IMMUNISATION COALITION

Influenza Update

10:00

A/Prof Paul Griffin

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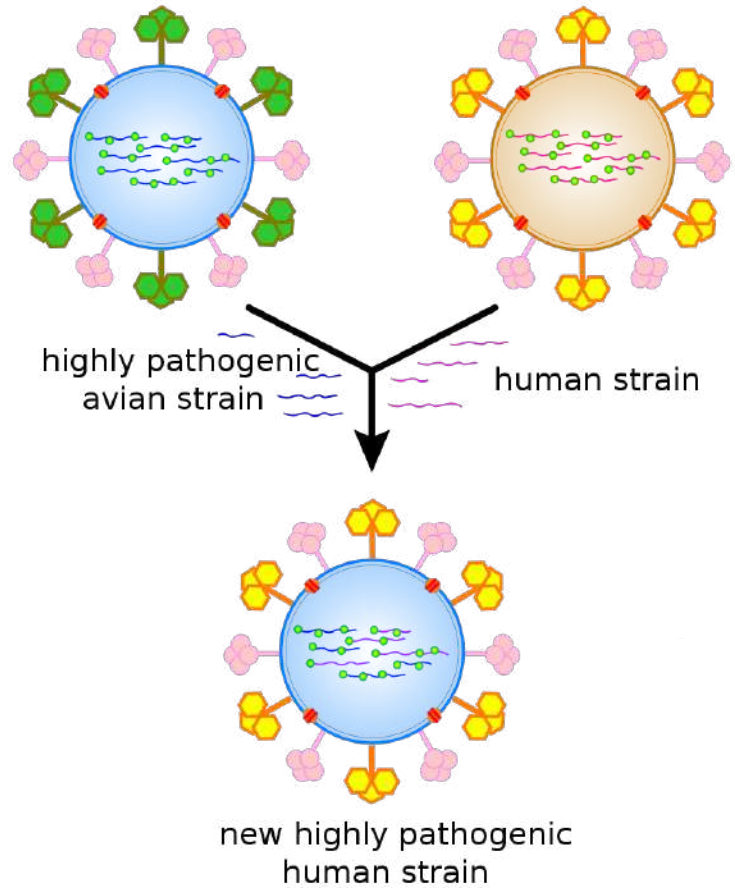
Disclosures

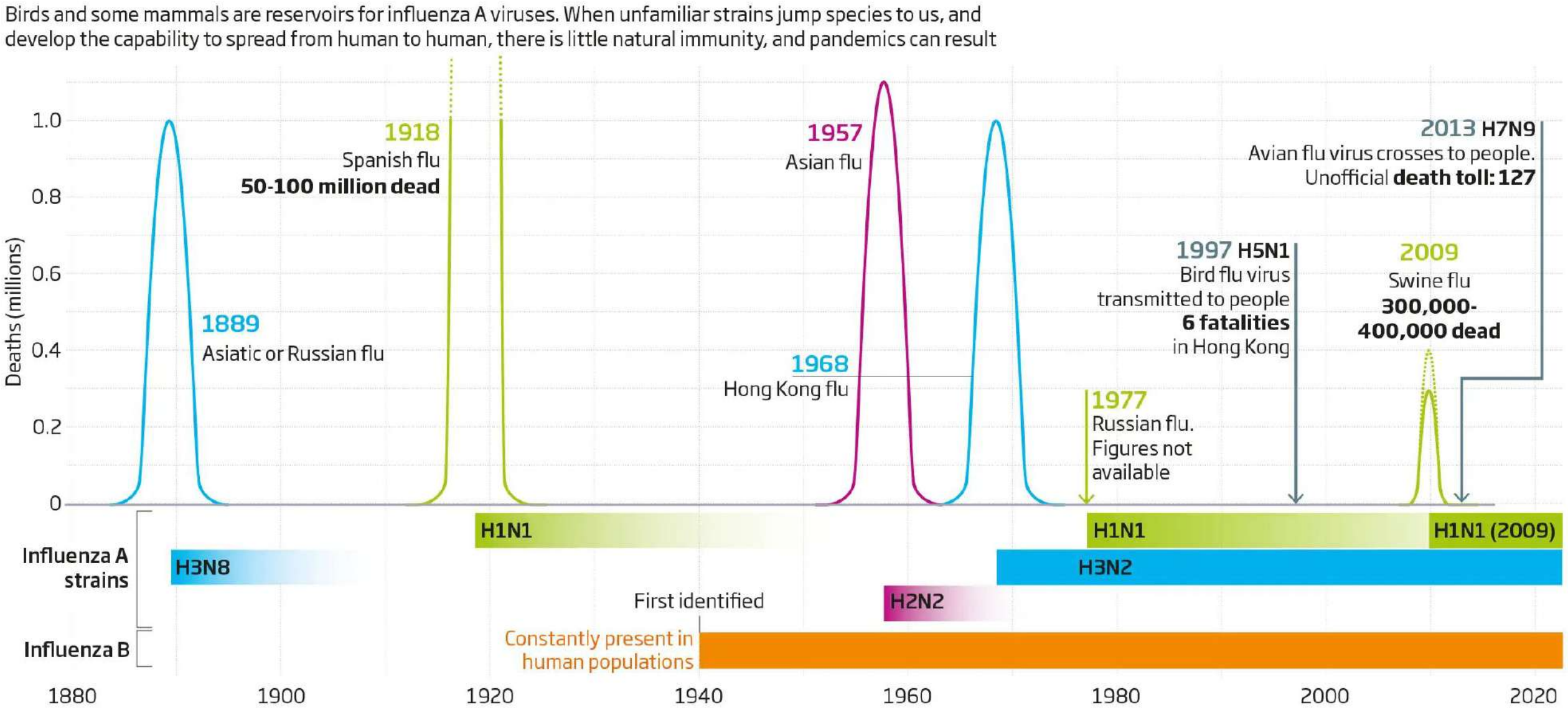
- Principal Investigator on numerous vaccine clinical trials
  - including the following SARS-CoV-2 vaccines;
    - UQ
    - Novavax (including approved vaccine and Omicron specific booster)
    - Serum Institute of India
    - Symvivo
    - Tetherex
    - Sanofi (mRNA and protein)
  - And many Influenza 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, MSD and Janssen
- Medical Advisory Board Memberships including AstraZeneca, GSK, MSD, Moderna, Biocelect/Novavax, Seqirus and Pfizer
- Content of this presentation is my own

