Immunisation in older women

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Declaration of interests:
- Zostavax Advisory Board
- Sequris Pneumococcal Advisory Board
- Sanofi High Dose Influenza vaccine Advisory Board
- Astra Zeneca Influenza vaccine Advisory Board

Acknowledgements
- Paul Van Buynder
- Janet McElhany

Learning Outcomes

- Review recommended immunisations for older women
- Outline vaccines under development and possible vaccines in the future

Overview

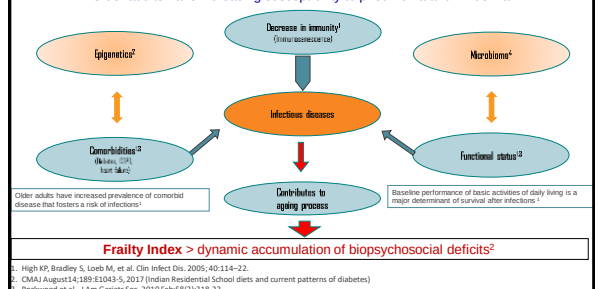
Vaccine-preventable disease in older women
- What's on the NIP schedule
- Update on influenza
- Update on pneumococcal vaccination rates

Other vaccines not on the NIP

Vaccines in the pipeline

Vaccine-preventable diseases

Older adults have increasing susceptibility to pneumonia and influenza



1. High KP, Bradley S, Loeb M, et al. Clin Infect Dis. 2005; 40:114–22.
2. CMAJ August14;189:E1043-5, 2017 (Indian Residential School diets and current patterns of diabetes)
3. Rockwood et al., J Am Geriatr Soc. 2010 Feb;58(2):318-23
4. Meehan et al., Interdiscip Top Gerontol Geriatr. 2015;41:54-65..

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"Hi! I'm the Flu! Do you have a couple of weeks free?"

Vaccine Preventable Disability[1]

Catastrophic disability

- Defined as a loss of independence in **≥ 3 basic** Activities of Daily Living[2]
- **15%** of older adults hospitalized with influenza **experience catastrophic disability**[3]
- Dysregulated immune responses are the 'geriatric giant' of chronic diseases: influenza wakes the giant **increasing the risk of catastrophic disability**[2] with:
  1. Strokes
  2. CHF
  3. Pneumonia and influenza [4,5]
  4. Ischemic heart disease
  5. Cancer
  6. Hip fracture

[1] McElhaney JE et al. Front Immunol. 2016;7:41.
[2] Ferrucci et al. JAMA 1997;277:728.
[3] Andrews MK et al. Canadian Immunization Conference. 12/7/2016.
[4] Barker et al. Arch Int Med 1998;158:645.
[5] Falsey et al. *N Engl J Med.* 2005;352:1749.

Review of influenza season 2017

Annual Australian Lab-confirmed Influenza Cases[1]

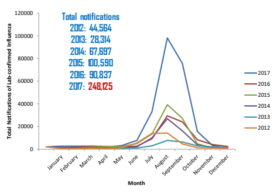


Figure adapted from Immunisation Coalition, 2017.[1]

- Highest level of activity since the 2009 pandemic year[2]
- Influenza A (H3N2) predominated[2]
- Vaccine effectiveness against this strain was low[2]

1. Immunisation Coalition. Annual Australian influenza statistics. Updated 18 Dec 2017. Available at: http://www.immunisationcoalition.org.au/wp-content/uploads/2017/12/18Dec-Flu-Stats-2017-PDF.pdf Accessed Feb 2018. Accessed February 2018. 2. Australian Government Department of Health. Information brief updated 22 Nov 2017. *2017 Influenza Season in Australia.* Available at: http://www.health.gov.au/internet/main/publishing.nsf/Content/cda-surveil-ozflu-flucurr.htm/$File/2017-season-summary-22112017.pdf. Accessed January 2018.

