Annual Scientific Meeting

2023

Latest in Influenza Prevention

PRESENTED BY
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Immunisation Coalition Director and Scientific Advisory Board Member

IMMUNISATION COALITION

Disclosures

- Principal Investigator on numerous vaccine clinical trials
  - including the following SARS-CoV-2 vaccines;
    - UQ
    - Novavax (including approved vaccine and Omicron specific booster)
    - Serum Institute of India
    - Symvivo
    - Tetherex
    - Sanofi (mRNA and protein)
  - And many Influenza and RSV vaccine and antibody studies
    - Including with Moderna, Novavax, Vaxxas, Vir, Visterra
- Immunisation Coalition Director and Scientific Advisory Board Member
- Speaker Honoraria includes Seqirus, Novartis, Gilead, Sanofi and Janssen
- Medical Advisory Board Memberships including AstraZeneca, GSK, MSD and Pfizer

Outline

- Background
  - Impact of Influenza in Australia
  - Limitations of current strategies
- Influenza prevention
  - NPI's
  - Antivirals
  - Monoclonal Antibodies
  - Vaccines
    - Augmented
    - Cell-based
    - Newer Platforms
    - Combination
    - Universal
    - Alternate route of administration
- Conclusion

Impact of Influenza in Australia

- Annual influenza attack rates in the community are typically **5–10%** but can be as high as **20%** in some years[1]
- Influenza contributes to more than 1/3 of the total burden due to all Vaccine Preventable Diseases in Australia.[4] (pre-COVID)

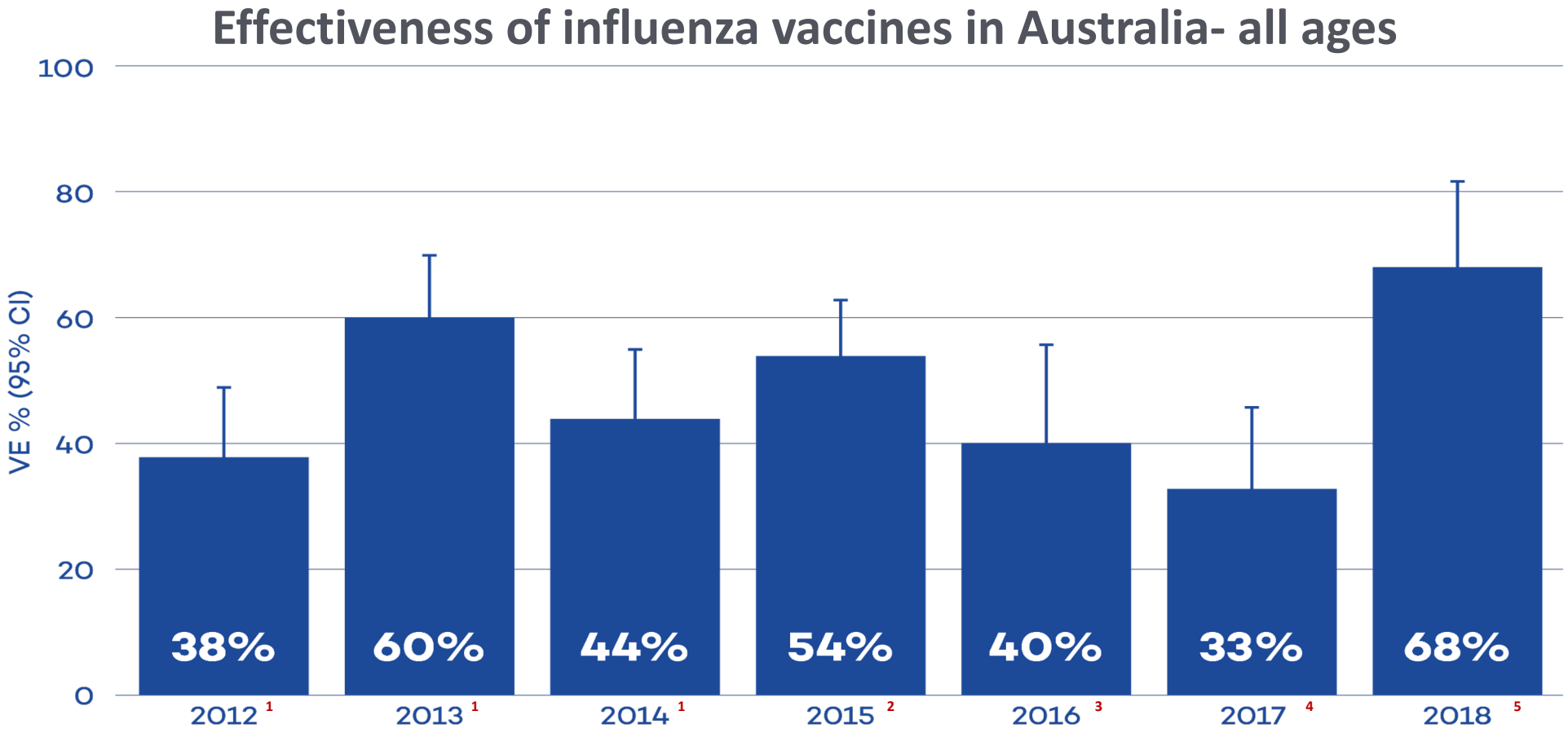
- Each year, influenza & associated complications are estimated to be responsible for approximately:
  - 3,000 deaths in older Australians[1]
  - 18,000 hospitalisations[2]
  - 300,000 doctor visits[2]
  - 1,500,000 lost work days[3]

1. ATAGI. Australian Immunisation Handbook, Australian Government Department of Health, Canberra, 2018, immunisationhandbook.health.gov.au. Accessed Jan 2021. 2. Newall, Anthony T, & Scuffham, Paul A. (2008). Influenza-related disease: The cost to the Australian healthcare system. Vaccine. 26(52), 6818-6823. 3. Mills J & Yapp T (1996). An Economic Evaluation of Three CSIRO Manufacturing Research Projects, CSIRO Australia. 4. AIHW 2019. The burden of vaccine preventable diseases in Australia. Cat. no. PHE 263. Canberra: AIHW.

Limitations of Current Strategies

- Both influenza A and influenza B viruses cause regular seasonal epidemics in humans
  - Seasonal influenza vaccines typically contain attenuated strains of both Influenza A and B viruses grown in eggs
  - The subtypes required to be contained in the seasonal vaccine often vary due to minor changes in the virus known as antigenic drift
    - mutations readily occur in HA and NA resulting in new antigenic variants (thus avoiding pre-existing host immunity);
    - the error prone nature of the viral polymerase is a significant factor in this
- Influenza A viruses particularly, also have the potential to undergo major changes known as antigenic shift which can result in a pandemic
  - i.e. reassortment of gene segments between two distinct influenza viruses within the same host giving rise to a novel strain
    - Last seen with H1N1 in 2009
- Vaccination remains our best defence against influenza, including pandemics, however there are limitations
  - Need to match circulating subtypes and update regularly
  - Relatively long lead time in a pandemic situation with existing platforms
  - Egg adaptation
  - Limited ability to protect those not able to respond to vaccination
  - Relatively low efficacy, ~ 20 to 60 % since 2010

Current vaccines have substantial impact on disease burden – but there is room for improvement



Note: Data pooled from multiple sources. Complete case analysis for 2012-2014, imputed analysis for 2015-2017.

1. Sullivan SG et al. Epidemiol Infect. 2016;144(11):2317-28. 2. Fielding JE et al. Vaccine. 2016;34(41):4905-12. 3. Regan AK et al. Vaccine. 2019;37(19):2634-41. 4. Sullivan SG et al. Euro Surveill. 2017;22(43):17-00707. 5. National Influenza Surveillance Committee. 2018 www1.health.gov.au/internet/main/publishing.nsf/Content/CA086525758664B4CA25836200807AF9/$File/2018-Season-Summary.pdf

