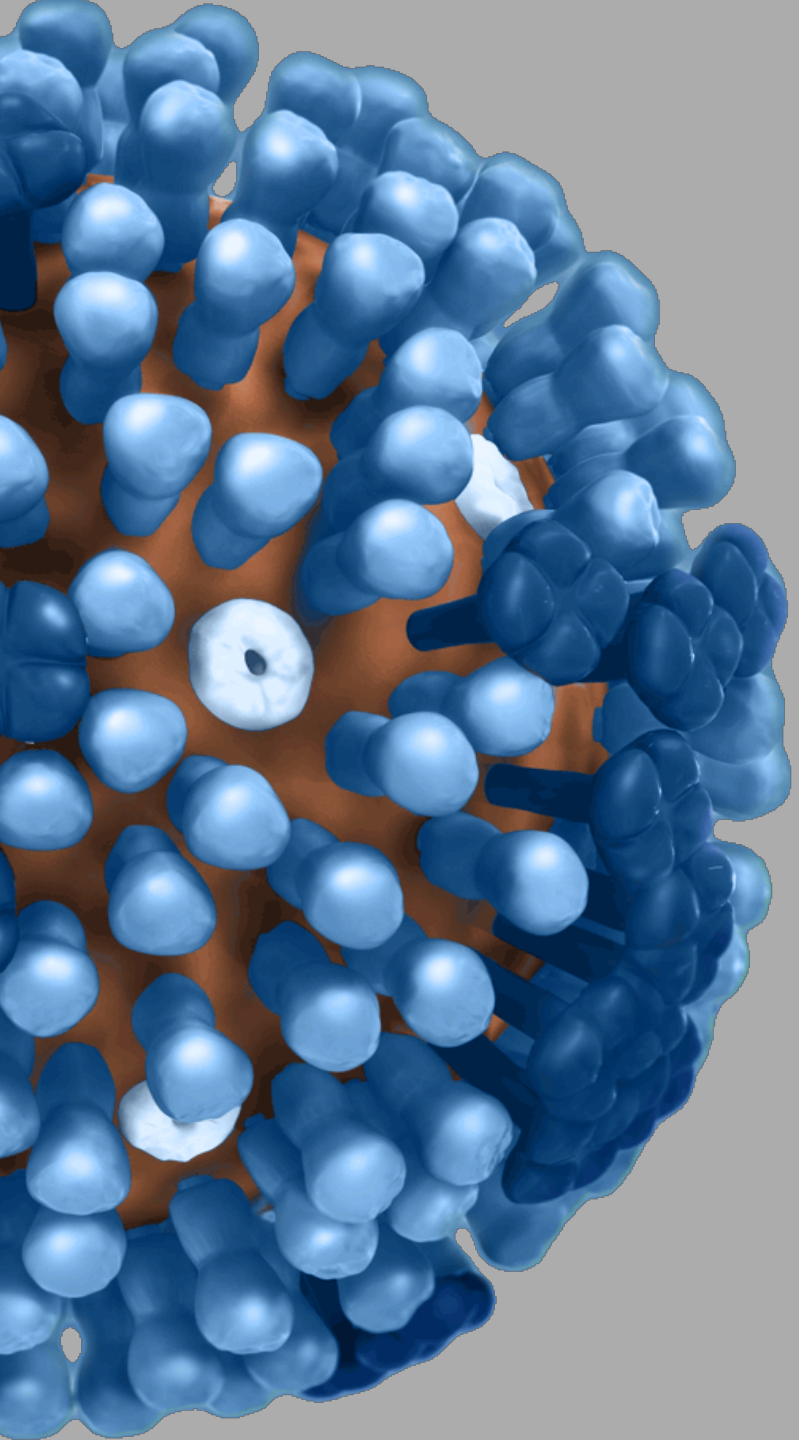
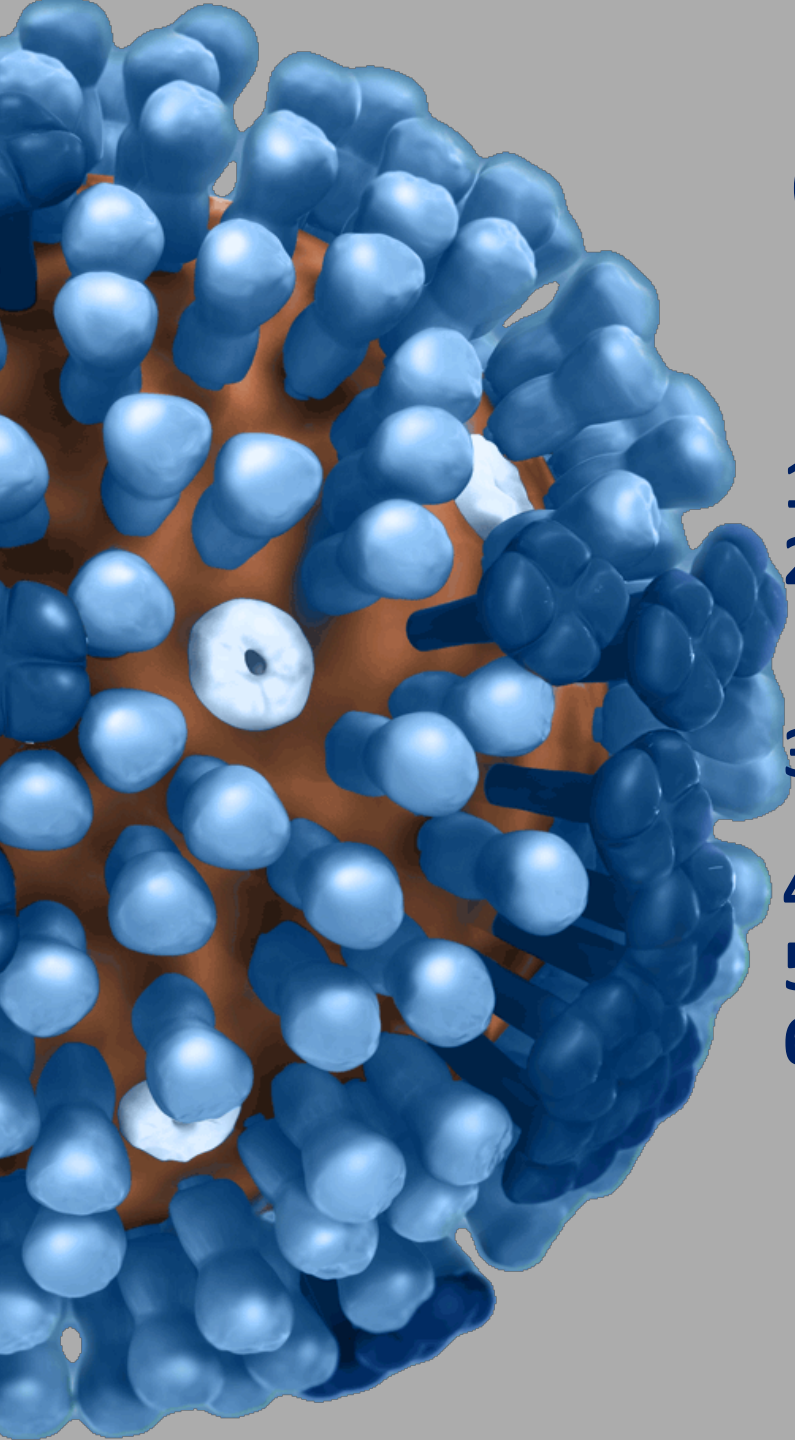


