Broadly protective vaccines for Flu and COVID: where are we and where should we go?

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A joint venture between The University of Melbourne and The Royal Melbourne Hospital

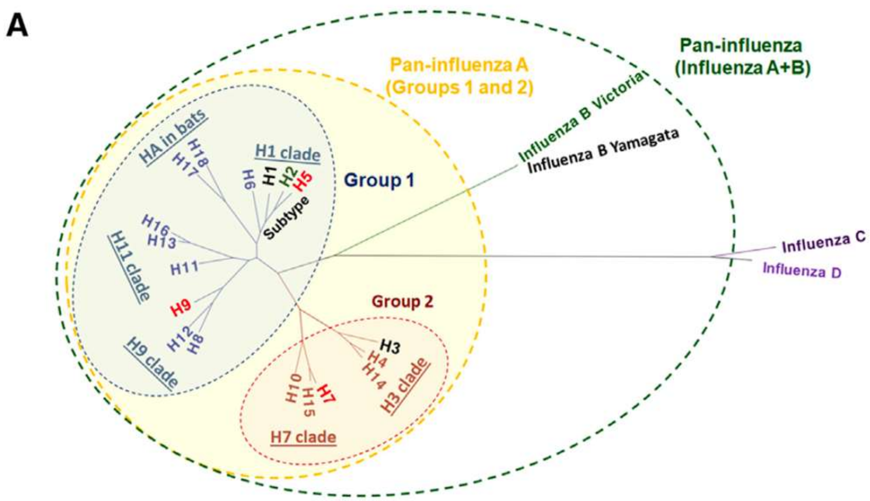
Key challenges for influenza and coronavirus vaccines

- Genetic diversity and animal reservoirs
- Antigenic change that allows escape from prior immunity
- Licensed, parenterally administered vaccines provide limited protection from infection and viral replication in the upper respiratory tract
- Strain-specific protection conferred by current vaccines

- Time to manufacture and deploy vaccines
- Poor vaccine effectiveness in vulnerable populations
- Poor immunogenicity of avian influenza vaccines

