Monitoring of Immunisation and Outcomes: Experience of the Canadian Serious Outcomes Surveillance Network

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2018 Adult Immunization Forum

Adelaide, Australia

June 8, 2018

Disclosures

- Research grants: GSK, Merck, Sanofi Pasteur, Pfizer
  - The SOS Network is funded by CIHR, PHAC and by collaborative research agreements with GSK (influenza) and Pfizer (CAP/IPD)
- Clinical trials: (all) vaccine manufacturers
- Chair, Immunize Canada
- Former member of National Advisory Committee on Immunization (NACI)

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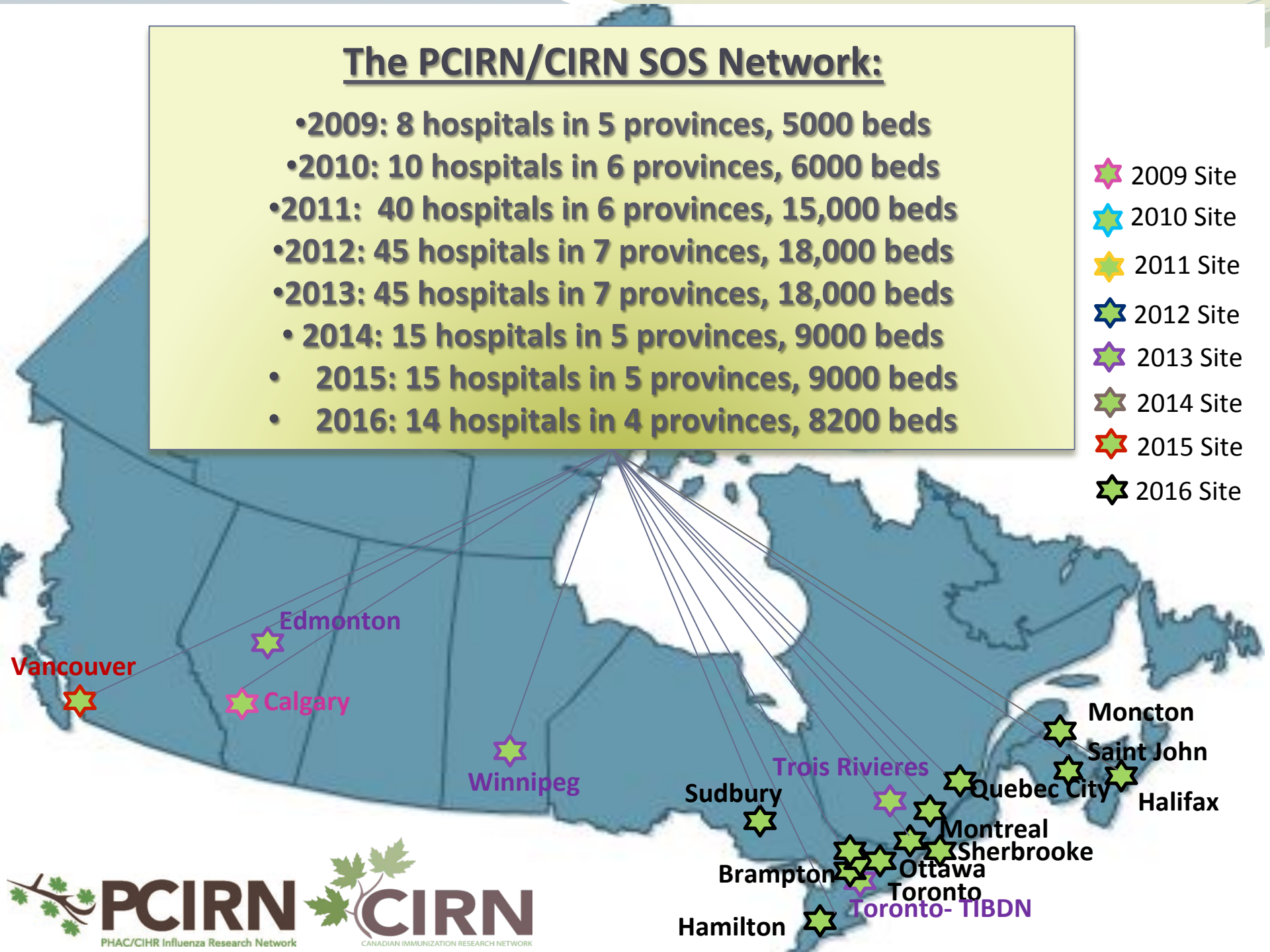
The PCIRN/CIRN SOS Network:

- 2009: 8 hospitals in 5 provinces, 5000 beds
- 2010: 10 hospitals in 6 provinces, 6000 beds
- 2011: 40 hospitals in 6 provinces, 15,000 beds
- 2012: 45 hospitals in 7 provinces, 18,000 beds
- 2013: 45 hospitals in 7 provinces, 18,000 beds
- 2014: 15 hospitals in 5 provinces, 9000 beds
- 2015: 15 hospitals in 5 provinces, 9000 beds
- 2016: 14 hospitals in 4 provinces, 8200 beds



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PHAC/CIHR Influenza Research Network
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SOS Objectives

- To assess the **effectiveness** of influenza vaccination in the prevention of influenza-related hospitalization in older Canadian adults (≥ 65y)
- To assess the **burden** of influenza diseases among older Canadian adults
- In doing so, consider measures and outcomes that are important for older people: frailty, mobility, function, social vulnerability
- Subsequently evolved to enable surveillance for CAP/ IPD and seroepidemiology of *S. pneumoniae*

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Methods

- 15-45 academic and community hospitals across Canada
- active surveillance for influenza infection in adults (≥ 16 years of age) (Nov. 15)
  - NP swab obtained from all patients with an admitting diagnosis of CAP, exacerbation of COPD/asthma, unexplained sepsis, any respiratory diagnosis or symptom
  - All NP swabs tested for influenza A & B by PCR
  - Influenza typing and B lineage characterization performed at CIRN SOS Central Lab, CCfV

McNeil SA et al. Euro Surveill. 2014 March 6;19(9).

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Methods

- **Case:**
  - Adult patients with positive test for influenza whose admission is attributable to influenza or a complication of influenza
- **Control:**
  - consenting adult patients at same site with:
    - diagnosis compatible with influenza (i.e. eligible for NP swab at admission)
    - NP swab obtained within 7 days of onset of symptoms, and test negative for influenza
    - Admission date within 14d of DOA of case
    - Same age strata as case (≥ 65y or <65y)

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Vaccine Effectiveness

- VE estimated as (1- matched OR of influenza in vaccinated vs unvaccinated)*100
  - assuming protection from vaccine from 14 days post vaccination
  - Unadjusted & Adjusted (conditional logistic regression with backward stepwise selection; $p \leq 0.1$)
  - VE point estimates and 95% CI presented
  - Overall VE and VE in age subgroups (< 65y, ≥65y) assessed
  - For the assessment of VE against death or need for mechanical ventilation or intensive care unit admission, only matched sets in which the case experienced the outcome were considered for the analysis
  - VE by influenza type/subtype assessed

Cases and Controls per season in SOS Network

Season	# of Cases	# of Controls	Dominant circulating strain(s)	Notes on Season/Vaccine
2011/2012	528	835	Influenza B (Yamagata)	B-lineage strain included in the TIV mismatched to B strain circulating
2012/2013	1292	1573	H3N2	Dominant H3N2 season
2013/2014	1574	2152	H1N1/ Influenza B (Yamagata)	Mixed H1N1, influenza B season
2014/2015	1262	1538	H3N2	Mismatch of H3N2 included in TIV to H3N2 strain circulating
2015/2016	1161	NA	H1H1/B	Good Match
2016/2017	687	807	H3N2/B	H3N2 matched/B mismatched to TIV component
2017/2018	1872	TBD	H3N2	25% mismatch