Current vaccines funded for older Australians under the National Immunisation Program (NIP)[1]

Disease	Age group	Vaccine brands[1]
Influenza	65 years and over	Fluad® (trivalent inactivated influenza virus)*; Fluzone® High-dose (inactivated trivalent influenza vaccine)*
Pneumococcal pneumonia	65 years and over 50 years and over (Aboriginal and Torres Strait Islanders)	Pneumovax®23 (pneumococcal vaccine, polyvalent)
Herpes-zoster (shingles)	70-79 years^	ZOSTAVAX® (Zoster Vaccine Live (Oka/Merck))

*Vaccine available under NIP from April 2018[2]. ^ZOSTAVAX® is funded for 70-year-olds, with a 5 year catch-up program for 71 to 79-year-olds until 31 October 2021[1] . Refer to the National Immunisation Program for the full Immunisation schedule[1]

1. Australian Government Department of Health. *National Immunisation Program Schedule.* Available at: https://beta.health.gov.au/topics/immunisation/immunisation-throughout-life/national-immunisation-program-schedule Accessed February 2018. 2. Prime Minster of Australia. Media Release. Ground-breaking flu vaccines to protect millions of Aussies, February 2018. Available at: https://www.pm.gov.au/media/ground-breaking-flu-vaccines-protect-millions-aussies Accessed February 2018.

Two new vaccines available on the National Immunisation program (NIP) from April 2018 for adults aged 65 and over:[1]

Vaccine	Type	Manufacturer	Route of administration
Fluad®[2]	Adjuvanted Inactivated TIV Influenza Vaccine	Seqirus	0.5mL IM
Fluzone® High-dose[3]	High-dose Inactivated TIV Influenza Vaccine	Sanofi	0.5mL IM

TIV = Trivalent; IM = intramuscular injection

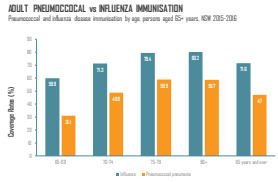
1. Prime Minster of Australia. Media Release. Ground-breaking flu vaccines to protect millions of Aussies, February 2018. Available at: https://www.pm.gov.au/media/ground-breaking-flu-vaccines-protect-millions-aussies Accessed February 2018. 2. Fluad. Product Information. Amended 16 Nov 2017. 3. Fluzone High-dose. Product Information. Amended 12 Jan 2018.

Invasive pneumococcal disease (IPD)

- Strep pneumoniae
  - 90 serotypes cause disease, 23 account for majority of infections
- IPD case fatality rate ~ 8-12 % (children with meningitis 30%)[1]
- Rates of highest disease
  - children aged < two years
  - persons > 65 years
- Increasing prevalence of antibiotic resistance
  - 2006: 11% Aust IPD isolates non-susceptible to penicillin and 3% non-susceptible to ceftriaxone/cefotaxime

1. Ludwig et al Eur Respir Rev. 2012 Mar 1;21(123):57-65

Adult pneumococcal vs influenza vaccination in Australia



Only 31% of 65-69 year olds received their free pneumococcal vaccine in 2015-2016[1]

Adapted from Centre for Centre for Epidemiology and Evidence, NSW Ministry of Health[1]

1. Centre for Epidemiology and Evidence. NSW Ministry of Health. Health Data NSW - Influenza and pneumococcal disease immunisation. Sydney: NSW Ministry of Health. Available at: http://www.healthstats.nsw.gov.au/Indicator/com_flupneumimms_age/com_flupneumimms_age_snap Accessed February 2018

Adult pneumococcal vaccination recommendations

- Pneumovax®23 is recommended and funded on the NIP for the following adults[1,2]:
  - All adults 65 years and over
  - Aboriginal and Torres Strait Islanders 50 years and over
  - Aboriginal and Torres Strait Islanders 15-49 years with a condition(s) associated with increased risk of IPD.
- Adults aged 18-64 years with a condition(s) associated with an increased risk of IPD can access Pneumovax®23 through the PBS.[1]

Refer to the Australian Immunisation Handbook for the full list of recommendations[1].