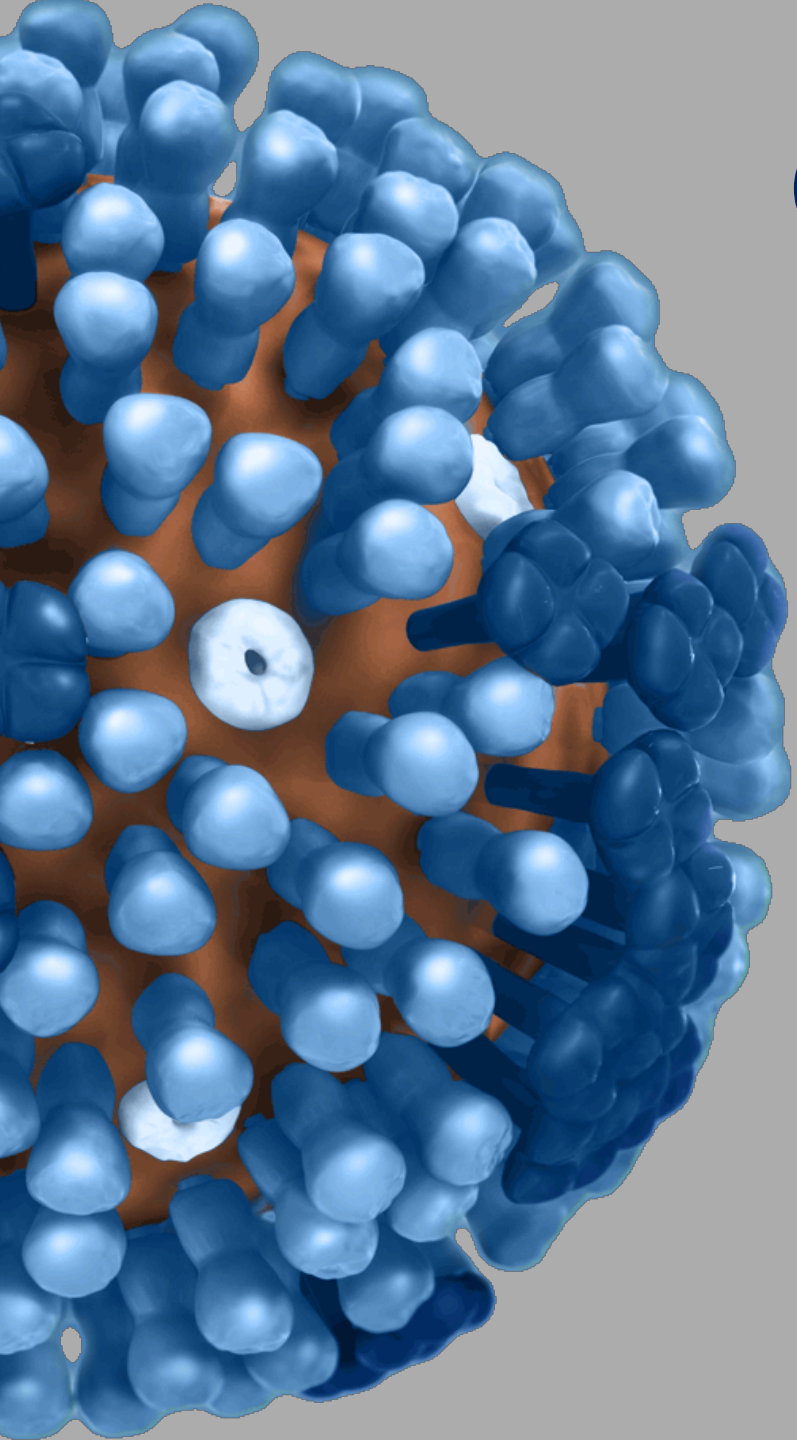
Influenza Vaccines in older persons 65+

Paul Van Buynder
Professor, Griffith University
Chairman, Immunisation Coalition



Outline

1. Influenza in older persons
2. Vaccine effectiveness in the elderly including duration of protection
3. Desirable attributes in influenza vaccines for older persons
4. aTIV
5. hdTIV
6. Recommendations



Outline

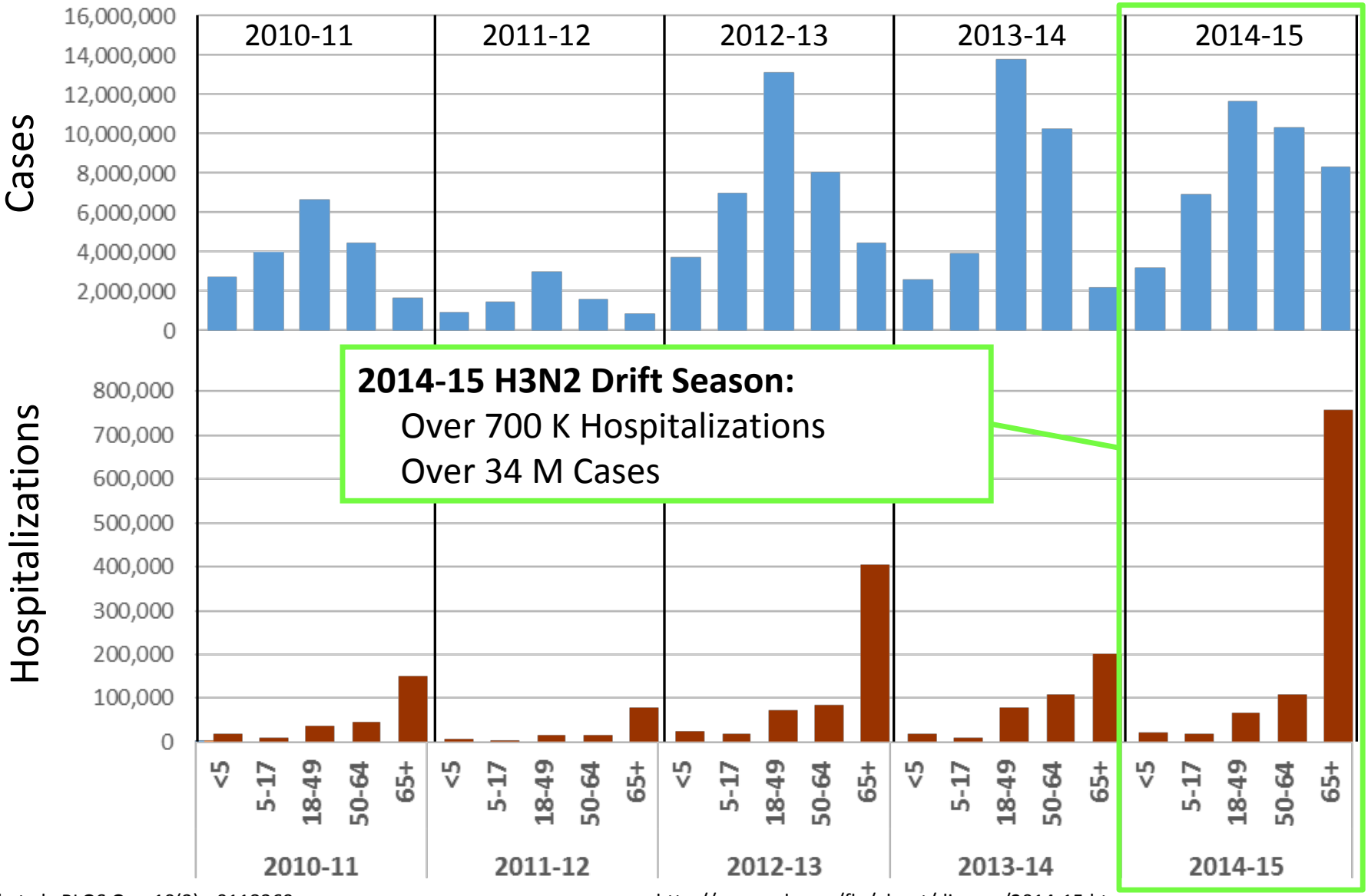
1. Influenza in older persons

2. Vaccine effectiveness in the elderly including duration of protection
3. Desirable attributes in influenza vaccines for older persons
4. aTIV
5. hdTIV
6. Recommendations

Burden of influenza in the elderly

- Influenza is a serious infectious disease and places a significant disease burden
  on the elderly
  - The incidence of influenza-related hospitalizations is highest in the elderly
  - Age-related immune vulnerability may result in serious complications associated with influenza in the elderly
  - Influenza in the elderly is associated with significant direct and indirect medical cost

Annual Influenza Impact Varies by Age Group



Reed et al. PLOS One 10(3):e0118369

http://www.cdc.gov/flu/about/disease/2014-15.htm

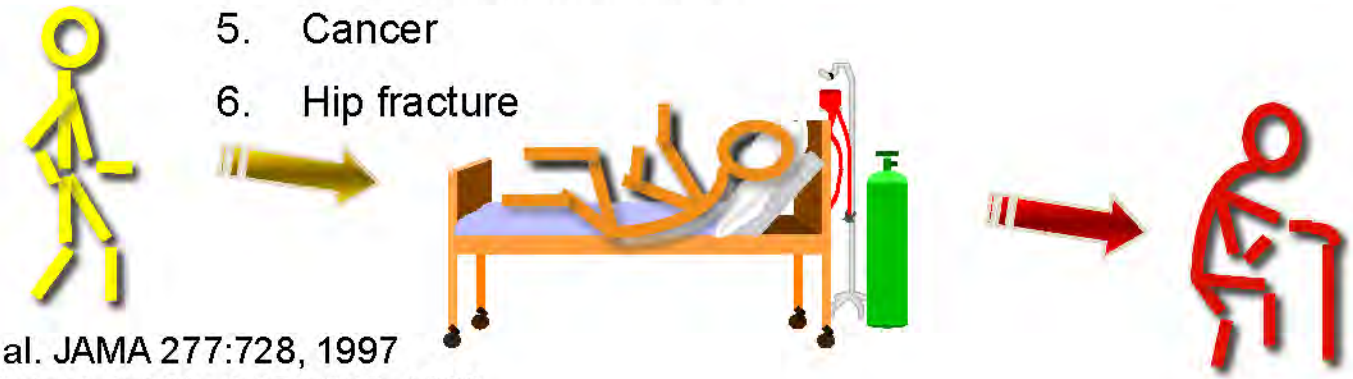
… and there are other impacts

- Influenza causes an inflammatory response which increases the chances of heart attack and stroke following infection
- Many infections and deaths go unrecognised as worsening of co-morbid cardiac neurological and respiratory diseases

