Influenza pre-immune ferrets vaccinated with computationally optimized recombinant HA proteins generate sero-protective antibody responses against H1N1 and H3N2 viruses from the last decade

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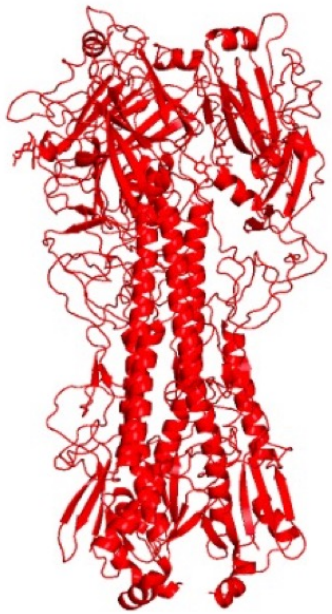
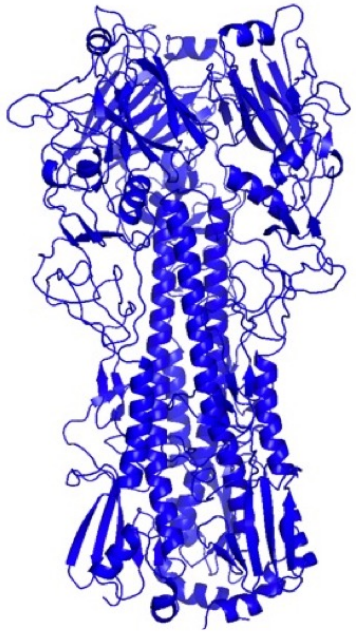
COBRA Approach for Designing Broadly Reactive Vaccines

- In-silico layered consensus building approach
  - Utilizes HA sequence data from flu surveillance databases (GISAID, GenBank)
    - Natural viral evolution dictates antigen design
- Capable of eliciting potent, broadly reactive HA-specific antibody responses
  - Effective against seasonal and pandemic influenza virus strains
    - H1, H3, & H5 subtypes
    - Mice, ferrets, non-human primates
      - Y2 H1 COBRA (2014-2016)
      - NG2 H3 COBRA (2016-2018)



Y2 H1 COBRA HA
(2014-2016)



NG2 H3 COBRA HA
(2016-2018)

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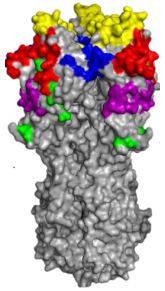
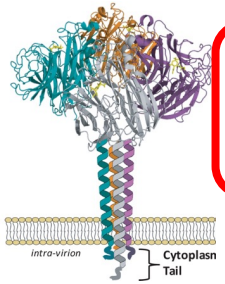
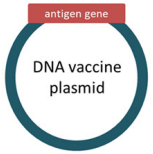
Allen 2021. *Journal of Virology*

Overview of different COBRA vaccine delivery platforms

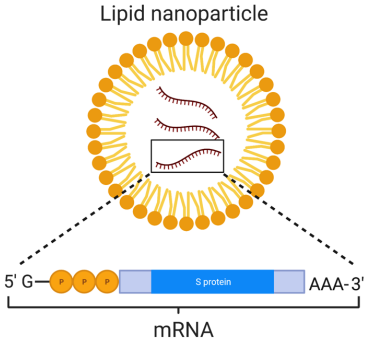




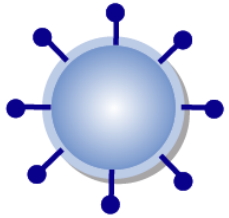
HA and NA recombinant proteins



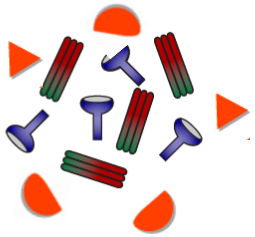
DNA vaccination



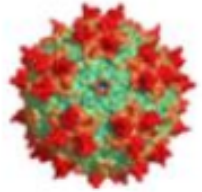
mRNA LNP



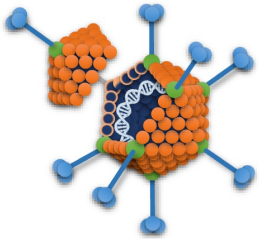
Nano, Micro, & Virus-like particles (VLP)