IPD = invasive pneumococcal disease

1. Australian Technical Advisory Group on Immunisation (ATAGI). *The Australian Immunisation Handbook* 10th ed (2017 update). Canberra: Australian Government Department of Health; *National Immunisation Program Schedule*. Available at: https://beta.health.gov.au/topics/immunisation/immunisation-throughout-life/national-immunisation-program-schedule. Accessed February 2018.

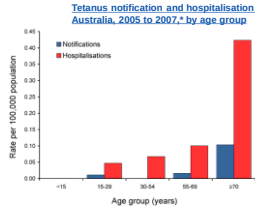
Non-NIP funded vaccines for older adults

- Diphtheria-tetanus-pertussis (dTpa): People aged >65 years are also advised to have a dTpa booster if they have not received one in the previous 10 years[1]
- Meningococcal disease: 4vMenCV and MenBV are available through private prescription for adults who wish to reduce their likelihood of becoming ill with meningococcal disease[2]

4vMenCV=quadrivalent (A,C,W,Y) meningococcal conjugate vaccine; MenBV=meningococcal B vaccine

1. Australian Government Department of Health. *Immunise Australia Program, Older Australians*. Available at: http://www.immunise.health.gov.au/internet/immunise/publishing.nsf/Content/older-australians. Accessed January 2018.
2. NCIRS Fact Sheet: Meningococcal vaccines for Australians. Feb 2018. Available at: http://ncirs.edu.au/provider-resources/ncirs-fact-sheets/ Accessed February 2018.

Tetanus



The ABS Causes of Death database recorded 1–4 deaths with tetanus as the underlying cause for the 4 years from January 2008 to December 2011, all deaths were in people aged >65 years.

Five vaccine doses and an interval of at least 10 years since the last dose are predictive of a long-term protective titre in absence of a booster (>1.97 IU/ml).

Notification where the diagnosis was between January 2006 and December 2007; hospitalisations where the date of separation was between July 2005 and June 2007

Changing pneumococcal serotypes with the introduction of conjugate pneumococcal vaccines

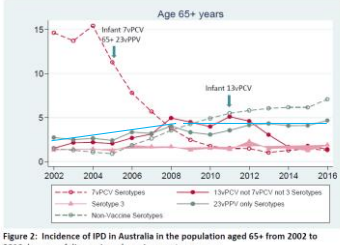


Figure 2: Incidence of IPD in Australia in the population aged 65+ from 2002 to 2016, by year of diagnosis and vaccine serotype group

The direct impact of 23vPPV is evident in the significantly lower rate of growth from 2005 in IPD attributable to its 11 exclusive serotypes (Incidence Rate Ratio (IRR)2016:2005 = 2.0 (1.5–2.7)) compared to IPD attributable to non-vaccine serotypes (IRR2016:2005 = 8.0 (5.2–12.9)), resulting in higher incidence of the latter from 2009

Immunosenescence

- Definition & mechanisms
  - The age-associated decline of the immune system and host defense mechanisms.
  - universal age-associated immune alteration
  - Reduced numbers and proportions of peripheral blood CD8+ naïve T cells are as a result of developmentally-programmed thymic involution
- Range of responses of the ageing immune system
  - poorer responses to vaccination,
  - lower capacity to mediate anti-cancer responses,
  - more inflammation and tissue damage,
  - Increased autoimmunity and,
  - loss of control of persistent infections

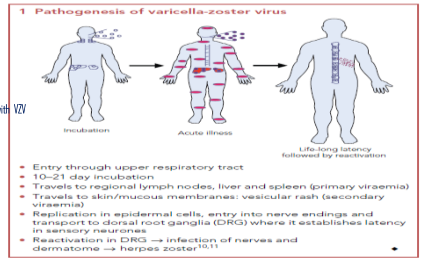
Pawelec Exp Gerontol. 2018 May;105:4-9. Del Giudice et al NPJ Aging Mech Dis. 2017 Dec 21;4:1.

