# Influenza vaccines for older Australians

Allen Cheng

Director, Infection Prevention and Healthcare Epidemiology Unit, Alfred Health

Professor of Infectious Diseases Epidemiology, Monash University

theAlfred

Part of AlfredHealth

# Declarations

- Co-Chair, ATAGI
- Chair, ATAGI Influenza Working Group
- Chair, ACV

- Opinions expressed do not represent views of committees or government

# 2017

| Sponsor | Tradename | Age group |
|---|---|---|
| **Quadrivalent vaccines** | | |
| GlaxoSmithKline | Fluarix Tetra | 3 years and over |
| Sanofi-Aventis | FluQuadri Junior* | 6-35 months (<3 years) |
| | FluQuadri | 3 years and over |
| Seqirus | Afluria Quad | 18 years and over |

# The 2017 flu season was the 'deadliest' since records began

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By Aisha Dow
May 31, 2018 — 6.56am

It was one of the worst weeks of Professor David Pilcher's working life.

Late in September last year, intensive care units around the country were floode
number of people experiencing severe complications from the flu.

Some patients suffered multiple organ failure.

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The Age 31/5/2018

# Melbourne girl, eight, dies as Australia's 'horror' flu season continues

**Victoria's health minister urges people to get vaccinated as eastern seaboard sees slight decline in cases**

▲ There have been more than 13,000 flu cases in Victoria over the past few months, including 95 deaths. Peo
have been urged to get vaccinated. Photograph: Evan Vucci/AP

An eight-year-old girl is the latest victim of Victoria's "horror" flu season, with people urged to get vaccinated and not ignore symptoms.

Guardian 18/9/2017

# Victorian mother Sarah Hawthorn remains in induced coma after contracting flu while pregnant

Updated 20 Sep 2017, 7:40pm

PHOTO: Sarah Hawthorn contracted the flu while in the later stages of pregnancy. (GoFundMe)

ABC 20/7/2017

# 2018

- For adults aged ≥65 years, in addition to the quadrivalent influenza vaccines (QIVs), two higher-immunogenicity trivalent influenza vaccine (TIV) formulations (one a 'high-dose' vaccine and another containing an adjuvant) are available and NIP-funded.
- *These TIVs are **preferentially recommended over QIVs** for adults aged ≥65 years. However, there is no preference for use between either of these two TIVs.*
- *There is an increased likelihood of injection site reactions and systemic symptoms with these two TIVs, but no increase in the risk of severe adverse effects compared with standard TIVs.*

| | Quadrivalent | | | | | Trivalent (for age ≥65 years only) | |
|---|---|---|---|---|---|---|---|
| Vaccine / Registered age group | FluQuadri Junior 0.25 mL (Sanofi) | FluQuadri 0.50 mL (Sanofi) | Fluarix Tetra 0.50 mL (GSK) | Afluria Quad 0.50 mL (Seqirus) | Influvac Tetra 0.50 mL (Mylan) | Fluzone High-Dose 0.50 mL (Sanofi) | Fluad 0.50 mL (Seqirus) |
| <6 months | x | x | x | x | x | x | x |
| 6 to 35 months (<3 years) | ✓ | x | x | x | x | x | x |
| ≥3 to 17 years | x | ✓ | ✓ | x | x | x | x |
| ≥18 years | x | ✓ | ✓ | ✓ | ✓ | x | x |
| ≥65 years | x | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |

# 2019

- For adults aged ≥65 years two higher-immunogenicity trivalent influenza vaccine (TIV) formulations (one 'high-dose' vaccine and another containing an adjuvant) are available, in addition to the quadrivalent influenza vaccines (QIVs).
- In 2019, only **Fluad® (TIV containing an adjuvant) is NIP-funded.**
- The higher immunogenicity TIVs are **preferentially recommended over QIVs for adults aged ≥65 years**. However, there is no preference for use between either of these two TIVs.
- The evidence around the use of higher immunogenicity TIVs is still evolving and ATAGI continues to review this evidence.

| | Quadrivalent | | | | | Trivalent (for age ≥65 years only) | |
|---|---|---|---|---|---|---|---|
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| <6 months | x | x | x | x | x | x | x |
| 6 to 35 months (<3 years) | ✓ | ✓ | x | x | x | x | x |
| ≥3 to <5 years | x | ✓ | ✓ | x | x | x | x |
| ≥5 to 17 years | x | ✓ | ✓ | ✓ | x | x | x |
| ≥18 years | x | ✓ | ✓ | ✓ | ✓ | x | x |
| ≥65 years | x | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |

* Vaccine funded under the NIP

# Adjuvated TIV - (PBAC July 2019)

- The PBAC did not recommend the requested price increase for aTIV (Fluad®) on the NIP for vaccination against influenza in adults aged 65 years and above. This was on the basis that the extent of **benefit of the aTIV over non-adjuvanted QIV was uncertain**, given that the impact of the loss of the additional B strain differed across influenza seasons.
- The PBAC considered that this uncertainty made it **difficult to assess the cost-effectiveness of the aTIV**, and that although a small price premium for the aTIV over QIV may be reasonable, the **proposed price premium was not justified**.
- The PBAC deferred making a recommendation for a new listing for aQIV (Fluad Quad®) …