Influenza, Background and Definitions

- 4 Influenza species, most important are Influenza A and Influenza B
  - Family *Orthomyxoviridae*
  - Negative sense single stranded RNA
  - Influenza A and B have 8 genome segments
    - 1 encodes the hemagglutinin (HA)
    - 1 encodes the neuraminidase (NA)
      - These are the main surface proteins
      - This is where the “H” and “N” come from in the names of the strains
- Changes readily
  - More subtle changes are called antigenic **drift**
    - Gradual accumulation of mutations, especially in the hemagglutinin
      - Error prone polymerase
    - Creates a degree of “immune evasion”
    - Leads to epidemics or seasonal increases in cases (with other factors)
  - Antigenic **shift** is a sudden drastic change, usually in the hemagglutinin
    - Different strains infect same cell and reassort genome segments
    - Occurs mostly in Influenza A
    - Very common in Avian Influenza viruses
    - Some animals have receptors for both mammalian and avian Influenza A viruses
      - Pigs and bats for example mixing vessels
    - Causes Pandemics (global epidemic)



Influenza Over Time



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.

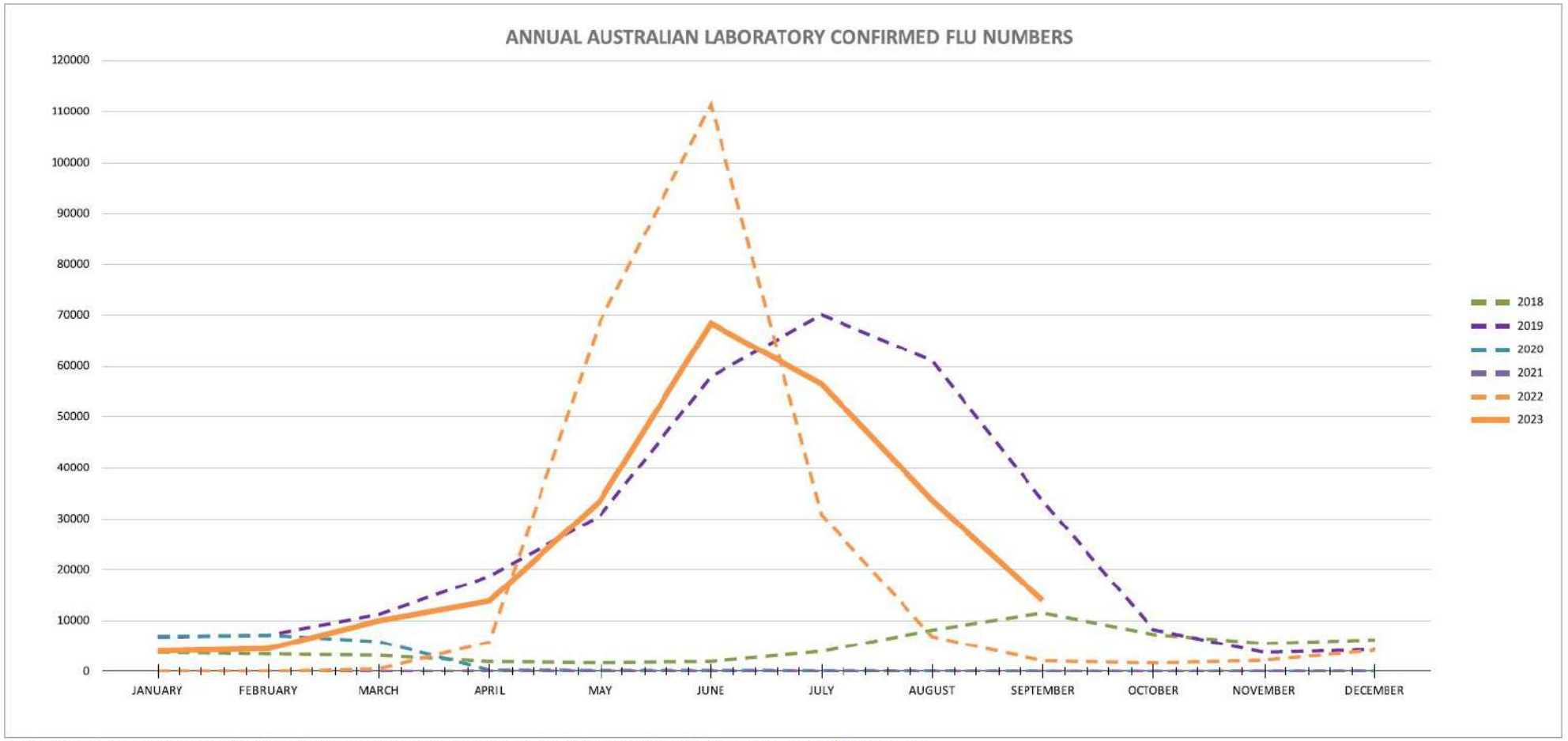
IMMUNISATION COALITION

The Immunisation Coalition is the leading voice in whole-of-life immunisation in Australia, protecting all Australians against communicable diseases.
For more information, please visit 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
2018	3,751	3,467	3,189	1,976	1,712	1,995	3,967	8,158	11,523	7,324	5,542	6,273	58,877
2019	6,808	7,185	11,234	18,745	30,650	57,951	70,100	61,090	33,531	8,257	3,742	4,322	313,615
2020	6,963	7,180	5,913	304	237	228	193	125	59	36	53	64	21,355
2021	56	48	56	64	72	71	60	53	56	51	68	98	753
2022	40	39	540	5,828	68,820	111,404	30,815	6,866	2,128	1,682	2,234	4,185	234,581
2023	**4,046**	**4,522**	**9,975**	**13,868**	**33,549**	**68,416**	**56,531**	**33,658**	**13,970**				**238,535**

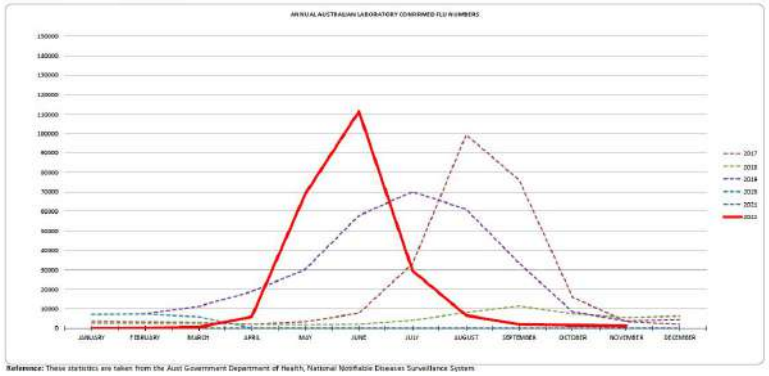
Data valid as at: **25 September 2023**



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

What Happened to Flu During COVID

- Marked decline in Influenza activity in Australia from April 2020 essentially until April 2022.
  - Only 753 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/air filtration
    - Isolation of symptomatic individuals