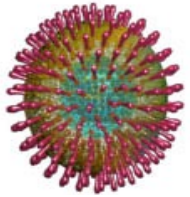
Inactivated/Split vaccine



AAV - Vectored



Recombinant ChAd3



Live or Attenuated Viruses

Self-amplifying mRNA

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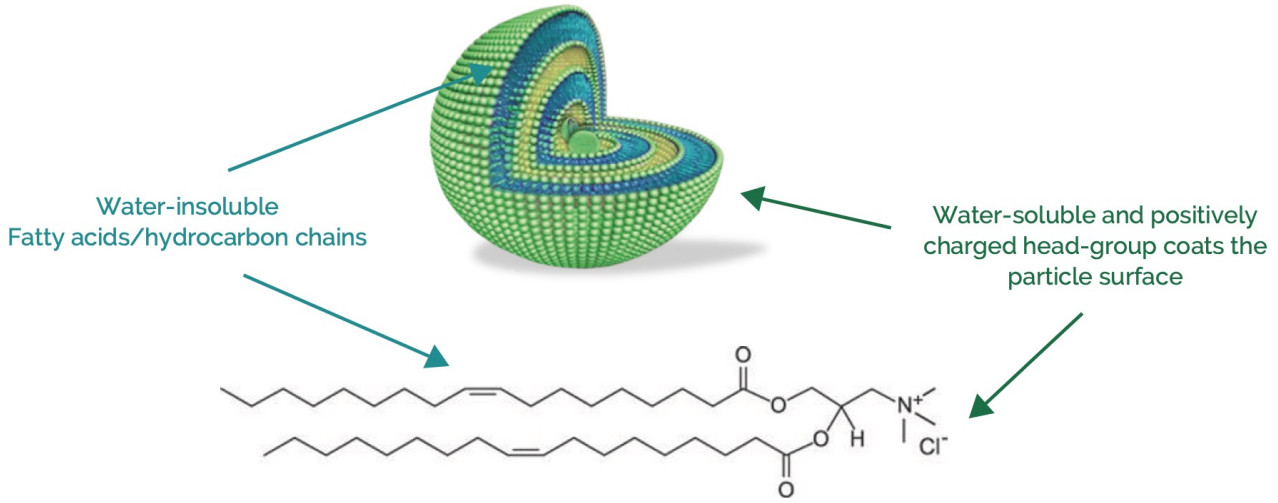
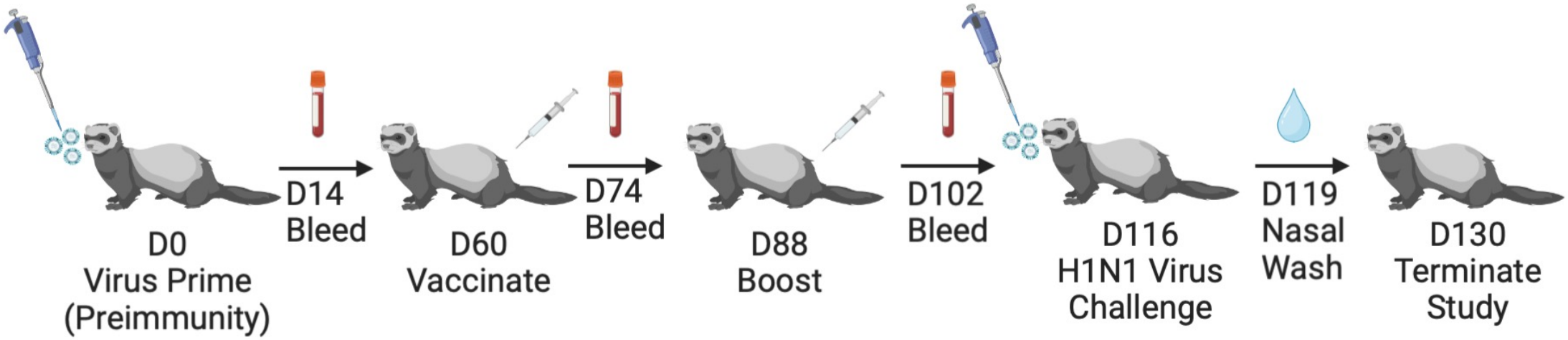
Infectimune® Adjuvant

- Infectimune® (R-enantiomer of DOTAP)
- Cationic lipid nanoparticle adjuvant
  - Quaternary ammonium head with two 18 carbon length unsaturated fatty acid (acyl) chains
  - Binds to surface of DCs and is endocytosed via a clathrin-mediated mechanism
  - Efficient at transporting protein or peptides into cells
  - Safe and effective at eliciting cellular and humoral immune responses in human clinical trials