# Adjuvanted QIV – PBAC outcome (Aug 2019)

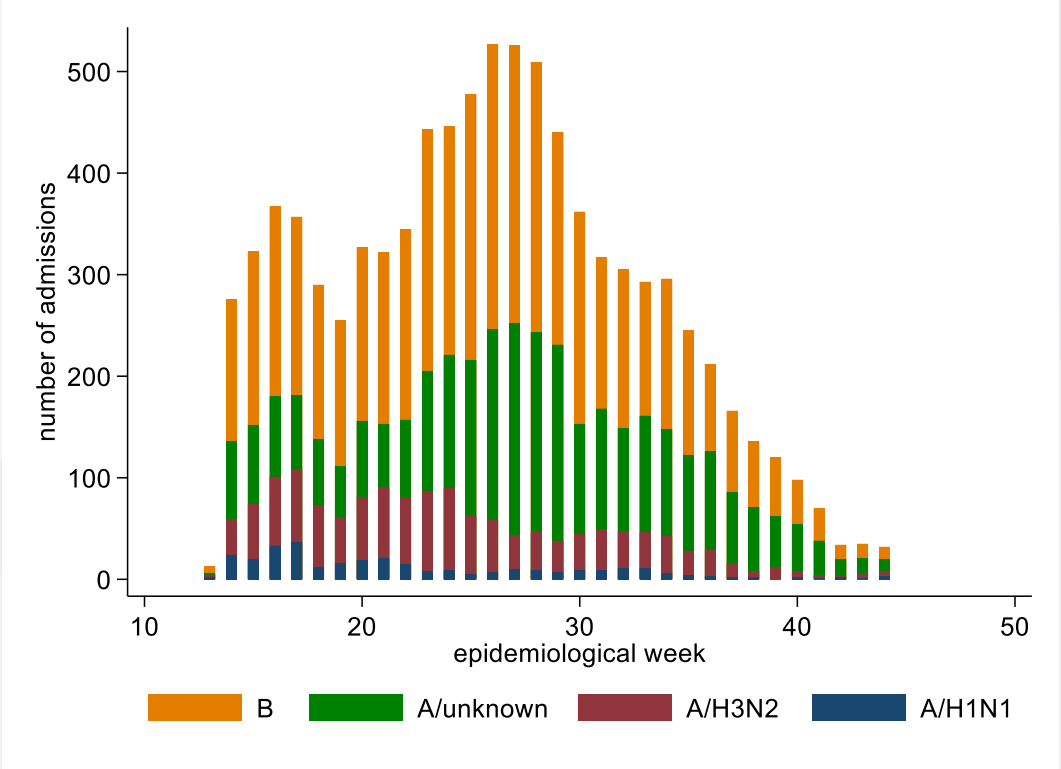
- The PBAC recommended the listing of adjuvanted quadrivalent influenza vaccine (aQIV, Fluad Quad®) … for vaccination against influenza in **adults aged 65 years and above**.
- The PBAC reiterated its July 2019 advice that it was satisfied that **aQIV provides**, for adults aged 65 and above, **a significant improvement in efficacy over non-adjuvanted QIVs** and that it considered that aQIV was **cost-effective at the proposed price**.

# FluCAN 2019

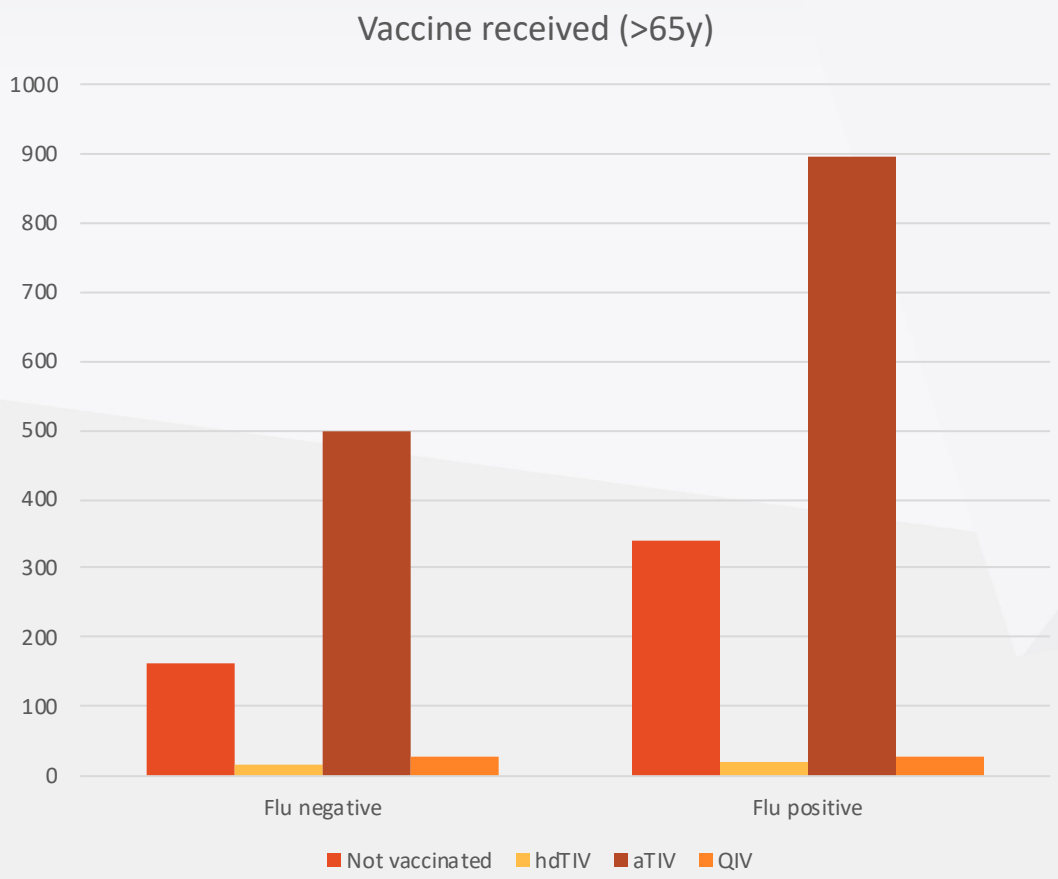
- 4155 cases total
- 2447 elderly
- 1993 vaccine status ascertained