Total: 8,277

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Immune function and influenza

Incidence of serious outcomes of influenza ↑

Most influenza deaths occur in older people (and other high risk groups)

For every influenza death, there are 3–4 influenza hospitalizations (most are ≥65)

Response to vaccination ↓

CURRENT INFLUENZA VACCINE

Effectiveness in preventing respiratory illness is lower in older people (and many high risk groups) than in healthy adults

BUT has benefit in prevention of poor outcomes

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So what does frailty have to do with influenza?

McElhaney fig 2

Figure credit: Janet McElhaney

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Definition of Frailty

Clegg et al., The Lancet, 2013

Frailty is a state of increased vulnerability to poor resolution of homoeostasis after a stressor event, which increases the risk of adverse ou

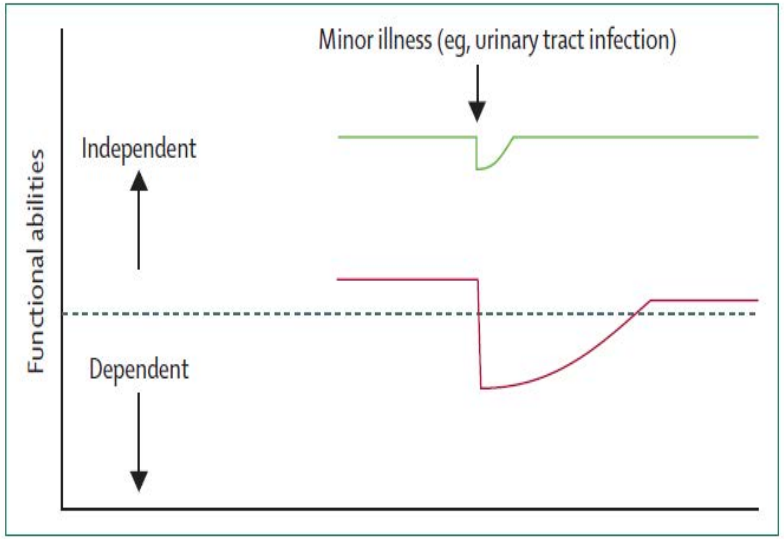

Figure 1: Vulnerability of frail elderly people to a sudden change in health status after a minor illness

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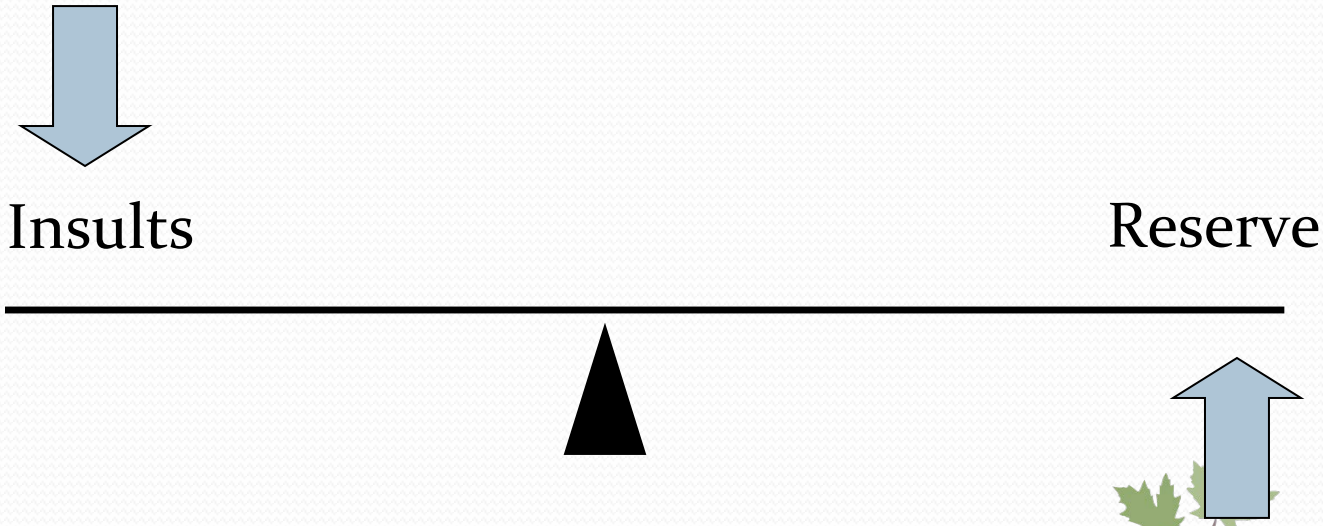
Frailty: it comes down to