Immunosenescence

- Impact on vaccine efficacy
  - lower vaccination efficacy in older adults does correlate with age-associated differences in the responses of CD4+ and CD8+ T cells to the vaccine
- Vaccine-related strategies to counter immunosenescence
  - Enhanced adjuvant eg FluAd (influenza), Shingrix (AS01B is a liposome-based adjuvant; Shingles)
  - Increased antigen dose eg Zostavax (14 x), Fluzone (4 x Ag dose: influenza)
  - Better targeting of antigen selected eg Shingrix (Glycoprotein E)
- Other strategies
  - Address Frailty:
    - Frailty increases with age as we accumulate social, physical and cognitive deficits and contributes to "inflammaging"

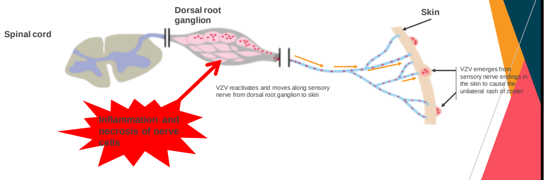
Zoster: pathogenesis

Varicella = *Chickenpox*
Primary infection with VZV



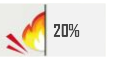
Cunningham et al Med J Aust 2008; 188: 171–176

VZV: REACTIVATION



Postherpetic neuralgia (PHN) is the most frequent debilitating complication of shingles[1]

- PHN can last for months, even years[2]
- Pain and nerve damage can begin before the shingles rash is visible[2]
- PHN may be severe[1,2]
- PHN patients report experiencing pain in the area of their shingles rash for an average of 3.5 years[3]



Up to 20% of shingles sufferers may go on to develop PHN[1,4]

1. Australian Technical Advisory Group on Immunisation (ATAGI). *The Australian immunisation handbook* 10th ed (August 2017 update). Canberra: Australian Government Department of Health, 2017. 2. Oxman MN et al. Arvin AM et al, editors, 2000 p246/75 3. Serpell M *et al. Health Qual Life Outcomes* 2014; 12: 92. 4. Harpaz R et al. MMRW 2008 Jun 6; 57(RR-5):1-30

Incidence of PHN

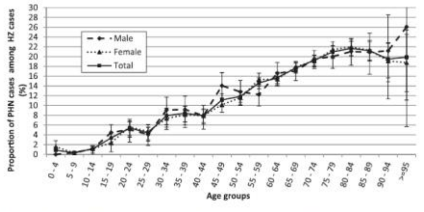


Figure 3 Proportion of PHN cases among all HZ cases by 5-year age groups and sex in 2009.

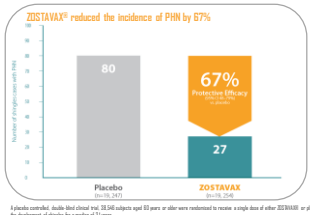
Hillebrand et al J Infect. 2015 Feb;70(2):178-86.

ZOSTAVAX®[1]

- ZOSTAVAX® is a live-attenuated varicella-zoster virus vaccine[1]
- ZOSTAVAX® is indicated for the prevention of:[1]
  - shingles in individuals 50 years of age and older
  - postherpetic neuralgia (PHN) and for reduction of acute and chronic zoster-associated pain in individuals 60 years of age and older
- ZOSTAVAX ® is funded on the National Immunisation Program for 70-79 year olds[2]

1. ZOSTAVAX Approved Product Information. Amended August 2017. 2. Department of Health. National Immunisation Program Schedule. https://beta.health.gov.au/topics/immunisation/immunisation-throughout-life/national-immunisation-program-schedule Accessed February 2018.