- Early season
- H3>H1
- Significant B

- VE = 1-aOR

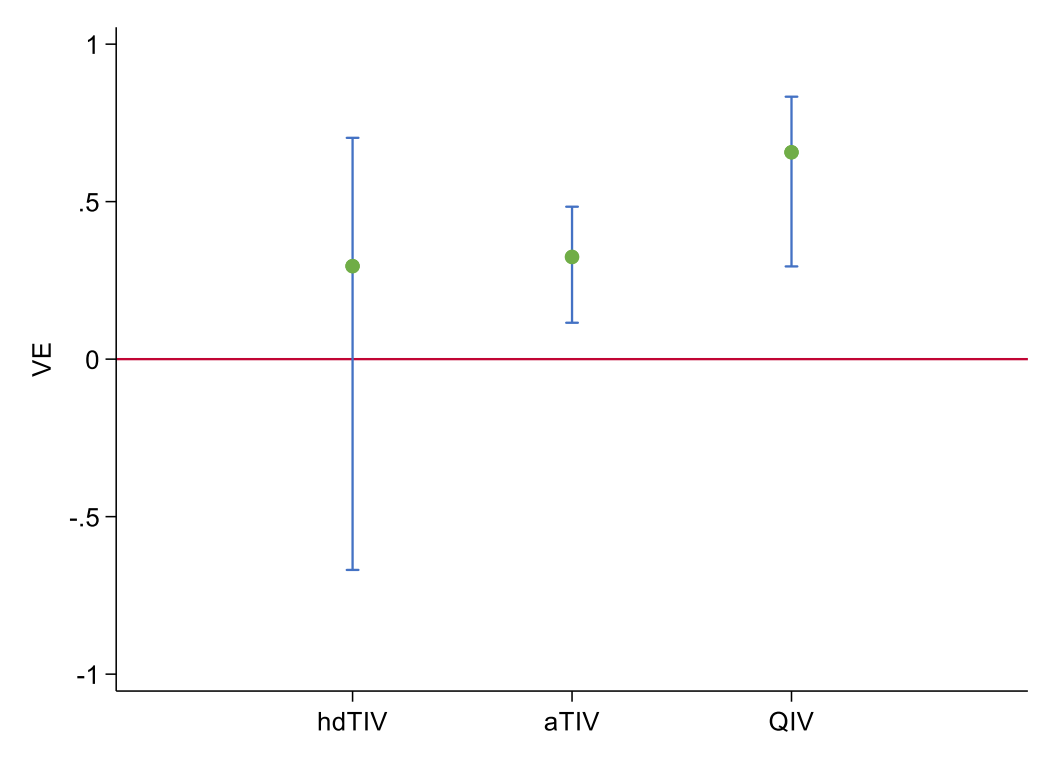


# FluCAN data: 2019




- N=1993 known vaccine >65 years
- Vaccination coverage (controls) 77%
- 93% of vaccinated received aTIV
- *small numbers received hdTIV, QIV

# Vaccine effectiveness in elderly




- Estimated VE
  - **aTIV vs no vaccine: 32% (12-48%)**
  - hdTIV vs no vaccine: 30% (-67, +70%)
  - QIV vs no vaccine: 66% (29, 83%)
- hdTIV vs aTIV: OR 1.05 (0.45, 2.4)
- *adjusted for comorbidities, Indigenous status

# Discussion

- Similar VE to previous years
- Many caveats about comparisons
  - Small numbers received hdTIV, QIV
  - Potential misascertainent of vaccination status
  - Only basic adjustment for confounders

