Current Status of Universal Influenza Vaccine Research and Development

Punnee Pitisuttithum, MBBS, DTM&H,RCPT
Vaccine Trial Centre,
Faculty of Tropical Medicine , Mahidol University
GVIRF, 28 March 2023, Seoul Korea

- Epidemiology and VE of current influenza vaccines.
- Need for universal influenza vaccines.
- Influenza vaccine research and development road map.
- Update on clinical trials of universal influenza vaccines.
- Ways forward

Effectiveness of the seasonal influenza vaccines varies

Table 1: Vaccine effectiveness against medically attended influenza A and A(H3N2), 2021–2022

Flu type	Flu-positive		Flu-negative		Adjusted Interim VE*	
	Total	Vaccinated no. (%)	Total	Vaccinated no. (%)	%	Confidence Interval
Flu A						
Overall	**468**	198 (42%)	**3,844**	2,265 (59%)	**36**	**(21–48)**
Flu A (H3N2)						
Overall	**440**	182 (41%)	**3,844**	2,265 (59%)	**36**	**(20–49)**

Abbreviations: VE = vaccine effectiveness.

https://www.cdc.gov/flu/vaccines-work/2021-2022.html#print

Flu type	Flu-positive		Flu-negative[1]		Adjusted Interim VE[2]	
	Total	Vaccinated no. (%)	Total	Vaccinated no. (%)	%	Confidence Interval
Influenza A(H3N2)						
Overall	440	182 (41%)	3,844	2,265 (59%)	36	(21–48)
6 mos – 8 years	95	33 (35%)	622	356 (57%)	51	(19–70)
9 – 17 years	117	39 (33%)	499	214 (43%)	34	(-7–59)
18 – 49 years	165	68 (41%)	1,685	935 (55%)	32	(3–52)
50 years and older	63	42 (67%)	1,039	760 (73%)	10	(-60-49)

[1] Persons testing negative for both influenza and SARS-CoV-2 using molecular assays.

[2] Multivariable logistic regression models adjusted for site, age, month of onset, self-rated general health status, and race/ethnicity.

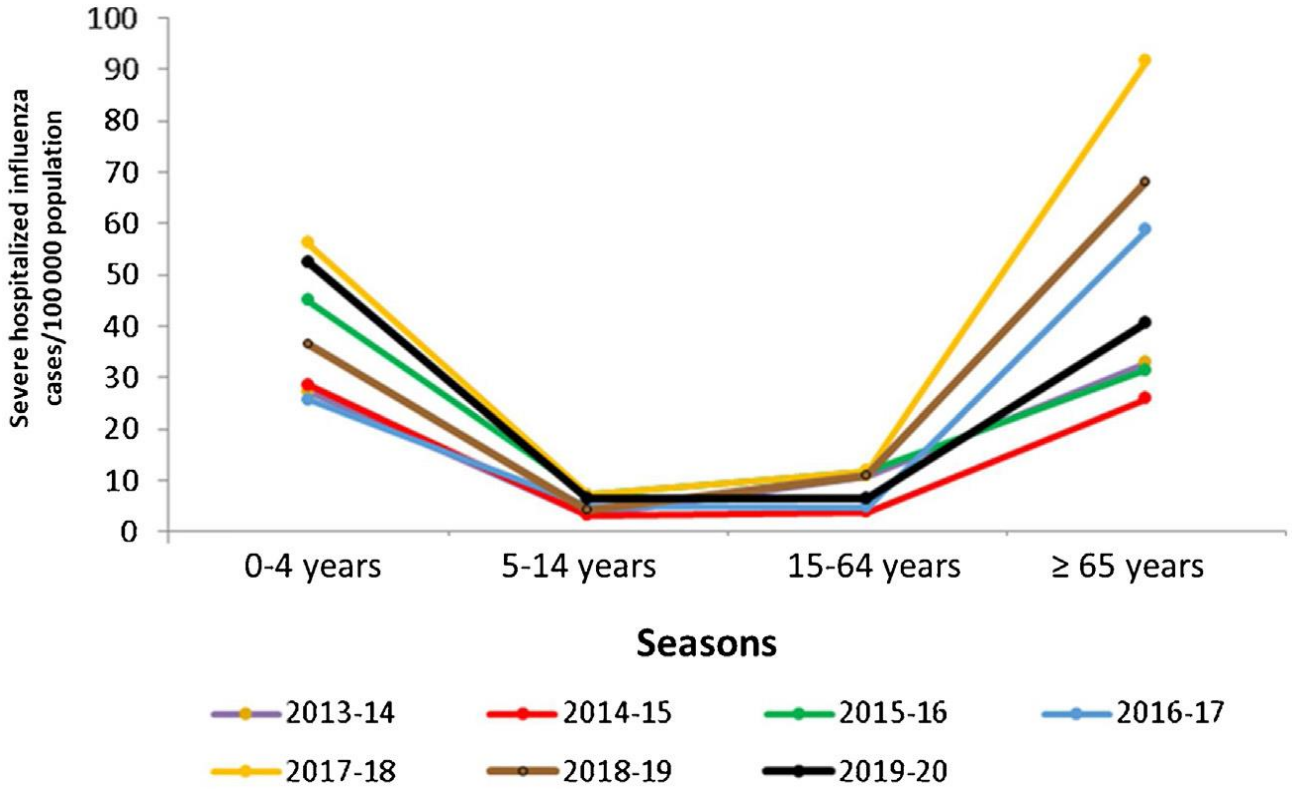
Last Reviewed: December 22, 2022

https://www.cdc.gov/flu/vaccines-work/2021-2022.html#print

Efficacy and effectiveness of influenza vaccination in healthy children. A review of current evidence