Non-Pharmaceutical Interventions

IMMUNISATION COALITION

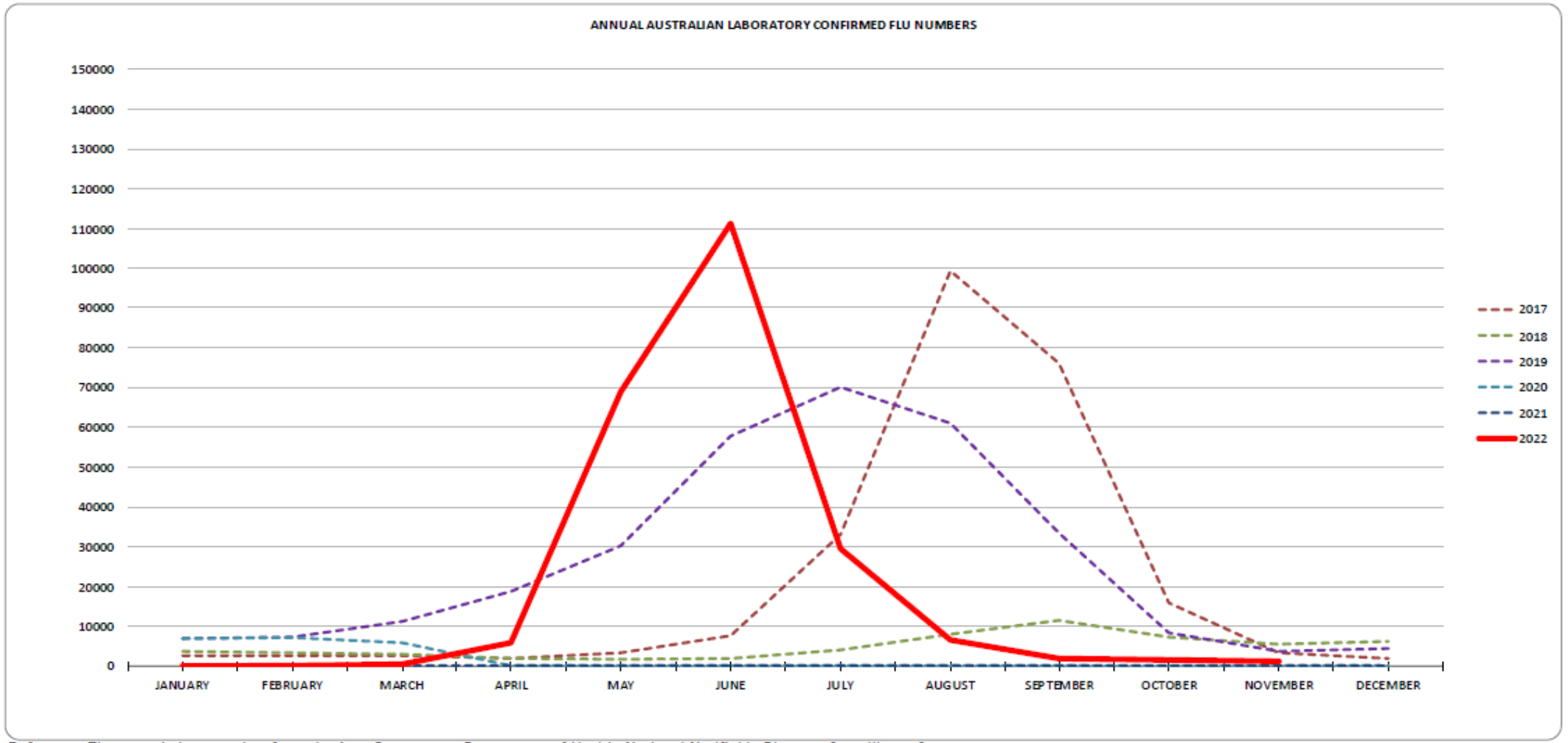
The Immunisation Coalition is the leading voice in whole-of-life immunisation in Australia, protecting all Australians against communicable diseases.

visit our website: https://www.immunisationcoalition.org.au/news-data/influenza-statistics/

ANNUAL AUSTRALIAN INFLUENZA STATISTICS

YEAR	JANUARY	FEBRUARY	MARCH	APRIL	MAY	JUNE	JULY	AUGUST	SEPTEMBER	OCTOBER	NOVEMBER	DECEMBER	TOTALS
2017	2762	2750	2815	1939	3285	7793	33207	99367	76060	15912	3369	2031	**251290**
2018	3746	3481	3174	1977	1717	1988	3969	8168	11506	7320	5548	6267	**58861**
2019	6829	7161	11158	18667	30372	57842	70151	60964	33572	8319	3734	4316	**313085**
2020	6861	7177	5912	304	237	228	193	125	59	36	53	64	**21249**
2021	56	48	56	64	72	71	60	53	56	51	68	97	**752**
2022	37	38	541	5826	68832	111309	29680	6669	2083	1664	1199		**227878**

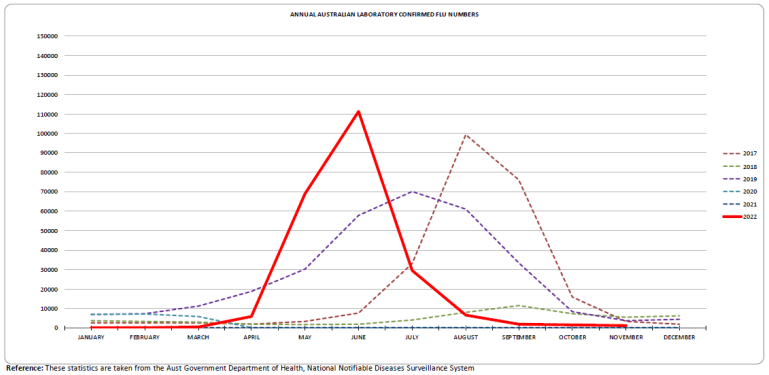
Data valid as at: **18 November 2022**



Reference: These statistics are taken from the Aust Government Department of Health, National Notifiable Diseases Surveillance System

Can NPI's Prevent Influenza

- Marked decline in Influenza activity in Australia from April 2020 essentially until April 2022.
  - Only 752 recorded cases in 2021
- Likely due to many COVID-19 mitigation strategies
  - Impossible to know the impact of each individual strategy
  - Closure of international borders likely the most important
  - Others include
    - Social distancing
    - Hand hygiene
    - Mask wearing
    - Ventilation
    - Isolation of symptomatic individuals
- Potential hope for these strategies to be more readily applied to influenza in the future
  - Although increasing resistance already



Antivirals

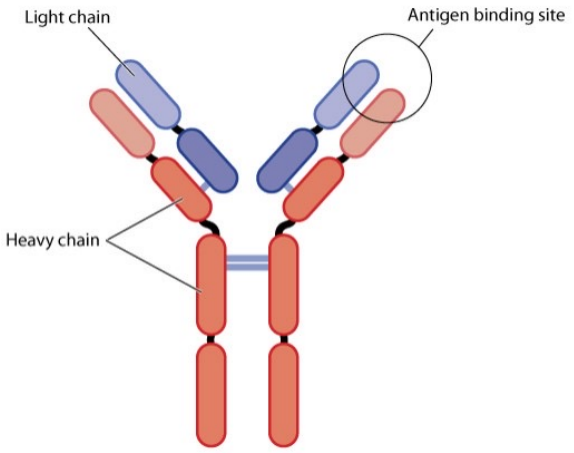
Antivirals

- A number of antivirals are approved for the treatment of influenza
- Antivirals are also approved for chemoprophylaxis in specific circumstances
  - Examples include exposed individuals at high risk for severe or complicated influenza or in an effort to address an institutional outbreak.
- Options include
  - Neuraminidase inhibitors→prevent the release of virions from the host cell
    - Oseltamivir
      - meta-analyses of trials for prophylaxis have shown a reduced risk of symptomatic laboratory confirmed influenza of 2.6 vs 5.6 % and in households 3.4 vs 17.0 %
    - Zanamivir
      - Available as dry powder and intravenous forms, both evaluated for prophylaxis
      - Effect similar to that of oseltamivir
    - Laninamivir
      - Long-acting neuraminidase inhibitor available for prevention of influenza in Japan
      - Similar to others
  - Baloxavir→ blocks influenza proliferation by inhibiting initiation of mRNA synthesis
    - Licensed in Japan and the USA for postexposure prophylaxis
    - Studies have shown decrease of lab confirmed influenza in household contacts compared to placebo of 1.9 vs 13.6 %

Monoclonal Antibodies

Monoclonal Antibodies

- Many highly effective examples applied to COVID-19
  - For both pre-exposure prophylaxis in individuals not able to be protected by vaccination and for treatment
    - Examples include Sotrivmab (GSK and Vir), Evusheld (tixagevimab/cilgavimab, AstraZeneca)
  - Unfortunately, ongoing immune evasion has significantly impacted efficacy
- Other examples include
  - Hep B, Varicella, CMV, Rabies
  - Palivizumab and now Nirsevimab for RSV (both target F protein) *
- Large number of monoclonal antibodies under development for influenza
  - VIR-2482, Vir (and GSK)
  - MHAA4549A (earlier known as 39.29), Genentech
  - VIS410, Visterra
  - CR6261, Crucell and NIAID
  - CR8020, Crucell and Retroscreen
  - TCN-032, Theraclone
  - CT-P27 Celltrion



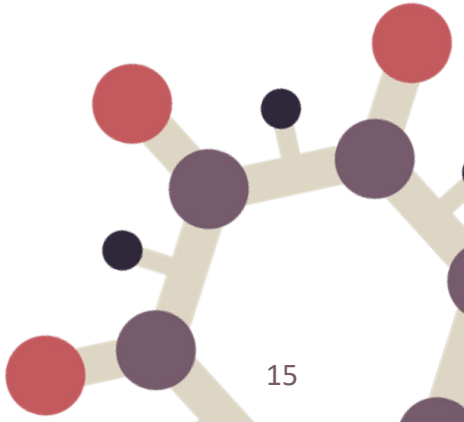
* Hammitt et al., Nirsevimab for Prevention of RSV in Healthy Late-Preterm and Term Infants

