Overview of investigational products including broad protection against influenzavirus A(H_5N_1)

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What research is important to prepare and respond to H_5N_1 influenza outbreaks?

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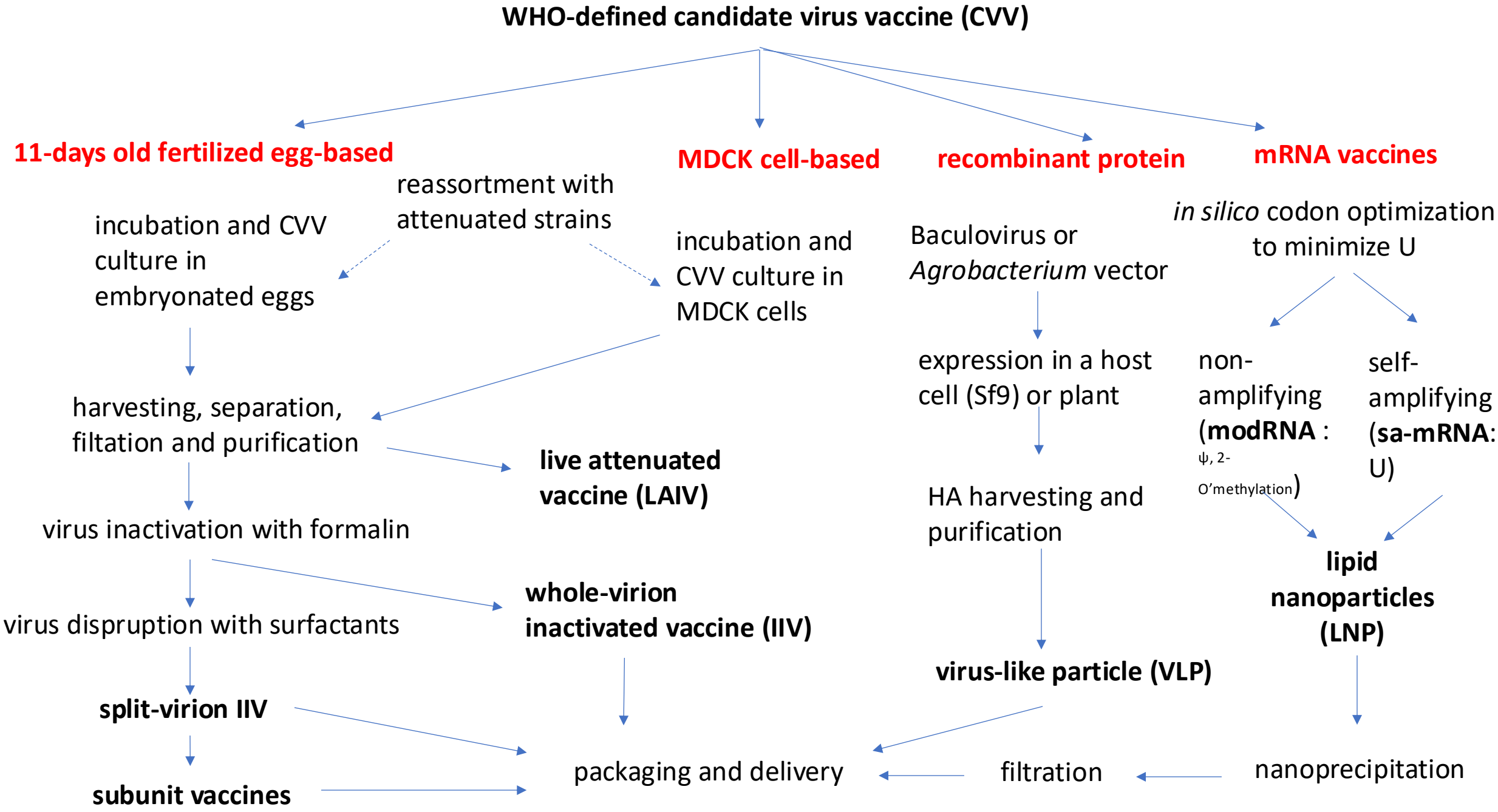
I declare I have no conflict of interest related to the content of my presentation.