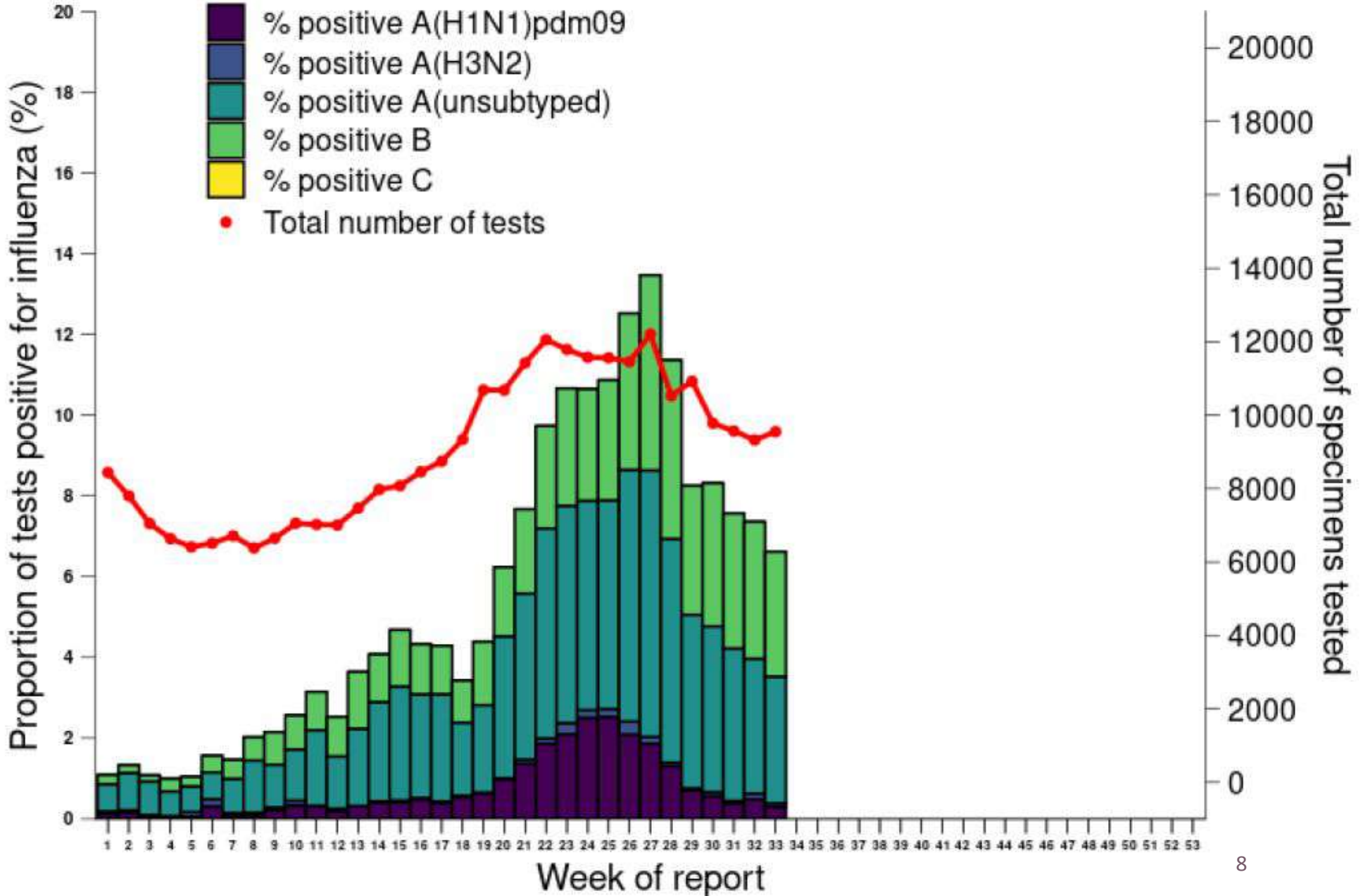


- Potential hope for these strategies to be more readily applied to influenza in the future
  - Although increasing resistance already
  - Useful to recommend some for high risk including during pregnancy to reduce risk

2023 Detail

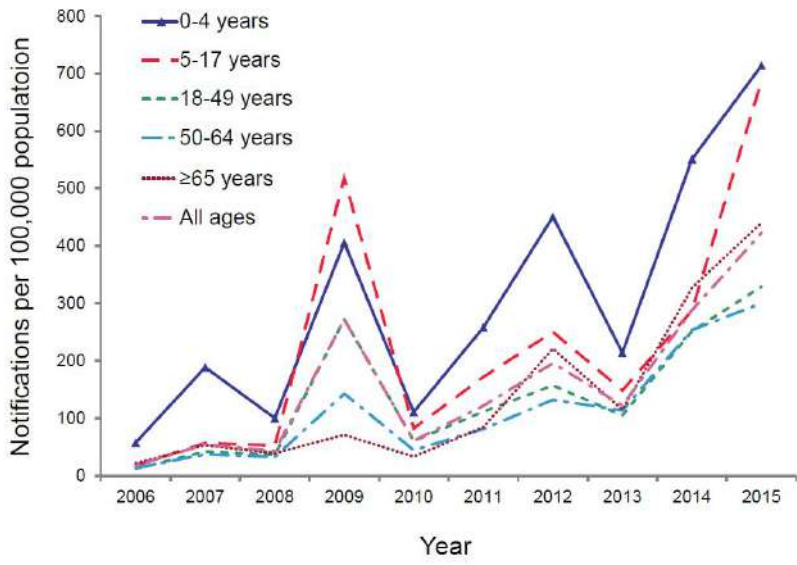
- Cases 211 491 lab confirmed
  - Rate highest in QLD
    - 1178 / 100K population
- Admissions 2787
  - Flu A 65%
  - Flu B 35%
  - Direct to ICU 190
- Deaths 214
  - 87% Flu A
    - Untyped 77%
    - H1N1 9%
    - H3N2 1%
  - 11% Flu B
  - 2 % untyped
  - Median age 75.5 years