Genetic relationship and conservation among influenza viruses

Influenza viruses

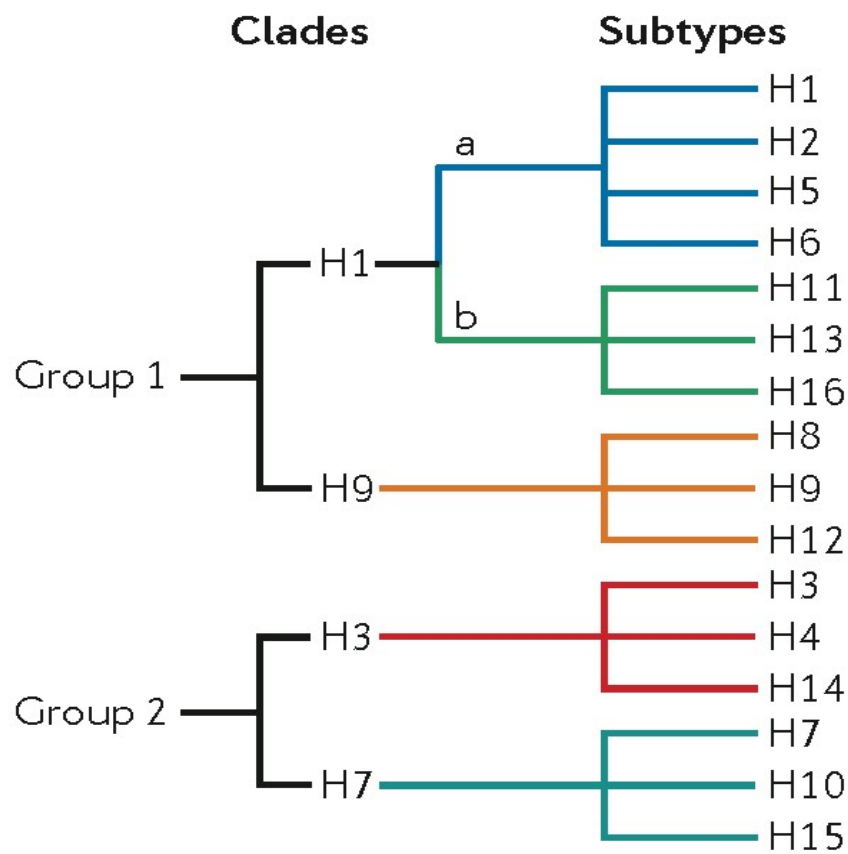


B

	HA	HA stalk	NA	M2e	M1	NP	PA	PB1	PB2	NS1	NS2
Pan *IAV and IBV*	24	27	26	12	25	34	33	60	36	12	17
Pan A *IAV H3 and H1*	37	47	38	79	92	89	93	97	94	77	90
Group *H1 and H5*	62	50	86	96	96	94	96	97	97	80	88
Subtype *H1N1-2022*	95	100	95	92	98	99	99	99	98	95	97