WHO-defined candidate virus vaccine (CVV)
11-days old fertilized egg-based
MDCK cell-based
recombinant protein
mRNA vaccines
reassortment with attenuated strains
incubation and CVV culture in embryonated eggs
incubation and CVV culture in MDCK cells
Baculovirus or Agrobacterium vector
in silico codon optimization to minimize U
harvesting, separation, filtation and purification
live attenuated vaccine (LAIV)
expression in a host cell (Sf9) or plant
non-amplifying (modRNA : ψ, 2-O'methylation)
self-amplifying (sa-mRNA: U)
virus inactivation with formalin
HA harvesting and purification
lipid nanoparticles (LNP)
virus dispruption with surfactants
whole-virion inactivated vaccine (IIV)
virus-like particle (VLP)
split-virion IIV
subunit vaccines
packaging and delivery
filtration
nanoprecipitation

Egg-based production makes up 84% of the global pandemic influenza H_5 vaccine manufacturing capacity

Manufacturer	Manufacturer location	Vaccine name	Vaccine type	Adjuvant	Age group indication*	Licensing authority
AstraZeneca	UK	Pandemic influenza vaccine H5N1 AstraZeneca	LAIV	None	Children†	EMA
Denka Seiken	Japan	Adsorbed influenza vaccine (H5N1) "Seiken"	IIV	Aluminium-based	Information unavailable	PMDA Japan
GC Biopharma	South Korea	GCFLU H5N1	IIV	Aluminium-based	Healthy adults	MFDS Korea
GlaxoSmithKline	UK (*ID Biomedical Corp (Vancouver, Canada), acquired by GSK in 2005)	**Adjupanrix™**	IIV	AS03	Healthy adults, children, older adults	EMA
		Arepanrix™ * Q Pan/Influenza A (H5N1) virus monovalent vaccine, adjuvanted	IIV, split	AS03	Healthy adults, children, older adults	FDA 2024 (US national stockpile)
Daiichi Sankyo	Japan	Adsorbed influenza vaccine (H5N1) "HOKKEN"	IIV	Aluminium-based	Healthy adults	PMDA Japan
Sanofi Pasteur	France	Influenza virus vaccine, H5N1	IIV, split	None	Healthy adults	FDA 2007 (US national stockpile)
CSL Seqirus	Australia	**Foclivia™**	IIV	MF59	Healthy adults, children, older adults	EMA
		Panvax™ H5N1 influenza vaccine	IIV	Information unavailable	Information unavailable	TGA Australia
		Zoonotic H5N8 influenza vaccine, Seqirus	IIV	MF59	Healthy adults, older adults	EMA
		Panvax™ H5N8 influenza vaccine	IIV	Aluminium-based	Healthy adults, children, older adults	TGA Australia
		Aflunov™	IIV, HA and NA	MF59C.1	Healthy adults, children, older adults	TGA Australia/EMA
Sinovac Biotech	China	**Panflu™**	IIV, whole virion	Aluminium-based	Healthy adults	SFDA China
The Research Foundation for Microbial Diseases for Osaka University	Japan	Adsorbed influenza vaccine (H5N1) "BIKEN"	IIV	Aluminium-based	Healthy adults	PMDA Japan

Modified from https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(25)00052-9/fulltext

Cell-based (IIV) production makes up 16% of the global pandemic influenza H_5 vaccine manufacturing capacity

Manufacturer	Manufacturer location	Vaccine name	Vaccine type	Adjuvant	Age group indication	Licensing authority
KM Biologics	Japan	Emulsion-adjuvanted cell-culture derived influenza HA vaccine	HA	AS03	Healthy adults	PMDA Japan
CSL Seqirus	Australia/USA/ Netherlands	Audenz™	HA	MF59C.1	Healthy adults, children, older adults	FDA 2020 (US national stockpile)
		Celldemic™	HA and NA			TGA Australia/EMA
		Incellipan™	HA and NA			EMA
Takeda Pharmaceutical	Japan	BLB-750	Whole virion	None	Information unavailable	PMDA Japan

Modified from https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(25)00052-9/fulltext

The current flu vaccine manufacturing capacity (including both egg-based and cell-based manufacture) is about 1.5 billion doses of trivalent vaccines, which *THEORETICALLY* corresponds to 4.13- billion doses of 15 µg monovalent (pandemic) vaccines, i.e., **2 billion of 15 µg 2-dose courses.**

Assuming that for a less immunogenic avian influenza vaccine we need a higher antigen level per dose, capacity drops :

