

**HKU Strategic Partnerships Fund with University College London**  
Final Report

**Project title**

Immune dynamics after repeated influenza vaccination

**Investigators**

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**Deliverable 1: Statistical analyses to study the effect of repeated influenza vaccination on antibody waning in both the HK and UK cohorts, specifically:**

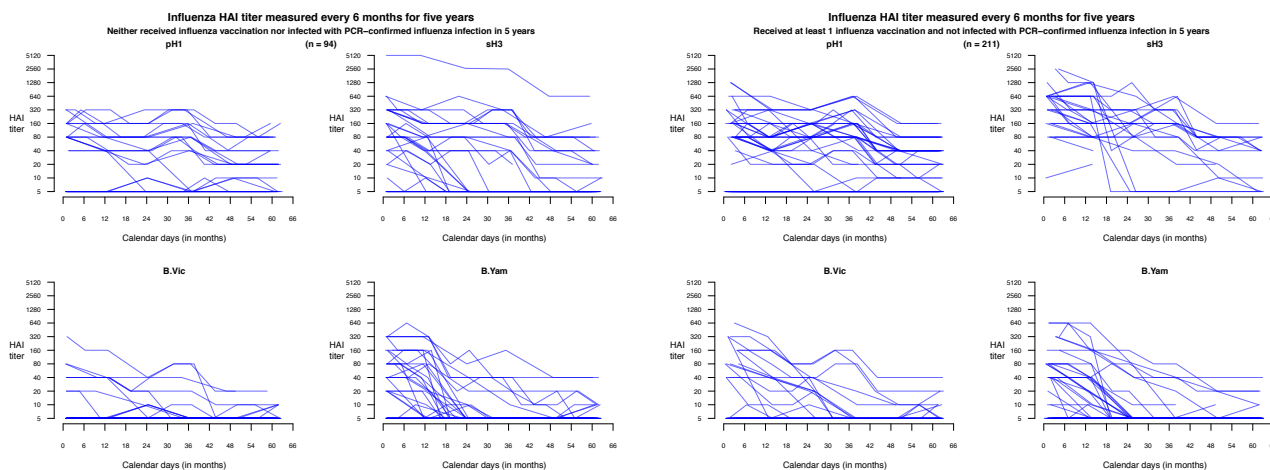
1. To estimate the antibody waning after repeated vaccination over time;
2. To estimate the correlation of HAI titer with protection against laboratory-confirmed infection; and
3. To determine whether this protection differs between individuals who received multiple influenza vaccinations over the years.

**Output:**

In the Hong Kong cohort (Kiddivax study), a total of 796 children were enrolled at the start of study before the 2009/10 influenza season, among which 367 (46%) were followed up and provided blood specimens every 6 months for 5 full years. From these, we explored the trajectories of HAI antibody titers since the last self-reported influenza vaccination or PCR-confirmed influenza A/B infection as identified from our active surveillance effort over the course of five years. For each strain, individuals who had 4-fold or greater increases in HAI titer between any consecutive sera collection were excluded to minimize bias from boosting due to infections that were not PCR confirmed. Waning rates of HAI titers were estimated with generalized estimating equations (GEE) with Gaussian distribution on the log scale using the R *gee* package. 249 (68%) received influenza vaccination at least once during the five years of follow-up period. We estimated HAI antibody declined by an average of around 0.1 to 0.2 logs per year, with no major differences in the waning rates between viruses, prior vaccination or PCR-confirmed infection (Figure 1). Except for influenza A(H3N2) virus, for all other influenza viruses there were around 4% of individuals who had undetectable HAI titer for the entire course of five years despite having received influenza vaccination. Further analyses are needed to estimate the duration that the HAI titer would decline to a level with sub-optimal protection, and to understand whether individuals who never had boosting in HAI titers were more susceptible to influenza virus infections.

The preliminary results were presented in the following two meetings, and we are writing these up for journal publications:

1. Leung NHL, Perera RAPM, Fang VJ et al. Waning of antibodies against influenza virus after vaccination or infection. 11<sup>th</sup> Annual CEIRS Network Meeting, 2018. New York, US. [Poster]
2. Leung NHL, Perera RAPM, Fang VJ et al. Waning of natural or vaccine-induced serum antibodies against human influenza virus over multiple years. São Paulo School of Advanced Sciences on Vaccines, 2018. São Paulo, Brazil. [Poster] **[Scholarship awarded]**



**Figure 1. Influenza HAI antibody titer measured in same individuals every 6 months over five years since their last influenza vaccination or PCR-confirmed influenza A/B virus infection. A)** Individuals who have reported never receive an influenza vaccination, nor had a PCR-confirmed influenza A/B virus infection. **B)** Individuals who had reported received at least once influenza vaccination but did not have a PCR-confirmed influenza A/B virus infection. pH1: Influenza A(H1N1pdm09); sH3: A(H3); B.Vic: Influenza B(Victoria); B.Yam: B(Yamagata).

**Deliverable 2: Organization of 2 virtual half-day workshops for convening a consortium of multi-disciplinary scientists, specifically:**

1. To identify a unifying research agenda and future funding opportunities; and
2. To establish a writing group to develop further grant applications based on the work initiated in Deliverable 1.

**Output:**

The team have met 3 times during academic meetings (New York, London and Stockholm) for the discussion of the project and future research direction. We identified important research questions to be addressed, including the waning of vaccine- or infection-induced serum antibodies against influenza hemagglutinin (HA) and neuraminidase (NA), which are being considered as additional candidate correlates of protection (CoPs) for universal influenza vaccine, and their contribution to protection.

These have contributed to the following grant applications:

1. Waning of vaccine- or infection-induced serum antibodies against influenza hemagglutinin and neuraminidase in children. **NIAID** Centers of Excellence for Influenza Research and Surveillance (CEIRS), United States. [Under consideration, HK\$3.5m]
2. Control of influenza: individual and population immunity. **Theme-based Research Scheme 2019/20**, Hong Kong. [Invited for full proposal, HK\$75m]