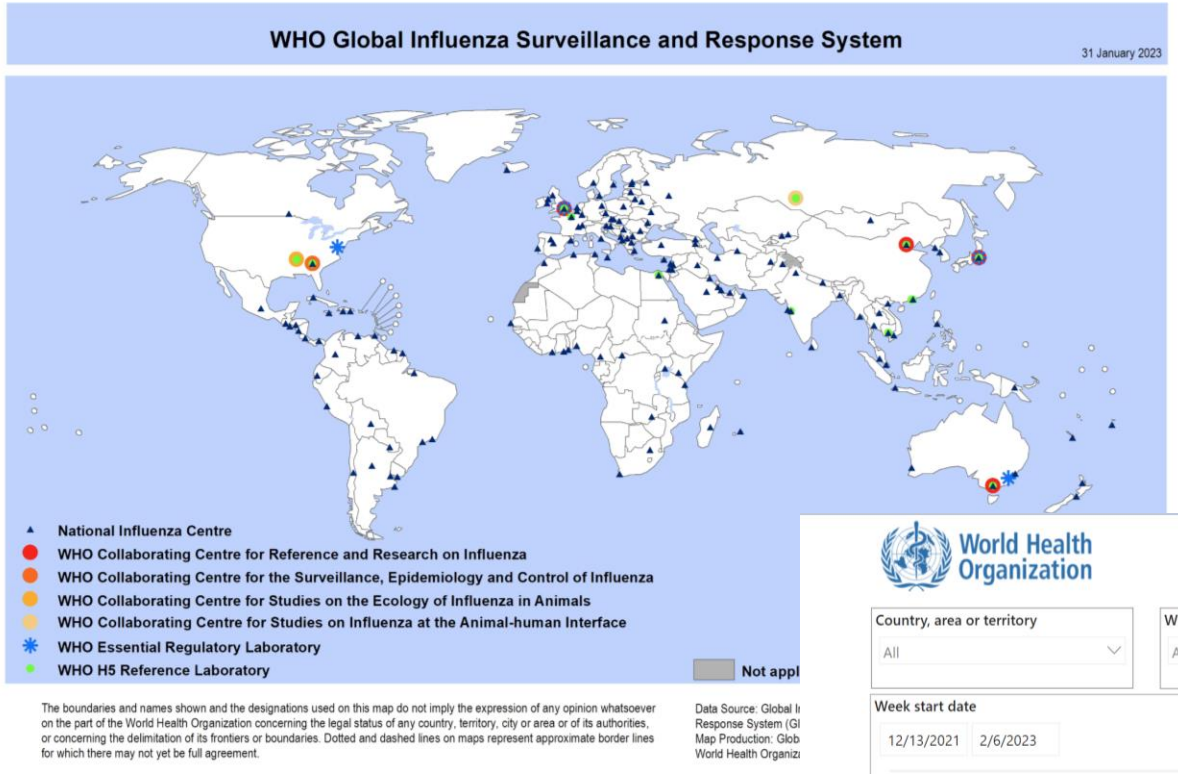
- The aim of this paper was to review the available evidence on the efficacy/effectiveness of influenza vaccination in healthy children <18 years of age through a non-systematic search of studies conducted between 2010 and 2020.

- Despite the 41 selected studies, statistically significant studies show efficacy values for the influenza vaccine of between 25.6% and 74.2%, and effectiveness from 26% to 78.8%.



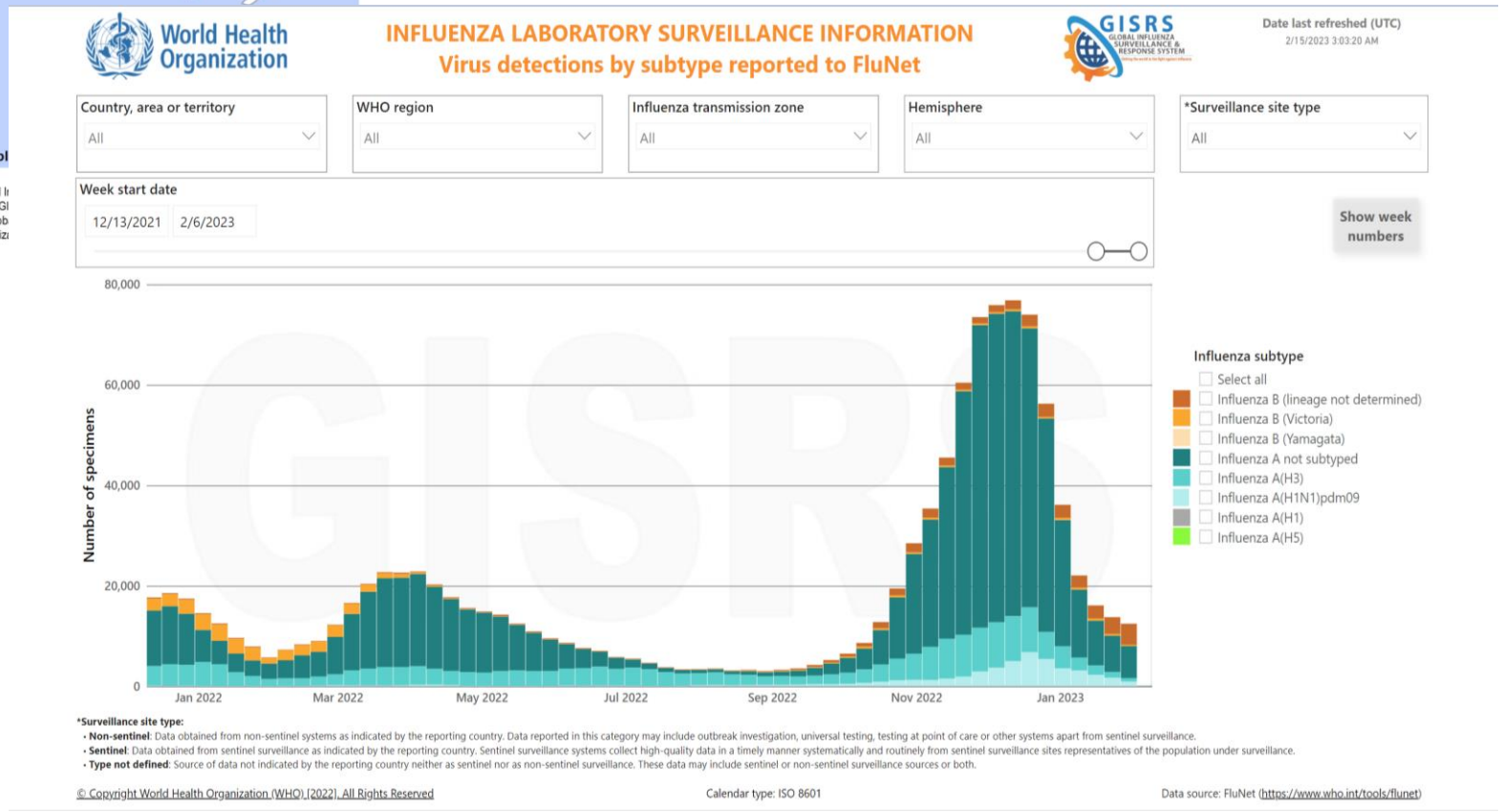
Severe hospitalized influenza cases in Spain in the seasons from 2013 to 2020 by age group