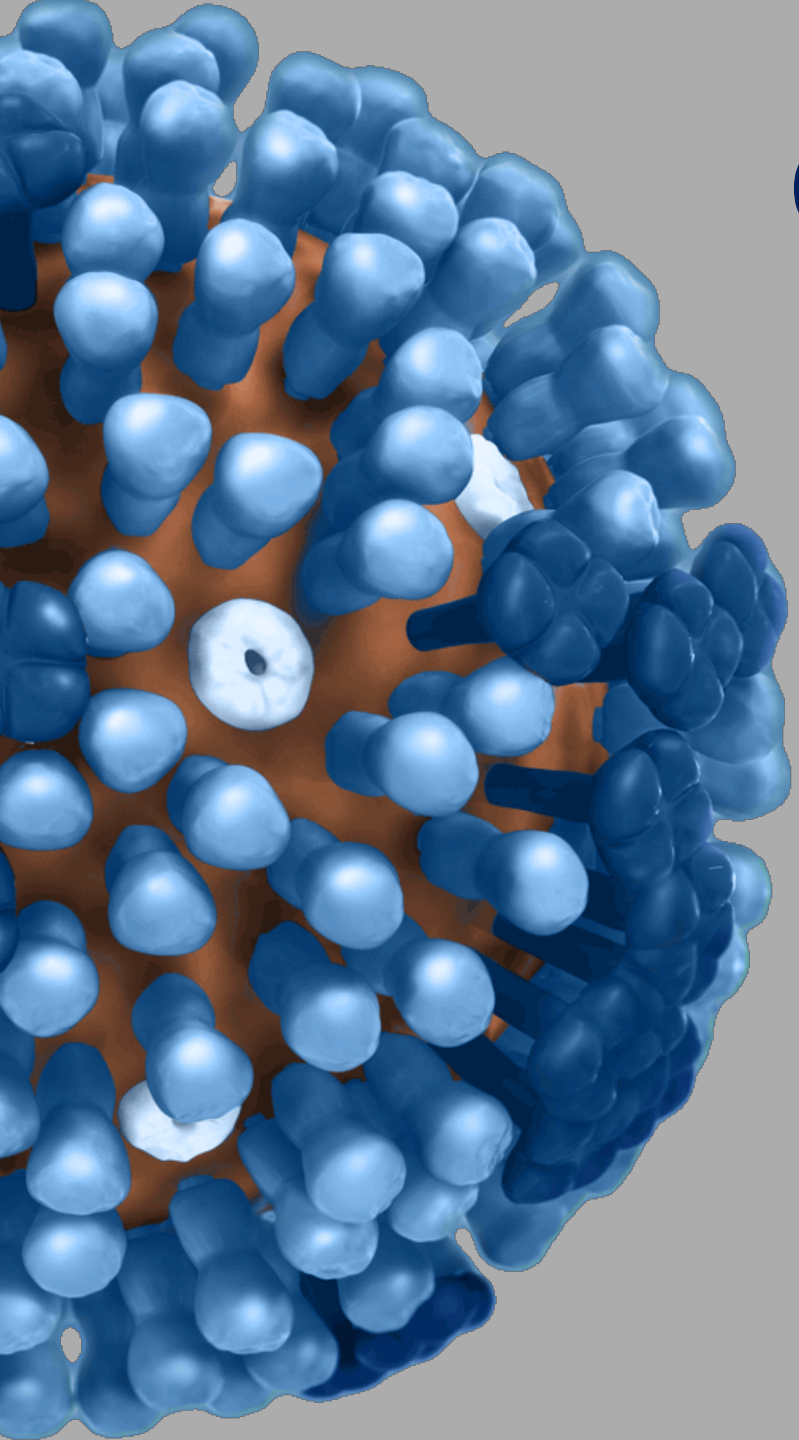
Vaccine Preventable Disability

Catastrophic disability

- Defined as a loss of independence in ≥ 3 ADL
- 72% who experience catastrophic disability have been hospitalized
- Leading causes of catastrophic disability
    1. Stroke
    2. CHF
    3. Pneumonia and influenza
    4. Ischemic heart disease
    5. Cancer
    6. Hip fracture



Ferrucci et al. JAMA 277:728, 1997
Barker et al. Arch Int Med 158:645, 1998
Falsey et al. *N Engl J Med*. 2005;352:1749



Outline

1. Influenza in the elderly
2. **Vaccine effectiveness in older persons including duration of protection**
3. Desirable attributes in older person' influenza vaccines
4. aTIV
5. hdTIV
6. Recommendations

The goal of vaccination is not only to prevent disease but to influence the trajectory of intrinsic capacity … dealing with the impacts on frailty important

Immunosenescence

- Increase in exhausted memory T cells
- Decrease in naïve T cells
- Decrease CD8 cell population
- CD8/CD4 ratio <1
- Decreased telomerase
- Telomere shortening
- … Decreased response to all vaccines

Effect of Immunosenescence

- **Effect of serious outcomes increases**
  - **90% of deaths in elderly**
  - **3-4 hospitalisations per death**
- **Response to vaccinations decreases**
  - **Efficacy about 60% in healthy adults**
  - **Efficacy 27-40% in elderly**
    - **..but are still cost saving so a margin for improvement**

2016-17 US data

- **VE all ages** **42%**
- **VE 6/12 to 8 years** **61%**
- **VE 65 yrs+** **25%**
- **Overall 30% against hospitalisations all ages**
- **Overall 37% against hospitalisations 65 years +**
- ***"You got the flu but you weren't hospitalised and you didn't die"***

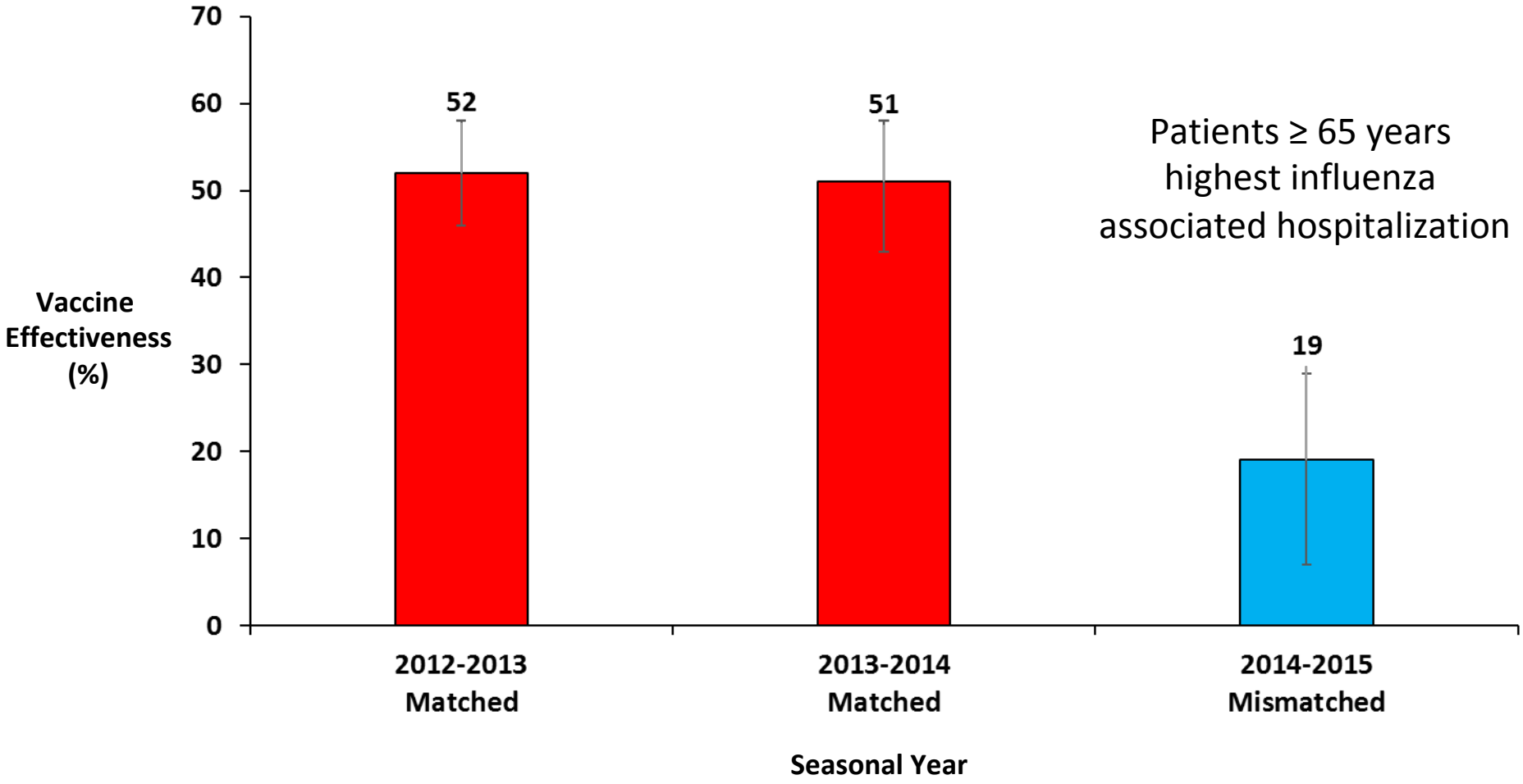
Duration of protection

- Two new CDC studies last twelve months
  - One in < 50 years
  - One in all ages
- VE declines progressively across the influenza season and this may be as much as 8% per month
- In elderly vaccine may have no effect after 3-4 months