ZOSTAVAX® significantly reduced the incidence of PHN by 67% vs. placebo in adults aged 60+[1,2]



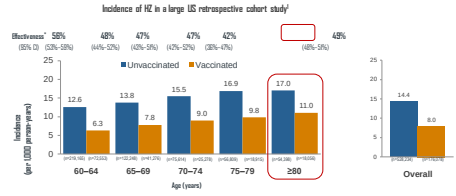
ZOSTAVAX® significantly reduced the incidence of shingles by 51% vs. placebo in adults aged 60+

Patients vaccinated with ZOSTAVAX® who did develop shingles had a significantly lower incidence of PHN compared to placebo

A placebo controlled, double-blind clinical trial; 38,546 subjects aged 60 years or older were randomised to receive a single dose of either ZOSTAVAX® or placebo and were monitored for the development of shingles for a median of 3.1 years.
PHN – post herpetic neuralgia defined as pain and discomfort associated with shingles rated as 3 or more, on a scale ranging from 0 (no pain) to 10 (pain as bad as you can imagine), persisting or appearing more than 90 days after the onset of rash. Graph adapted from Oxman et al NEJM 2005.

1. ZOSTAVAX Approved Product Information. Amended August 2017. 2. Oxman MN et al. NEJM 2005; 352:2271-84

Effectiveness of ZOSTAVAX® in Adults Aged ≥60 Years (2007-2015)

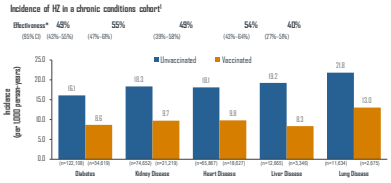


Survey of the electronic records of 178 078 vaccinated and 529 234 unvaccinated members of Kaiser Permanente Southern California (KPSC). The vaccinated cohort had been vaccinated against HZ between 1 January 2007 and 31 December 2009 at the age of ≥60 years. Unvaccinated cohort consisted of randomly sampled members who were matched at a ratio of 3:1 to the vaccinated cohort. Electronic medical records were used to identify episodes of HZ.

*Calculated vaccine effectiveness is adjusted for age, sex, race/ethnicity, healthcare utilization, length of membership prior to index date, and chronic disease. CI=confidence interval; HZ=herpes zoster.

2. Tseng HF, et al. J Infect Dis. First published online February 9, 2016; doi:10.1093/infdis/jiw047

Effectiveness of ZOSTAVAX® in Adults Aged ≥60 Years with Chronic Disease Conditions. KPSC (2007-2015)



Survey of the electronic records of 178 078 vaccinated and 529 234 unvaccinated members of Kaiser Permanente Southern California (KPSC). The vaccinated cohort had been vaccinated against HZ between 1 January 2007 and 31 December 2009 at the age of ≥60 years. Unvaccinated cohort consisted of randomly sampled members who were matched at a ratio of 3:1 to the vaccinated cohort. Electronic medical records were used to identify episodes of HZ.

*Calculated vaccine effectiveness is adjusted for age, sex, race/ethnicity, healthcare utilization, length of membership prior to index date, and chronic disease.
*Patients could have more than 1 co-morbid chronic disease.
CI=confidence interval; HZ=herpes zoster.

2. Tseng HF, et al. J Infect Dis. First published online February 9, 2016; doi:10.1093/infdis/jiw047

ZOSTAVAX uptake in those aged 70-79 years

- Unprecedented uptake at launch
- At June 2017 doses distributed reflected 54% of cohort size[1]
- At December 2017 doses distributed reflected 60%.[1]

Vaccine uptake has slowed down significantly.

How can we encourage the remaining eligible patients to get vaccinated?

1. Seqirus Data on file

Almost the entire adult population is at risk of Zoster[1]

- **97% of adults** have the virus that causes shingles within them[2]
- An estimated **120,000 to 150,000 new cases** of shingles occur per year in Australia[1-3]
- Shingles may affect **1 in 3 people** in their lifetime[4]
- About **half** of people who live to 85 will develop shingles[1]

1. NCIRS. Zoster vaccine for Australian adults. NCIRS Fact sheet. August 2017. Available at: http://www.ncirs.edu.au/assets/provider_resources/fact-sheets/zoster-vaccine-fact-sheet.pdf Accessed Jan 2018. 2. Gidding et al. Epidemiol Infect. 2003;130(1):133-8. 3. Macintyre R et al. PLoS ONE 2015; 10(4):e0125123. 4. Harpaz R et al. MMWR 2008; 6;57(RR-5):1-30.