Orrico-Sánchez A, Valls-Arévalo Á, Garcés-Sánchez M, Álvarez Aldeán J, Ortiz de Lejarazu Leonardo R. Efficacy and effectiveness of influenza vaccination in healthy children. A review of current evidence. Enferm Infecc Microbiol Clin (Engl Ed). 2023.



https://www.who.int/initiatives/global-influenza-surveillance-and-response-system

https://www.who.int/tools/flunet



Challenges

- Strain-specific seasonal flu vaccines do not provide broad protection- NEED annual immunization
- Vaccine-induced immunity is short-lived.
- Vaccine effectiveness is suboptimal
- Lengthy production times for vaccines may not keep pace with antigenic changes in the vaccine viruses resulting from egg based vaccine production can also results in antigenic mismatches
- Efforts have been made , moving toward cell culture based technology, adding adjuvants, alternative vaccine delivery

With the antigenic shift , led to new policies, initiatives and funding programs. Innovations in various field like systems biology, structure biology, immunology, vaccinology

Organization	Initiative
World Health Organization (WHO)	***Global Influenza Strategy 2019-2030*** • Promotes research and innovation to develop novel, improved, and universal influenza vaccines • Strategies to reduce global morbidity and mortality from influenza.
US National Institute for Allergy and Infectious Diseases (NIAID)	***Strategic Plan for Universal Influenza Vaccine*** Serves as a foundation for NIAID's research investments and envisions a transformative effort toward the development of a universal influenza vaccine that improves the breadth and durability of protection against seasonal influenza and provides protection from pandemic strains.

Organization	Initiative
Sabin Vaccine Institute and the Aspen Institute	***Sabin-Aspen Vaccine Science and Policy Group*** Published a 2019 report, Accelerating the Development of a Universal Influenza Vaccine, proposing the creation of a new collaborative entity to spearhead universal influenza vaccine development, mobilize funding, advance research that enables transformational change in influenza vaccine technology, and implement a communications strategy reflecting the scale and urgency of the public health need for universal influenza vaccines.
Task Force for Global Health	***Global Funders Consortium for Universal Influenza Vaccine Development*** **Convenes stakeholders to share information about ongoing investments and strategic plans, facilitate collaboration** to address challenges, coordinate funding guided by a common vision, and raise awareness of the importance of universal influenza vaccine research and development (R&D) .

Bill and Melinda Gates Foundation (BMGF)	***Universal Influenza Vaccine Development Grand Challenge*** Supports novel, transformative research leading to the development of universal influenza vaccine candidates, aligned with the characteristics outlined in BMGF's intervention target Product profile(TPP).
Wellcome Trust University of Minnesota, Center for Infectious Disease Research & Policy (CIDRAP)	***Influenza Vaccines Research and Development Roadmap*** An international collaborative effort to develop an R&D roadmap aimed at accelerating progress to ward improved influenza vaccines, balancing transformative and pragmatic changes in vaccine technology to improve breadth and durability of protection from influenza infection and/or severe disease.
US Government (USG)	***Executive Order 13887: Modernizing Influenza Vaccines in the United States to Promote National Security and Public Health*** Directs USG actions to reduce reliance on egg-based influenza vaccine production; expand capacity for more agile and rapid vaccine production methods; advance the development of broadly protective vaccine candidates;and expand influenza immunization across recommended populations.

Global Stakeholder Engagement

147 international subject matter experts
100 organizations
20+ countries
online consultations and public comments

2019

The Global Funders Consortium for Universal Influenza Vaccine Development initiated development of the IVR

2021

The Influenza Vaccines R&D Roadmap was launched

2022

IVR Monitoring, Evaluation, and Adjustment (ME&A) phase began

2023

IVR Funding Tracker and Dashboard to be launched.