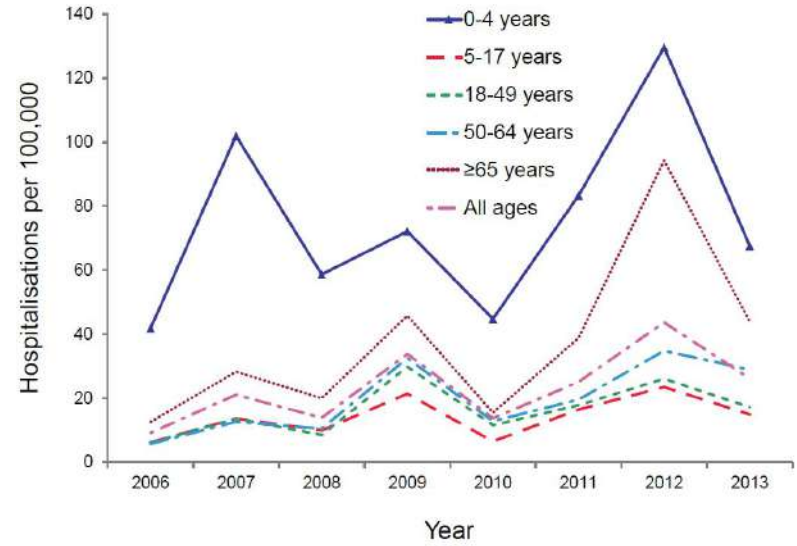
Figure 4: Proportion of sentinel laboratory tests positive for influenza and total number of specimens tested, 1 January to 20 August 2023, by subtype, year and week*



At Risk Groups

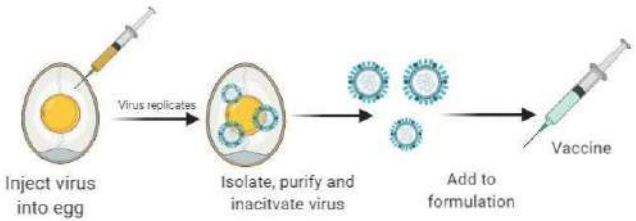
- Different to COVID-19, for Flu
  - Children impacted more significantly
    - Contribute to spread
    - Highest rates of notifications and hospitalisations
      - Notifications 2023
        - Highest in 5 to 9 years at 2563 per 100 000 population
        - Followed by 0 to 4 at 1761
    - Rates of deaths low
  - Pregnancy also high risk
    - Manifestations similar however typically more severe
      - During 2009 H1N1 pandemic, pregnant 5% of all influenza deaths despite being 1% of population
- Although similar to COVID-19 that age is greatest risk for death
  - Children ≤ 5 ~ 0.2 per 100 000
  - 75 years or more 3.66 per 100 000
- Similar list of comorbidities
  - Including chronic lung, metabolic, cardiovascular, metaplastic and immunosuppressing conditions





