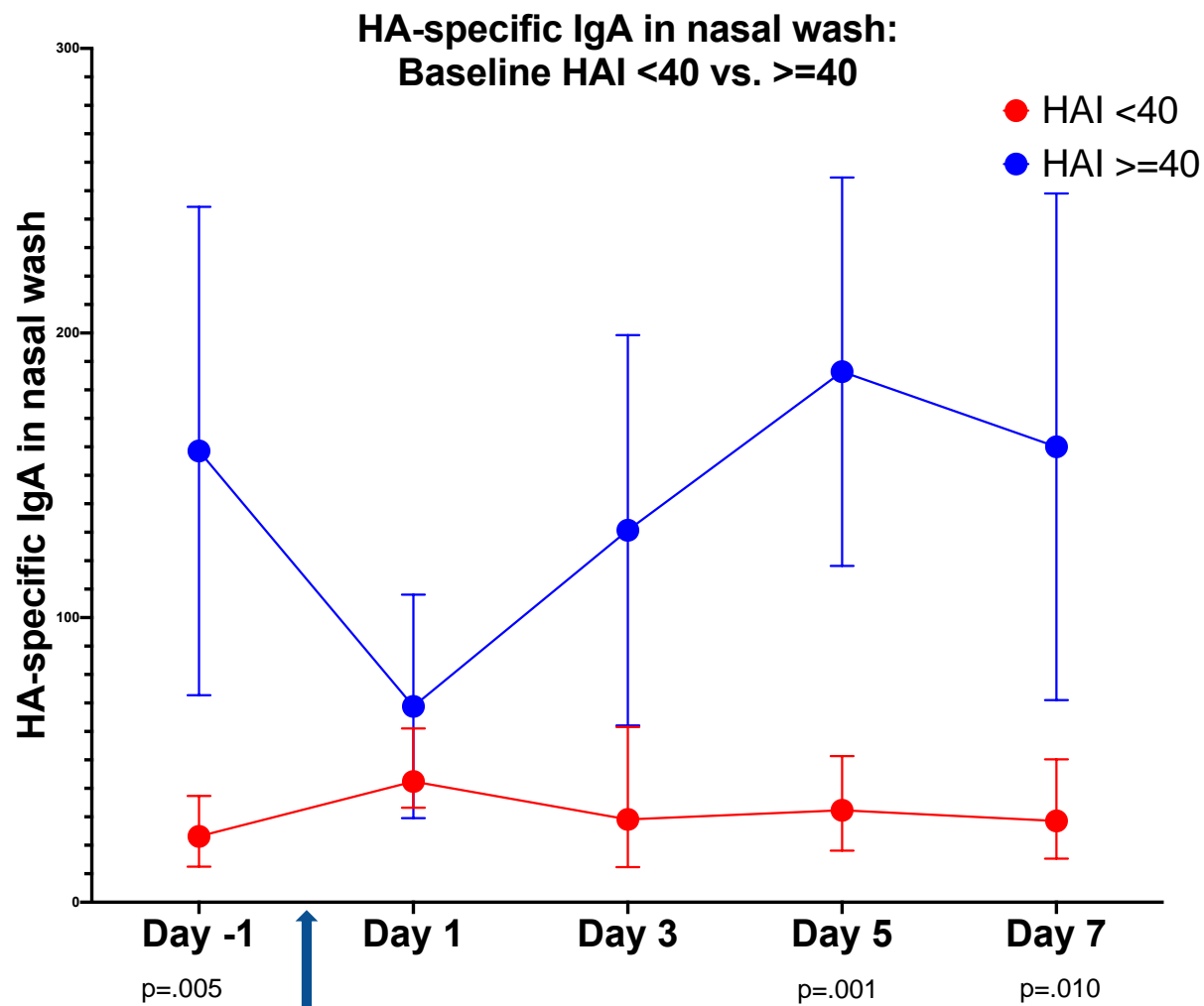# Mucosal immunity in viral challenge

Title: Mucosal Antibodies to Influenza as Correlates of Protection in a Healthy Volunteer Challenge with Influenza A/H1N1pdm Virus