Other zoster vaccines – not on NIP

- Herpes zoster subunit vaccine (HZ/su) - SHINGRIX®
  - Contains $AS01_B$ adjuvant designed to increase vaccine immunogenicity
  - IM injection given as 2 doses 2 months apart (no efficacy data published for single dose)
- Efficacy and safety tested in two large phase 3 trials (ZOE-50 and ZOE-70)[1,2] which showed an overall vaccine efficacy of:
  - **97.2% (95% CI, 93.7 to 99.0; P<0.001 vs placebo)** in age group >50 years[1]
  - **89.8% (95% CI, 84.2 to 93.7; P<0.001 vs placebo)** in age group >70 years[2]
  - **91.3% (95% CI, 86.8 to 94.5; P<0.001 vs placebo)** in age group >70 years (pooled results from ZOE-50 and ZOE-70)[2]
- No safety concerns related to vaccination were identified[1,2]
- However the HZ/su vaccine was more reactogenic than placebo:*[1]
  - Solicited injection site reactions (81.5% vs 11.9%)
  - Systemic reactions (fatigue, fever, gastrointestinal symptoms, headache, myalgia, and shivering) (53% vs 25%) HZ/su group vs placebo

*Most common reactions were pain at injection site and myalgia!

1. Lal et al. NEJM 2015; 372: 2087-96. 2. Cunningham et al. NEJM 2016; 375: 1019-32. 3. US Food and Drug Administration. Shingrix BLA Approval letter. Available at: https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM581232.pdf. Accessed February 2018.

The most important predictor of vaccination is a health care provider recommendation[1,2]

Factors that increase HZ vaccine uptake[3]	Factors that decrease uptake[3]
• Older age • Female • Higher level of education • Regularly gets other vaccines • Higher awareness of shingles vaccine • Belief that shingles can be a severe condition • Has a usual GP • GP recommendation to get vaccine • Family or friends previously affected by shingles • Availability of vaccine	• Low perceived risk of getting shingles • Beliefs that: the vaccine is unnecessary, they never get sick, they already have good immunity, natural immunity is better • Concerns about: vaccine efficacy, adverse effects, allergic reaction to vaccine, vaccine causing shingles • GP did not discuss need for vaccine • Difficulty getting to GP

1. Litt JCB, *et al. Int J Infect Diseases* 2014; 21:436-7.
2. Menzies R *et al Med J Aust* 2017; 206:238-39.
3. Litt JCB, et al. Update on Herpes Zoster. Health Ed 2017

Vaccines in the pipeline

Dementia

- Alzheimers Disease is characterized by both extracellular depositions of Amyloid beta as well as intracellular tau depositions that form neurofibrillary tangles (NFT) in neurons
- Need to commence therapy before any memory loss (preclinical stage)
  - The earlier, the safer it needs to be
  - Likely a cocktail, from start or sequentially
    - β-secretase (BACE) inhibitor (reducing beta amyloid (Aβ) by inhibiting its production)
    - Monoclonal Ab against amyloid (attacking beta amyloid (Aβ) plaques)
    - Anti-tau therapies? (vaccination against the intracellular proteins tau)
- Several anti-amyloid and now anti-tau vaccination trials proceeding, but all completed are negative so far, including solanezumab

Bracyynski et al J Neurochem. 2017 Dec;143(5):467-488. Bittar et al NPJ Vaccines. 2018 Feb 27;3:9. doi: 10.1038. Schilling et al Molecules. 2018 May 3;23(5).