30 µg per dose → **1 billion 2-dose courses**

90 µg per dose → 0.3 billion 2-dose courses

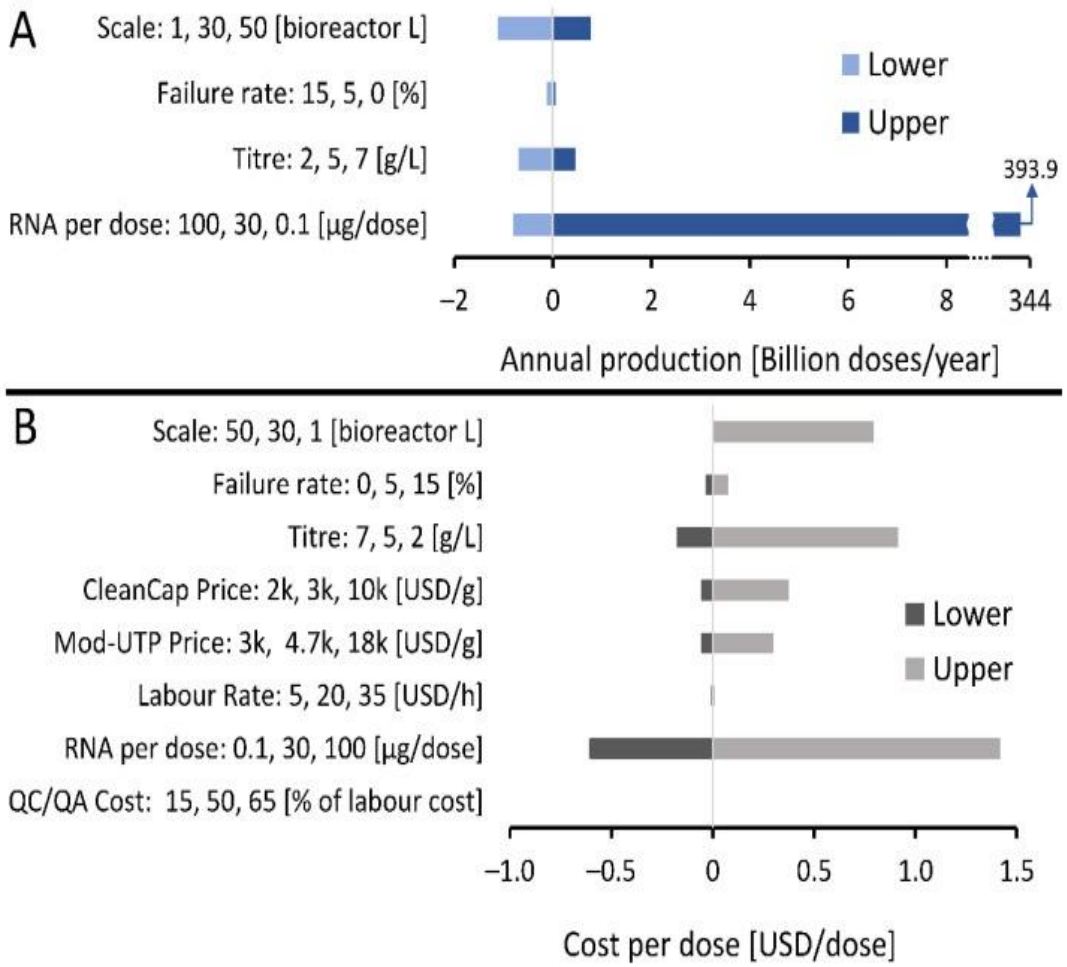
Egg availability during an avian flu pandemic remains unpredictable.

In case we can spare antigens (down to 7.5 µg per dose) by using adjuvants (which are currently available to only 4 suppliers), this estimate could be increased to 4 billion 2-dose courses.