Importance of Persistence

- Influenza immunization occurs early in autumn
- Period of influenza circulation varies yearly
- May leave large time period between immunization and exposure

Importance of Breadth of Response

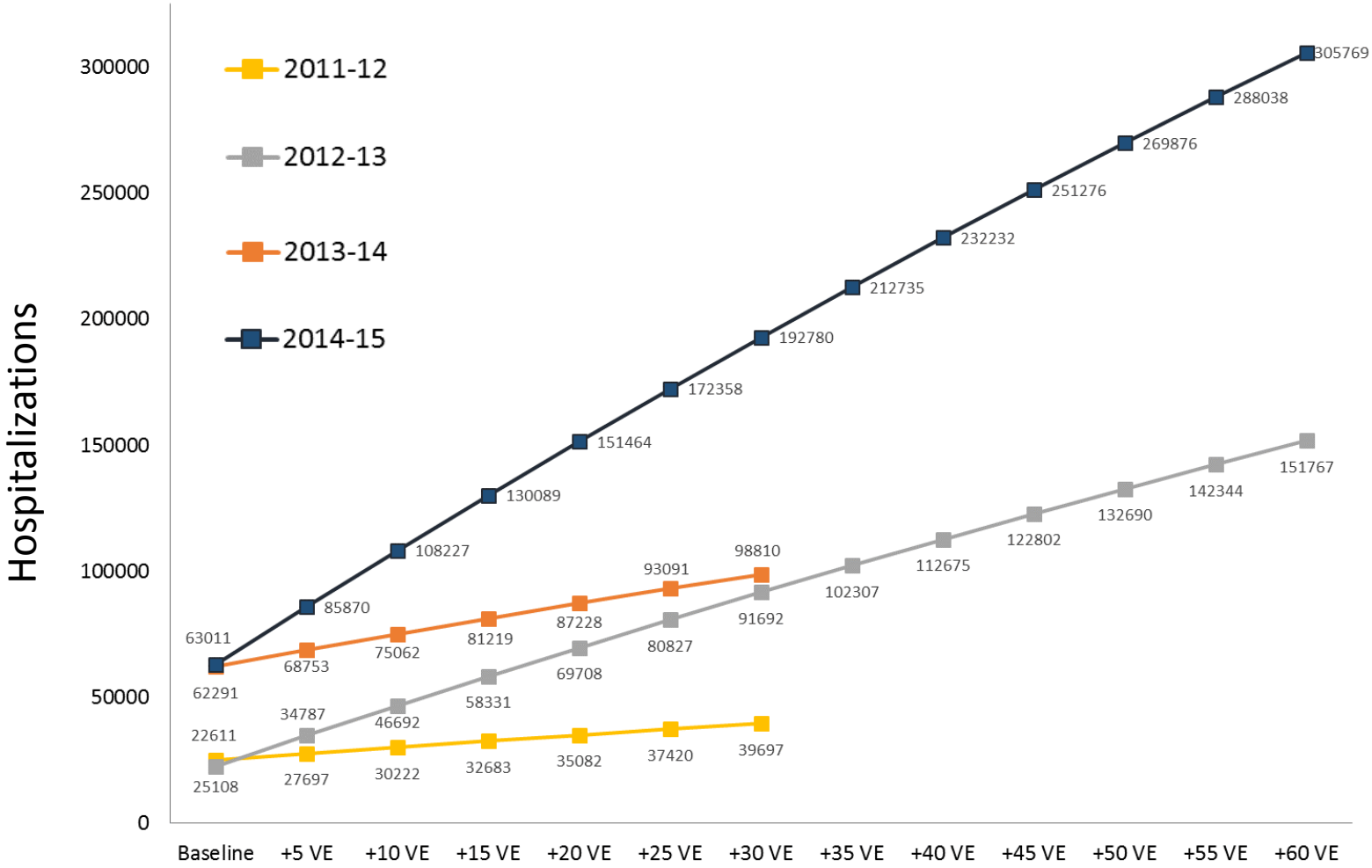


1. MMWR, 2013; CDC 2015; 2. MMWR 2014; CDC 2015; 3. MMWR 2015.

Conclusions

- Influenza is a key contributor to morbidity and mortality in the elderly
- Increases in coverage likely might have modest gains; however, improvement in VE would have greatest impact
- Even at low VE, vaccination can be cost-effective in 65+

Averted Hospitalizations for Incremental VE Improvements 2011-15 Influenza Seasons, U.S.



- For the 2014-15 drift H3 season, an improvement of +5% averts 86K hospitalizations, +10% averts 108K, and +40% averts 232K
- Even at low VE, influenza morbidity in 65+ may be reduced with incremental VE increases

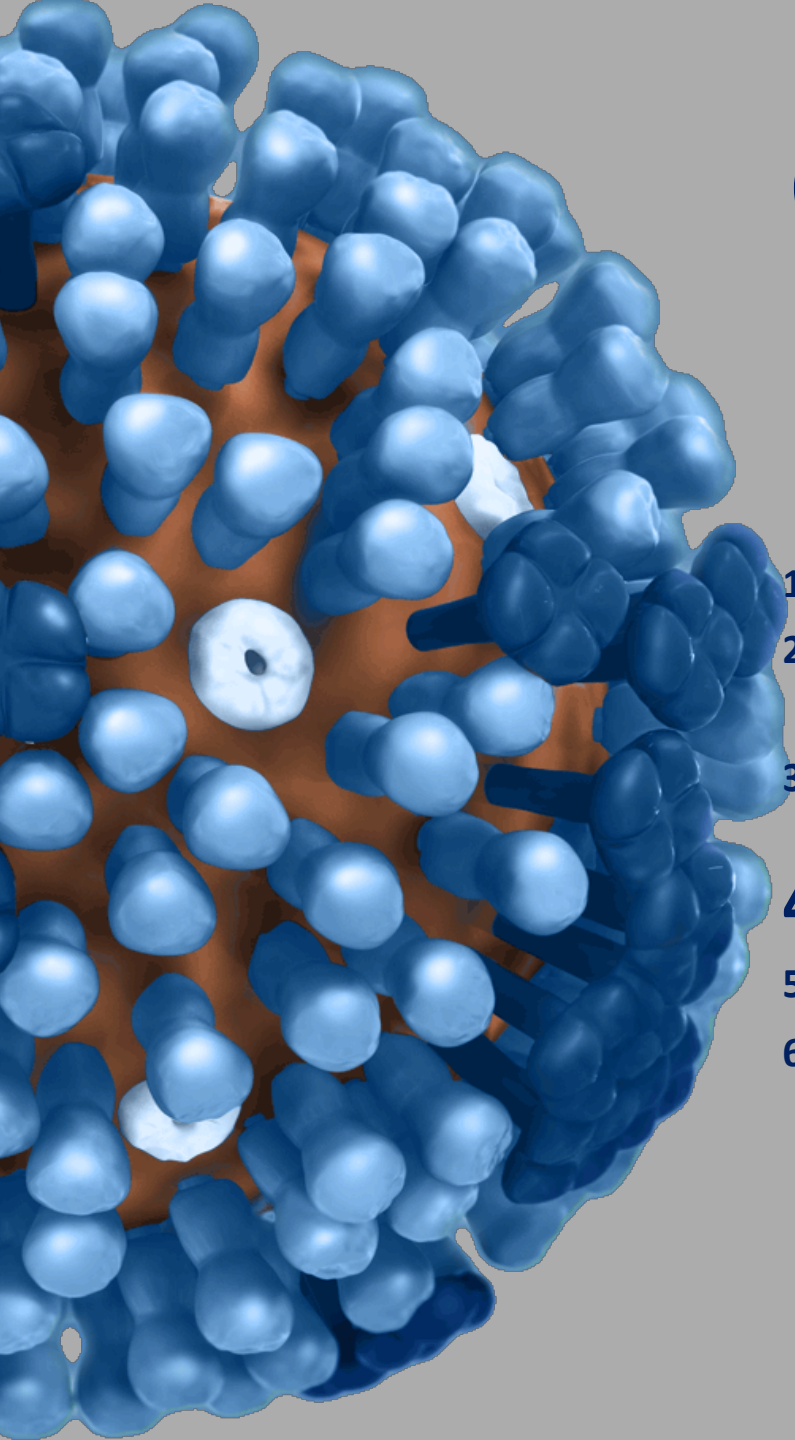
Biggerstaff et al. CDC unpublished data. 2016

Desirable Characteristics of an enhanced flu vaccine for older persons

- Influenza vaccines are less effective in the elderly due to immune senescence
- Influenza vaccines are even more ineffective in the elderly during seasons when there is a strain mismatch
- Influenza vaccine effectiveness wanes significantly during the season
- Improved influenza vaccines need to:
  - **Enhance immune responses in susceptible populations**
  - **Provide broader cross-protection when vaccine strain mismatch occurs**
  - **Improve the duration of protection during the flu season**
  - **Offer improved clinical outcomes against influenza**