Vaccines and cancer: immunotherapy

- Convincing effectiveness in:
  - NSCLC (non-small cell Lung cancer)[1,]
  - Renal cancer[2]
  - Melanoma [3]
- Efficacy in other settings (eg Intravesical BCG in bladder cancer) still needs to be demonstrated[4]

1. Herbst et al Nature. 2018 Jan 24;553(7689):446-454
2. Tsaitas et al Ann Transl Med. 2016 Jul;4(14):270. doi: 10.2103
3. Pasquali et al Cochrane Database Syst Rev. 2018 Feb 6;2:CD011123
4. Poletajew et al Urol Int. 2017;99(1):1-5

Other conditions where a vaccine in humans may be possible

- RSV
  - Vaccines and antiviral agents for the prevention and treatment of RSV infections in elderly adults are currently not available, but they are being developed
- Metapneumovirus (hMPV)
  - Several hMPV vaccine candidates are under development with the potential to progress into clinical trial; none yet tested in humans
- Pseudomonas
  - Very early days; no vaccine against this bacteria is currently available in the clinical setting
- Staphylococcus aureus
  - Lack of known correlates of protection against S. aureus in humans is delaying development of efficacious vaccines
- Hypertension
  - Angiotensin II (AngII) vaccine has shown variable effectiveness in Phase II trials

1. Haber Med Mal Infect. 2018 Mar 13. pii: S0399-077X(16)30734-X. doi: 10.1016. 2. Márquez-Escobar VA[1]. Expert Rev Vaccines. 2017 May;16(5):419-431
3. Grimwood et al Hum Vaccin Immunother. 2015;11(1):14-20. doi: 10.4161/hv.34296. Epub 2014 Nov 1. 4. Pozzi et al Curr Top Microbiol Immunol. 2017;409:491-528.
5. Nakagami et al Curr Hypertens Rep. 2018 Mar 19;20(3):2

Resources

NCIRS Fact sheets

- Zoster: http://www.ncirs.edu.au/assets/provider_resources/fact-sheets/zoster-vaccine-FAQ.pdf
- Influenza: http://www.ncirs.edu.au/assets/provider_resources/fact-sheets/Influenza-FAQs.pdf

www.communityimmunity.com.au

- Recall resources
- Vaccine management resources

www.shingles.com.au

- Download patient education information about shingles

Litt, JCB. Cunningham, T. Van Buynder, P. Update on Zoster, HealthEd, December 2017. https://www.healthed.com.au/monographs/update-herpes-zoster/

The Australian Immunisation Handbook 10th Edition

- http://www.immunise.health.gov.au/internet/immunise/publishing.nsf/Content/Handbook10-home

Adjuvanted influenza vaccine: Fluad (Seqirus)

Systematic review of MF59 adjuvanted influenza vaccine (Fluad)

Methods
- 11 (6 case-control, 3 cohort and 2 prospective case-control) studies

Results
- Vaccine effectiveness of 51% (95% CI: 39–61%) against hospitalizations for pneumonia/influenza among community-dwelling seniors

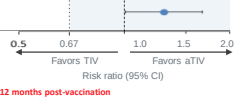
- Adjuvanted influenza vaccine is more effective than TIV in preventing :
  - hospitalizations due to pneumonia/influenza [adjusted risk ratio 0.75 (95% CI: 0.57–0.98)] and
  - laboratory-confirmed influenza [adjusted odds ratio 0.37 (0.14–0.96)].

I. Domnich et al Vaccine. 2017 Jan 23;35(4):513-520.

Persistence of Results:

Higher GMTs Against Homologous H3N2 Strain

H3N2	aTIV:TIV	Non-inferiority Bound
Day 22	1.42 (1.11-1.81)	
Day 181	1.35 (1.06-1.71)	
Day 366	1.3 (1.01-1.67)	



Higher antibody titers for H3N2 up to 12 months post-vaccination

Frey SE, et al. *Vaccine*. 2014;32:5077-5084.