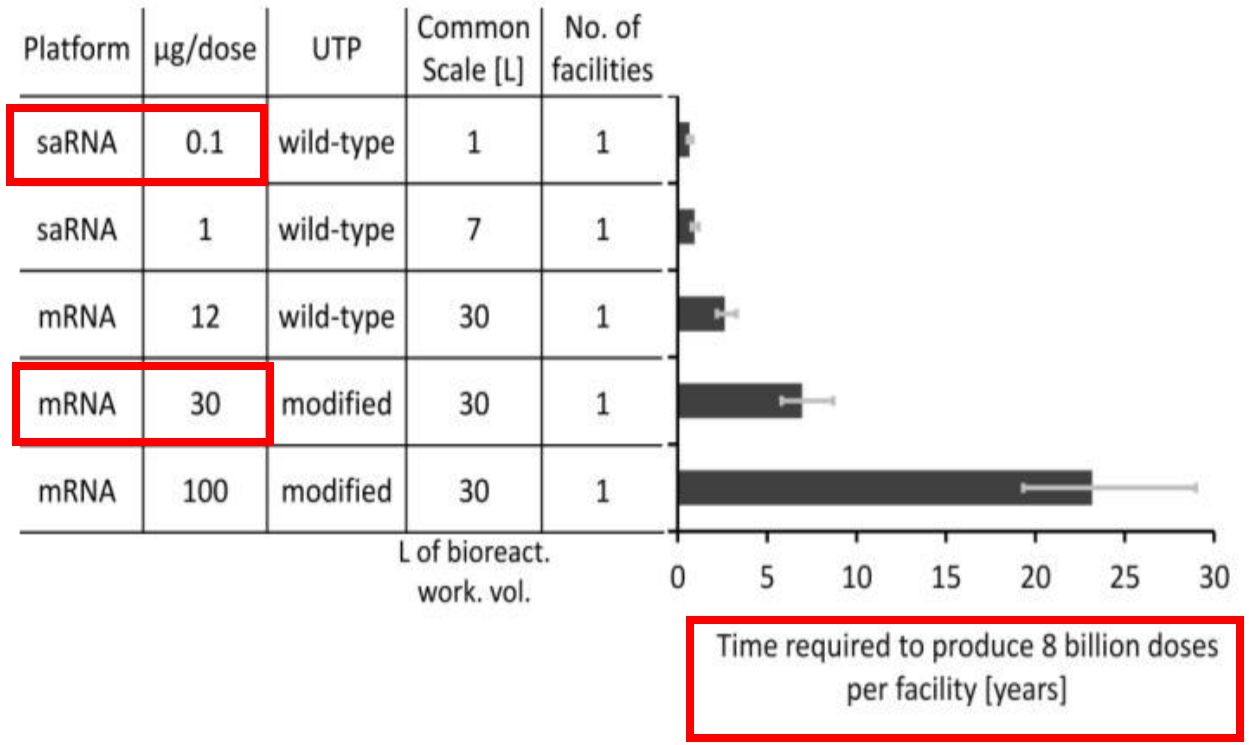
>80% of this manufacturing capacity stays with 7 producers, and only 0.5% stays in low- and low-to-middle-income countries (LMICs) (which make up 9% and 38% of the world's population, respectively).

It takes 4-6 months to have the first doses (21 weeks (LAIV)-24 weeks (IIV)). We clearly need faster platforms.