Vulnerability



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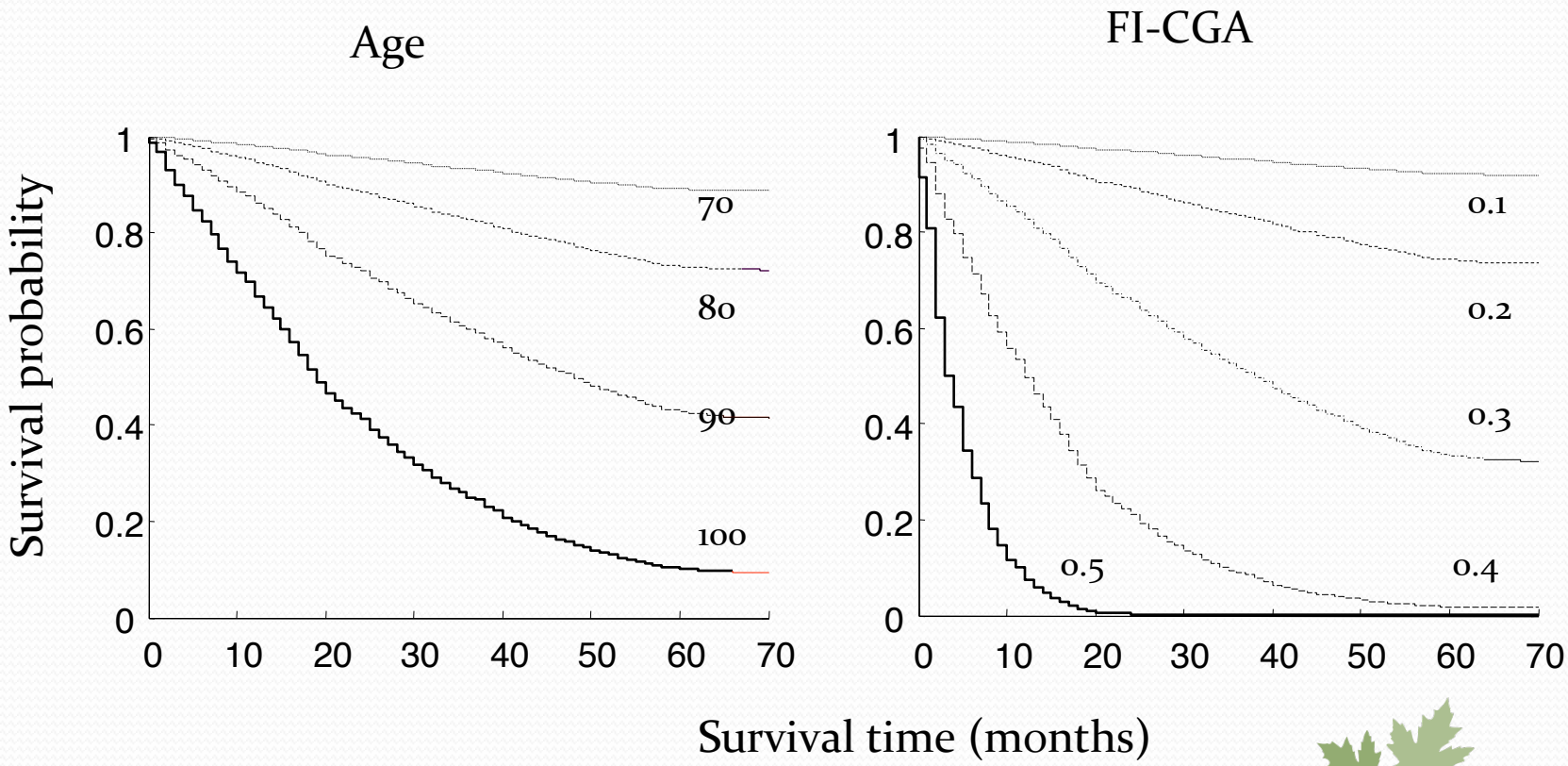
A frailty index based on a Comprehensive Geriatric Assessment (FI-CGA) better stratifies 70-month survival than does age