Monoclonal Antibodies

- VIR-2482
  - Intramuscularly administered investigational monoclonal antibody that has demonstrated in vitro the ability to neutralize all major strains of influenza A that have arisen since the 1918 Spanish flu pandemic
  - engineered to have an extended half-life, providing the potential for protection throughout an entire flu season
  - Phase 1 completed in Brisbane (PI)
  - Target of 3000 participants enrolled in phase 2 PENINSULA trial (**P**reve**n**tio**n** of **I**ll**n**e**s**s **D**u**e** to Inf**l**uenza **A**)
    - First Phase 2 outpatient trial to evaluate the role of a monoclonal antibody in the prevention of influenza A illness
    - First participant dosed October 2022
    - Data expected mid 2023
  - Like sotrovimab, collaboration agreement with GSK to lead post-Phase 2 development and commercialization

Monoclonal Antibodies

- MHAA4549A (earlier known as 39.29)
  - Genentech
  - Cloned from a single-human plasmablast isolated from a vaccinated donor
  - Binds highly conserved epitope on the stalk of HA blocking HA-mediated membrane fusion in the endosome
    - Capable of neutralizing all known human influenza A strains
  - Clinical trials
    - Safe and well tolerated in phase 1
    - Phase 2 treatment study did not improve clinical outcomes
- VIS410
  - Visterra, US biotech
  - Engineered IgG1 Monoclonal Antibody for treatment of Influenza A
    - Also have an Envelope protein antibody for Dengue
  - VIS410 broadly neutralizing antibody targeting the hemagglutinin stem
  - Animal models resulted in complete protection of mice (H7N9 challenge)
  - Clinical trials
    - Safe and effective in human H1N1 challenge
    - Phase 2 study completed for treatment, 150 participants (PI)
      - Favorable effects on symptom resolution and virus replication



Monoclonal Antibodies

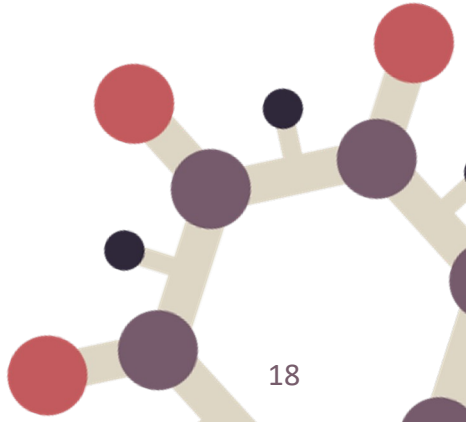
- CR6261
  - Crucell and NIAID
  - Isolated from combinatorial display libraries that were constructed from human IgM(+) memory B cells of seasonal influenza vaccinees
    - Originally found in 2008
  - neutralizes the virus by blocking conformational rearrangements associated with membrane fusion
  - recognizes a highly conserved helical region in the membrane-proximal stem of HA1 and HA2
  - protective in mice when given before and after lethal H5N1 or H1N1 challenge
  - Clinical trials
    - Human challenge in 2015 showed limited efficacy
- CR8020
  - Crucell and Retroscreen
  - isolated from a B cell of a donor vaccinated against influenza.
  - IV infusion
  - Structural and computational analyses indicate that CR8020 targets HA residues that are prone to antigenic drift and host selection pressure
    - escape mutation seen in certain H7N9 viruses
  - Clinical trials
    - 2 phase 2 challenge trials and 1 hospitalized patient trial
      - Residues prone to antigenic drift so effectiveness reduced by escape mutants

Monoclonal Antibodies

- TCN-032
  - Theraclone
  - Isolated from an IgG(+) memory B cell of a healthy human subject
  - Recognizes a previously unknown conformational epitope within the ectodomain of the influenza matrix 2 protein, M2e
    - highly conserved in influenza A viruses.
  - protected mice from lethal challenges with either H5N1 or H1N1 influenza viruses
  - Clinical trials
    - Phase 1 clinical study showed safe, with no evidence of immune exacerbation based on serum cytokine expression.
    - also showed that the antibody may provide immediate immunity and therapeutic benefit in influenza A infection, with no apparent emergence of resistant virus

Monoclonal Antibodies

- CT-P27
  - Celltrion (South Korea)
  - 2 antibodies, bind to the stem part of hemagglutinin
  - Reportedly effective against most influenza that affects humans -- H1, H2, H3, H5, H7, and H9 -- in various non-clinical and clinical trials conducted with the U.S. Centers for Disease Control and Prevention and Chinese government's research institutes
  - Clinical trials
    - Phase 1 successful but in press releases
    - 2a in the UK in 2014 apparently safe and effective
    - 2b trials
      - Some promising results at ESCMID in 2019 but no publications
        - Well tolerated, no major safety issues (diarrhoea 5%)
        - Reduced time to resolution of symptoms including fever



Vaccines

Opportunities to improve influenza vaccine effectiveness

Patient Factors

Reduced immune response to the vaccine[2]

e.g. immunosenescence (declining immune function in the elderly)

Adjuvant & high-antigen vaccines[1]

Viral Factors

Potential for vaccine-virus mismatch[3]

e.g. antigenic drift (natural mutation in circulating flu strains)

Universal vaccines??[4]

Vaccine Factors

Potential for vaccine-virus mismatch[5]

e.g. egg-adaptation (changes introduced during egg-based manufacturing)

Non egg-based vaccines[5]

Utilisation Factors

e.g. lack of patient demand and/or provider recommendation leading to under-vaccination[6,7]

1. ATAGI. Australian Immunisation Handbook, Australian Government Department of Health, Canberra, 2018, immunisationhandbook.health.gov.au. Accessed Sept 2020. 2. McElhaney JE. Aging Health. 2008;4(6):603-13. 3. Ansaldi et al. Vaccine. 2010;s8:4123-29. 4. Nachbagauer R et al. Annu Rev Med. 2020;71:315-27. 5. Skowronski DM et al. PLoS One. 2014;9(3):e92153. 6. Menzies RI et al. Med J Aust. 2017;206(6):238-239. 7. Rao S et al. Hosp Pediatr. 2016;6(9):513-519.

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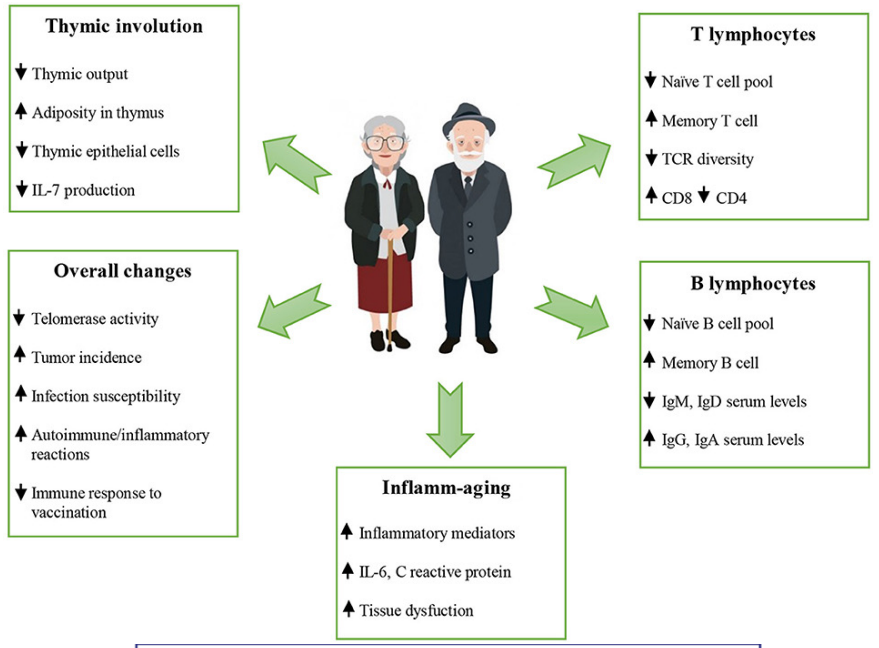
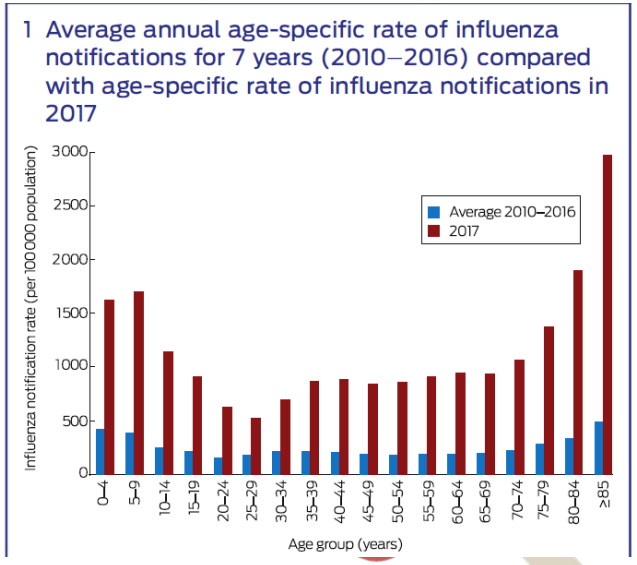
Vaccines-augmented vaccines for the elderly