Gandhapudi et. al. *J Immunology*. 2019

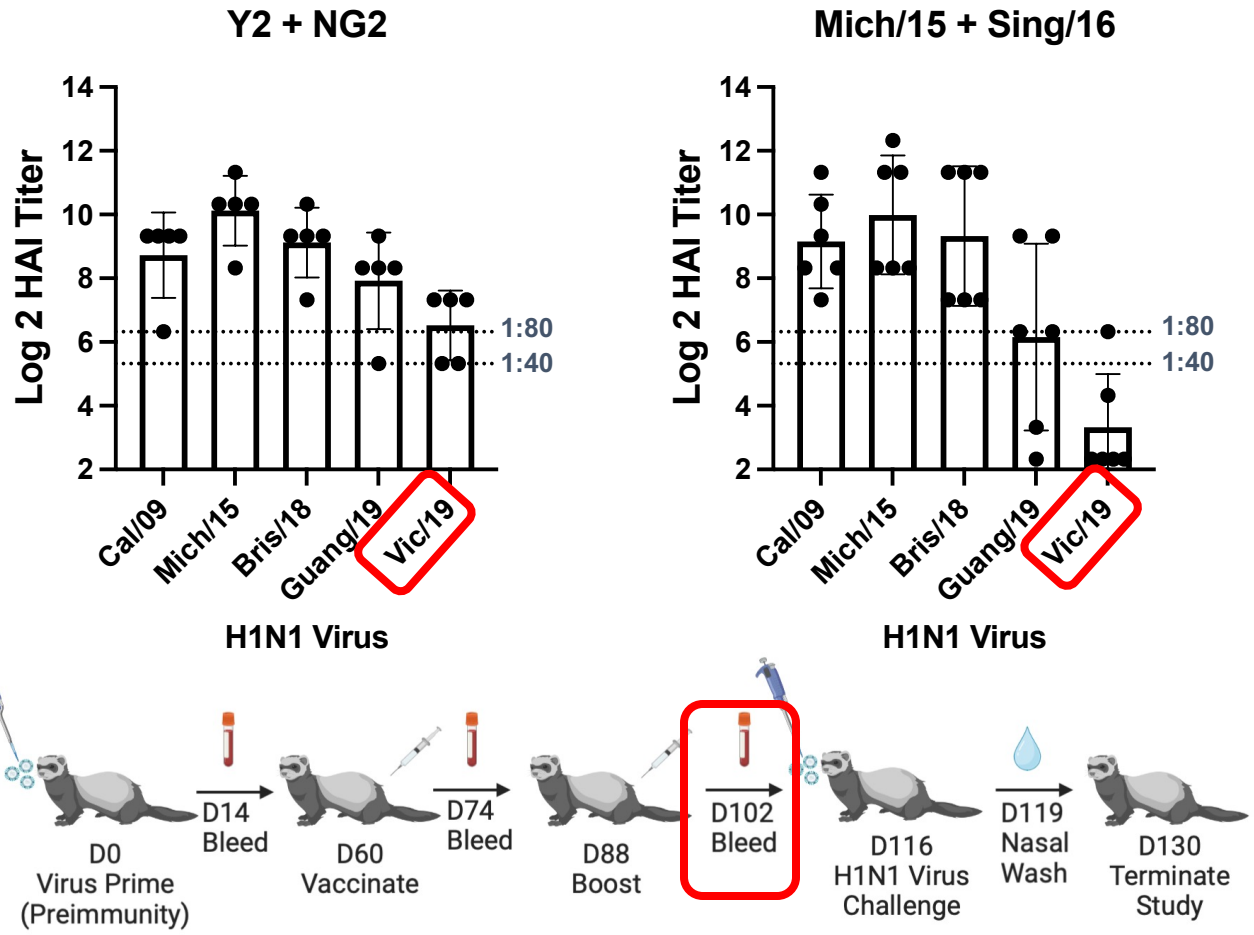
Pre-immune Ferret Model



- Mimic human response to vaccination by first infecting ferrets with influenza viruses
  - H1N1 (A/Singapore/6/1986)
  - H3N2 (A/Panama/2007/1999)