The Roadmap is a 10-year plan for prioritizing and coordinating global influenza vaccine R&D

- **Issues, knowledge gaps, and barriers to development**
- **24 strategic goals**
- **113 milestones, including 37 high-priority**
- **Additional research priorities**

6 key topic areas with goals and milestones for each

Vaccinology for universal influenza vaccines

Vaccinology for seasonal influenza vaccines

Virology applicable to vaccine development

Immunology and correlates of protection

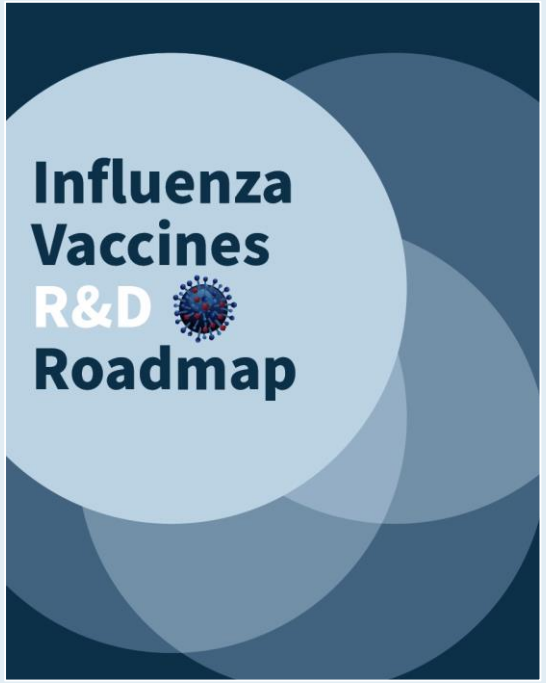
Animal and human infection models

A Framework to Prioritize R&D

Goal

1. Improve the production and effectiveness of strain-specific **seasonal influenza vaccines.**

2. Advance the development, licensure, manufacturing, and distribution of durable **broadly protective or universal influenza vaccines.**



CONCEPT of universal influenza vaccine varies

WHO working definition (Global vaccine action plan):

- Protection against influenza A virus illness at least 5 years.
- Suitability for high risk groups in low income and middle income countries. World Health Organization: WHO Preferred Product Characteristics for Next Generation Influenza Vaccines. WHO; 2017.

The Bill and Melinda Gates Foundation's Grand Challenges initiative :

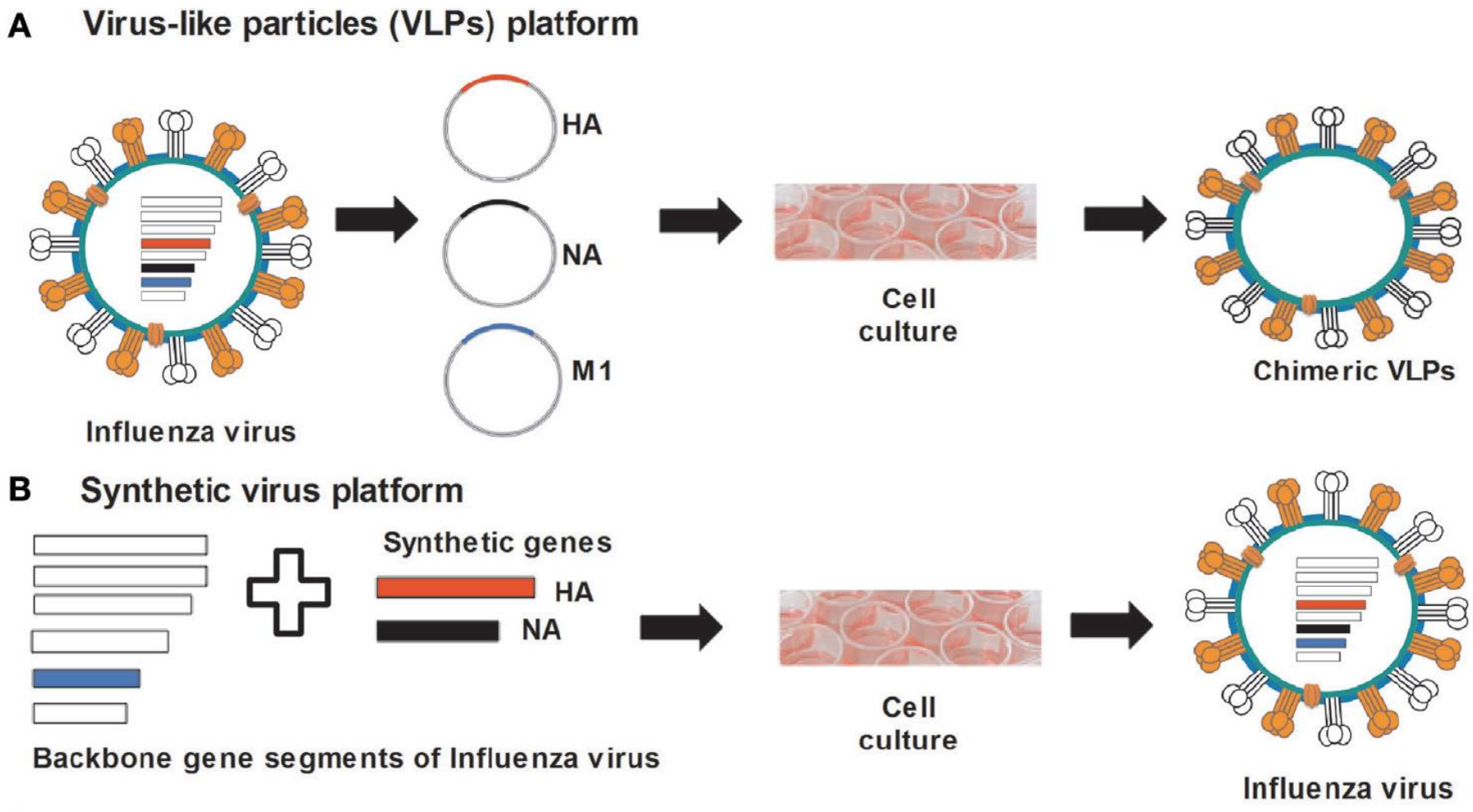
- Protection from morbidity and mortality caused by all subtypes of circulating and emerging (drifted and shifted) influenza A subtype viruses and influenza B lineage viruses for at least 3–5 years. Bill and Melinda Gates Foundation: Ending the Pandemic Threat: A Grand Challenge for Universal Influenza Vaccine Development. 2018.