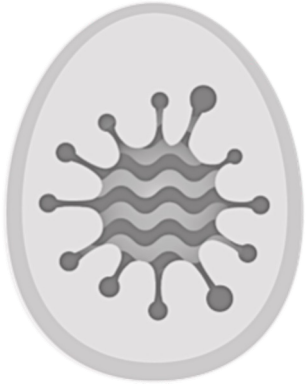
- Elderly are at increased risk of influenza, increased risk of complications and also known to respond less well to vaccination due to immunosenescence
- Recently enhanced vaccines have become available to address
  - Fluad Quad (Seqirus)
    - Adjuvanted, MF59
  - Fluzone (Sanofi)
    - High dose, 4 times the amount of adjuvant
- Studies suggest a relative improvement in effectiveness of approximately 20 to 25%





Vaccines-Cell Based

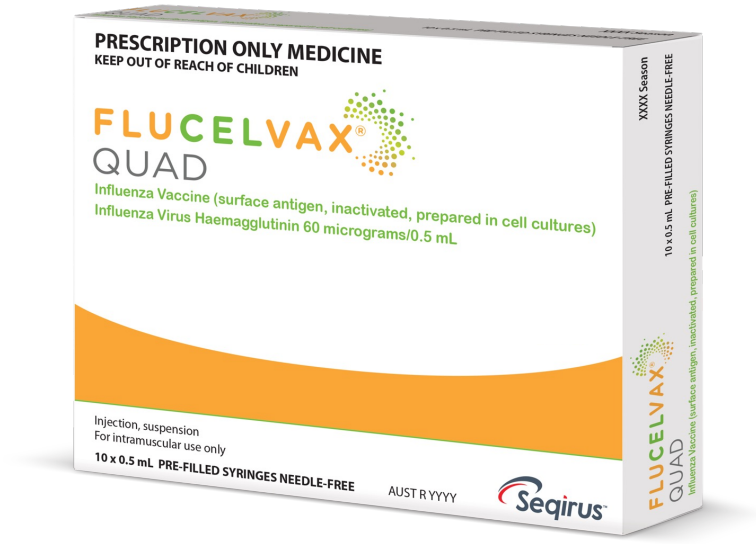
- Egg adaptation
  - Human flu viruses don't always grow well in eggs[1,2]
  - When grown in eggs, the viruses can adapt to that environment, this can cause mutations[3-5]
  - These mutations can result in viruses that differ from the WHO-selected reference strains[6-8]
  - This can contribute to vaccine-virus mismatch which may impact vaccine effectiveness in some seasons[1,2,6,9]



1. Harding AT et al. Vaccines. 2018;6(2):19. 2. CDC. www.cdc.gov/flu/vaccines-work/vaccineeffect.htm Accessed Sept 2020. 3. Wu NC et al. PLoS Pathog. 2017;13(10):e1006682. 4. Zost SJ et al. Proc Natl Acad Sci USA. 2017;114(47):12578-83. 5. Barr I et al. Vaccine. 2014;32(37):4713-25. 6. Skowronski DM et al. PLoS One. 2014;9(3):e92153. 7. WHO. www.who.int/influenza/vaccines/virus/candidates_reagents/summary_a_h3n2_cvv-cell_sh20.pdf?ua=1 Accessed Sept 2020. 8. WHO. www.who.int/influenza/vaccines/virus/recommendations/201909_recommendation.pdf?ua=1 Accessed Sept 2020. 9. Rajaram S et al. Ther Adv Vaccines Immunother. 2020;8:1-10.

FLUCELVAX® QUAD -

Australia's first and only cell-based influenza vaccine



- **Indicated for use in adults and children 2 years of age and older[1]**
- **Administered by intramuscular injection only[1]**
- **Each 0.5 mL dose contains four influenza virus surface antigens for 2022 season[1]**
  - Sub-unit Vaccine
  - Propagated in Madin Darby Canine Kidney (MDCK) cells
- **Contraindicated in individuals with known severe allergic reactions (e.g. anaphylaxis) to:**
  - any component of the vaccine[1]
  - a previous dose of any influenza vaccine[1]

First licensed in 2016 (USA) and >100 million doses distributed worldwide[2]

Available in Australia by private prescription only in 2022

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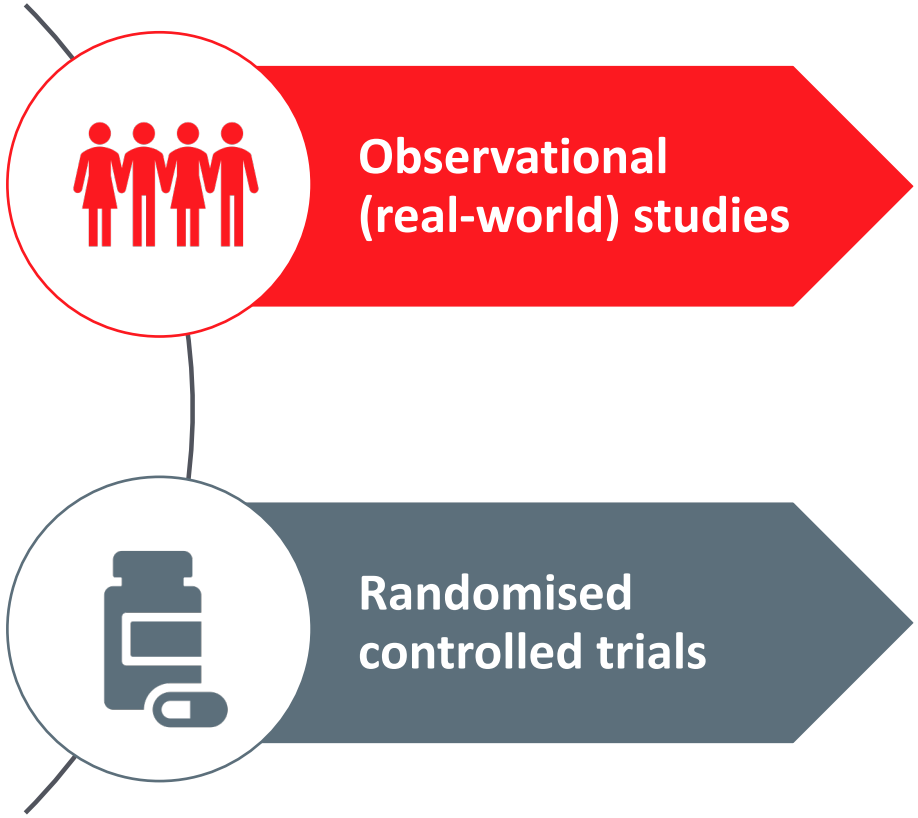
1.FLUCELVAX® QUAD Approved Product Information. 2. Seqirus Data on File.

FLUCELVAX® QUAD - Comparative effectiveness vs quadrivalent egg-based influenza vaccines



- **Six retrospective cohort studies**
  assessing effect on influenza-related GP diagnoses and Hospital diagnoses in US 2017/18, 2018/19 and 2019/20 seasons[1-6] *
- **Three test-negative design studies**
  assessing effect on lab-confirmed influenza in the US 2017/18 season (not presented)[7-9]
- **No head-to-head randomised controlled comparative efficacy studies**

* Three additional studies published, exclusively examined use in adults >65 years (not presented)[10-12]

1. Boikos C et al. Clin Infect Dis. 2020 Apr 7;ciaa371. 2. Divino V et al. Vaccine. 2020;38(40):6334-43. 3. Boikos C et al. Clin Infect Dis. 2021 Jan 5; ciaa1944 4. Krishnarajah G et al. Vaccines. 2021; 9(2):80. 5. Seqirus 2021a [Relative effectiveness of the cell-derived versus egg-derived quadrivalent influenza vaccines in the US during the 2019-20 influenza season [unpublished] 6. Seqirus 2021b [Flucelvax Compared to Standard-Dose Egg-Based Quadrivalent Influenza Vaccines during the 2019-20 Flu Season: A Real-World Analysis. [unpublished]. 7. Bruxvoort KJ et al. Vaccine. 2019; 37(39):5807-5811. 8. DeMarcus L et al. Vaccine. 2019;37(30):4015-21. 9. Martin ET et al. J Infect Dis. 2021; 223(12): 2062-2071. 10. Izurieta HS et al. J Infect Dis. 2019;220(8):1255-64. 11. Izurieta HS et al. J Infect Dis. 2020;222(2):278-87. 12. Izurieta HS et al. Clin Infect Dis. 2020 Nov 19;ciaa1727.