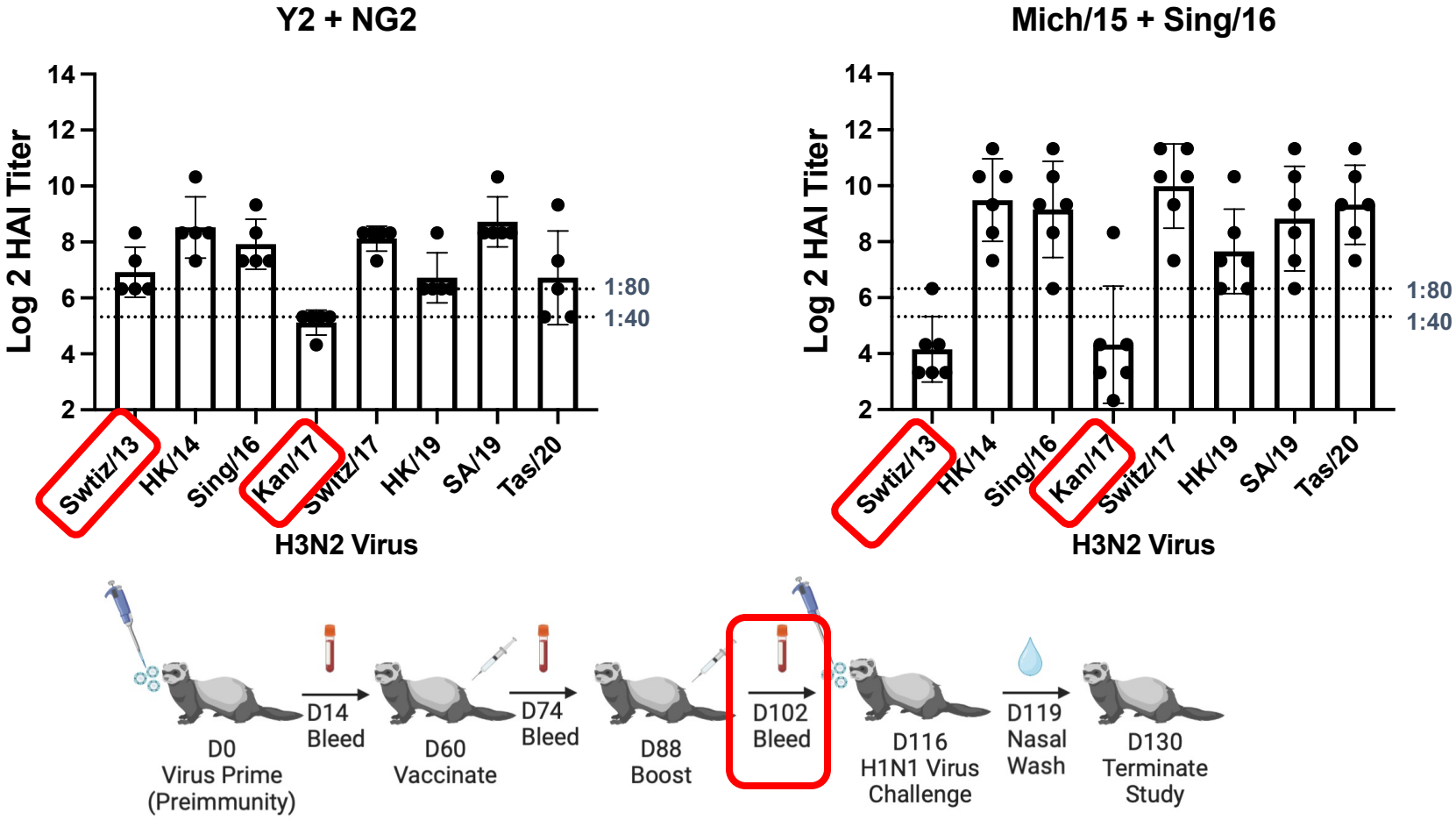
H1N1 HAI Response

- H1/H3 Pre-immune ferrets vaccinated 2x with Y2/NG2 rHA (15ug) + Infectimune® or wild-type rHA + Infectimune®