Rockwood, Rockwood, Mitnitski., *J Am Geriatrics Soc*, 2010;58:318-323.

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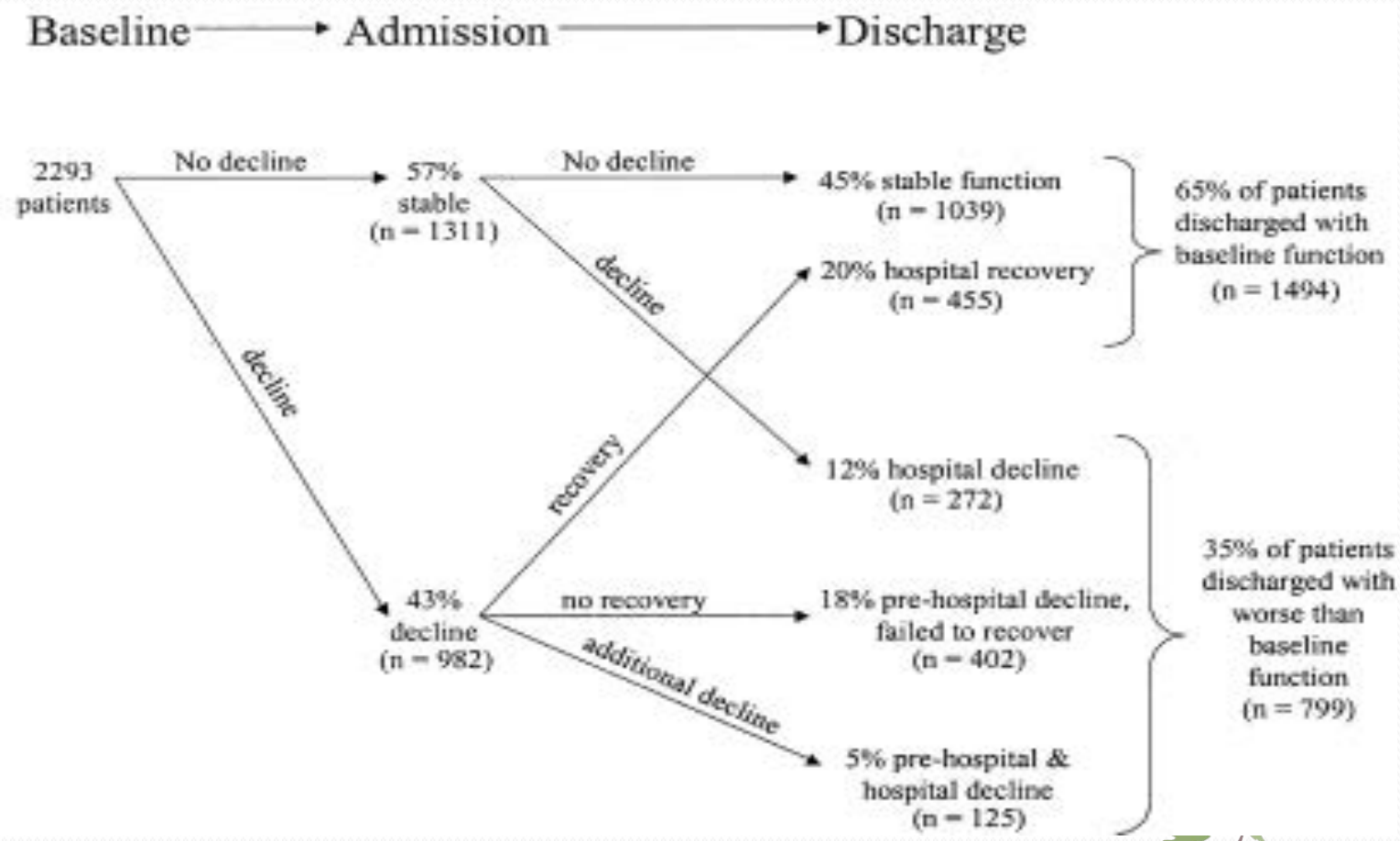
Functional loss is common when older people are in hospital