https://www.sciencedirect.com/science/article/pii/S0264410X25001367

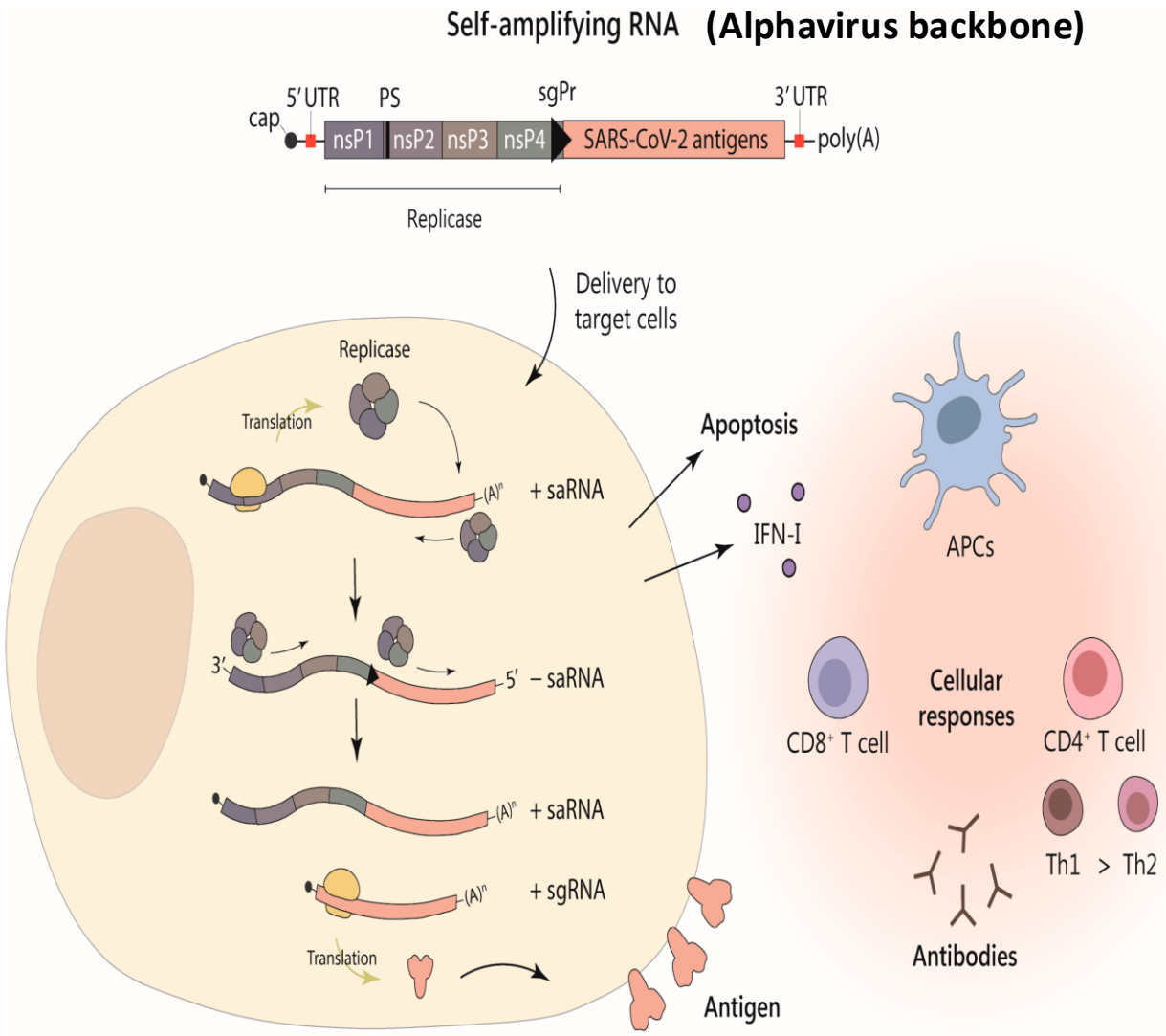


Platform	µg/dose	UTP	Common Scale [L]	No. of facilities
saRNA	0.1	wild-type	1	1
saRNA	1	wild-type	7	1
mRNA	12	wild-type	30	1
mRNA	30	modified	30	1
mRNA	100	modified	30	1



https://www.mdpi.com/2076-393X/9/1/3

How sa-RNA vaccines work?



https://www.mdpi.com/2076-393X/12/3/318

Primary developer	Number of pipeline/ marketed infectious disease candidates	Number of pipeline cancer therapy candidates	Highest developmental stage achieved
Arcturus Therapeutics	6		Approved Kostaive™
Gritstone Bio	4	2	Phase III
VLP Therapeutics	3	1	Phase III
Gennova Biopharmaceuticals	1		Phase II/approved
Strand Therapeutics		4	Phase II
Elixirgen Therapeutics	1		Phase II
Pfizer	7		Phase I
Immorna Hangzhou Biotechnology	2	1	Phase I
MRC/UVRI	1		Phase I

MRC/UVRI, The Medical Research Council/Uganda Virus Research Institute
Source: GlobalData's Pharmaceutical Intelligence Centre