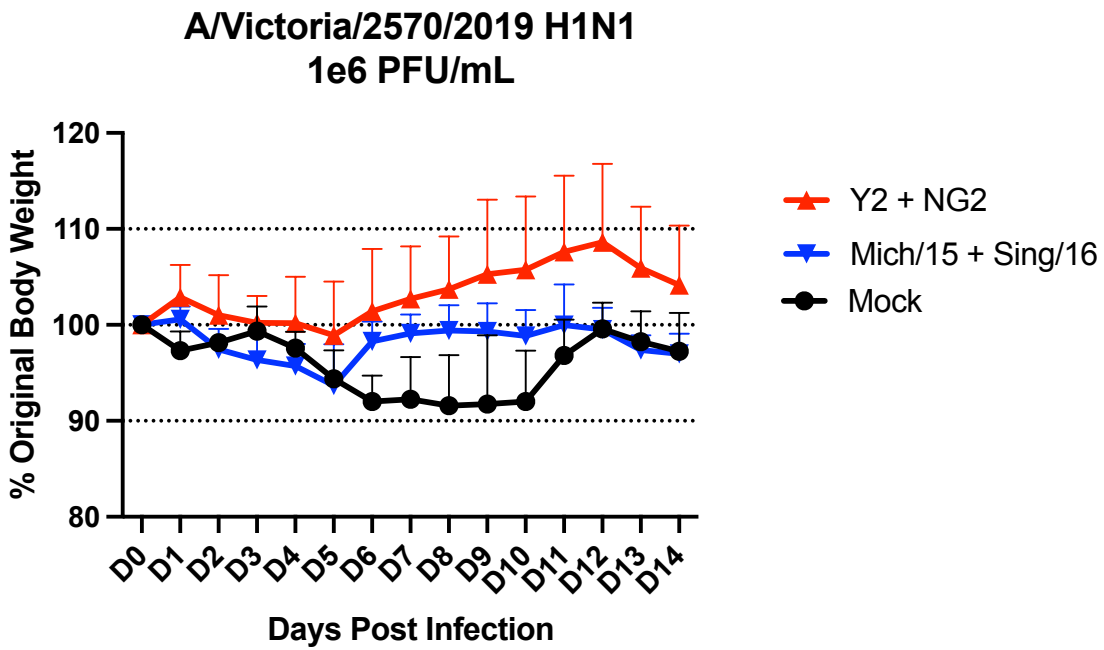


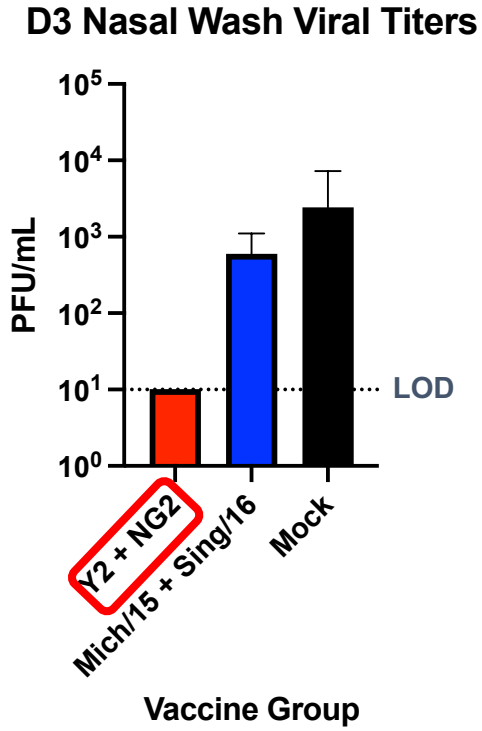
H3N2 HAI Response

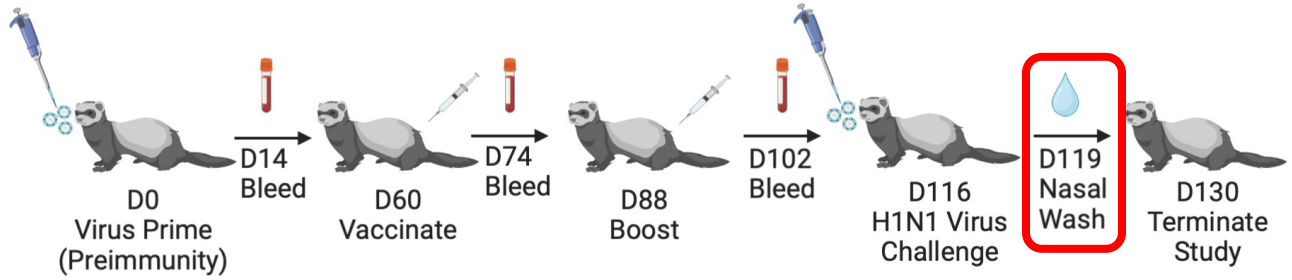
- H1/H3 Pre-immune ferrets vaccinated 2x with Y2/NG2 rHA (15ug) + Infectimune® or wild-type rHA + Infectimune®



H1N1 Infection Results







Conclusions

- COBRA rHA vaccines adjuvanted with Infectimune® capable of eliciting protective HAI antibody responses in pre-immune ferrets across panels of viruses from the last decade
  - Also elicit HAI reactive antibodies against future drifted viral isolates from 2019-2020
  - Prevent weight loss and H1N1 viral replication in the lungs of vaccinated animals
- In a population that has a more extensive pre-immune background to influenza, like humans, we expect these vaccines to generate a more broadly reactive antibody profile due to the recall of a more diverse population of memory B cells

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