# MF59-adjuvanted TIV - Italy

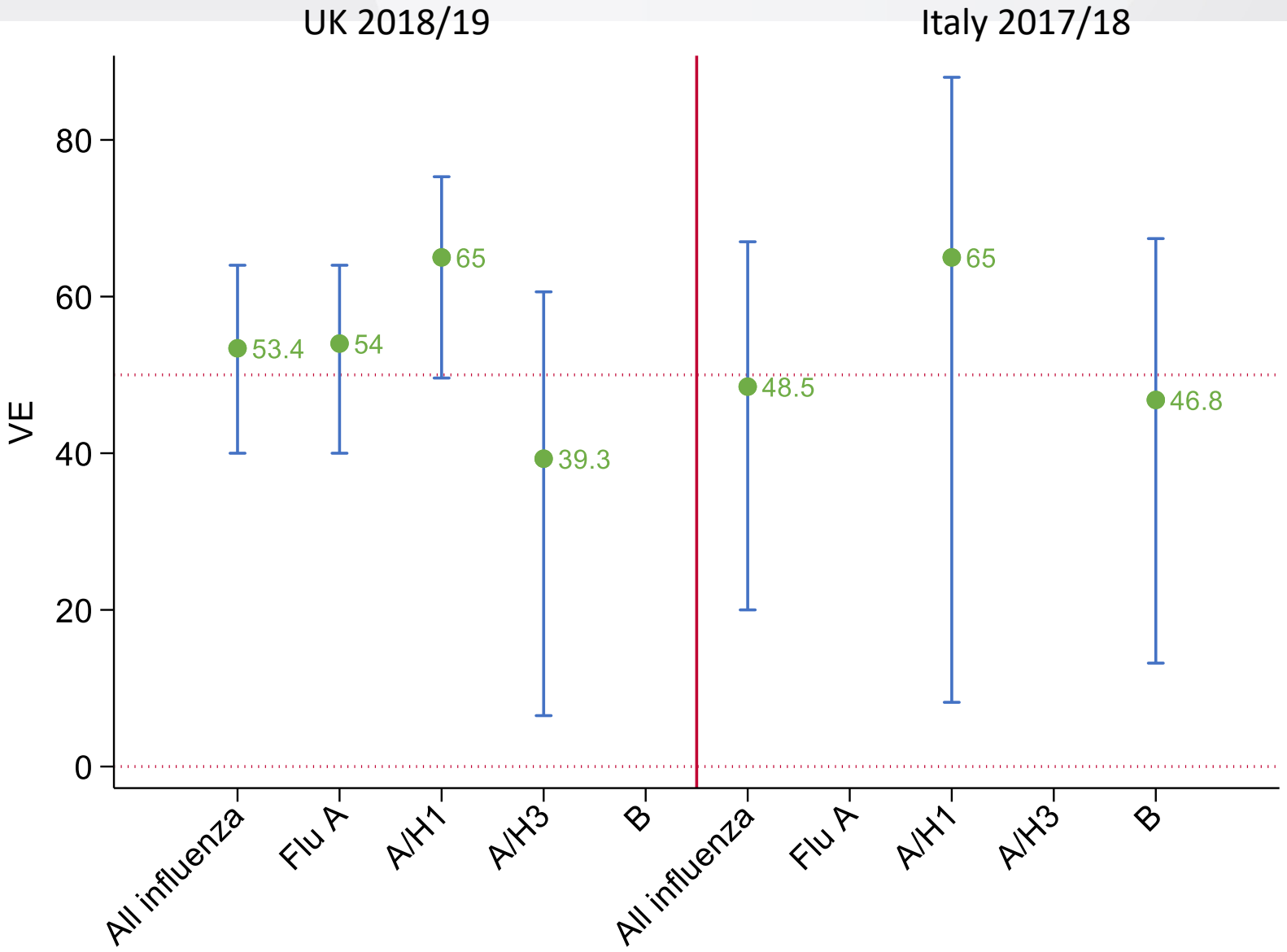
- Test negative (case control)
- Hospitalized patients, Italy
- 2017/18 season: B>H1>H3
- SARI case definition

- 502 patients with SARI
  - 118 (24%) flu positive
  - 384 (76%) flu negative
- 50% vaccinated
  - Almost all Fluad

# MF59-adjuvanted TIV - UK

- Test negative (case control)
- Hospitalized elderly patients, UK
- 2018/19 season: H1>H3
- SARI case definition, vaccine status from GP

- 428 cases
- 1013 controls (75% vaccinated)
- Most vaccinated with aTIV


UK 2018/19
Italy 2017/18
VE
80
60
40
20
0
53.4
54
65
39.3
48.5
65
46.8
All influenza
Flu A
A/H1
A/H3
B
All influenza
Flu A
A/H1
A/H3
B