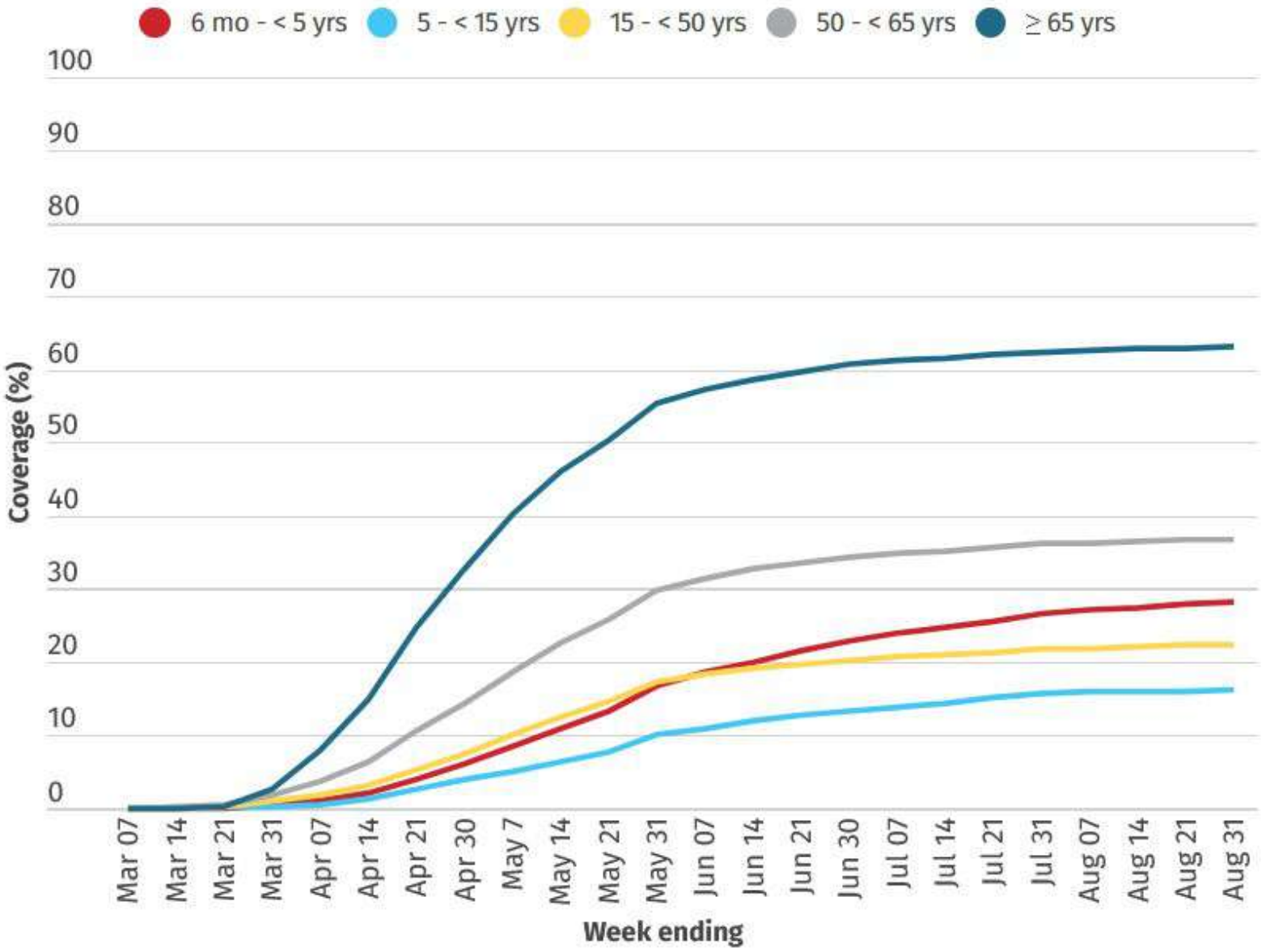
Current Vaccination Strategy

- Seasonal influenza vaccines typically contain attenuated strains of both Influenza A and B viruses
  - grown in eggs and inactivated
- AIVC meet in ~ October to decide what to include based on
  - Epidemiology, antigenic and genetic data of recent isolates in Australia and southern hemisphere
  - Serologic responses to the previous years' vaccines
  - Availability of candidate vaccines viruses
- 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
  - Uptake suboptimal
  - Relatively low efficacy, ~ 20 to 60 % since 2010
    - Need to be prepared to discuss this in the context of heightened awareness of these issues from COVID-19 vaccines