- Hypothesis: Nasal mucosal antibody levels predict clinical symptoms and/or viral shedding.
  - Correlate with previously published clinical and lab data
  - Compare pre-existing with post-challenge antibody levels
    - Time points: challenge day -1, 1, 3, 5, 7

- Evaluate nasal wash samples for total and influenza-specific antibodies (IgG/A/M) using ELISA technique
  - Ab's targeting HA, stalk and NA

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Results

HA-specific IgA in nasal wash:
All Subjects

HA-specific IgA in nasal wash:
MMID vs. no MMID

Results

HA-specific IgA in nasal wash:
Baseline HAI <40 vs. >=40

Clinical Trial

Title: Mucosal Correlates of Protection after Influenza Viral Challenge of Vaccinated and Unvaccinated Healthy Volunteers
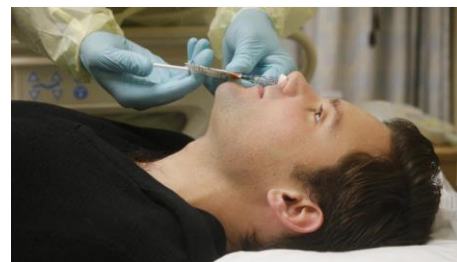
Study population: 80 healthy adults, with any level of pre-existing HAI titers
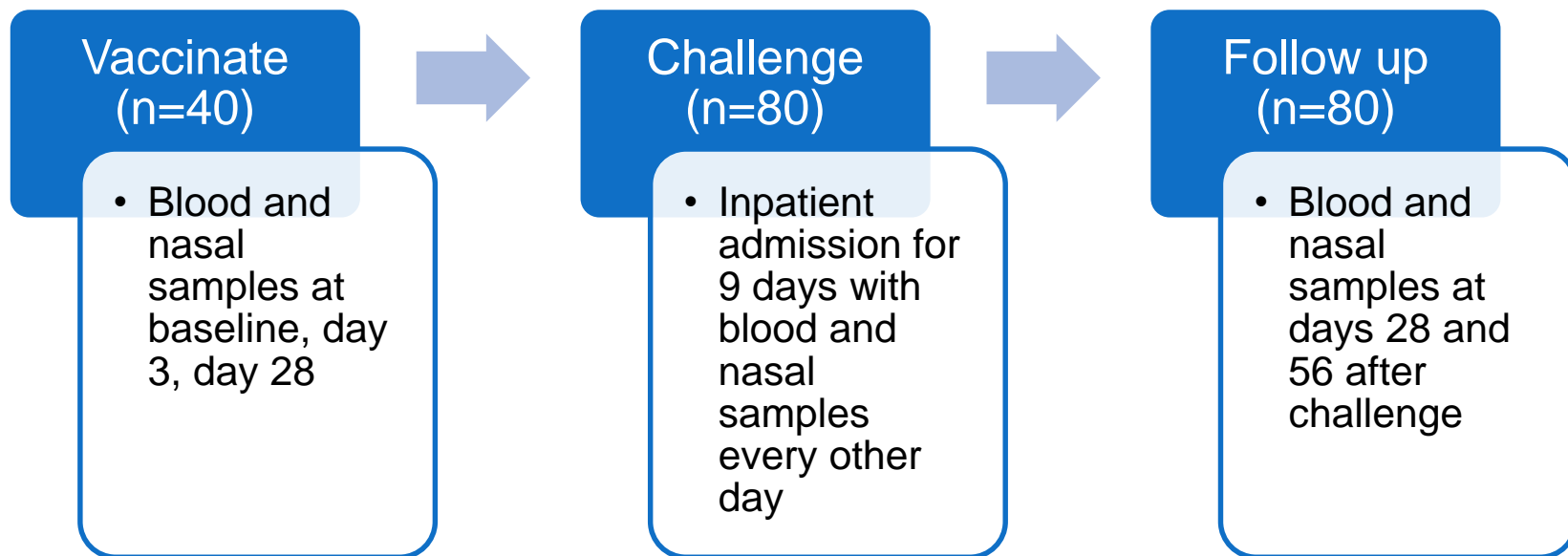
Interventions:
- Half of participants receive FDA-approved IM seasonal quadrivalent inactivated flu vaccine at enrollment; half remain unvaccinated.
- All participants undergo viral challenge with recombinant live influenza A/H1N1 (derived from 2009 pandemic H1N1).
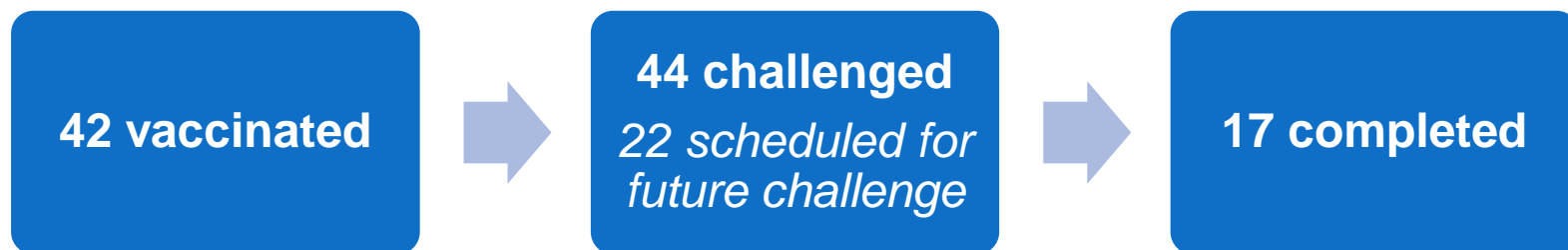
Samples:
- Serum
- Nasal samples via SAM strip and cytology brush
- Nasal washes for viral PCR