20 40 60 80 100
% conservation

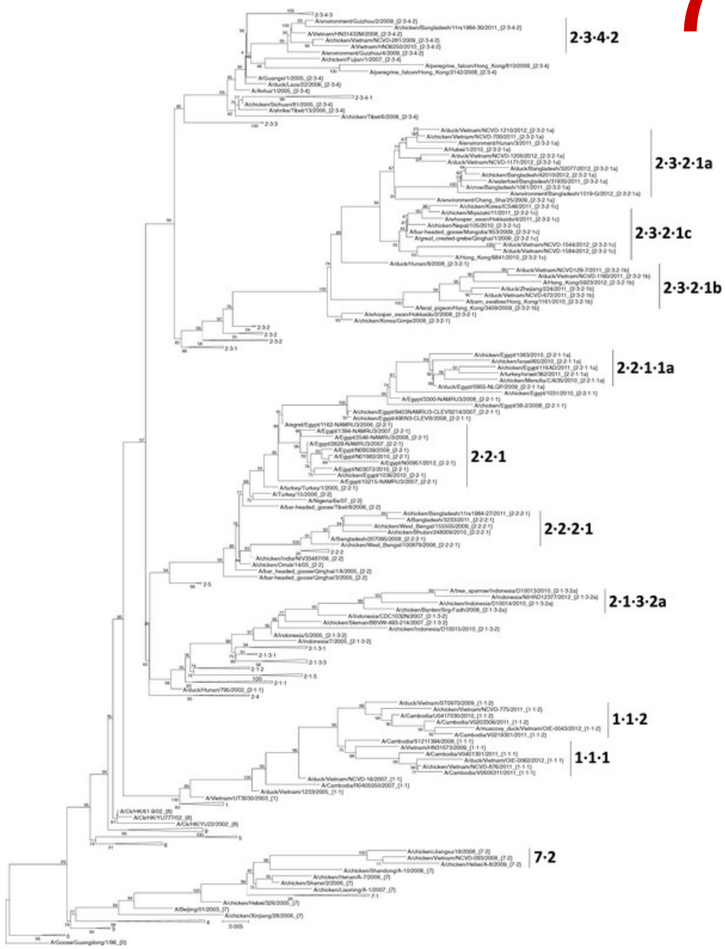
Influenza A HAs

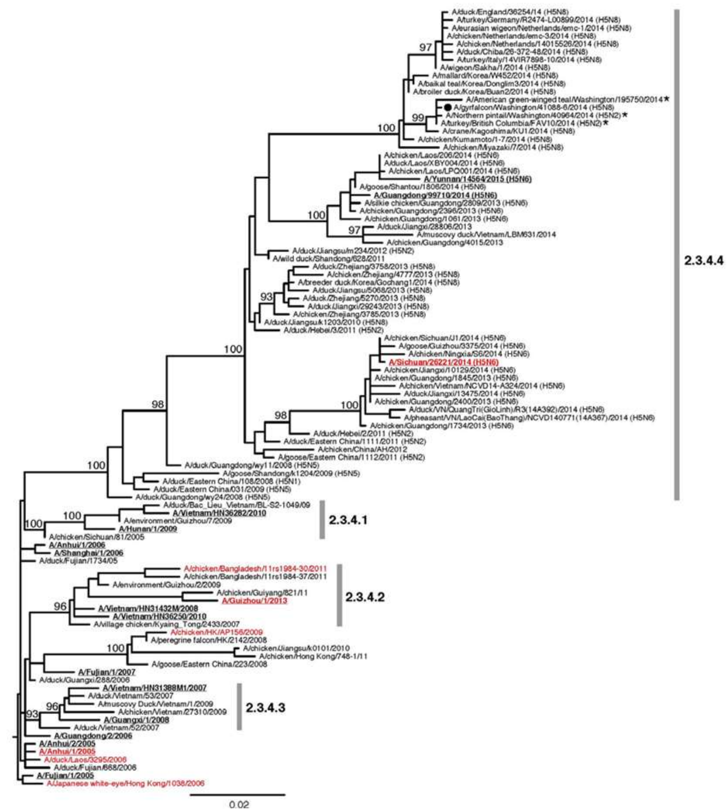


Tan et al *Cell Host and Microbe* 2023

Medina and Garcia-Sastre *Nat Rev Microbiol* 2011

The Diversity of H5N1 viruses





Influenza and Other Respiratory Viruses 8: 384-388; 2014

http://www.who.int/influenza/vaccines/virus/201502_zoonotic_vaccinevirusupdate.pdf?ua=1

Goals of vaccination

Durable broad-spectrum immunity that is effective against currently circulating strains, future variants and viruses that circulate in animals and pose a zoonotic/pandemic threat

- Preventing severe illness and death
- Preventing disease
- Preventing transmission (will require control of viral replication)
- Preventing infection

Ideal Properties of a Universal Coronavirus Vaccine

Individual Protection

Necessary
- Prevents clinical disease
- Prevents infection by all sarbecoviruses and merbecoviruses
- Prevents infection by viral drift and recombination variants
- Elicits a rapid and robust immune response
- Does not have limited vaccine immunogenicity in persons with preexisting immunity
- Induces immunity to multiple viral components
- Is safe and acceptable to the public
- Is safe for pregnant women
- Does not induce antibody-dependent enhancement with subsequent wild-type virus exposure
- Can be used in persons of all ages

Desirable
- Is highly efficacious in one dose
- Induces robust lifelong systemic immunity
- Induces robust lifelong mucosal immunity
- Induces a boost in immunity with subsequent wild-type virus exposure
- Does not alter the respiratory microbiome
- Is affordable and can be used in low-income countries
- Is efficacious in persons with immunosuppression

Morens *NEJM* 2022

Ideal Properties of a Universal Coronavirus Vaccine-2

Community Protection

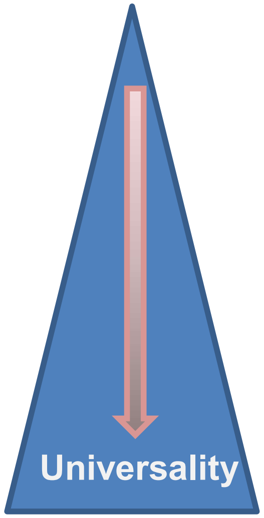
Necessary
- Covers all sarbecoviruses and merbecoviruses
- Covers all endemic human coronaviruses
- Can be used for pandemic prevention
- Is based on a platform that is easily upgraded with new antigens

Desirable
- Prevents transmission
- Reduces or shortens viral shedding
- Creates durable herd immunity
- Does not elicit neutralization escape mutants
- Is stable in storage
- Induces a boost in immune protection with sequential vaccination

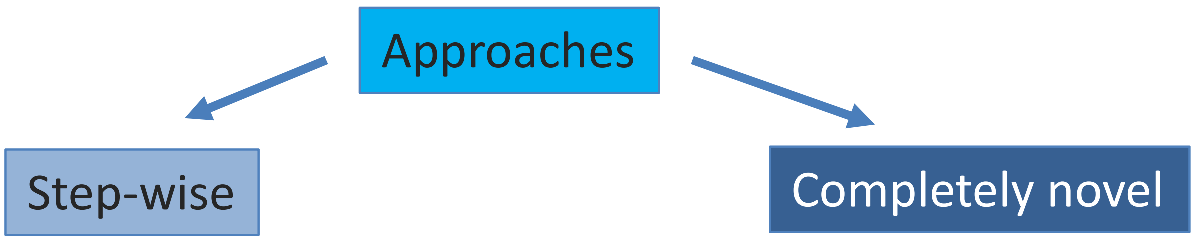
* The features listed describe a truly universal vaccine, although current vaccine approaches are unlikely to achieve all these goals. The highest priority should be universal coverage of betacoronaviruses, with additional coverage of endemic and other coronaviruses.