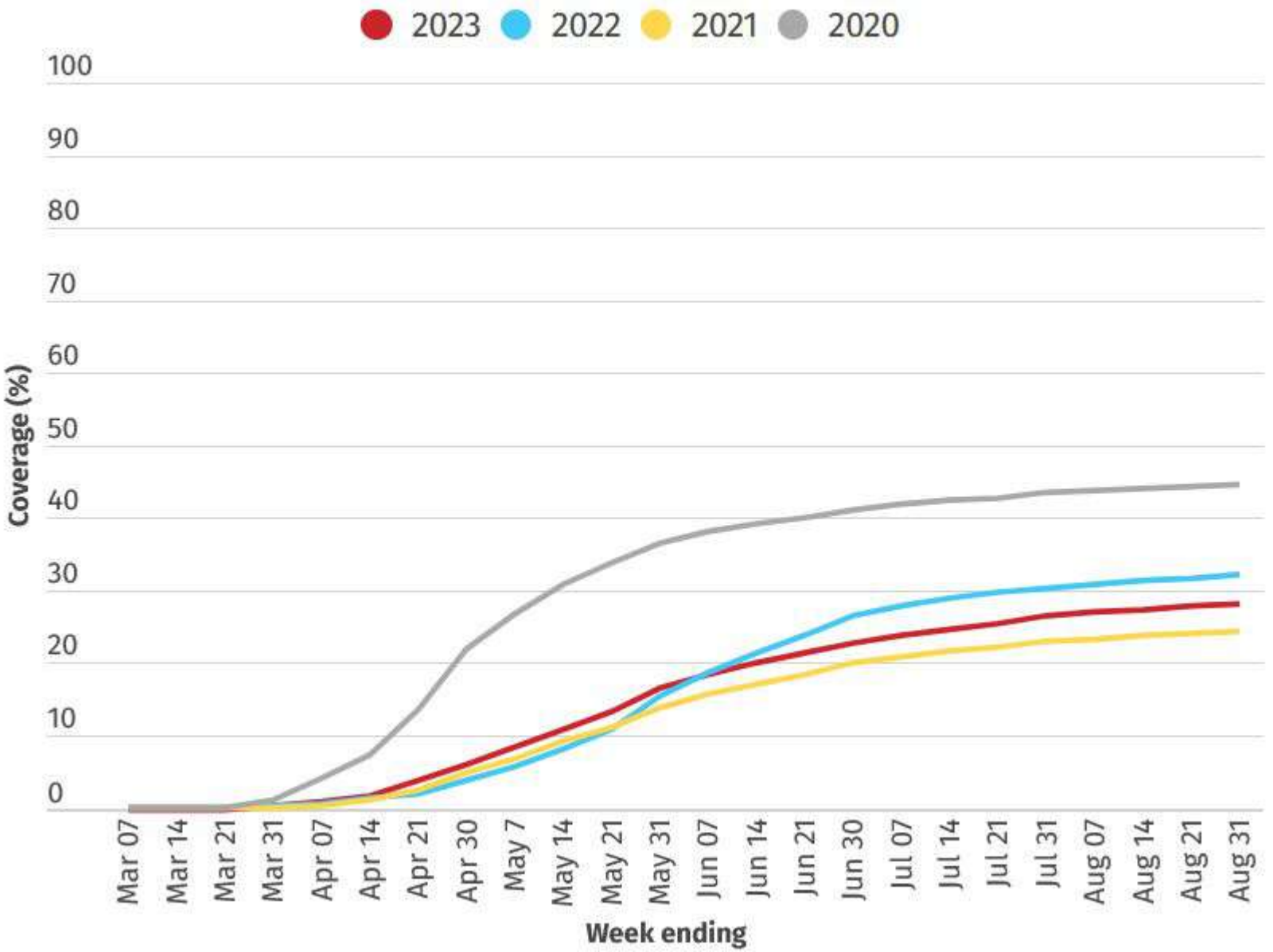
Australian Flu Vaccine Coverage-2023

- Highest in over 65's
  - Still less than 70%
- < 65 years
  - < 40%



Comparative Rate 6 m to < 5 years

- This group: high risk and NIP funded
- Uptake in 2023 second only to 2021 at less than 30%



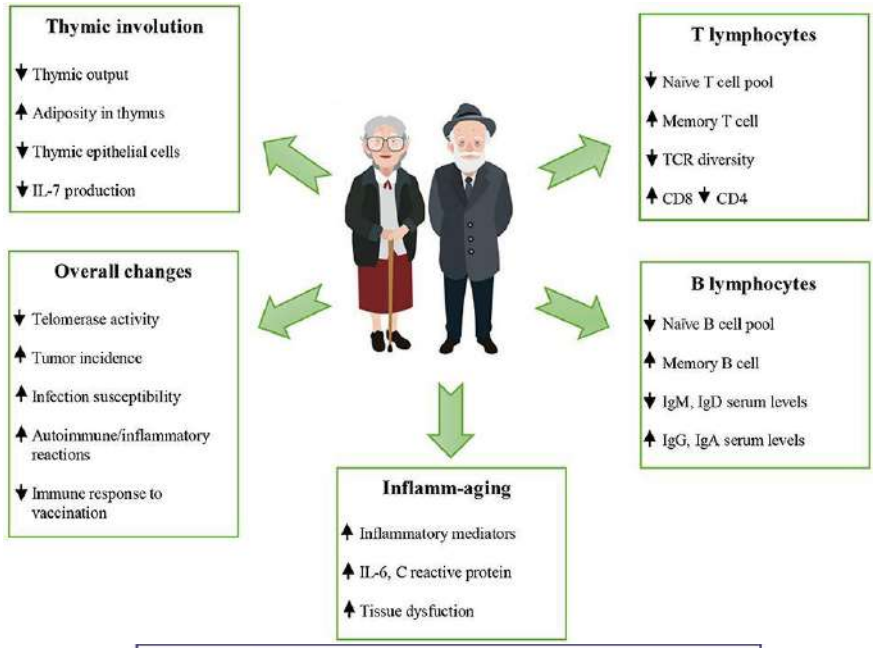
ATAGI Clinical Advice 2023