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Study Schedule & Progress

Vaccinate (n=40)
- Blood and nasal samples at baseline, day 3, day 28

→

Challenge (n=80)
- Inpatient admission for 9 days with blood and nasal samples every other day

→

Follow up (n=80)
- Blood and nasal samples at days 28 and 56 after challenge

Progress to Date:

42 vaccinated

→

44 challenged
22 scheduled for future challenge

→

17 completed

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Goals

Primary objective:
- Identify **mucosal correlates of protection against influenza infection** in each cohort
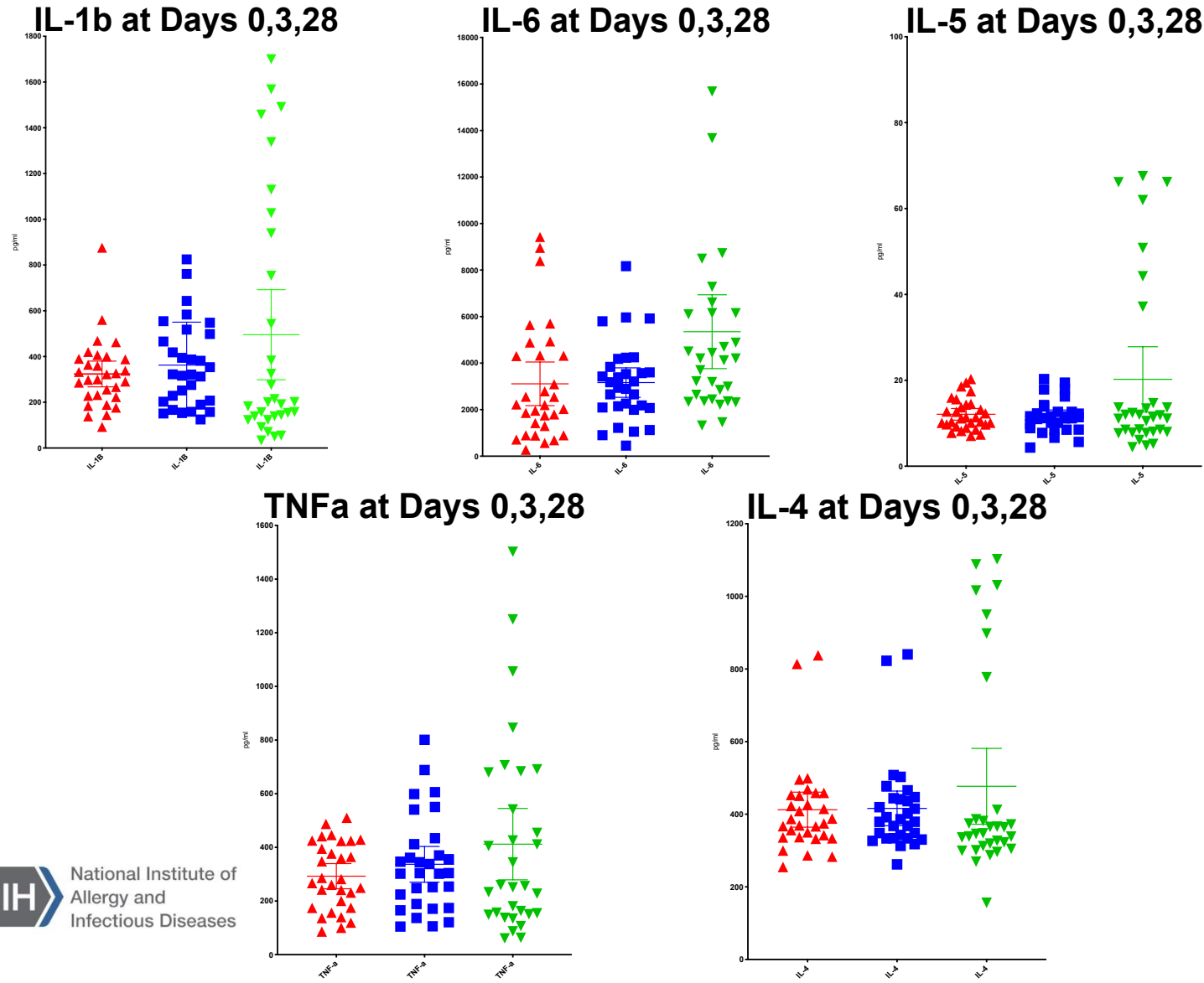
Secondary objectives:
- Characterize mucosal and systemic immune responses of vaccinated and unvaccinated cohorts