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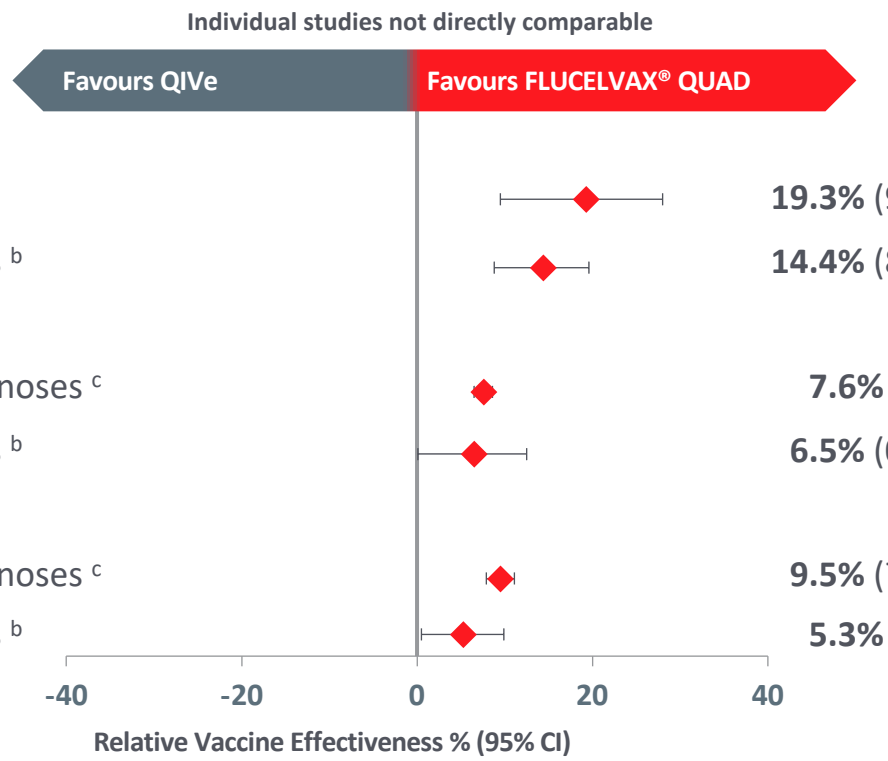
FLUCELVAX® QUAD – Relative vaccine effectiveness

3 years of comparative data vs QIVe (retrospective cohort analyses)



				Vaccinated subjects	
				FLUCELVAX® QUAD	QIVe
2017/18					
Boikos 2020[1]	≥4 years	GP diagnoses [a]	**19.3%** (9.5, 28.0)	92,187	1,261,675
Divino 2020[2]	4-64 years	Hospital diagnoses [b]	**14.4%** (8.8, 19.6)	555,538	2,528,524
2018/19					
Boikos 2021[3]	≥4 years	GP & hospital diagnoses [c]	**7.6%** (6.5, 8.6)	2,125,430	8,000,903
Krishnarajah 2021[4]	4-64 years	Hospital diagnoses [b]	**6.5%** (0.1, 12.5)	665,047	3,062,843
2019/20					
Seqirus 2021[5]	≥18 years	GP & hospital diagnoses [c]	**9.5%** (7.9, 11.1)	1,499,215	4,126,263
Divino 2021[6]	4-64 years	Hospital diagnoses [b]	**5.3%** (0.5, 9.9)	1,150,134	3,924,819

a GP visits with ICD code for influenza (ICD-10: J09.xx, J10.xx, J11.xx)
b Inpatient stays/ED visits with ICD code for influenza (ICD-10: J09.x, J10.x, J11.x)
c GP visits or Inpatient stays/ED visits with ICD code for influenza (ICD-10: J09.xx, J10.xx, J11.xx)
QIVe: quadrivalent egg-based influenza vaccine
ED: Emergency Department

1. Boikos C et al. Clin Infect Dis. 2020 Apr 7;ciaa371. 2. Divino V et al. Vaccine. 2020;38(40):6334-43. 3. Boikos C et al. Clin Infect Dis. 2021 Jan 5; ciaa1944 4. Krishnarajah G et al. Vaccines. 2021; 9(2):80. 5. Seqirus 2021 [Relative effectiveness of the cell-derived versus egg-derived quadrivalent influenza vaccines in the US during the 2019-20 influenza season [unpublished] 6. Divino V et al. Open Forum Infect Dis. 2021;9(1):ofab604.

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Vaccines, Newer Platforms

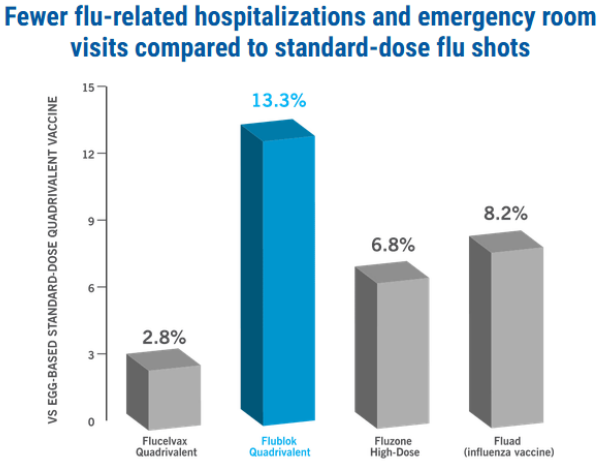
- COVID-19 accelerated the development of a number of newer vaccine platforms
  - perhaps most importantly mRNA, but also others
- mRNA not necessarily new technology
  - BioNTech, German Biotech, founded 2008
    - In addition to COVID-19, over 20 other candidate products including influenza
      - Phase 3 first participants dosed September 14, 2022
  - Moderna, American Biotech, founded 2010
    - Also over 20 other candidate products including influenza
      - Most advanced is mRNA-1010 in phase 3 (commenced June 2022)
        - Includes mRNA encoding hemagglutinin glycoproteins of the four influenza strains recommended by WHO
      - 4 other candidates
        - some with additional HA antigens for broader coverage (mRNA-1011 and mRNA-1012)
        - Some that incorporate both HA and neuraminidase (NA) antigens to reduce the potential of viral antigenic escape (mRNA-1020 and mRNA-1030)

Pfizer

moderna

Vaccines, Newer Platforms

- Recombinant Protein not a new platform
  - previous examples include hepatitis B, HPV and others
- First recombinant influenza vaccine “Flublok” (Sanofi)
  - Licensed by FDA in 2013
  - Quadrivalent haemagglutinin recombinant
  - Registered on the Australian register therapeutic goods 12th May 2021
  - Suggested to be 30% more effective at preventing flu in 50+ y.o.a. than Fluarix
- Other protein-based vaccines
  - Novavax, American biotech founded in 1987
    - COVID-19 vaccine approved and in use in Australia
    - ~10 other vaccines in pipeline including influenza
    - “NanoFlu” quadrivalent nanoparticle hemagglutinin proteins with Matrix-M adjuvant
      - Phase 3 trials underway



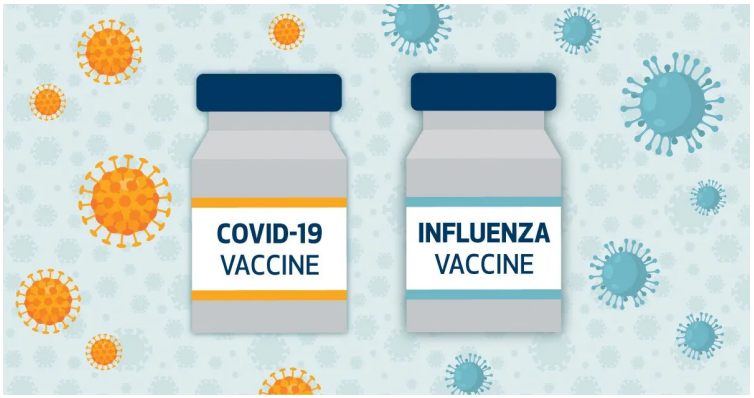
novavax
Creating tomorrow's vaccines today.