The NIAID strategic plan for guiding research toward improved influenza vaccines:

- At least 75% effective against symptomatic influenza infection, protective against phylogenetic groups 1 and 2 influenza A viruses, provide durable protection for at least 1 year, and suitable for all age groups

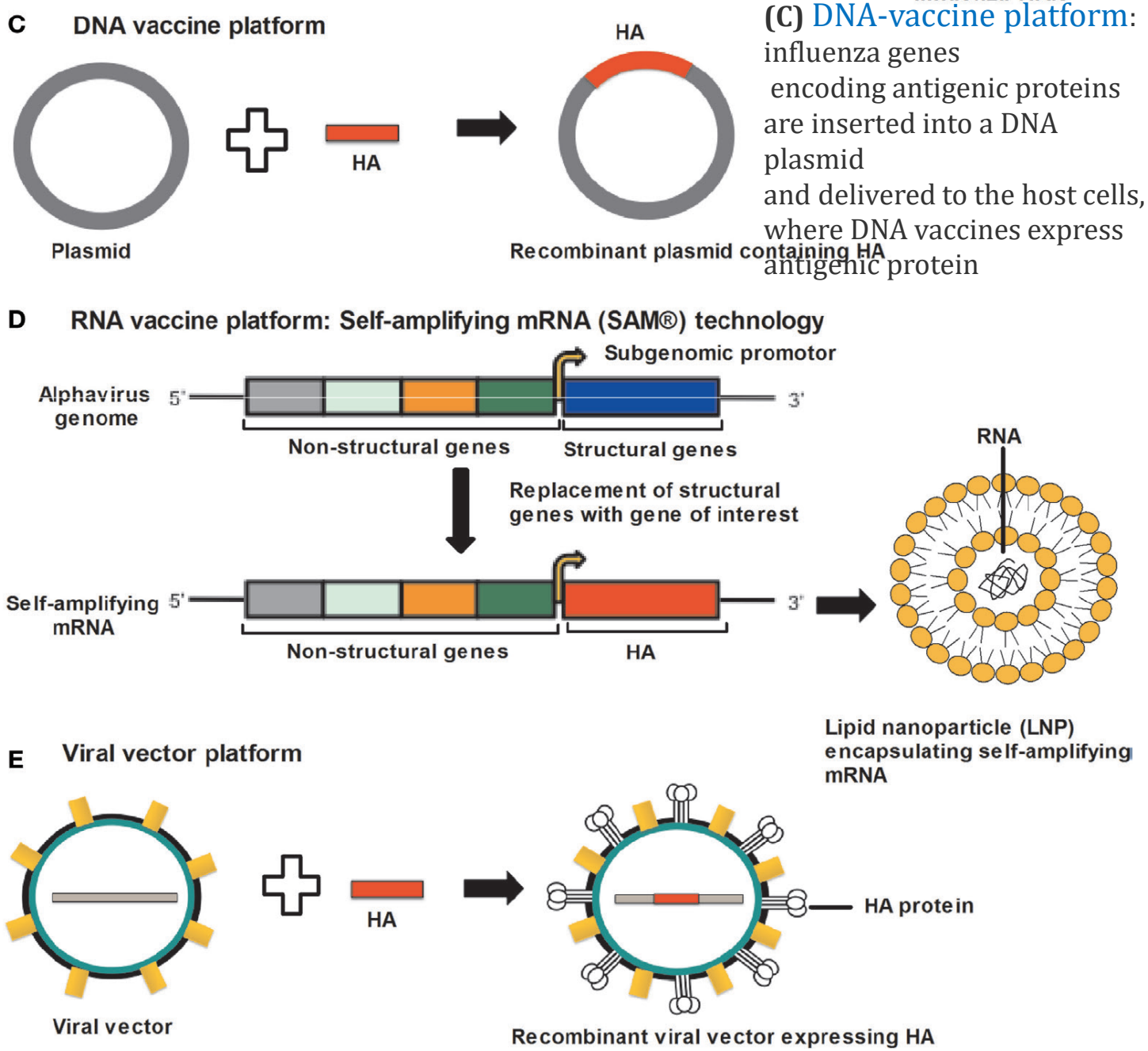
Novel Platforms for the Development of a Universal Influenza Vaccine

Kumar A, Meldgaard TS, Bertholet S. Novel Platforms for the Development of a Universal Influenza Vaccine. Front Immunol. 2018;9:600.



A) VLP platform: VLPs produced by cloning of HA, NA, and M1 gene sequences of influenza virus into the expression vector followed by transfection in to insect cells. Co-expression of HA, NA, and M1 proteins allows self-assembly of VLPs.
(B) Synthetic-virus platform: MDCK cells are transfected with plasmid DNA encoding influenza-virus backbone genes and error-free HA and NA gene segments, synthesized by an enzymatic and cell-free assembly technique. After transfection, vaccine viruses are rescued from MDCK cells.

Kumar A, Meldgaard TS, Bertholet S. Novel Platforms for the Development of a Universal Influenza Vaccine. Front Immunol. 2018;9:600.



(C) DNA-vaccine platform: influenza genes encoding antigenic proteins are inserted into a DNA plasmid and delivered to the host cells, where DNA vaccines express antigenic protein

D) RNA-vaccine platform: self-amplifying RNA expressed from an alphavirus genome in which structural genes are replaced by genes supporting the amplification of the RNA and the gene encoding the antigen. Self-amplifying mRNA (SAM) composed of a 5′ cap, genes encoding non-structural genes (NSP 1–4), a subgenomic promoter, the antigen-encoding gene, and a 3′ poly(A) tail. Diagrammatic representation of a lipid nanoparticle (LNP) encapsulating SAM.