Vaccine Products for Older Adults

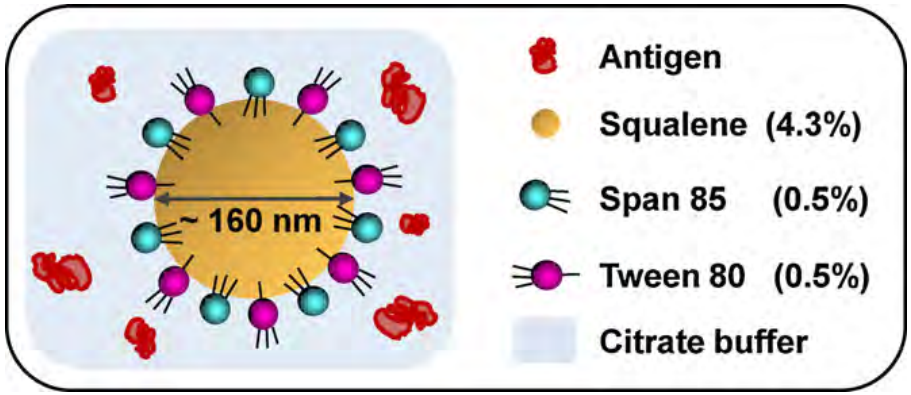
	Product Type (abbreviation)	Product Type
	TIV	trivalent influenza vaccine
	QIV	quadrivalent influenza vaccine
Enhanced vaccines for older adults	**aTIV (>30 countries)**	MF59-adjuvanted trivalent influenza vaccine
	hdTIV (available in USA and Canada)	trivalent influenza vaccine, high dose



Outline

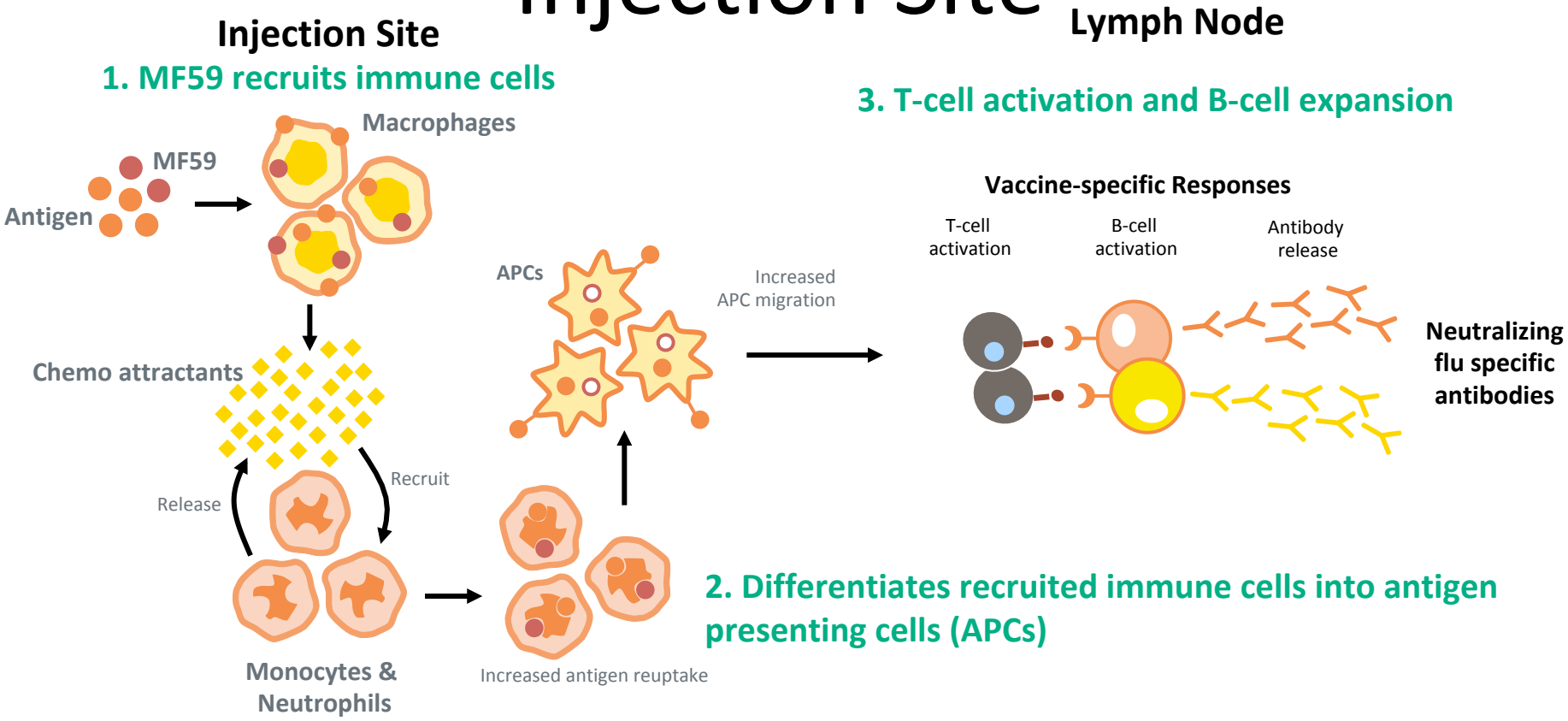
1. Influenza in older persons
2. Vaccine effectiveness in the elderly including duration of protection
3. Desirable attributes in influenza vaccines for older persons
4. **aTIV**
5. hdTIV
6. Recommendations

Adjuvanted Trivalent Influenza Vaccine



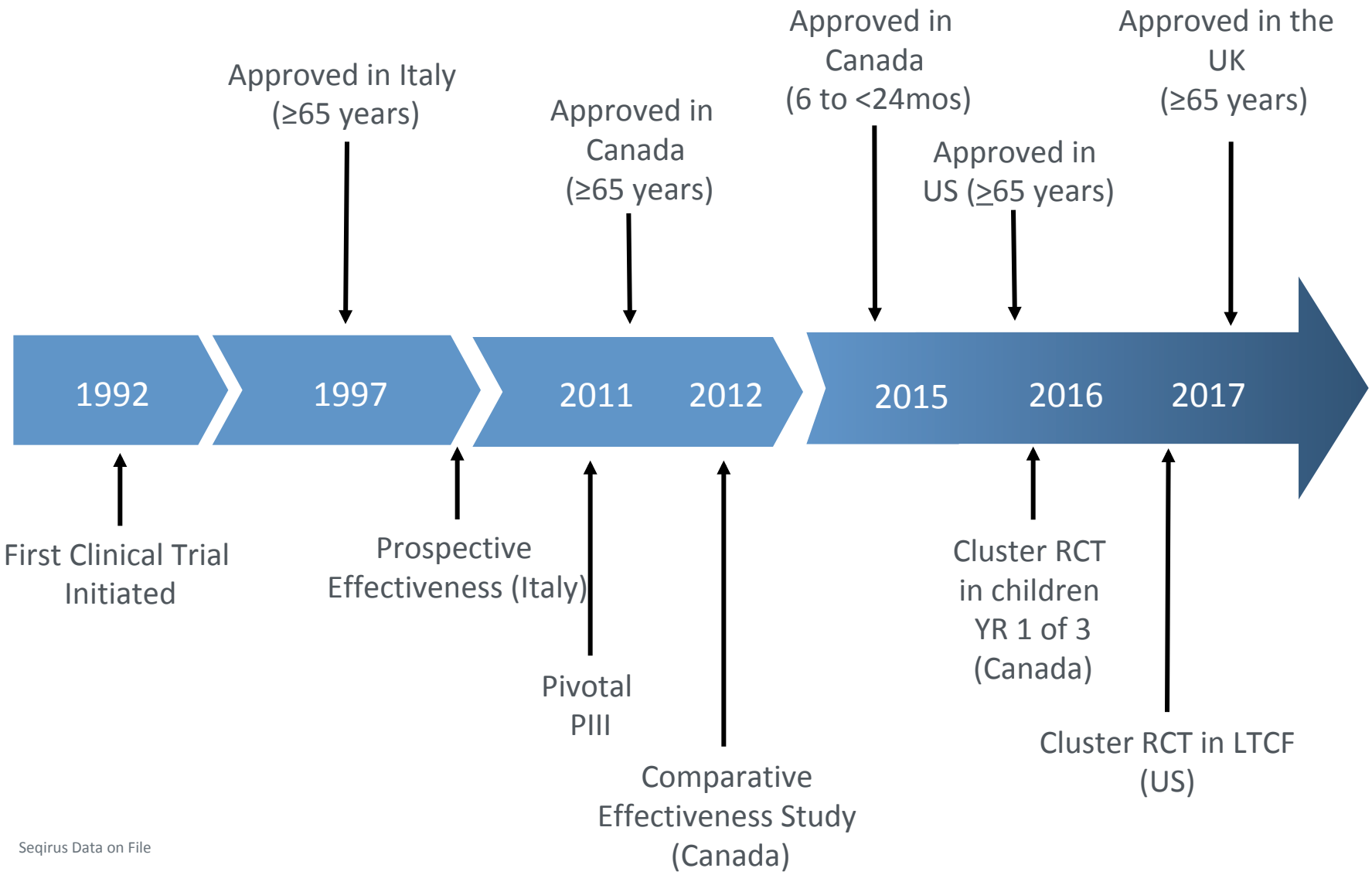
The MF59® adjuvant contained in aTIV is an oil-in-water emulsion composed of squalene as the oil phase, stabilized with the surfactants polysorbate 80 and sorbitan trioleate, in citrate buffer

Proposed MF59 Mode of Action at Injection Site



Seubert et al., J Immumol, 2008; Schultze et al., Vaccine, 2008.
Khurana et al., Sci Transl Med, 2010.
Calabro et al., Vaccine, 2011.
Vono et al., Proc Natl Acad Sci USA, 2013.