  - **After IM vaccination**, prior to challenge
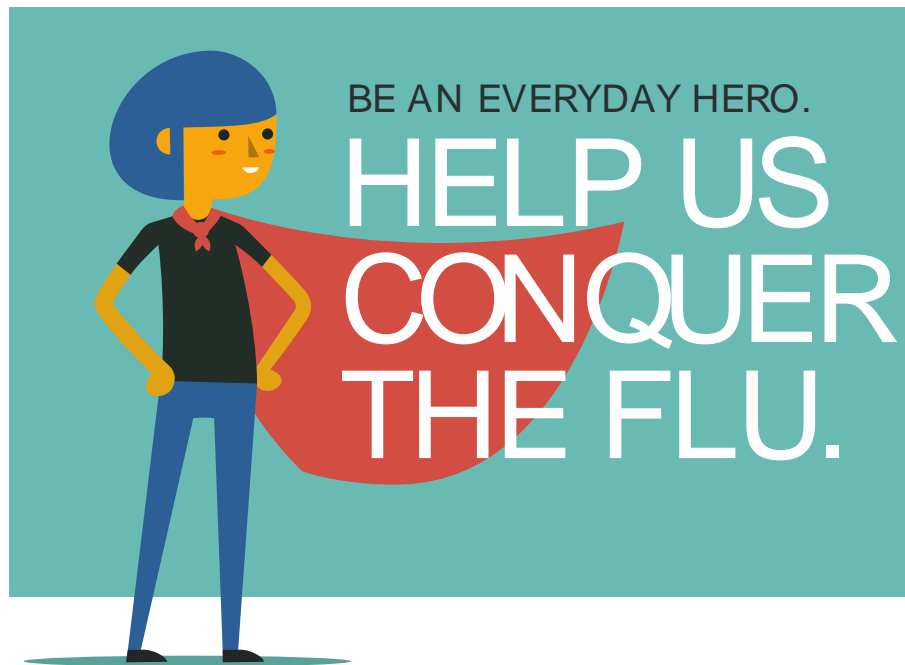 - **After influenza challenge**

Exploratory objectives:
- Identify **correlates of clinical disease severity** through analysis of clinical outcomes and correlation to mucosal and systemic immune responses to influenza challenge

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Results: Pre- and post-vax PBMC stimulation, for T cell cytokines

Thank you!

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- Kristina Edwards
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- Susan Reed
- Rani Athota, PhD

BE AN EVERYDAY HERO.
HELP US CONQUER THE FLU.

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