E) Viral-vector platform: viral vector-based influenza vaccine uses a non-influenza “carrier” virus to express antigenic protein. Influenza genes encoding HA protein are placed in to the carrier virus vector to express HA protein on the virus surface

Kumar A, Meldgaard TS, Bertholet S. Novel Platforms for the Development of a Universal Influenza Vaccine. Front Immunol. 2018;9:600.

mRNA Influenza vaccine

ADVANTAGES

- This can also improve manufacturing, because making mRNA is less cumbersome compared to recombinant technology, facilitating vaccine approval and distribution.
- Second, vaccine immunity may be better or broader because the viral proteins will be expressed at high fidelity by human cells likely preserving the natural structure.
- Third, mRNA makes it easier to incorporate a larger number of antigens, which may stimulate cellular immunity or expand protection beyond HA and NA.

There are other hurdles too.

The immune responses induced by mRNA-based SARS-CoV-2 vaccines seem to tail off rather quickly following vaccination

UNIVERSAL INFLUENZA VACCINE TECHNOLOGY LANDSCAPE

159
Vaccine Candidates

28
Vaccines in Clinical Trials

128
Developers

6
Platforms

https://ivr.cidrap.umn.edu/universal-influenza-vaccine-technology-landscape-access on Feb 7 2023

Novel Influenza Vaccine Candidates in Active Clinical Development

Recombinant proteins

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

Recombinant influenza virus-based

FluGen (US)
RedeeFlu M2SR

Vivaldi Biosciences (US), Icahn School of Medicine at Mount Sinai (US)
deltaFLU

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

Icahn School of Medicine at Mount Sinai (US), GSK (US)
cHA-based LAIV combinations

Codagenix (US)
CodaVax

Virus-vectored

Vaxart (US)
VXA-A1.1 oral tablet

Jenner Institute, University of Oxford (UK)
MVA/ChAdOx2-NP+M1

Virus-like particles (VLP)

Russian Academy of Sciences (Russia), VA Pharma (Russia
M2e based recombinant fusion proteins/VLP

Non-VLP nanoparticles

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

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)
mRNA vaccines

Pfizer (US)
Self-amplifying RNA

Sanofi Pasteur (US), Translate Bio (US)
mRNA NA

Phase 3 vaccine candidate recently discontinued

	Phase 3
Recombinant proteins	1
Virus-like particles (VLP)	1
Non-VLP nanoparticles	1
Nucleic acid-based	2

- BiondVax P-Multimeric- 001-stopped
- Medicago (Canada), Quadrivalent VLP (QVLP) plant-based virus-like particle vaccine candidate

2023: Medicago closed after deciding not to produce its COVID-19 vaccine

Vaccine status: *inactive*

Comparison of the safety and immunogenicity of a novel Matrix-M-adjuvanted nanoparticle influenza vaccine with a quadrivalent seasonal influenza vaccine in older adults: a phase 3 randomised controlled trial

- qNIV was well tolerated
- Produced a qualitatively and quantitatively enhanced humoral and cellular immune response in older adults.
- These enhancements may be critical to improving the effectiveness of currently licensed influenza vaccines.

Funded by Novavax

Shinde V, Cho I, Plested JS, Agrawal S, Fiske J, Cai R, et al. Comparison of the safety and immunogenicity of a novel Matrix-M-adjuvanted nanoparticle influenza vaccine with a quadrivalent seasonal influenza vaccine in older adults: a phase 3 randomised controlled trial. Lancet Infect Dis. 2022;22(1):73-84.

Table: Summary of day 28 haemagglutination-inhibiting GMTs, GMTRs, SCRs, and SCR difference for vaccine-homologous strains with qNIV and IIV4

qNIV vs IIV4	A/Brisbane (H1N1)		A/Kansas (H3N2)		B/Maryland (B/Victoria)		B/Phuket (B/Yamagata)	
	HAI (egg)	HAI (wtVLP)	HAI (egg)	HAI (wtVLP)	HAI (egg)	HAI (wtVLP)	HAI (egg)	HAI (wtVLP)
Day 28 baseline-adjusted $GMTR_{(qNIV/IIV4)}$	1·09 (1·03–1·15)	1·24 (1·17–1·32)	1·19 (1·11–1·27)	1·66 (1·53–1·79)	1·03 (0·99–1·07)	1·32 (1·26–1·39)	1·23 (1·16–1·29)	1·47 (1·40–1·55)
p value	0·0027	<0·0001	<0·0001	<0·0001	0·15	<0·0001	<0·0001	<0·0001
Day 28 absolute SCR % difference	5·0% (1·9 to 8·1)	11·4% (7·9 to 14·7)	7·3% (3·6 to 11·1)	20·4% (16·6 to 24·1)	0·5% (−1·9 to 2·9)	11·6% (8·6 to 14·6)	8·5% (5·0 to 11·9)	17·7% (14·3 to 21·0)
p value	0·0017	<0·0001	<0·0001	<0·0001	0·72	<0·0001	<0·0001	<0·0001

Data are mean (95% CI) unless otherwise stated.