# Adjuvanted quadrivalent vaccine

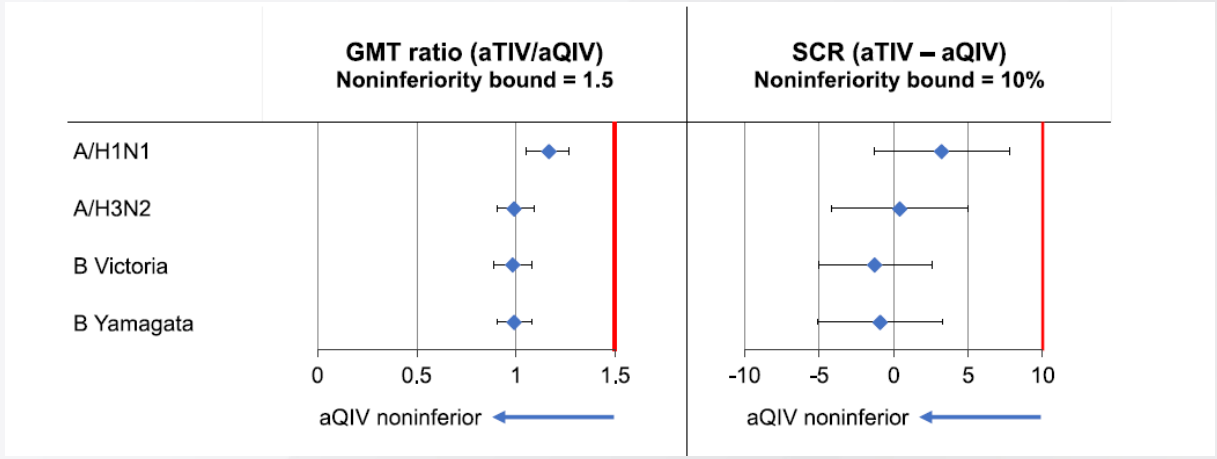
- No epidemiological data

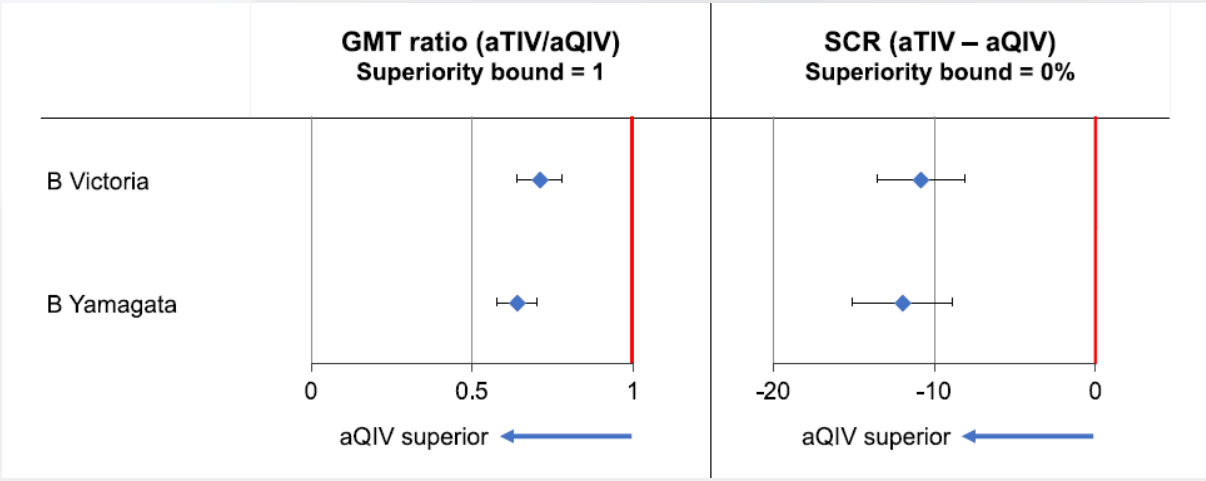
- Immunogenicity data
  - US elderly, 2017/18
  - aQIV (n=889) vs aTIV1 (n=445) vs aTIV2 (n=444)

- Primary outcomes:
  - GMT ratio (aTIV/aQIV) ie higher means aQIV is worse
  - SCR difference (aTIV – aQIV) ie >0 means aQIV is worse

# Immunogenicity

- aQIV as immunogenic as aTIV for A/H3, B/Vic, B/Yam.
- Meets non-inferiority criteria for A/H1
- Better than vaccine with alternate B strain



# High dose - PBAC outcome (Nov 2019)

- The PBAC recommended an increase in the price of inactivated trivalent influenza vaccine (Fluzone® High-Dose, TIV-HD), on the NIP for active immunisation against influenza in adults aged ≥ 65 years.
- The PBAC recommendation was on the basis that, on balance, **TIV-HD was at least as effective as adjuvanted quadrivalent influenza vaccine (Fluad® Quad, aQIV)**. The PBAC considered a claim of superior effectiveness compared with aQIV could not be adequately supported by the clinical evidence presented and therefore a cost-minimisation approach in which TIV-HD was the same price as aQIV would be appropriate

# High dose vs adjuvanted

- Several studies
  - Population
  - Adjustment for confounders
  - Analysis method
  - Endpoint

# Van Aalst (Vaccine 2020)

- Population – US elderly, Optum Clinfomatics Data Mart (admin claims), 2016/17, 2017/18
- Analysis method: PERR (baseline adjusted)
- Endpoint: respiratory admission (UTI as negative control)

**Table 4**
Relative vaccine effectiveness (rVE) with 95% confidence intervals of high dose (HD-IIV3) versus adjuvanted influenza vaccine (aIIV3) for respiratory seasons 2016–17, 2017–18 and the two seasons combined (summary rVE), adjusted for baseline characteristics.

| Hospitalizations | 2016–17 season | 2017–18 season | Summary rVE |
|---|---|---|---|
| Respiratory disease | 13% (−6.3%, 32%) | 12% (2.1%, 21%) | 12% (3.3%, 20%) |
| Cardio-respiratory disease | 13% (2.3%, 23%) | 6% (0.6%, 11%) | 7.0% (2.3%, 12%) |
| Urinary Tract Infection | −20% (−59%, 19%) | 2.5% (−12%, 17%) | −0.7% (−14%, 13%) |

Confidence intervals were calculated using a robust variance estimator. We applied the Previous Event Rate Ratio (PERR) to address unmeasured confounders by including an interaction term of Period (observation versus baseline period) and treatment (HD-IIV3 versus aIIV3). The PERR was adjusted for observed confounding factors by including all the baseline characteristics of Table 1 as covariates, except for Age Groups and the Deyo-Charlson Score, to prevent collinearity with Age and individual comorbid conditions. Hospitalizations were classified using the principal discharge diagnosis.