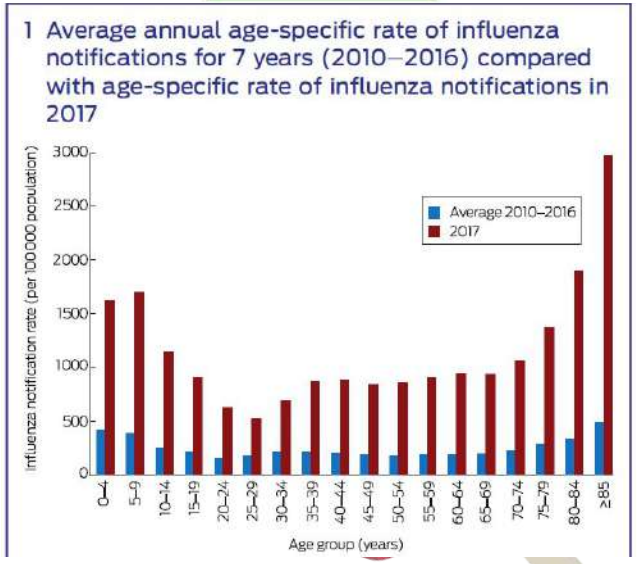
- Annual vaccination recommended for all ≥ 6 months of age
  - NIP funding: < 5 or > 65 y.o.a., comorbidities, pregnancy, Aboriginal and Torres Strait Islander people
- Vaccinations recorded in Australian Immunisation Register
- Can be co-administered with any COVID-19 vaccine
- Adults ≥ 65 augmented vaccine