Covinsky JAGS 2003

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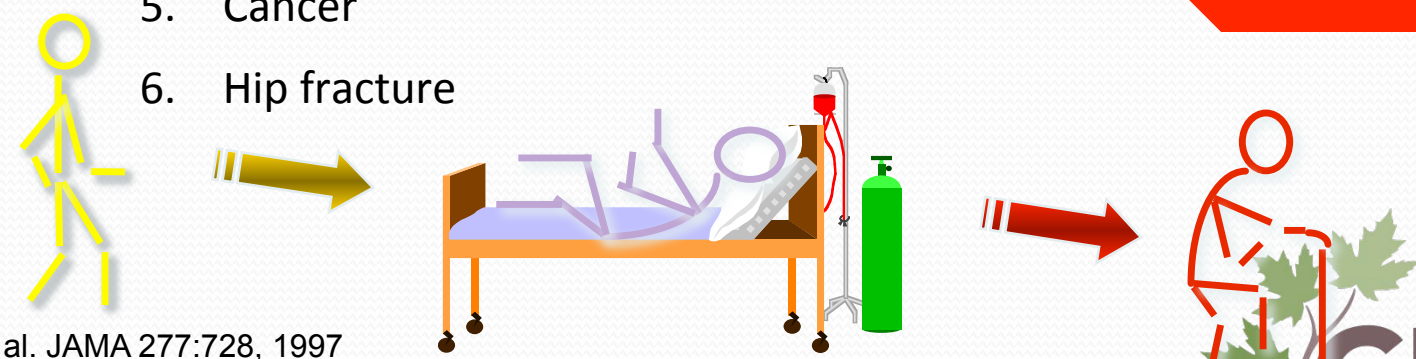
Vaccine Preventable Disability

Catastrophic disability

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

15% of 65+ hospitalized with influenza



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
Andrew et al, IDWeek 2016

Figure credit Dr. Janet McElhaney

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The problem of BIAS: how do vaccinated and unvaccinated people differ?

- **Bias** is any factor independently associated with risk of disease and vaccination status
  - Healthy user bias- persons more likely to be vaccinated are less likely to develop disease-
    - OVER-estimates VE
  - Indication (frailty) bias- persons more likely to be vaccinated (e.g. frail elderly people) are more likely to have suboptimal vaccine response and experience adverse more influenza outcomes
    - UNDER-estimates VE

Quantifying Frailty

- The Frailty Index (FI) is calculated by adding the number of deficits a person has divided by the total possible deficits