Timeline of aTIV Experience

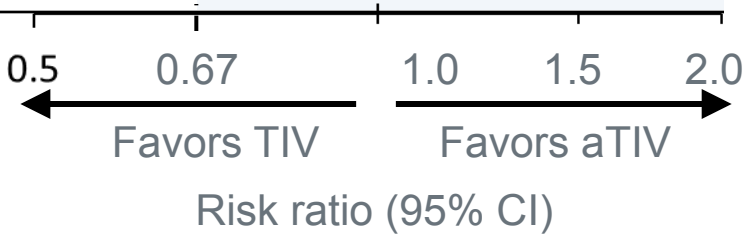


Seqirus Data on File

Persistence of Results:

Higher GMTs Against Homologous H3N2 Strain

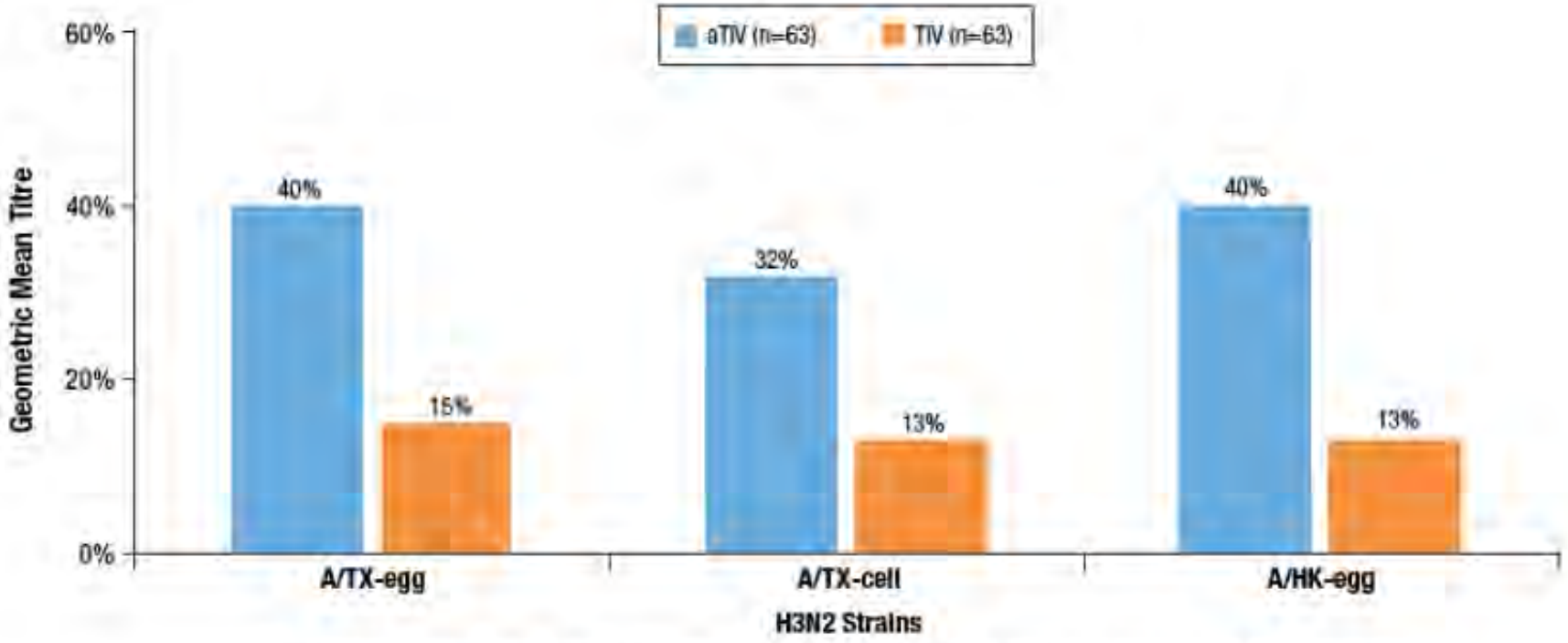
H3N2	aTIV:TIV	Non-inferiority Bound
Day 22	**1.42** (1.11-1.81)	
Day 181	**1.35** (1.06-1.71)	
Day 366	**1.3** (1.01-1.67)	



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

Frey SE, et al. *Vaccine*. 2014;32:5027-5034.

aTIV Expands Serologic Coverage of 14/15 NH H3N2 Mismatch – Microneutralisation



Adjuvanted vaccine generated a higher percentage of significant titer increase against both matched and mismatched strains.

Lower Influenza-related Hospitalization Risk for aTIV

*Adjusted risk ratio for pneumonia or influenza hospitalization**

17% higher risk for hospitalization† at baseline

- (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)

25% reduction in risk for hospitalization† post-vaccination with aTIV

- (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.

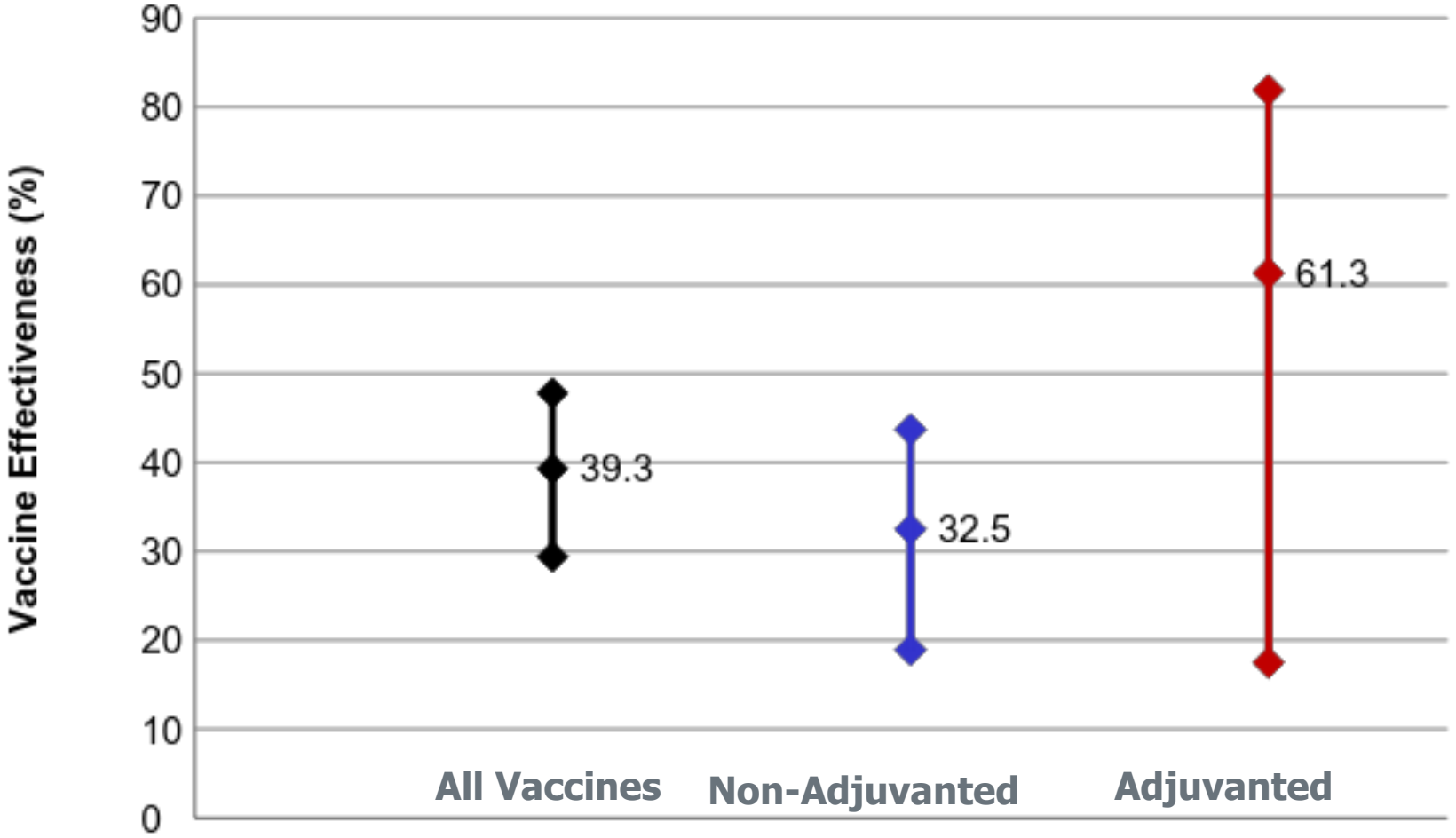
Comparative Influenza Vaccine Effectiveness 2011-12 aTIV vs TIV

Protection Against Laboratory Confirmed Influenza	Odds Ratio (VE)	95% CI for Odds Ratio		Significance
		Lower	Upper	
Overall aTIV (n = 282)	0.65 (35%)	0.34	1.25	<0.194
Overall TIV	1.12 (0)	0.52	2.38	0.774
Overall aTIV (corrected)	0.42 (58%)	0.19	0.95	0.038
Overall TIV (corrected)	1.02 (0)	0.32	2.39	0.970
Community dwelling aTIV	0.27 (72%)	0.08	0.86	0.030
Comparative aTIV over TIV	0.37 (63%)	0.14	0.96	0.040

- Among the vaccinated study population (n=227), the relative vaccine efficacy was 63% (4-86%, p=0.04) when comparing aTIV to TIV directly.
- The absolute vaccine efficacy for aTIV was 58% (5-82%, p=0.04) overall and 72% (2-93%, p=0.047) for non-long term care residents.
- aTIV appeared to provide a significant improvement on the protection available against the known hospitalizations and death in this group.