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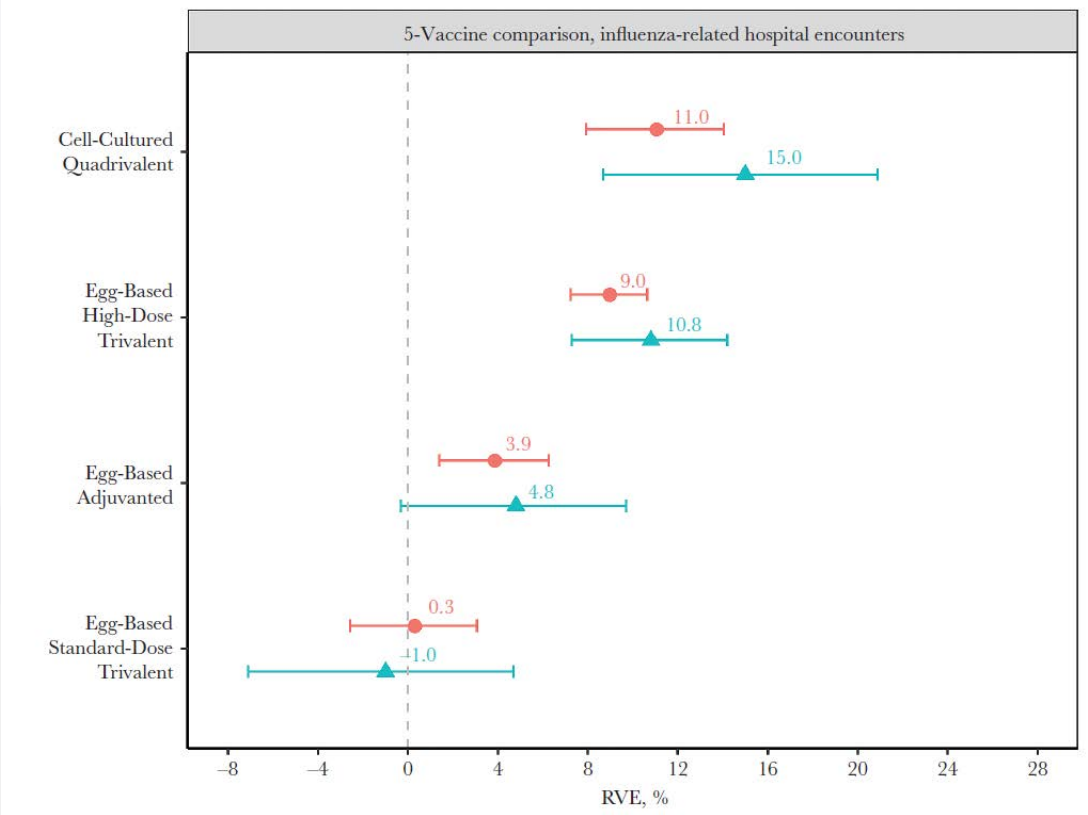
# Izureita (JID 2019)

- Population – US elderly – Medicare data, 2017/18
- Analysis method: Propensity score IPTW
- Endpoints: influenza-related presentation (ED+IP) based on coding

- >16 million individuals; 13 million included in analysis
  - 5% cell-cultured QIV
  - 14% egg cultured QIV, 7% TIV
  - 63% hdTIV
  - 11% aTIV

# Comparisons

- Cell cultured QIV – VE 11%
- hdTIV - VE 9.0%
- aTIV - VE 3.9%
- aTIV and aQIV – referent (1)




Comparator: egg based QIV

| Cohort | RVE by Reference Group (95% CI), % | | | |
|---|---|---|---|---|
| | Egg-Based Quadrivalent | Egg-Based SD Trivalent | Egg-Based Adjuvanted Trivalent | Egg-Based HD Trivalent |
| Cell-cultured quadrivalent | 11.0 (7.9–14.0)[a] | 10.8 (7.4–14.1)[a] | 7.5 (4.1–10.7)[a] | 2.3 (–.8, to 5.3) |
| Egg-based HD trivalent | 9.0 (7.2–10.6)[a] | 8.7 (6.5–10.9)[a] | 5.3 (3.3–7.3)[a] | … |
| Egg-based adjuvanted trivalent | 3.9 (1.4–6.3)[a] | 3.6 (.7–6.4)[a] | … | … |
| Egg-based SD trivalent | 0.3 (–2.6 to 3.1) | … | … | … |

Abbreviations: CI, confidence interval; HD, high-dose; IPTW, inverse probability of treatment weighting; RVE, relative vaccine effectiveness; SD, standard-dose.

[a]Pairwise comparison RVE estimates that are significant at the $P \leq .05$ level.

**Table 4. IPTW-Adjusted Pairwise RVE Estimates for Influenza-Related Office Visits and Inpatient Stays in the 2017–2018 Season**

| Outcome by Cohort | RVE by Reference Group (95% CI), % | | | |
|---|---|---|---|---|
| | Egg-Based Quadrivalent | Egg-Based SD Trivalent | Egg-Based Adjuvanted Trivalent | Egg-Based HD Trivalent |
| Influenza-related office visits | | | | |
| Cell-cultured quadrivalent | 5.7 (1.9–9.4)[a] | 1.0 (–3.5 to 5.3) | 11.5 (7.9–15.0)[a] | 5.1 (1.6–8.4)[a] |
| Egg-based HD trivalent | 0.7 (–1.5 to 2.9) | –4.3 (–7.4 to –1.3)[a] | 6.8 (4.6–8.9)[a] | … |
| Egg-based adjuvanted trivalent | –6.6 (–9.7 to –3.5)[a] | –11.9 (–15.9 to –8.1)[a] | … | … |
| Egg-based SD trivalent | 4.8 (1.5–8.0)[a] | … | … | … |
| Influenza-related inpatient stays | | | | |
| Cell-cultured quadrivalent | 9.5 (5.3–13.4)[a] | 11.4 (7.0–15.7)[a] | 7.1 (2.7–11.3)[a] | –0.7 (–4.8 to 3.4) |
| Egg-based HD trivalent | 10.0 (7.8–12.3)[a] | 12.0 (9.2–14.8)[a] | 7.7 (5.1–10.2)[a] | … |
| Egg-based adjuvanted trivalent | 2.5 (–.8 to 5.8) | 4.7 (.9–8.3)[a] | … | … |
| Egg-based SD trivalent | –2.2 (–6.1 to 1.5) | … | … | … |

Abbreviations: CI, confidence interval; HD, high-dose; IPTW, inverse probability of treatment weighting; RVE, relative vaccine effectiveness; SD, standard-dose.

[a]Pairwise comparison RVE estimates that are significant at the $P \leq .05$ level.

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| Influenza-related inpatient stays | | | | |
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Abbreviations: CI, confidence interval; HD, high-dose; IPTW, inverse probability of treatment weighting; RVE, relative vaccine effectiveness; SD, standard-dose.