FI = # deficits/total possible deficits

- Can include as many possible deficits as available data allows; ideally ~40

Rockwood CMAJ Aug 2005
Searle BMC Geriatrics 2008

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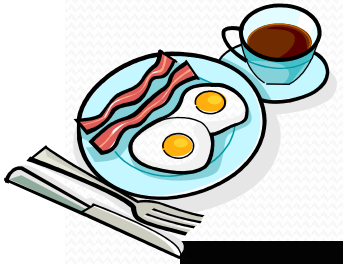
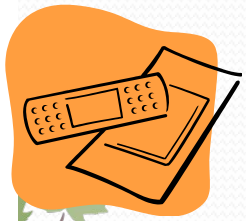
APPENDIX 6: Frailty Index and Frail Scale





Frailty Index (for patients 65 years and older)		Check if Frailty Index was not done: ☐
	Two Weeks Prior to Admission	**On Admission**
A. Cognition	☐ WNL ☐ CIND ☐ Dementia ☐ Delirium due to illness? ☐ unk If dementia, type _____	☐ WNL ☐ CIND ☐ Dementia ☐ Delirium due to illness? ☐ unk If dementia, type _____
C. Mood	☐ WNL ☐ Low mood ☐Depression ☐ Anxiety ☐ unk	☐ WNL ☐ Low mood ☐Depression ☐ Anxiety ☐ unk
D. Sensory	Hearing ☐ WNL ☐ Impaired ☐ unk Vision ☐ WNL ☐ Impaired ☐ unk Speech ☐ WNL ☐ Impaired ☐ unk	Hearing ☐ WNL ☐ Impaired ☐ unk Vision ☐ WNL ☐ Impaired ☐ unk Speech ☐ WNL ☐ Impaired ☐ unk
E. Mobility	Transfers ☐ I ☐ A ☐ D ☐ unk Ambulates ☐ I ☐ A ☐ Non-amb ☐ unk Aid ☐ Y ☐ N ☐ unk If yes, aid type: ☐ Cane ☐ 2ww ☐ 4ww ☐ unk Balance ☐ WNL ☐ Impaired ☐ unk Falls ☐ Y ☐ N ☐ unk	Transfers ☐ I ☐ A ☐ D ☐ unk Ambulates ☐ I ☐ A ☐ Non-amb ☐ unk Aid ☐ Y ☐ N ☐ unk If yes, aid type: ☐ Cane ☐ 2ww ☐ 4ww ☐ unk Balance ☐ WNL ☐ Impaired ☐ unk Falls ☐ Y ☐ N ☐ unk
F. Nutrition	Weight ☐ Stable ☐ Loss ☐ Gain ☐ unk	Weight ☐ Stable ☐ Loss ☐ Gain ☐ unk
G. Function	Bathing ☐ I ☐ A ☐ D ☐ unk Toileting ☐ I ☐ A ☐ D ☐ unk Meds ☐ I ☐ A ☐ D ☐ unk Dressing ☐ I ☐ A ☐ D ☐ unk Eating ☐ I ☐ A ☐ D ☐ unk Finances ☐ I ☐ A ☐ D ☐ unk I =Independant , A=Assisted, D =Dependant	Bathing ☐ I ☐ A ☐ D ☐ unk Toileting ☐ I ☐ A ☐ D ☐ unk Meds ☐ I ☐ A ☐ D ☐ unk Dressing ☐ I ☐ A ☐ D ☐ unk Eating ☐ I ☐ A ☐ D ☐ unk Finances ☐ I ☐ A ☐ D ☐ unk I =Independant , A=Assisted, D =Dependant
H. Skin	Ulcers ☐ Y ☐ N ☐ unk Edema ☐ Y ☐ N ☐ unk	Ulcers ☐ Y ☐ N ☐ unk Edema ☐ Y ☐ N ☐ unk
I. Continence (ostomy managed by patient = continent)	Bladder : ☐ Continent ☐ Incontinent ☐ unk Bowel : ☐ Continent ☐ Incontinent ☐ unk	Bladder: ☐ Continent ☐ Incontinent ☐ unk Bowel : ☐ Continent ☐ Incontinent ☐ unk
J. Frailty Scale	1 to 9: _____	1 to 9: _____