Van Buynder et al., Vaccine, 2013.

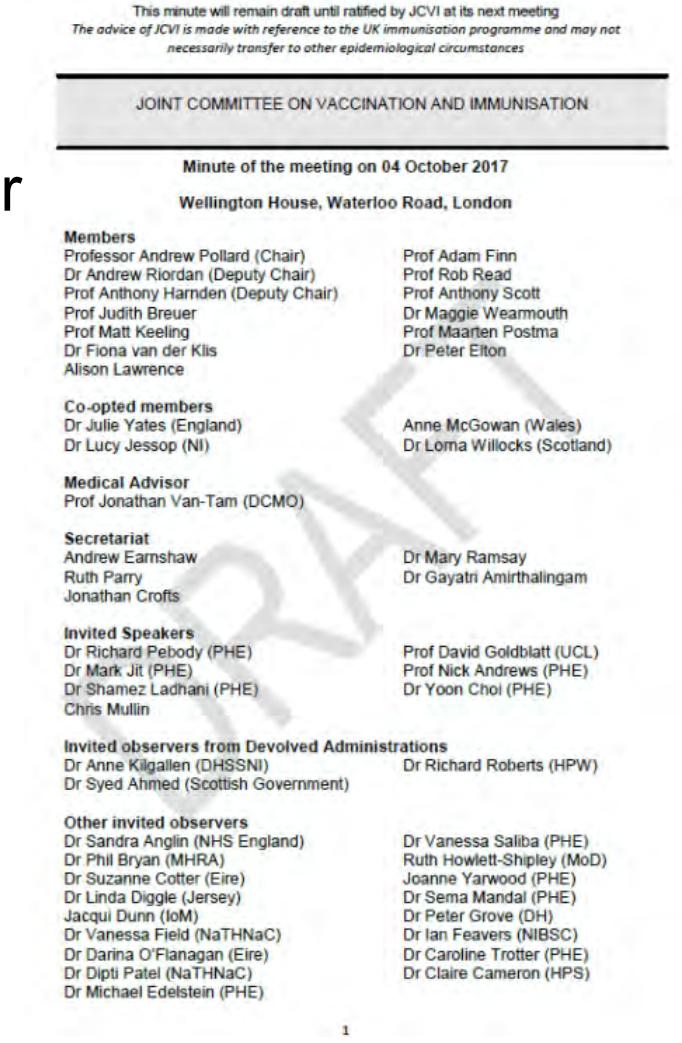
VE against influenza hospitalisations in patients 65 years and older in SOS network, 2011-2014



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

Joint Committee on Vaccination and Immunisation

- Available evidence indicated better immunogenicity and effectiveness for aTIV in comparison with IIV in the elderly
  - The MHRA also indicated there were no concerns about its safety.
- aTIV, under quite conservative estimates of effectiveness, would be highly cost-effective in both the 65-74 and 75 and over age groups



This minute will remain draft until ratified by JCVI at its next meeting
The advice of JCVI is made with reference to the UK immunisation programme and may not necessarily transfer to other epidemiological circumstances

JOINT COMMITTEE ON VACCINATION AND IMMUNISATION

Minute of the meeting on 04 October 2017

Wellington House, Waterloo Road, London

Members
Professor Andrew Pollard (Chair)
Dr Andrew Riordan (Deputy Chair)
Prof Anthony Harnden (Deputy Chair)
Prof Judith Breuer
Prof Matt Keeling
Dr Fiona van der Klis
Alison Lawrence
Prof Adam Finn
Prof Rob Read
Prof Anthony Scott
Dr Maggie Wearmouth
Prof Maarten Postma
Dr Peter Elton

Co-opted members
Dr Julie Yates (England)
Dr Lucy Jessop (NI)
Anne McGowan (Wales)
Dr Lorna Willocks (Scotland)

Medical Advisor
Prof Jonathan Van-Tam (DCMO)

Secretariat
Andrew Earnshaw
Ruth Parry
Jonathan Crofts
Dr Mary Ramsay
Dr Gayatri Amirthalingam

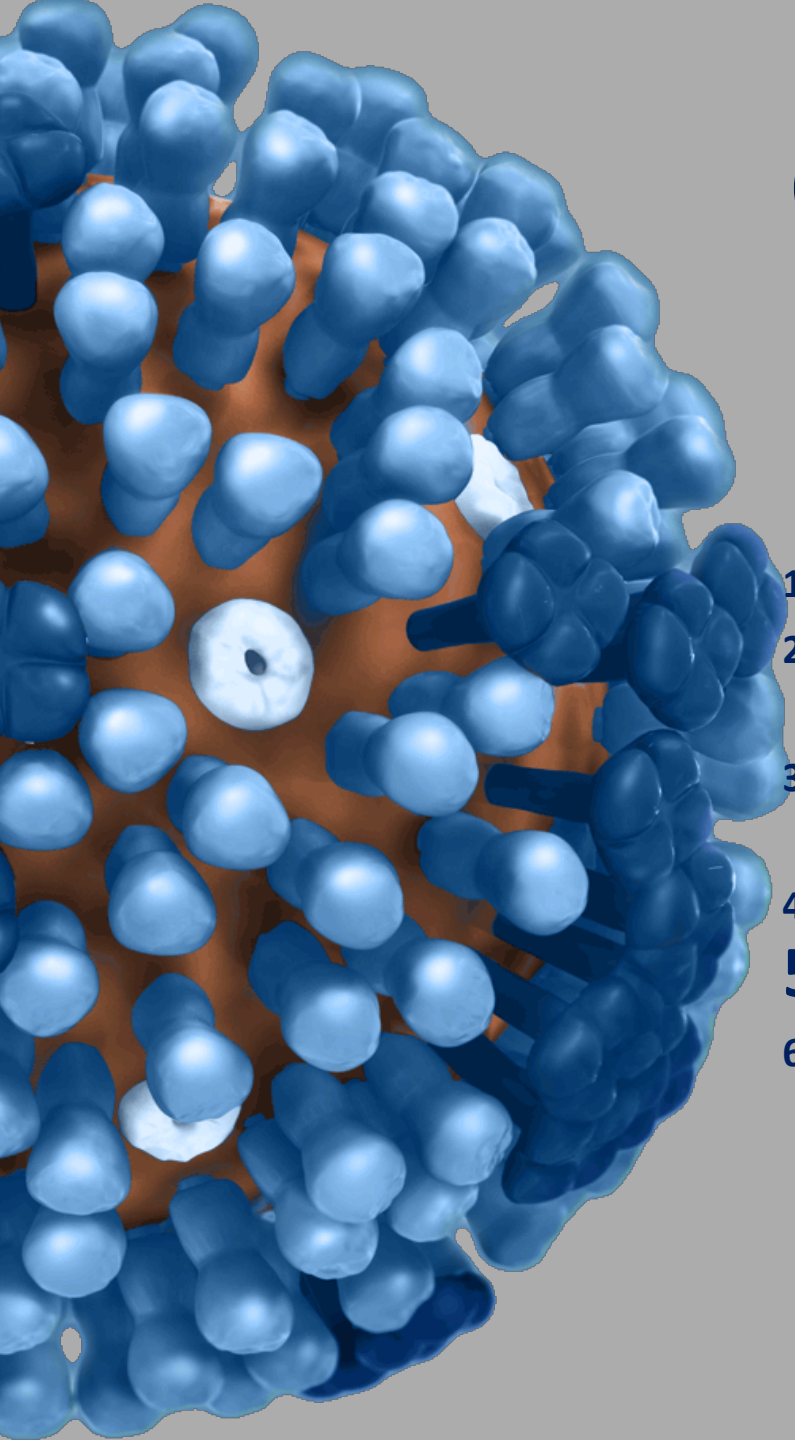
Invited Speakers
Dr Richard Pebody (PHE)
Dr Mark Jit (PHE)
Dr Shamez Ladhani (PHE)
Chris Mullin
Prof David Goldblatt (UCL)
Prof Nick Andrews (PHE)
Dr Yoon Choi (PHE)

Invited observers from Devolved Administrations
Dr Anne Kilgallen (DHSSNI)
Dr Syed Ahmed (Scottish Government)
Dr Richard Roberts (HPW)