Egg-based influenza vaccines	Cell-based influenza vaccines
A/Sydney/5/2021 (H1N1) pdm09-like virus	A/Sydney/5/2021 (H1N1) pdm09-like virus
A/Darwin/9/2021 (H3N2)-like virus	A/Darwin/6/2021 (H3N2)-like virus
B/Austria/1359417/2021 (B/Victoria lineage)-like virus	B/Austria/1359417/2021 (B/Victoria lineage)-like virus
B/Phuket/3073/2013 (B/Yamagata lineage)-like virus	B/Phuket/3073/2013 (B/Yamagata lineage)-like virus

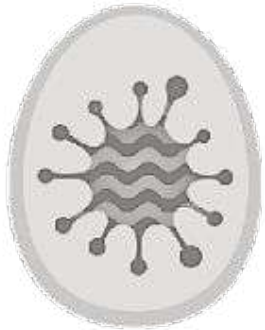
Vaccines-Augmented Vaccines for the Elderly

- 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 antigen
- 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]
    - can contribute to vaccine-virus mismatch
      - may impact vaccine effectiveness in some seasons[1,2,6,9]
- Cell-based vaccines potentially over come this
  - Sub-unit vaccine propagated in Madin Darby Canine Kidney (MDCK) cells
  - Indicated for use in adults and children 2 years of age and older
    - First available in Australia in 2021, approval extended to 2 years of age last year
  - Private prescription, not yet funded

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.

New Vaccines

- COVID-19 accelerated the development of many vaccine platforms
  - mRNA not necessarily new
    - Both BioNTech and Moderna
      - Founded over 10 years ago
      - Have over 20 other candidate vaccines including Influenza
        - Influenza vaccines in Phase 3
          - Includes mRNA encoding hemagglutinin glycoproteins of the four influ WHO
          - Have other candidates with additional HA and NA antigens
      - Combinations also progressing well through clinical trials
        - Focusing on COVID-19 with Flu and some also with RSV
  - Similar with other platforms including novel protein based
    - Novavax
      - ~10 other vaccines in pipeline including influenza
      - "NanoFlu" quadrivalent nanoparticle hemagglutinin proteins with Matrix-M adjuvant
        - Phase 3 trials underway


Human Vaccines & Immunotherapeutics

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/khvi20

A phase 1, randomized, placebo-controlled study to evaluate the safety and immunogenicity of an mRNA-based RSV prefusion F protein vaccine in healthy younger and older adults

Antonios O. Aliprantis . Christine A. Shaw . Paul Griffin . Nicholas Farinola .

Treatment

- Most cases self-limiting and uncomplicated
- Antivirals have 2 main roles
  - Early treatment of high risk to reduce likelihood of progression
  - Treatment of severe disease to likely improve outcomes
  - Can also be used for prophylaxis in specific circumstances
    - Including addressing institutional outbreak

- Some controversy as to benefit
  - Cochrane reviews failed to clearly demonstrate benefit for complications such as pneumonia, mostly due to “lack of diagnostic definitions”
    - Did show reduced time to alleviation of symptoms and when used as prophylaxis reduced the risk of developing symptomatic influenza
    - Like essentially all antivirals (and as demonstrated with COVID-19), time to initiation, patient selection and other factors all relevant

Testing and treatment

- Most guidelines recommend initiating treatment within 48 hours of symptom onset
  - In highest risk, particularly pregnancy, start anyway, even if later
  - Logistics can be challenging, particularly if delay in accessing testing
    - In very high-risk patients, particularly at times of higher transmission, commence empirically whilst awaiting results
    - Increasingly RAT's also test for Influenza
      - Laboratory based testing still has a significant role however
        - Increased sensitivity
        - Typing
        - Ability to find other pathogens
        - Data

Conclusion

- Despite
  - Majority of the focus being on COVID-19 recently
  - Very low influenza numbers from early 2020 to April 2022
    - Influenza has returned and is once again a very significant disease with high impact
- Children and pregnant women are both important subsets of the population with significant risks
  - Children have the highest rates of notifications and hospitalisations and contribute significantly to transmission
    - The elderly have the highest burden in terms of deaths
  - Influenza in pregnancy associated with more severe disease in the mother and pregnancy complications including preterm birth and pregnancy loss
- Vaccination is an important tool to reduce the impact of influenza
  - Due to risk of severe disease, many groups NIP funded
  - Other simple measures to reduce risk should also be recommended
- Some new vaccine options are available, and more are under development
- Antiviral therapy is also an important strategy to reduce risk of complications in high-risk individuals including in pregnancy