Morens *NEJM* 2022

Breadth of protection from influenza vaccines



Vaccine	Coverage
Strain Specific	Current circulating strains
Subtype Specific	All strains within a single HA subtype (e.g. H3)
Multisubtype	Multiple HA subtypes within a group (e.g. H1/H2/H5)
Pan-group	Covering all influenza A viruses (group 1 & group 2)
Universal	All influenza A viruses (with or without influenza B)



Adapted from Gary Nabel; Erbelding *JID* 2018

Immune responses

- Systemic antibodies (IgG)
  - Neutralising Abs in the systemic circulation protect the lower respiratory tract (influenza, SARS-1, SARS-CoV-2)
  - Non neutralising antibodies mediate pan-sarbecovirus protection in a mouse model*
- Mucosal antibody (IgA)
  - Critical for protection in the upper respiratory tract
  - Difficult to elicit, measure and sustain
- T cell responses
  - CD4 help for B cells and antibody
  - CD8 T cells clear virus infected cells (influenza)

*Adams Cell Reports 2023

Viral targets

- Influenza:
  - Hemagglutinin: full length/HA stem
  - Neuraminidase
  - M2
  - NP
- Coronaviruses
  - Spike: full length/RBD/S2 domain

Vaccine strategies

Achieving breadth:

- Mixture of antigens eg different HAs or RBDs
- Computationally optimised broadly reactive antigens (COBRA)
- Present a conserved region eg HA stem or S2 stem-helix

Vaccine presentation:

- Modified nucleic acid nanoparticles
- Protein: purified or on nanoparticles; adjuvants
- Vectored
- Inactivated virus vaccines
- Live virus vaccines
- Virus like particles

Experience with influenza

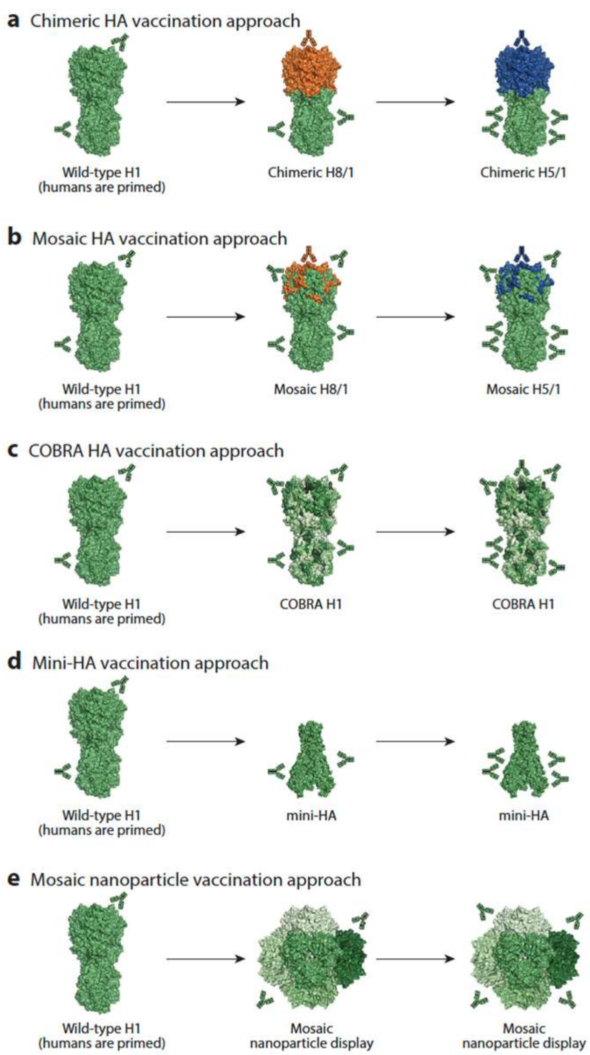
Universal influenza vaccines

are novel vaccine candidates designed to provide broader and more durable protection against circulating and pandemic influenza viruses, compared with current strain-specific seasonal influenza vaccines.