[a]Pairwise comparison RVE estimates that are significant at the $P \leq .05$ level.

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# Discussion

- Two large, well conducted observational studies suggest
  - Cell based QIV, hdTIV and aTIV better than QIV
  - hdTIV is better than aTIV
- Seasons with dominant A/H3
- Magnitude of benefit is not large
- BUT hospitalisation endpoint is clinically important (and has cost effectiveness implications)
- Other studies suggest better protection

# hdTIV vs TIV/QIV - effectiveness

H3 dominant seasons
Similar VE to RCTs
VE flu = VE hospitalisation
Some heterogeneity

| | Year/dominant strain | VE against probable influenza | VE against flu-related hospitalisation |
|---|---|---|---|
| Izurieta et al. 2015 | 2012/13 (A/H3) | 22.6% (15.7–29.0) | 20.6% (14.9–24.8) |
| Richardson et al. 2015 | 2010/11 (A/H3) | | 2% (-40 to 32) |
| Shay et al. 2017 | 2012/13 (A/H3) | 22.0% (14.8–28.6) | 22.1% (16.6–27.3) |
| | 2013/14 (A/H1) | 6.8% (–2.3 to 15.1) | 12.7% (4.9–19.9) |
| Doyle 2018 (abstract only)[9] | 2015/16 (A/H1) | | 28% (-1 to 48%) |
| Saade 2018 (abstract only)[13] | 2013/14 (A/H1) | | Acute CV events: 8% (5–15) |
| Young-Xu et al 2018[17] | 2015/16 (A/H1) | Influenza/pneumonia outpatient visit: 14% (-8 to 32)<br>Confirmed influenza: 38% (-5 to 35) | 25% (2–43%) |
| Young-Xu 2018 [16] | 2011/12 (A/H3) & 2012/13 (A/H3) | | Flu/pneumonia: 22% (CI 11–31)<br>Cardiorespiratory: 10% (2–17)<br>All-cause: 11% (8–15) |
| Young-Xu 2018 [15] | 2014/15 (A/H3) | | Flu/pneumonia: 7% (5–9)<br>Cardiorespiratory: 15% (10–17)<br>All-cause: 13% (8–17) |
| Lu 2018 (hdTIV vs QIV) | 2017/18 (A/H3) | 0.8% (CIs not reported) | 8.4% (6.6–10.1) |

# aTIV vs TIV - effectiveness

**Table 4**
Relative effectiveness of MF59-TIV (MF59-TIV versus other vaccines).

| Study [Ref.] | Design | Setting | Comparator | Outcome | ES (95% CI) | aES (95% CI) |
|---|---|---|---|---|---|---|
| Iob [25] | Prospective | Long-term care facility | IM-TIV | Influenza-like illness | **0.66 (0.53–0.82)**[a,b] | N/A |
| Mannino [28] | Prospective | Community | IM-TIV | Hospitalization for pneumonia and influenza | 0.97 (0.74–1.25)[c] | **0.75 (0.57–0.98)**[c] |
| Puig-Barberà [31] | Retrospective | Community | Virosomal TIV | Influenza-related hospitalization | 0.53 (0.53–1.30)[c] | 0.85 (0.54–1.34)[c,d]<br>0.94 (0.37–2.38)[c,e] |
| Puig-Barberà [31] | Retrospective | Community | Virosomal TIV | Laboratory-confirmed influenza | 0.72 (0.44–1.18)[c] | 0.75 (0.46–1.24)[c,d]<br>0.84 (0.31–2.26)[c,e] |
| Gasparini [30] | Case-control | Community | ID-TIV | Hospitalization for pneumonia and influenza | **0.43 (0.20–0.91)**[a,f] | 0.54 (0.22–1.29)[a,f] |
| Van Buynder [29] | Prospective case-control | Mixed | IM-TIV | Laboratory-confirmed influenza | 0.58 (0.31–1.09)[a] | **0.37 (0.14–0.96)**[a] |

Range of analytical methods
Most estimates around VE 20-25%, although some considerably higher

Domnich Vaccine 2017

# How much does this matter?

- AIHW: hospital admissions with influenza: 1600 per million in 2016
- Assume
  - VE ~40%
  - Coverage ~70%

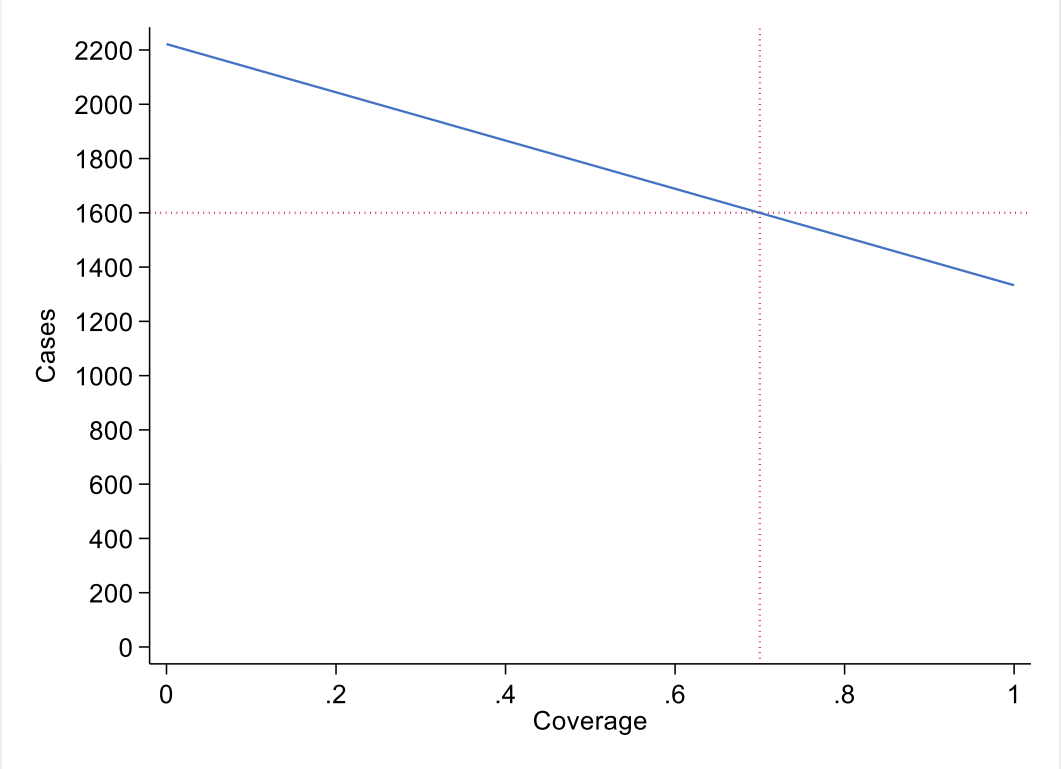
- [coverage x (1-VE) x R] + [(1-coverage) x R] = 1600