Main advantage: mRNA dose sparing

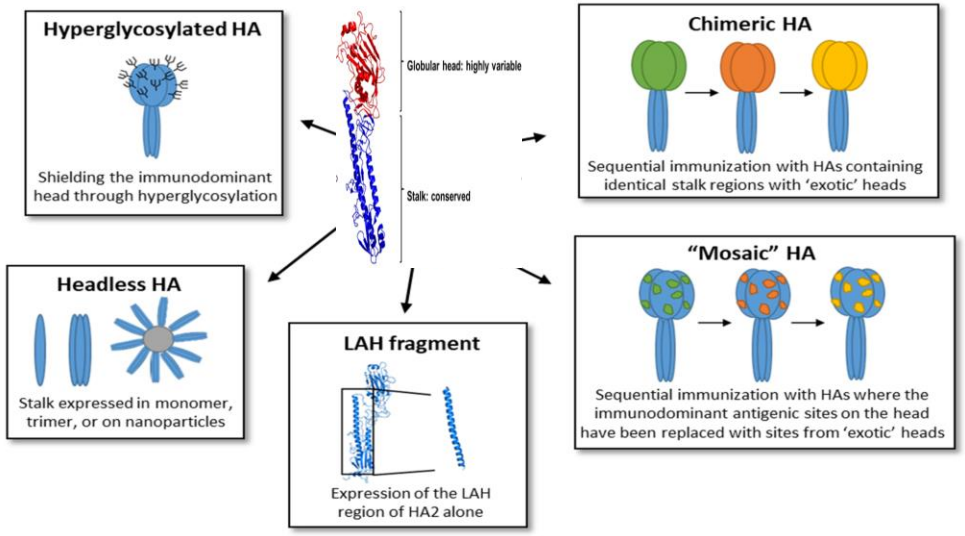
Main hurdles:

- You can't replace U with pseudo-U → reactogenic
- Immunogenicity of the RNA polymerase may hurdle efficacy of boosters
- Longer mRNA (4000 nt) →higher likelihood of degradation and reduced immunogenicity

The H_5N_1 vaccine pipeline is dominated by RNA vaccines

manufacturer	country	name	vaccine type	advancement
CSL	Australia	**CSL406** Influenza (H_5N_1) Vaccine	sa-mRNA	Phase I (NCT06028347)
		CSL400 (TIV) Trivalent Influenza Vaccine	sa-mRNA	Phase I
Pfizer	USA	**pdmFlu**	modRNA	Phase I (NCT06179446)
Moderna	USA	**mRNA-1018** (against H_5 and H_7, and soon against 5 serotypes upon BARDA funding)	modRNA	Phase I/II (NCT05972174**)**
CureVac/GSK	Germany	mRNA influenza A (H_5N_1) pre-pandemic vaccine candidate	(codon-)optimized mRNA	Phase I/II (NCT06382311)
Sanofi	France	**SP0289**	mRNA	Phase I
Arcturus Therapeutics	USA	**ARCT-2304** (aka LUNAR®-H_5N_1)	sa-mRNA (STARR®) into LUNAR® LNP	Phase I (NCT06602531)
Novavax	USA	Highly pathogenic H_5N_1 avian pandemic influenza vaccine	protein subunit with Matrix-M® adjuvant	preclinical
CyanVac + BlueLake Biotechnology	USA	Parainfluenza virus 5 (PIV5) intranasal against H_5N_1+H_7N_9	none	preclinical

How to develop universal influenza vaccines

<table>
<tr><th colspan="2">Strategy</th><th>Pros</th><th>Cons</th></tr>
<tr><td>combination of HA heads</td><td>mixtures of VLPs that express multiple subtypes of HA</td><td>neutralizing and cytotoxic</td><td>Strain specific</td></tr>
<tr><td rowspan="2">HA stalk-directed immunity
 

https://www.frontiersin.org/journals/microbiology/articles/10.3389/fmicb.2020.00135/full</td><td>recombinant stalk-specific HA</td><td>generates antibodies toward a region conserved across subtypes</td><td>deletion of the globular head changes the structure of HA → antibodies against cryptic epitopes. Weakly immunogenic, multiple boosts required</td></tr>
<tr><td>chimeric recombinant HA (heads from exotic subtypes and stalk from common subtypes)</td><td>native HA structure, but with hyperglycosylated globular head.</td><td>does not enrich for stalk-specific antibodies.</td></tr>
<tr><td rowspan="2">Non-HA proteins</td><td>M1 + NP</td><td rowspan="2">conserved structures</td><td>nonneutralizing (ADCC only)</td></tr>
<tr><td>tandem-repeated recombinant extracellular domain of M2 (M2e)</td><td>weak neutralization</td></tr>
</table>