Vaccines, Newer Platforms

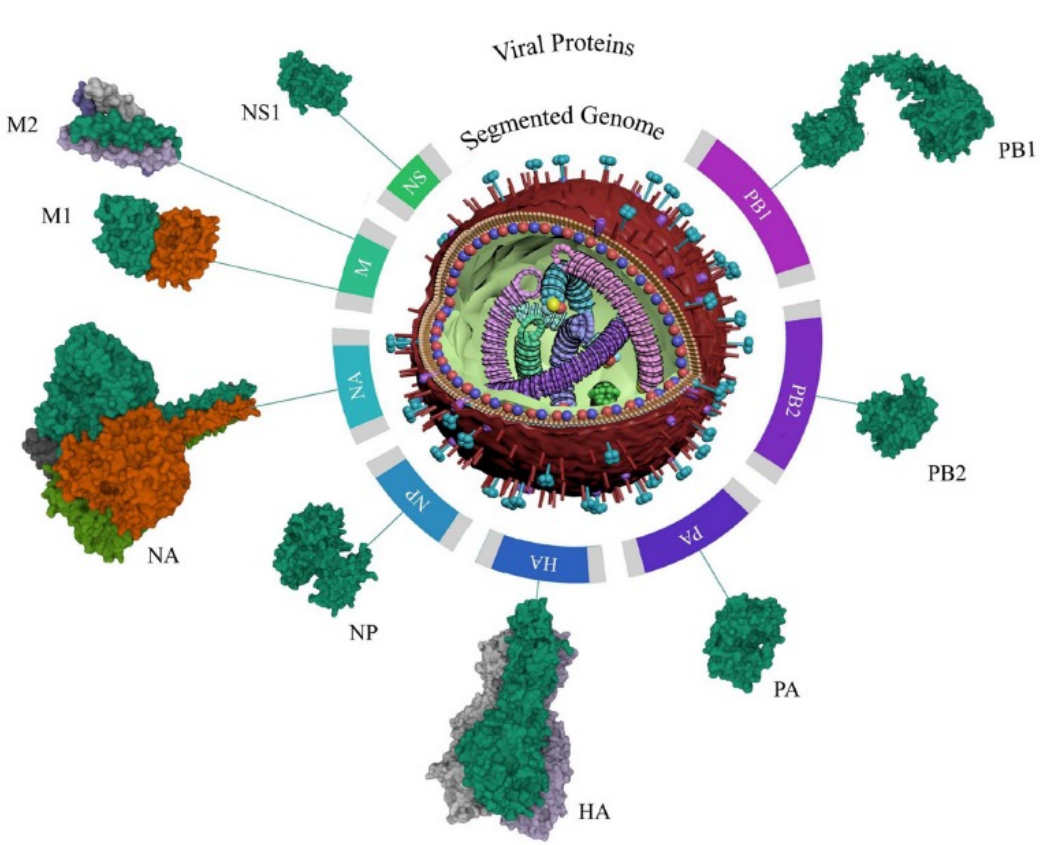
- Viral vector
  - Many different vectors in use including adenovirus, arenavirus, Newcastle disease virus, baculovirus, and herpesvirus vectors
  - Potential advantages include ability to induce strong humoral and cellular adaptive immune responses against the immunogenic proteins
  - Can also be used to construct polyvalent or multicomponent vaccines
    - Adenovirus vectored influenza vaccines have been constructed to express conserved antigenic regions such as hemagglutinin stem region, M2 (gives good humeral responses), NP (T cell responses)
  - Examples include
    - MVA NP+M1 by Vaccitech (spin-out University of Oxford)
      - Vector: Modified Vaccinia Ankara-very commonly used vector, generates strong T cell responses
      - Vaccine is a recombinant, replication deficient MVA vector expressing antigens for NP and M1 as a fusion protein
      - Phase 2b failed to achieve primary endpoint of reduction of incidence compared to licensed seasonal Quadrivalent

Vaccines-Combination

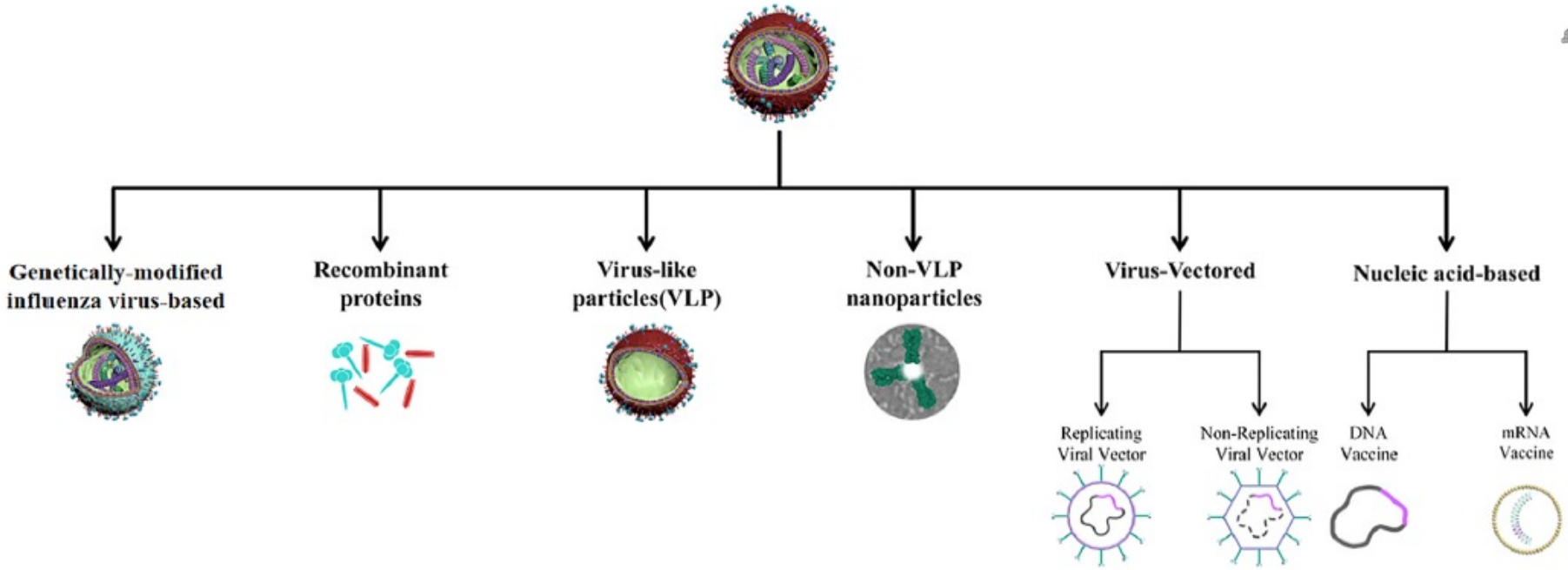
- A number of vaccines combining Influenza with Covid-19 (and some with RSV) are in clinical trials
  - Novavax
    - COVID + Flu – Phase 2 recruitment just completed
      - 1500 participants from 25 Aus and 9 NZ sites (Lead site)
  - Moderna
    - COVID + Flu vaccine (mRNA-1073) – Phase 1
    - COVID + Flu + RSV vaccine (mRNA-1230) – Phase 2
  - Pfizer
    - Combines quadrivalent modRNA-based influenza candidate, qIRV (22/23) which alone is in phase 3 trials with approved BNT162b2 (Original/Omicron BA.4/BA.5) vaccine
      - Phase 1 commenced Nov 2022



Vaccines-Universal



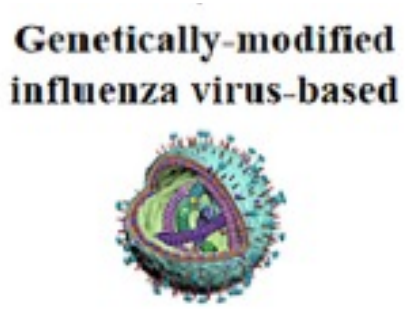
- 6 platforms utilized for universal candidates



Vaccines-Universal

- Genetically modified influenza virus based

Phase	Developer	Vaccine Name	Antigen	Injections/ Route	Adjuvant	Trial ID	Ref.
II	FluGen	RedeeFlu M2SR	M2-deficient replication-deficient H3N2	1/IN	None	2017-004971-30 (18–55 years)	Eiden et al. (2022)
	Vivaldi Biosciences & Icahn School of Medicine at Mount Sinai	deltaFLU	NS1-deficient, replication-deficient (H1N1)-like virus	1/IN	None	NCT01078701 (18–50 years)	(Krenn et al., 2011; Rathnasinghe et al., 2021)
I	Codagenix	CodaVax	De-optimized live-attenuated HIN1	1/IM	None	NCT05223179 (18–45 years)	(Broadbent et al., 2016; Stauft et al., 2019; Yang et al., 2013)
	Icahn School of Medicine at Mount Sinai & GSK	cHA-based LAIV combinations	Chimeric HA LAIV and IIV	2/IN and IM	ASO3A	NCT03300050 (18–39 years)	(Bernstein et al., 2020; Guthmiller et al., 2022; Nachbagauer et al., 2021)
	NIAID	BPL-1357	Four inactivated whole AIV	2/IM or IN	None	NCT05027932 (18–55 years)	(Larkin, 2022; Park et al., 2022)