Other invited observers
Dr Sandra Anglin (NHS England)
Dr Phil Bryan (MHRA)
Dr Suzanne Cotter (Eire)
Dr Linda Diggle (Jersey)
Jacqui Dunn (IoM)
Dr Vanessa Field (NaTHNaC)
Dr Darina O'Flanagan (Eire)
Dr Dipti Patel (NaTHNaC)
Dr Michael Edelstein (PHE)
Dr Vanessa Saliba (PHE)
Ruth Howlett-Shipley (MoD)
Joanne Yarwood (PHE)
Dr Sema Mandal (PHE)
Dr Peter Grove (DH)
Dr Ian Feavers (NIBSC)
Dr Caroline Trotter (PHE)
Dr Claire Cameron (HPS)

1

https://app.box.com/s/iddfb4ppwkmtjusir2tc/file/247634612957



Outline

1. Influenza in older persons
2. Vaccine effectiveness in the elderly including duration of protection
3. Desirable attributes in influenza vaccines for older persons
4. aTIV
5. **hdTIV**
6. Recommendations

IIV3-High-Dose Vaccine: Timeline

- **1999:** Concept proposed by Wendy Keitel, MD (Baylor U.) and Fred Ruben, MD (Sanofi Pasteur)
- **2000-2003:** Developmental work and dose-ranging (Phase I) studies[1]
- **2005-2006:** Phase II study[2]
- **2006-2007:** Phase III study[3]
- **2009:** Licensure plus commitment to post-licensure efficacy study
- **2009-2010:** FIM07 Efficacy Trial[4]
- **2011-2013:** FIM12 Efficacy Trial[5]
- **2014:** Publication of FIM12 Efficacy Results[5]
  Addition of Efficacy Data to Prescribing Information

1. Keitel WA, et al. *Arch Intern Med*. 2006;166(10):1121-1127. **2.** Couch RB, et al. *Vaccine*. 2007;25(44):7656-7663. **3.** Falsey A, et al. *J Infect Dis.* 2009;200(2):172-180. **4.** DiazGranados C, et al. *Vaccine*. 2013;31(6):861-866. **5.** DiazGranados CA, et al. *N Engl J Med.* 2014;371(7):635-645.

hdTIV Efficacy and Safety

- Phase III trials: higher antibody response and reduced laboratory-confirmed influenza versus standard TIV
- Enhanced protection against serious, life-threatening pneumonia associated with influenza.
- The safety profile of high-dose TIV is similar to that of standard TIV

hdTIV Success in Older Adults

- Retrospective cohort study of over 2.5 million people in the US: significantly more effective than standard-dose vaccine in prevention of influenza-related hospital admissions
  - 22% more effective than the standard TIV
  - 22% more effective for prevention of influenza hospital admissions

Izurieta HS, et al. *N Engl J Med*. 2000;342(4):232-239.

Ever hospitalized

	Odds Ratio*	LCL	UCL	p-value
Treatments				
High dose vs. standard dose vaccine	0.930	0.875	0.988	0.0195
Free staff vaccine vs. usual staff care	1.018	0.958	1.081	0.572

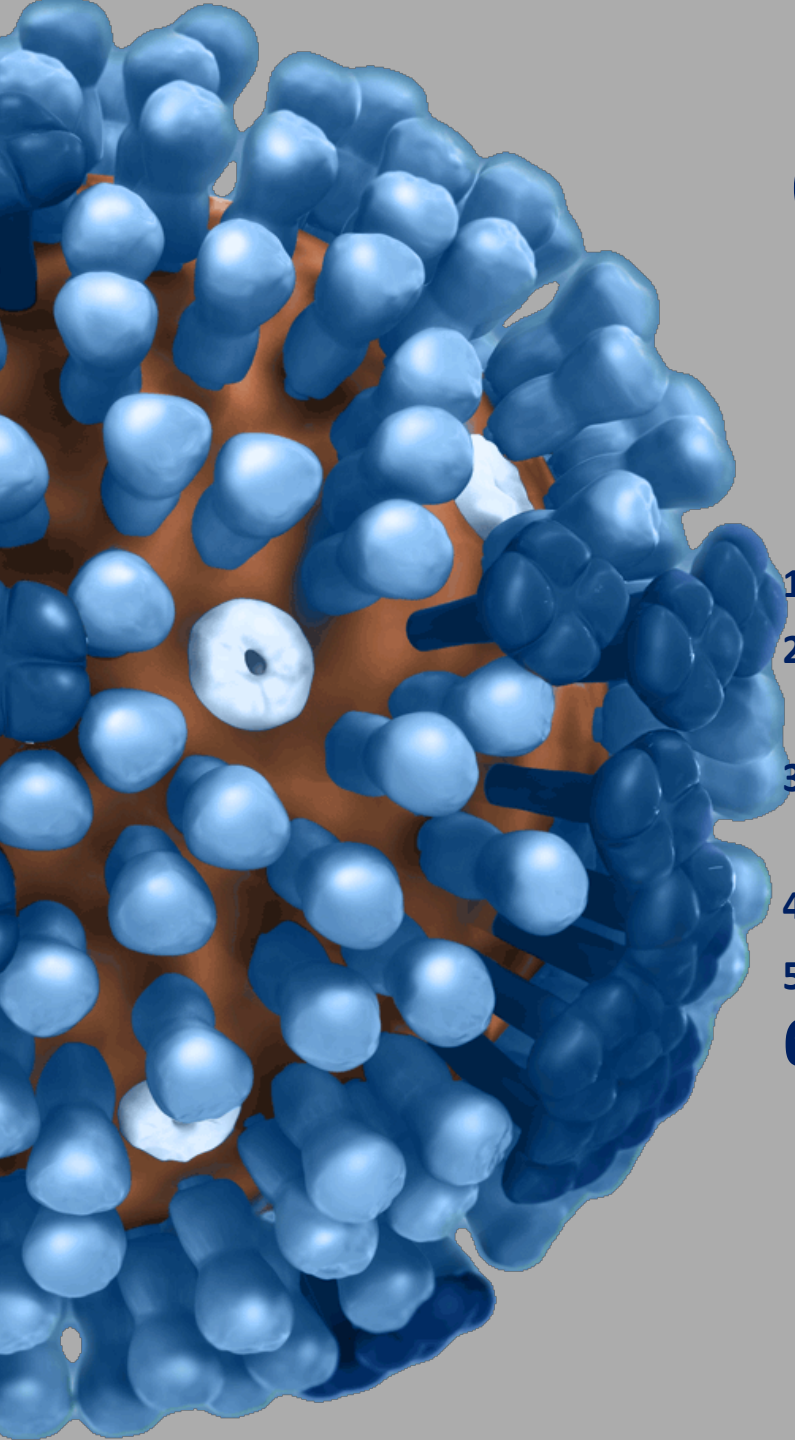
* Adjusted for prior year NH hospitalization rate, age of resident, mean age of residents in NH, individual ADL score, mean ADL score in NH, Cognitive Function Score (CFS), Mean CFS in NH, history of CHF risk-group, prevalence of CHF risk-group in NH

- Statistically significant effect of high dose vaccine for NH residents
- No evidence of effect for providing free vaccine to NH staff.

hdTIV Success in Older Adults

- Cluster nursing home study by Gravenstein 2017 Lancet resp Med
  - 12.5% decrease in any hospitalization with hdTIV
- Real world studies: significantly more effective than standard TIV in the prevention of influenza-related medical encounters, hospitalisations, and death

Izurieta HS, et al. *N Engl J Med*. 2000;342(4):232-239.



Outline

1. Influenza in older persons
2. Vaccine effectiveness in the elderly including duration of protection
3. Desirable attributes in influenza vaccines for older persons
4. aTIV
5. hdTIV
6. **Recommendations**

So

- Magnitude of benefit from enhanced vaccines will vary with season match and circulating strains
- Appears to be of the order of 25%
- Data insufficient to recommend one over other
- Must use one of them in elderly

Table 2. Regression analysis of the factors influencing uptake of flu vaccination

	Odds ratio	P
Did you receive a flu vaccine in the year before you were pregnant?		
No	1	
Yes	5.47 (3.67-8.17)	<0.001
Did any doctor recommend you receive flu vaccine in pregnancy?		
No	1	
Yes	13.94 (8.79-22.11)	<0.001
Season		
Jan-Mar	1	
Apr-Jun	1.69 (0.99 – 2.88)	0.05
Jul-Sep	5.21 (3.15-8.64)	<0.001
Oct-Dec	2.68 (1.69-4.48)	<0.001
Education		
Tertiary	1	
High school	1.13 (0.67-1.91)	0.65
Some tertiary	.36 (0.18 – 0.71)	0.003
Income		
80001 or more	1	
20000-40000	1.03 (0.44-2.39)	0.94
40001-80000	0.68 (0.43-1.06)	0.09
Age		
18-24 Years	1	
25-34 Year	0.91 (0.31-2.68)	0.86
35 and more	0.70 (0.23-2.14)	0.53
Constant	0.02	<0.001

Classification is 78.9%, Hosmer and Lemeshow Test is 0.13, Nagelkerke R Square is 50.1%

The Study

1028 pregnant women in 2017
85% had a pertussis vaccine
35% had an influenza vaccine

3 Major factors

- **Belief in vaccine**
- **Physician**
- **Season**

2018

- **Dedicated bi level marketing**
- **Extended shelf life**