Vaccinated  Unvaccinated

- R = 2222 admissions/million/year in unvaccinated

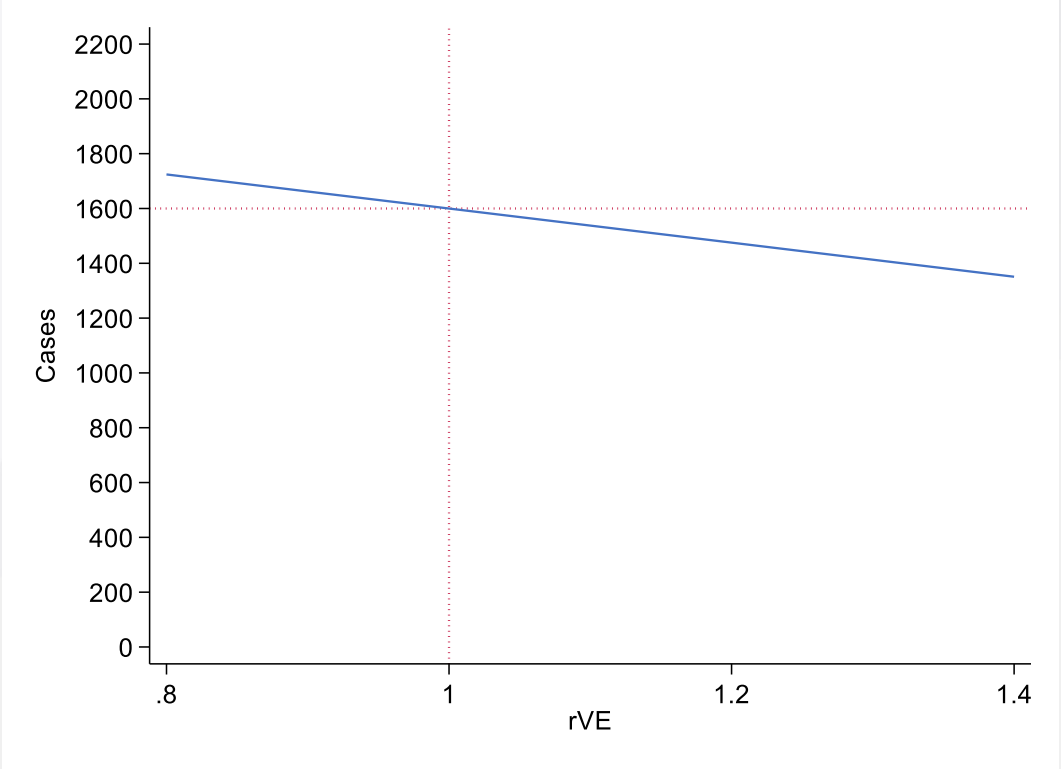
# Changing coverage

- No vaccination: 2222 admissions
- Coverage (at VE 40%)
  - 70%: 1600 admissions
  - 80%: 1510 admissions
  - 100%: 1333 admissions



# Improved relative VE

- QIV: 1600 cases
- Enhanced vaccine at 70% coverage
  - 10% better: 1537 admissions
  - 20% better: 1475 admissions
  - 30% better: 1413 admissions



# Other guidelines

- ACIP (US) – 2019/20
  - No preference is expressed for any one vaccine type.
  - For persons aged ≥65 years, any age-appropriate IIV formulation (standard dose or high dose, trivalent or quadrivalent, unadjuvanted or adjuvanted) or RIV4 are acceptable options.
- NACI (Canada) – 2019/20
  - When available, IIV3-HD should be used over IIV3-SD, given the burden of influenza A (H3N2) disease and the evidence for better efficacy compared with IIV3-SD in this age group
  - There is insufficient evidence to make comparative individual-level recommendations on the use of IIV3-Adj or IIV4-SD over IIV3-SD or between IIV3-Adj, IIV3-HD and IIV4-SD

# Conclusions

- For 2020, we have aQIV (and standard QIV) on the NIP
  - Enhanced vaccines provide some marginal improvements
  - PBAC have determined that hdTIV is not cost effective compared to current vaccines
- Emerging data that hdTIV may be better than aTIV or QIV
  - US administrative data
  - H3 dominant seasons
- Future developments – cell-based QIV, hdQIV?
- Need to monitor and improve coverage