Vaccines-Universal

- Recombinant

Phase	Developer	Vaccine Name	Antigen	Injections/ Route	Adjuvant	Trial ID	Expression Platform	Ref.
III	BiondVax Pharmaceuticals	Multimeric-001 (M-001)	Conserved epitopes of M1, NP, and HA	2/IM	None	NCT03450915 (50 years and older)	*E. coli*	(Atsmon et al., 2012, 2014; Gottlieb and Ben-Yedidia, 2014; Lowell et al., 2017; van Doorn et al., 2017a)
II	ConserV Bioscience & Imutex	FLU-v	Conserved epitopes of M1, IAV-NP, IBV-NP, and M2	1 or 2/SC	Montanide ISA-51	NCT03180801 (18–55 years) NCT02962908 (18–60 years)	Synthetic peptides	(Pleguezuelos et al., 2012, 2015b; van Doorn et al., 2017b)
I	Russian Academy of Sciences & VA Pharma	M2e based recombinant fusion proteins	Four tandem copies of M2e and conserved fragments of HA stem	2/IM	Flagellin	NCT03789539 (18–60 years)	*E. coli*	(Mardanova et al., 2015, 2016; Mardanova and Ravin, 2018; Stepanova et al., 2015, 2018a, 2018b; Tsybalova et al., 2018)
	Immune Targeting Systems (Acquires by Altimmune)	FP-01.1	Conserved epitopes of NP, M, and PB1/PB2	2 or 3/IM	None/ unknown	NCT01265914 (18–55 years) NCT02071329 (18–45 years) NCT01677676 (18–55 years) NCT01701752 (65–74 years)	Synthetic peptides	Francis et al. (2015)
	VaxInnate Corp	VAX102	Four tandem copies of the M2e	2/IM or SC	Flagellin	NCT00921973 (18–49 years) NCT00921947 (18–49 years) NCT00921206 (18–49 years) NCT00603811 (18–49 years)	*E. coli*	(Talbot et al., 2010; Turley et al., 2011)

Vaccines-Universal

- Virus like particles

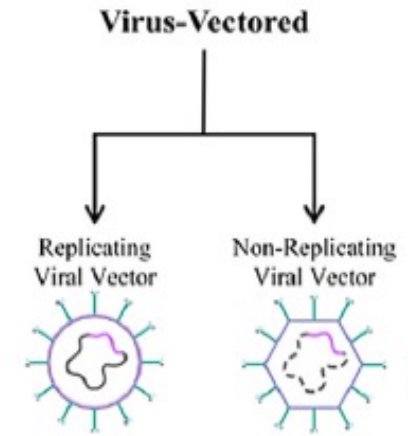
Phase	Developer	Vaccine Name	Antigen	Injections/ Route	Adjuvant	Trial ID	VLP Platform	Ref.
III	Medicago	Quadrivalent VLP (QVLP)	Quadrivalent HA	1/IM	Alhydrogel	NCT03739112 (65 years and older) NCT03301051 (18–64 years) NCT03321968 (18–49 years)	Plant-derived VLPs	(Alvarez et al., 2022; Hendin et al., 2022; Ward et al., 2020, 2021; Won et al., 2018)
I	Ghent University & Sanofi Pasteur	M2e-based VLPs (ACAM-FluA)	M2e	2/IM	Alhydrogel or Stimulon QS-21	NCT00819013 (18–40 years)	HBc-based VLPs	(De Filette et al., 2008; Ibanez et al., 2013; Schotsaert et al., 2016)

Vaccines-Universal

- Non VLP Nanoparticle based

Phase	Developer	Vaccine Name	Antigen	Injections/ Route	Adjuvant	Trial ID	Nanoparticle Platform	Ref.
III	Novavax & Emergent BioSolutions	Nano-Flu (qNIV)	Quadrivalent HA	1/IM	Matrix-M	NCT04120194 (65 years and older)	PS 80-based nanoparticles	(Portnoff et al., 2020; Shinde et al., 2022; Smith et al., 2017)
II	Osivax	OVX836	NP	1/IM	None	NCT05284799 (15–55 years) NCT05060887 (18 years and older) NCT05569239 (18–55 years) NCT04192500 (18–65 years)	OVX313- based nanoparticles	(Del Campo et al., 2019, 2021)
I	Emergent BioSolutions	EBS-UFV-001	HA stem	1 or 2/IM	Aluminum hydroxide and CpG	NCT05155319 (18–45 years)	Ferritin-based nanoparticles	*N.A.*
	NIAID	FluMos-v1	Quadrivalent HA	1/IM	SAS	NCT04896086 (18–50 Years)	I53_dn5 based nanoparticles	(Boyoglu-Barnum et al., 2021; Georgiev et al., 2018; Kanekiyo et al., 2019; Nelson et al., 2022)
	NIAID & Sanofi Pasteur	VRC-FLUNPF0103-00-VP	HA stem	1 or 2/IM	None	NCT04579250 (18–70 years)	Ferritin-based nanoparticles	(Corbett et al., 2019; Darricarrere et al., 2018, 2021; Yassine et al., 2015)

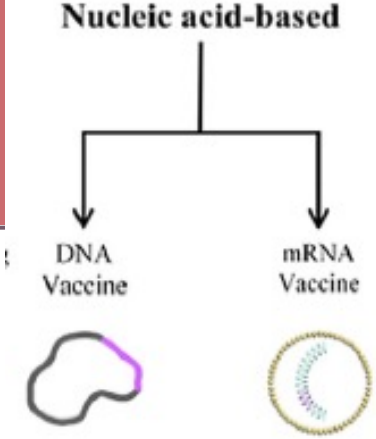
Vaccines-Universal



- Viral vectored

Phase	Developer	Vaccine Name	Antigen	Injections/ Route	Adjuvant	Trial ID	Viral Vector	Ref.
II	DEVELOPER Vaxart	VXA-A1.1 oral tablet	HA	1/Oral	TLR3 agonist	NCT02918006 (18–49 years)	Replication-defective Ad5	(Kim et al., 2016; Liebowitz et al., 2015, 2020; McIlwain et al., 2021; Scallan et al., 2016)
	Altimmune	NasoVAX	HA	1/IN	None	NCT03232567 (18–49 years) NCT03760549 (18–49 years)	Replication-deficient Ad5	(Tasker et al., 2021; Zhang et al., 2011)
	Vaccitech	MVA-NP + M1 (VTP-100)	NP and M1	1/IM	None	NCT00993083 (18–45 years) NCT03300362 (65 years and older) NCT03883113 (18–55 years)	MVA	(Antrobus et al., 2012, 2014a; Berthoud et al., 2011; Folegatti et al., 2019; Lillie et al., 2012; Mullarkey et al., 2013; Mullin et al., 2016; Powell et al., 2013; Puksuriwong et al., 2020; Swayze et al., 2019)
I	Jenner Institute, University of Oxford	MVA/ChAdOx2-NP + M1 (2-dose heterologous regimen)	NP and M1	2/IM	None	NCT01818362 (18–50 years) NCT01623518 (18–50 years)	MVA and ChAdOx2	(Antrobus et al., 2014b; Coughlan et al., 2018; Lambe et al., 2013)
	NIAID & Sanofi Pasteur	Ad4-H5-VTN	H5 HA	1 or 2/Oral or via tonsillar swab or IN	None	NCT01806909 (18–49 years) NCT01443936 (19–49 years)	Ad4	Matsuda et al. (2021)