Slide adapted from Chris Chadwick, WHO; https://ivr.cidrap.umn.edu/universal-influenza-vaccine-technology-landscape

Experience with influenza

- Chimeric HAs with a conserved HA stem epitope
- Headless HAs
- Bacterially expressed soluble trimers
- Stem-only immunogen on ferritin nanoparticles
- Co-immunization with group 1 and group 2 HA stem immunogens
- Mosaic display of diverse HAs on nanoparticles
- Computationally optimised HAs
- Multivalent whole virus vaccine
- Neuraminidase based vaccines
- Multivalent VLPs
- Multivalent mRNAs
- Peptide vaccine



Krammer and Palese *Ann Rev Med* 2020

Number of Universal Influenza Vaccine Candidates *by platform and phase*

	Preclinical	Phase 1	Phase 2	Phase 3	Approved
Recombinant proteins	36	0	3	1	0
Recombinant influenza virus-based	13	2	3	0	0
Virus-vectored	21	2	3	0	0
Virus-like particles (VLP)	26	2	0	1	0
Non-VLP nanoparticles	36	4	2*	1	0
Nucleic acid-based	22	6*	5	3*	0

* Combined influenza and COVID vaccine

Slide adapted from Chris Chadwick, WHO

Universal influenza vaccine candidates in clinical development (active)

Recombinant proteins

ConserV Bioscience (UK), Imutex (UK)
FLU-v

Janssen Vaccines and Prevention J&J (Netherlands)
G1 mHA

Recombinant influenza virus-based

FluGen (US)
RedeeFlu M2SR

Vivaldi Biosciences (US)
deltaFLU

Icahn School of Medicine at Mount Sinai (US)
Chimeric HA constructs

National Institute of Allergy and Infectious Diseases (US)
BPL-1357

Codagenix (US)
CodaVax

Virus-vectored

Vaxart (US)
VXA-A1.1 oral tablet

Virus-like particles (VLP)

Russian Academy of Sciences (Russia), VA Pharma (Russia)
HBc-4M2eh (Uniflu)

Non-VLP nanoparticles

Novavax (US), Emergent BioSolutions (US)
Nano-Flu (qNIV)

Novavax (US)
CIC

Osivax (France)
OVX836

Emergent BioSolutions (US)
EBS-UFV-001

National Institute of Allergy and Infectious Diseases (US)
FluMos-v1

National Institute of Allergy and Infectious Diseases (US), Sanofi Pasteur (US)
Stabilized headless HA stem nanoparticles