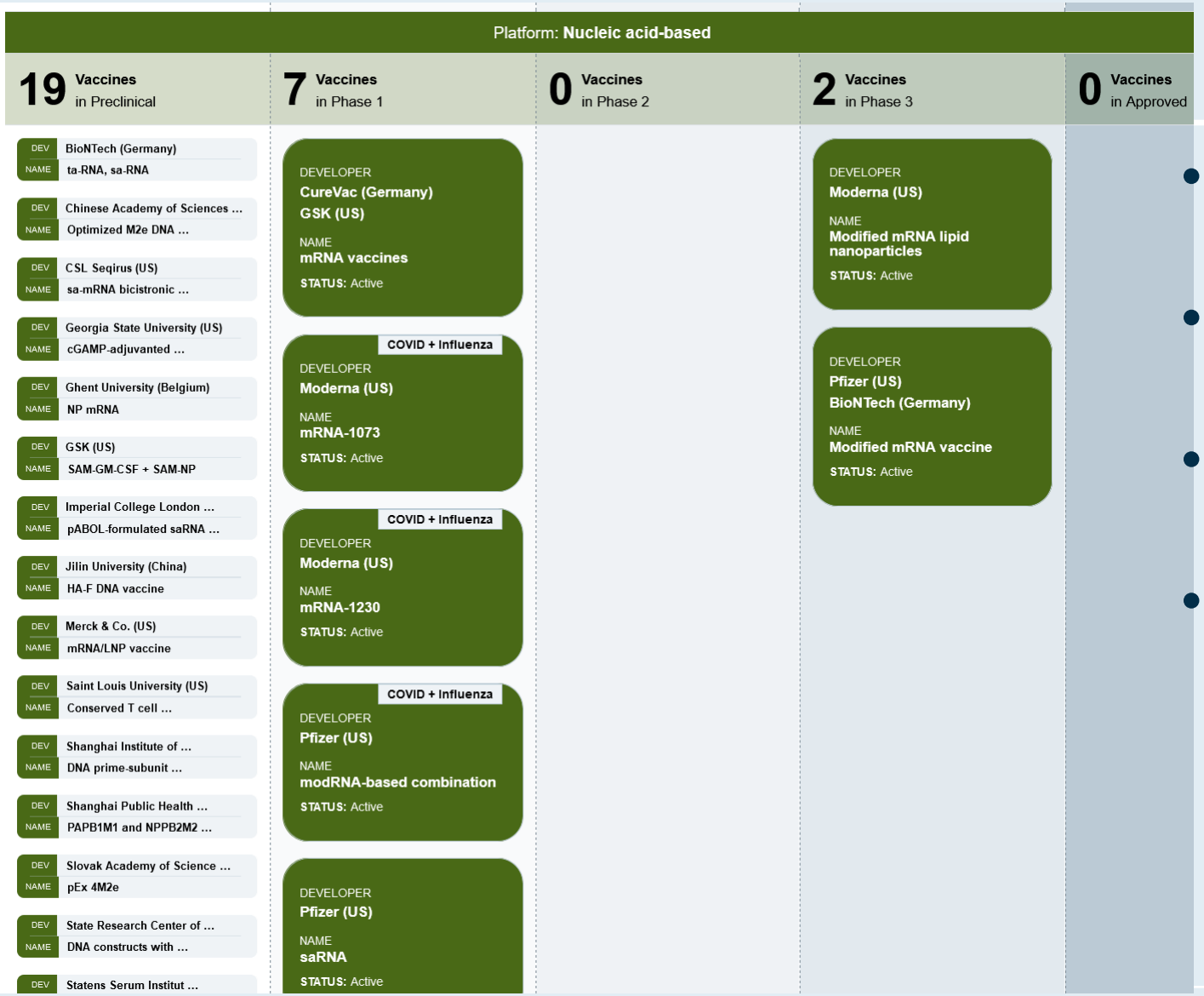
SCR was defined as percentage of participants with either a baseline haemagglutination-inhibiting titre of less than 1/10 and a post-vaccination titre of at least 1/40, or a baseline haemagglutination-inhibiting titre of at least 1/10 and a four-fold increase in post-vaccination haemagglutination-inhibiting titre relative to baseline. Percentages were based on the number of participants with non-missing haemagglutination-inhibiting titre values in the per-protocol population who received that treatment.

GMTR(qNIV/IIV4) was defined as the ratio of the GMTs of the two specified treatment groups at day 28. A mixed-effects model with treatment group and baseline haemagglutination-inhibiting antibody titres as covariates was done. The ratios of geometric least square, means, and 95% CIs for the ratio were calculated by back transforming the mean differences and 95% confidence limits for the differences of log (base 10) transformed total haemagglutination-inhibiting antibody titres between two specified treatment groups.

A/Brisbane=A/Brisbane/02/2018 H1N1 pdm09. A/Kansas=A/Kansas/14/2017 H3N2. B/Maryland=B/Maryland/15/2016 (Victoria lineage). B/Phuket=B/Phuket/3073/2013 (Yamagata lineage). GMFR=geometric mean fold rise. GMTR=geometric mean titre ratio. GMT=geometric mean titre. HAI=haemagglutination-inhibiting. IIV4=quadrivalent inactivated influenza vaccine. LLoQ=lower limit of quantitation. qNIV=quadrivalent nanoparticle influenza vaccine. SCR=seroconversion rate. SPR=seroprotection rate. VLP=virus-like particle. wt=wild-type.

Shinde V, Cho I, Plested JS, Agrawal S, Fiske J, Cai R, et al. Comparison of the safety and immunogenicity of a novel Matrix-M-adjuvanted nanoparticle influenza vaccine with a quadrivalent seasonal influenza vaccine in older adults: a phase 3 randomised controlled trial. Lancet Infect Dis. 2022;22(1):73-84.

Combination **COVID + Influenza** Vaccines



- Moderna mRNA-1073
- Moderna mRNA-1230
- Pfizer modRNA
- Novavax CIC recombinant HA nanoparticle, adjuvanted

Visit the IVR initiative at ivr.cidrap.umn.edu

COVID + Flu vaccine (mRNA-1073) Phase 1/2 is fully enrolled

Population

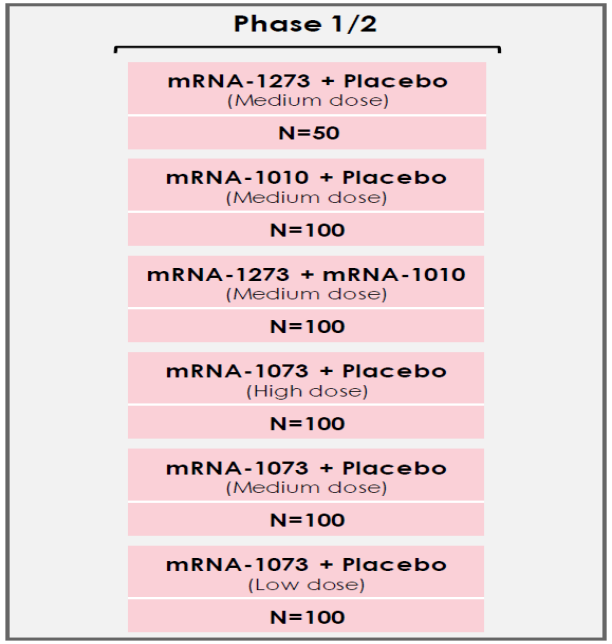
- Healthy adults aged 18 to 75 years old
- Must have received COVID-19 primary series