Lower Influenza-related Hospitalization Risk for aTIV

*Adjusted risk ratio for pneumonia or influenza hospitalization**

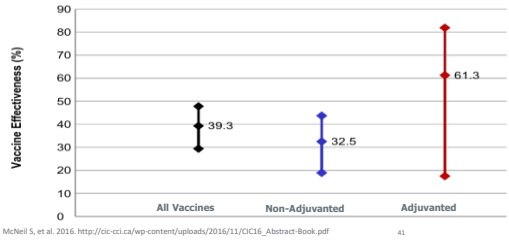
17% higher risk for hospitalization† at baseline	25% reduction in risk for hospitalization† post-vaccination with aTIV
• (Hospitalizations occurring before influenza season) • Prior to flu-season, subjects in the aTIV group were at greater risk of hospitalizations than those in the TIV group • RR=1.17 (95% CI=0.96, 1.43)	• (Hospitalizations occurring during peak of season) • Vaccination with aTIV significantly reduced the risk of hospitalizations vs TIV • RR=0.75 (95% CI=0.57, 0.98)

- Vaccination policies preferentially recommend aTIV to high-risk patients in Italy
- Thus, patients receiving aTIV were generally older, had more functional limitations and higher rates of comorbidities. These patients may therefore have had more baseline hospitalizations

*Risk ratios were adjusted to account for confounding factors.
†Risk for influenza or pneumonia-related hospitalization.
aTIV=adjuvanted trivalent inactivated influenza vaccine; CI=confidence interval; RR=relative risk; TIV=trivalent inactivated influenza vaccine.

Mannino S, et al. Am J Epidemiol. 2012;176:527-533.

VE against influenza hospitalisations in patients 65 years and older in the Serious Outcomes Surveillance (SOS) network, 2011-2014



McNeil S, et al. 2016. http://cic-cci.ca/wp-content/uploads/2016/11/CIC16_Abstract-Book.pdf 41

High dose influenza vaccine: Fluzone (Sanofi)

hdTIV Efficacy and Safety

- 4 x Ag dose for each flu strain in the vaccine
- Phase III trials: higher antibody response and reduced (24.2%; 95% CI 9.7-36.5) laboratory-confirmed influenza versus standard TIV[1]
- Enhanced protection (39.8%; 95% CI, 19.3–55.1%) against serious, life-threatening pneumonia associated with influenza[2].
- The safety profile of high-dose TIV is similar to that of standard TIV [3]

1. DiazGranados et al N Engl J Med. 2014 Aug 14;371(7):635-45.
2. Diazgranados et al Vaccine. 2015 Sep 11;33(38):4988-93
3. DiazGranados et al N Engl J Med. 2014 Aug 14;371(7):635-45. Gravenstein et al Lancet Respir Med. 2017 Sep;5(9):738-746

hdTIV Success in Older Adults

- Retrospective cohort study of over 2.5 million US Medicare beneficiaries: significantly more effective than standard-dose vaccine in prevention of influenza-related hospital admissions
  - 22% (95% CI 15–29%) more effective than the standard TIV in preventing influenza
  - 22% (95% CI 16–27%) more effective for prevention of influenza hospital admissions

Izurieta HS, et al. *N Engl J Med*. 2000;342(4):232-239. Izurieta et al Lancet Infect Dis. 2015 Mar;15(3):293-300

hdTIV Success in Older Adults

- Cluster nursing home study[1]
  - 8% decrease in any hospitalization with hdTIV (12.5% reduction for hospitalizations for respiratory illness) when compared with standard dose TIV
  - NNT to prevent all-cause hospital admissions for the season is 83·7
- Real world studies[2]: significantly more effective than standard TIV in the prevention of influenza-related medical encounters, hospitalizations, and death

1. Gravenstein et al Lancet Respir Med. 2017 Sep;5(9):738-746;
2. Izurieta HS, et al. *N Engl J Med*. 2000;342(4):232-239. Shay et al J Infect Dis. 2017 Feb 15;215(4):510-517. Diazgranados et al Vaccine. 2015 Sep 11;33(38):4988-93. Izurieta et al Lancet Infect Dis. 2015 Mar;15(3):293-300.