Vaccines-Universal

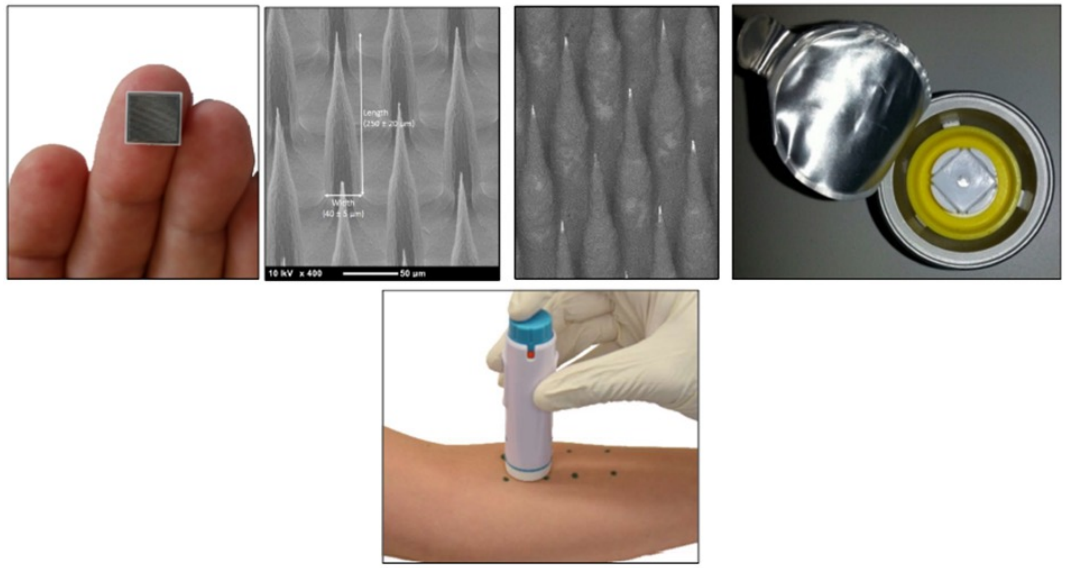


- Nucleic acid based

Phase	Developer	Vaccine Name	Antigen	Injections/ Route	Trial ID	Delivery	Ref.
III	Moderna	mRNA-1010	Quadrivalent HA	1/IM	NCT05415462 (18 years and older) NCT05566639 (50 years and older)	LNP	(Bahl et al., 2017; Liang et al., 2017; Lindgren et al., 2017)
	Pfizer & BioNTech	Modified mRNA vaccine	Quadrivalent HA	1/IM	NCT05540522 (18 years and older)	LNP	(Abbasi, 2021; Dolgin, 2021)
I	CureVac & GSK	CVSQIV	Quadrivalent HA	1/IM	NCT05252338 (18 years and older)	LNP	Petsch et al. (2012)
	Pfizer	Self-Amplifying RNA	*N.A.*	*N.A.*/IM	NCT05227001 (18–49 years)	*N.A.*	*N.A.*
	Sanofi Pasteur & Translate Bio	MRT5400 and MRT5401	Monovalent NA	1/IM	NCT05426174 (18 years and older)	LNP	(Chivukula et al., 2021; Dolgin, 2021)
	Wistar Institute & Inovio Pharmaceuticals	Micro-consensus DNA vaccine	Bivalent HA	3/IM	NCT01405885 (18–55 years)	Electroporation	(Elliott et al., 2018; Kichaev et al., 2013; Xu et al., 2020; Yan et al., 2014, 2018)
	University of Manitoba	FVH1	Bivalent HA	3/IM	NCT01587131 (65 years and older)	Electroporation	*N.A.*

Vaccines-alternate route of admin

- Skin
  - Nanopatch - UQ/Vaxxas
    - Solid, high density micro projection array patch
    - Dried vaccine formulation coated onto micro-projections
    - Replace one big needle with thousands of microscopic needles
    - Stable at room temperature for 6 months
    - High speed patch application to enable micro-projections to enter skin
    - Studies showed safe effective
      - Initially with no vaccine then flu vaccine



vaxxas

4

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Safety, acceptability and tolerability of uncoated and excipient-coated high density silicon micro-projection array patches in human subjects

Paul Griffin [a,b,c,d], Suzanne Elliott [b], Kenia Krauer [b], Cristyn Davies [e,f], S. Rachel Skinner [e,f], Christopher D. Anderson [g,h], Angus Forster [i,*]

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Safety, tolerability, acceptability and immunogenicity of an influenza vaccine delivered to human skin by a novel high-density microprojection array patch (Nanopatch™)

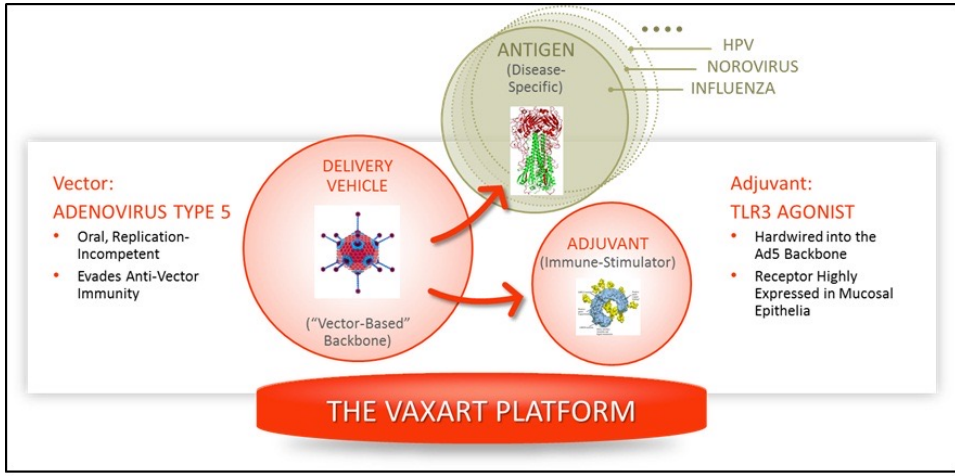
Germain J.P. Fernando [a], Julian Hickling [b], Cesar M. Jayashi Flores [a], Paul Griffin [c,d,e,f], Christopher D. Anderson [g,h], S. Rachel Skinner [i,j], Cristyn Davies [i,j], Katey Witham [a], Melinda Pryor [k], Jesse Bodle [l], Steve Rockman [l,m], Ian H. Frazer [f], Angus H. Forster [a,*]

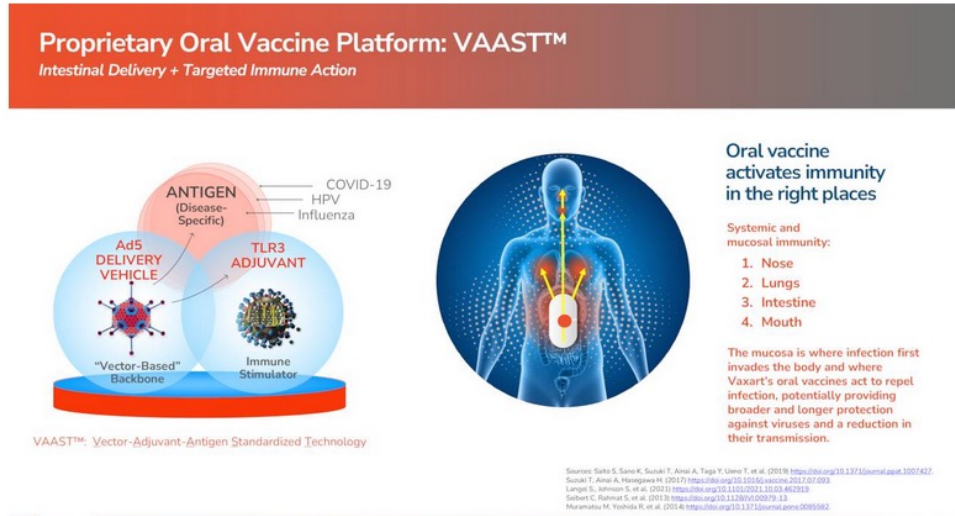
Vaccines-alternate route of admin

- FluMist (MedImmune, subsidiary of AZ)
  - Live attenuated Quadrivalent administered intranasally
  - Recommendations fluctuated over time
    - Approved in USA in June 2003
    - July 2014 recommended as preferred alternative in children 2 to 8 after many studies, particularly from 2007, suggested higher efficacy than injectable
      - 55 % reduction in cases in children compared to those who received injectable
    - Recommended to no longer be used for the 2016/17 season
      - During 2013/14 season no measurable effectiveness against H1N1 in children 2 to 8
    - Included in recommendations again for the 2018/19 season
      - Studies presented at the ACIP meeting showed that the new H1N1 LAIV strain induced improved antibody responses
  - In Australia
    - TGA approved registration in 2016
      - 24 months to 18 years of age

Vaccines-alternate route of admin

- Oral
  - Vaxart
    - San Francisco based, specializing in oral vaccines
    - Tablet form, room temperature stable
    - VAAST = Vector-Adjuvant-Antigen Standardised Technology
    - Replication deficient adenovirus type 5 vector
      - Delivers genes for target and adjuvant to the epithelial cells lining the mucosa of the small bowel
    - Human challenge studies showed safe and effective
    - Phase 2 studies showed a 39% reduction in clinical disease compared to placebo
      - Fluzone comparator was 27%
      - Safety profile similar to placebo





Conclusion

- A number of vaccine (and therapeutic) options for Influenza exist, however are not without limitations
- There are a number of monoclonal antibodies under investigations with many currently in phase 2 trials
- Recent additions that are available for use include augmented vaccines to address immunosenescence and a cell-based vaccine to address egg-adaptation
- COVID-19 likely temporarily slowed the development of new interventions for Influenza
  - however also likely subsequently hastened the development of additional options
    - particularly mRNA and other newer vaccine platforms
- This will also facilitate combination vaccines with a number of options in phase 2 trials (including 1 underway in Australia)
- Universal vaccine efforts continue with at least 3 now in phase 3 trials (using 3 different platforms)
- Non-needle and syringe options are also likely to soon be increasingly available

END

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