Universal influenza vaccines pipeline

UNIVERSITY OF MINNESOTA

the IVR initiative
INFLUENZA VACCINES ROADMAP

https://ivr.cidrap.umn.edu/universal-influenza-vaccine-technology-landscape

Platform	Preclinical	Phase 1	Phase 2	Phase 3	Approved
Influenza-virus based	17	2	5	0	0
Nucleic acid-based	30	6	6	4 Moderna • **mRNA-1010** (quadrivalent seasonal HA) • **mRNA-1083** (mRNA-1010+COVID19) Pfizer/BioNTech	0
Non-VLP nanoparticles	50	4	1 Osivax **OVX836**	2 (Novavax/Emergent BioSolutions **NanoFlu** : trivalent HA or quadrivalent+COVID19)	0
Recombinant proteins	39	1	3	1 (BiondVax Pharma, Israel : **Multimeric-001** is a linear polypeptide with 3 repetitions of 9 conserved sequences from M1, NP and HA), failed phase 3 in 2020	0
Virus-like particles (VLP)	22	1	0	1 (Medicago, Canada)	0
Virus-vectored	21	2	3 • VaxArt **VXA-A.1** • Vaccitech **MVA-NP+M1**	0	0

Monoclonal antibodies in clinical trials for the treatment of influenza.

target	cocktail	ingredients	specificity	manufacturer	prior clinical studies
anti-H	CT-P27 (fully human IgG with half-life of only 6 days)	CT-P22/CT120/ firivumab	H_1, H_2, H_5, and H_9	Celltrion (Korea)	NCT0001179 NCT02071914 KCT0001617 NCT03511066
		CT-P23/CT149/ navivumab	H_1, H_2, H_5, and H_9 (stem fusion domain in HA2)		Preclinical only [170]
	CR6261/diridavumab		group 1 influenza viruses [32], and binds a highly conserved epitope in the HA stalk/stem)	Crucell / Janssen Vaccines (Netherlands)	NCT01406418 phase II NCT02371668 challenge [130]
	CR8020		group 2 viruses (HA stem near the viral membrane)		NCT01756950 NCT01938352 NCT02015533
	MHAA4549A / 39.29		H_1, H_2, H_3, H_5, and H_7 (stalk)	Genentech (USA)	NCT01877785 and NCT02284607 phase I [171] NCT01980966 [172] NCT02293863 [173] NCT02623322
	MHAB5553A (IgG_1)		influenza B		NCT02528903 phase I [174]
	MEDI8852 / 46B8 (FY1-derived IgG_1 kappa)		inhibits the host cell protease cleavage of H_1 and H_3 HA0 to prevent membrane fusion	MedImmune / AstraZeneca (USA)	NCT02350751 [177] NCT02603952 [178]
	VIS410		broad IgG_1 (stem) against group 1 and group 2, including H_7N_9 [179]	Visterra (USA)	NCT02045472 [180] NCT02468115 [181] NCT02989194 [182] NCT03040141
	VIR-2482		fully human IgG_1 with extended half-life for prophylaxis [183]	Vir Biotechnology, Inc. (USA)	NCT04033406 NCT05567783
anti-NA	FNI9		H_5	Vir Biotechnology (Humabs BioMed SA)	preclinical
ectodomain of the matrix protein 2	TCN-032			Theraclone Sciences (USA)	NCT01390025 NCT01719874 [184]
TSG101 (human protein flipped on surface of influenza-infected cells)	FGI-101-1A6 (fully human IgG_1)			Functional Genetics (USA)	NCT01299142