Nucleic acid-based

Moderna (US)
Modified mRNA lipid nanoparticles

Pfizer (US), BioNTech (Germany)
Modified mRNA

CureVac (Germany), GSK (US)
Flu-SV-mRNA vaccines

Pfizer (US)
Self-amplifying RNA

Sanofi Pasteur (US)
mRNA

CSL-Seqirus (US), Arcturus Therapeutics (US)
sa-mRNA

NIAID, NIH (US)
DCVC H1 HA mRNA-LNP

NIAID, NIH (US)
VRC H1ssF mRNA-LNP

Slide adapted from Chris Chadwick, WHO

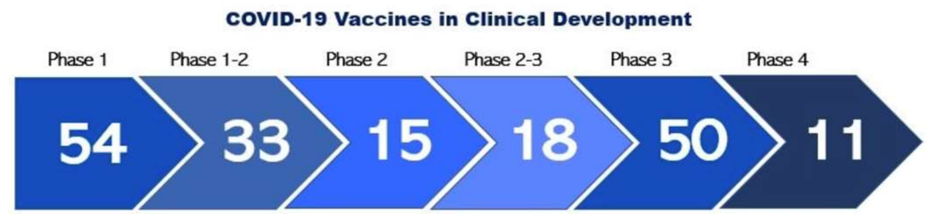
Coronaviruses vaccine development

COVID-19 vaccine tracker and landscape

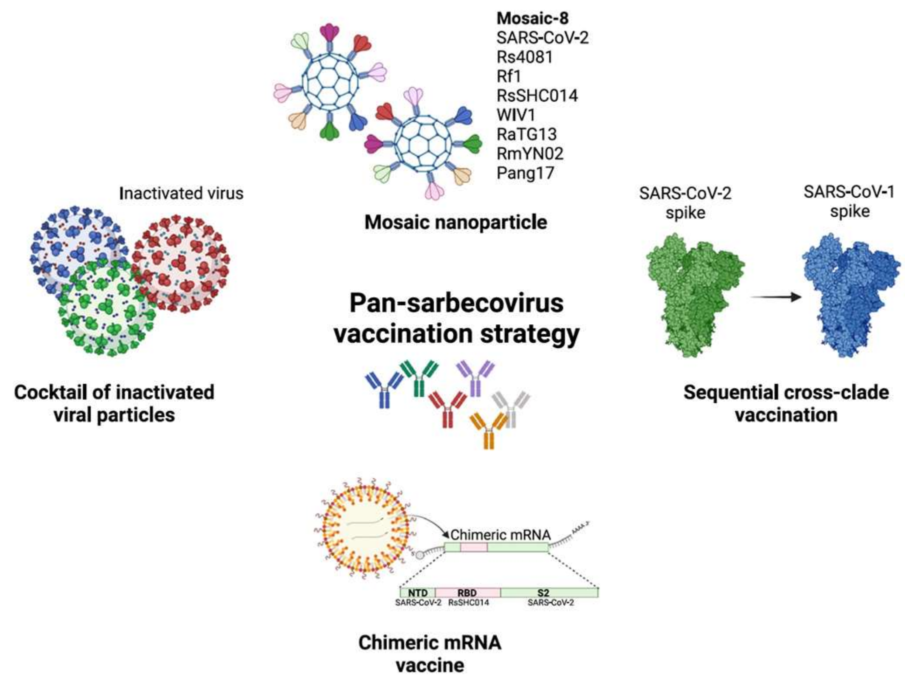
382 Total candidate vaccines

183 Clinical phase

199 Pre-clinical phase



Strategies for developing pan sarbecovirus vaccines



https://www.who.int/teams/blueprint/covid-19/covid-19-vaccine-tracker-and-landscape; Tan *CHM* 2023

Experience with broadly protective CoV vaccines

- Cross-clade boosting elicited by serial administration of vaccines based on distantly related S or RBD (Tan NEJM 2021)
- Characterisation of stem-helix human bnAbs that target conserved S2 sequences from different sarbeco- and merbeco- viruses and from use of multimeric RBD immunogens: lessons from structural biology (Liu STM 2022, Zhou Immunity 2023, Zang PNAS 2023)
- Multivalent VLP-S2 nanoparticle vaccines with adjuvants protected mice and hamsters against SARS-CoV-2 VOCs and pangolin CoVs (Halfmann eBioMedicine 2022)
- RBD-sortase conjugated ferritin nanoparticle vaccine with adjuvant, RBD conjugated with an Fc fragment and STING agonist, Mosaic RBD nanoparticles were evaluated in mice and NHPs (Li Nat Comms 2022, Zhou J Med Virol 2022, Fan Immunity 2022)

Knowledge gaps

- Strategies to induce lasting mucosal immunity
- Can S2 stem-helix bnAbs be induced in people who have not been infected with SARS-CoV-2?
- Strategies to subvert immunodominance and allow subdominant cross-reactive B cell response to emerge*
- Potential for escape from stem-binding antibodies**
- Vaccine Design:
  - Applying lessons learned from studies of the molecular basis for broad protection from passive Ab prophylaxis with bnAbs to immunogen design for vaccines
  - Mosaic nanoparticle design that confers breadth while preserving protective efficacy

*Kanikeyo *Nat Imm* 2019; **Lee *PNAS* 2023