Vaccine composition

- Ability to update combination vaccine to latest approved regulatory products
- mRNA-1073 currently combines the prototype COVID-19 vaccine with the 2022 southern hemisphere flu vaccine composition

Trial update

- Trial is fully enrolled



moderna

A Study to Evaluate the Safety and Immunogenicity of a Single Dose of H1ssF-3928 mRNA-LNP in Healthy Adults supported by NIH

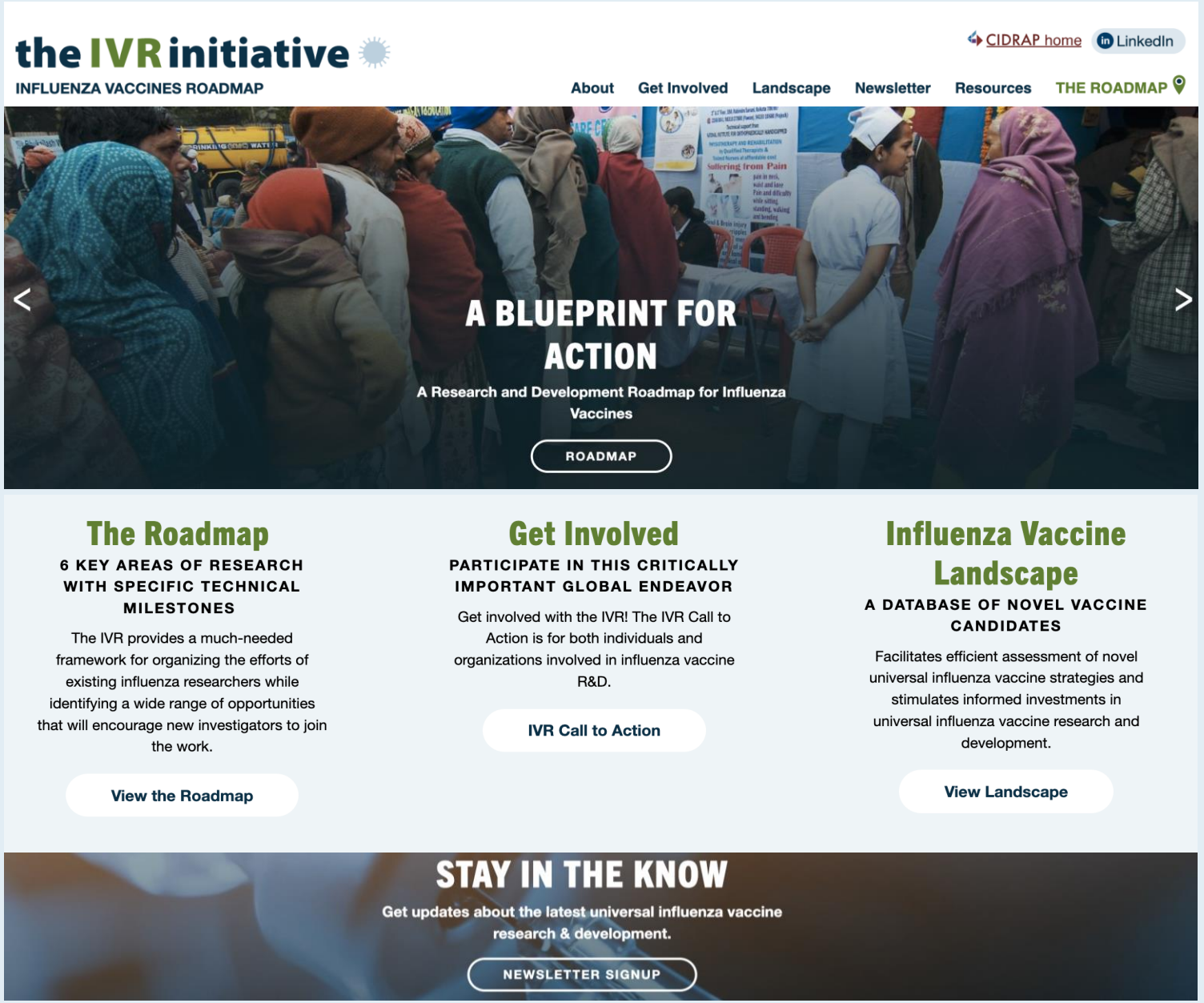
https://clinicaltrials.gov/ct2/show/NCT05755620

Condition or disease	Intervention/treatment	Phase
Influenza	Biological: Influenza Virus Quadrivalent Inactivated VaccineOther: Sodium Chloride, 0.9%Biological: VRC-FLUNPF099-00-VP (H1ssF_3928)	I

Conclusion

- The search for Universal Influenza continues
- Mostly focus on mRNA
- Working with available resources , collaborations, networking ,sharing , harmonizing

Together we can



ivr.cidrap.umn.edu

- View and download the IVR
- Resources
- Latest News
- Sign up for the IVR Newsletter
- Dashboard, coming soon
- **View the Influenza Vaccine Technology Landscape**
- **Sign the IVR Call to Action**

Acknowledgment

WHO
US CDC
NIH

University of Minnesota:
Kristine Moore,
Julie Ostrowsky,
Angela Ulrich,
Anje Mehr,
Eve Lackritz,
Michael Osterholm

Task Force for Global Health
(provides support for the Universal Influenza Vaccine Technology Landscape)
Wellcome Trust (provides support for the IVR initiative)
All the task Force members and Partners

Thanks for your attention