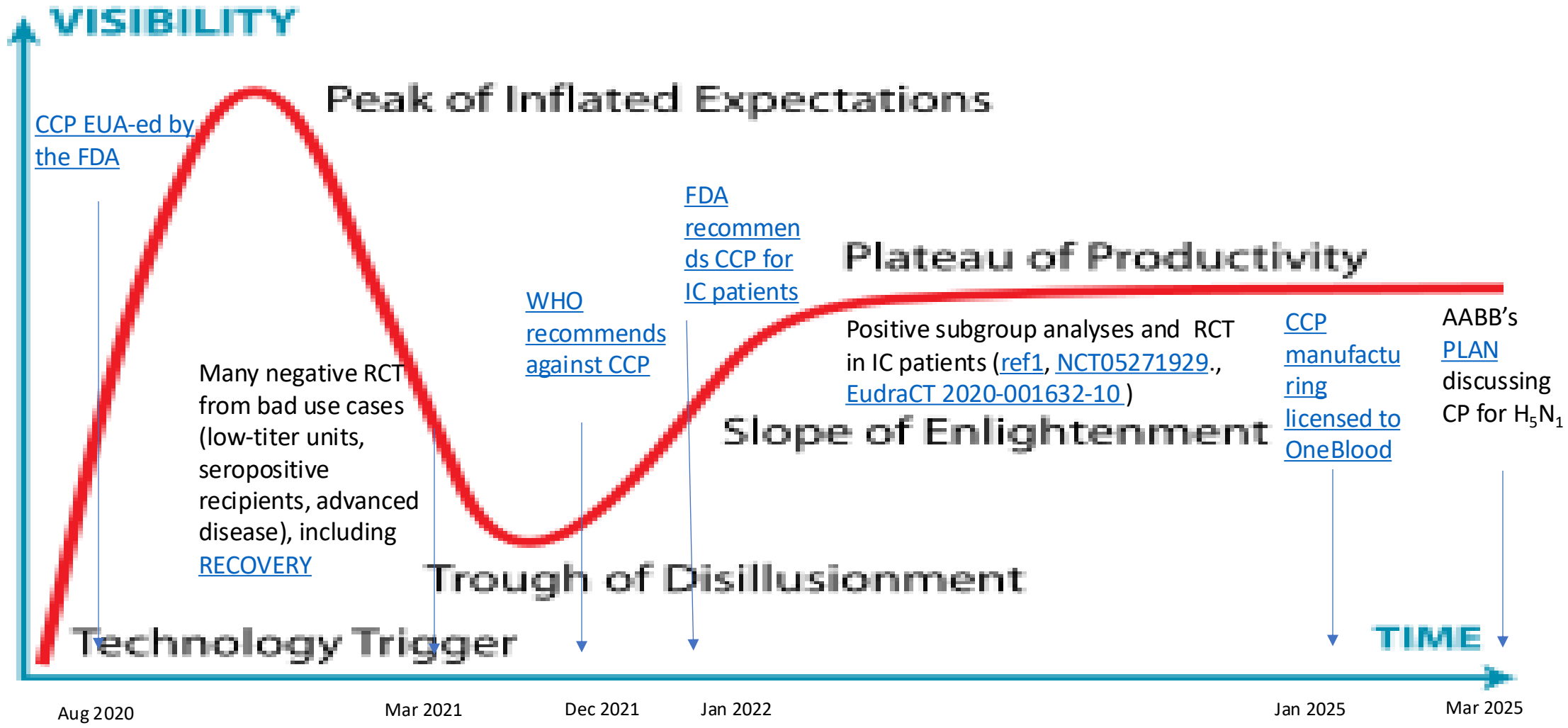
Focosi *et al*, *Rev Med Virol* (2024)

Polyclonal antibody preparations in clinical trials for the treatment of influenza.

Product	Specificity	NCT	Study design	N	outcome
equine F(ab')2 (FBF00, Fab'entech)	H_5N_1	NCT02295813	double-blind, placebo-controlled phase I	16	safe
convalescent plasma (CP)	seasonal flu	NCT01306773	nonrandomized, parallel assignment	80	n/a
		NCT01052480	phase II	98	Statistically nonsignificant trends towards normalized respiratory functions, day in hospital, days on mechanical ventilation, and mortality with CP
		NCT02572817	phase III	140	83% under oxygen, underpowered to detect benefits, terminated for futility
	H_1N_1pdm09	PMID 21248066	non-randomized, matched corhort study	93	Treatment of severe infection reduced respiratory tract viral load, serum cytokine response, and mortality (20 vs. 54.8%).
hyperimmune immunoglobulins (0.25 g/kg) (HIG)	H_1N_1pdm09 (CSL Biotherapies)	NCT01617317	double-blind, IVIG-controlled phase III	35	mortality benefit if < 5 days (0/12 vs. 4/10)
	2013-2019 seasonal flu (Emergent Biosolutions)	NCT02008578	double-blind phase II	31	safe
		NCT02287467	double-blind, placebo-controlled phase III FLU-IVIG	347	no benefit compared to placebo
		NCT03315104	double-blind, placebo-controlled phase II	65	n/a

WHO has secured access to 11% of pandemic influenza vaccine production for allocation and distribution to "developing countries" via SMTA2s, but what about therapeutics ? With such a low vaccine coverage, therapeutics will invariably be required there. Convalescent plasma will likely represent the only antiviral therapy affordable in low-and-middle income countries along a future pandemic.

COVID-19 convalescent plasma (CCP) has followed a Gartner hype cycle



Updated regulatory framework is required for convalescent plasma : Europe is lacking a CP monography in both European Pharmacopeia and the EDQM guidelines. CP usage remains hurdled by bureaucracy.