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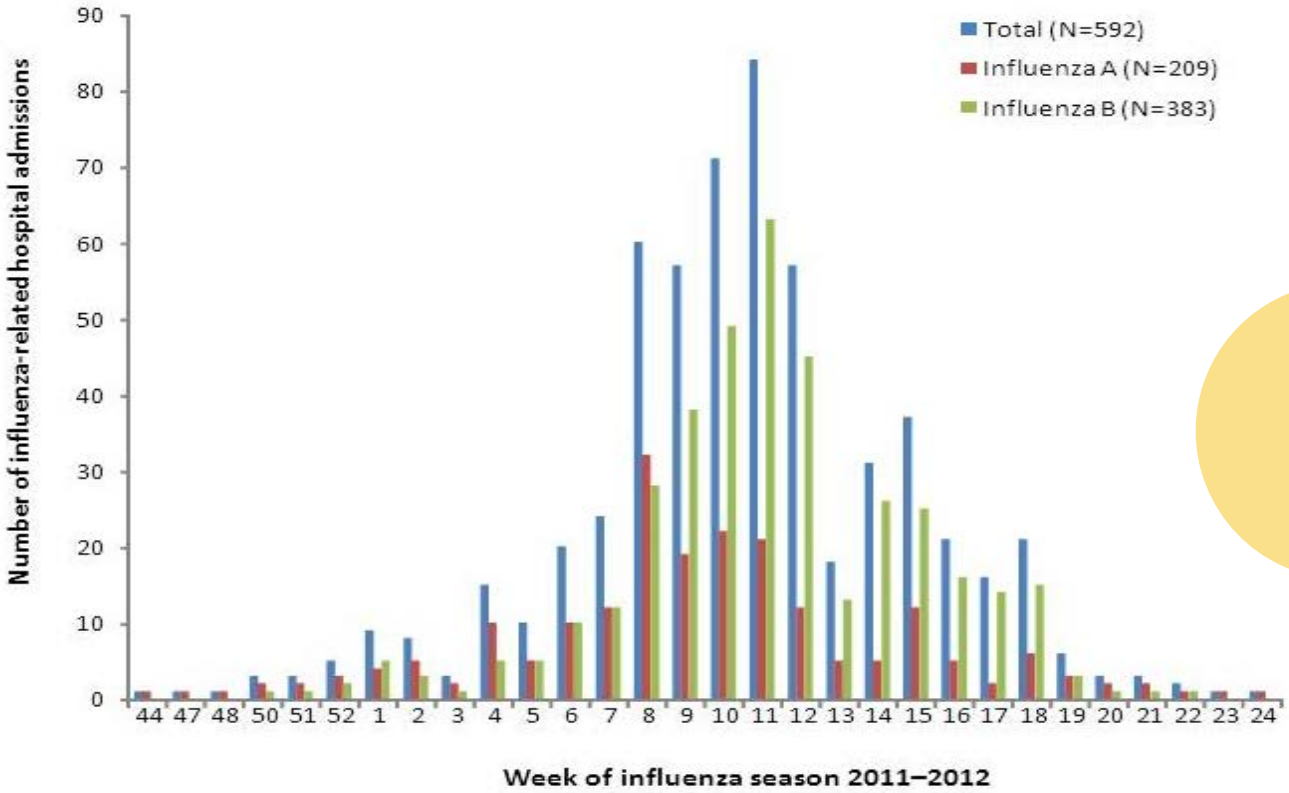
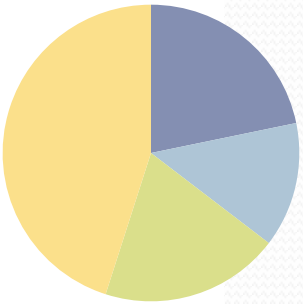
Function

- Barthel Index: collected at 3 time points, baseline (prior to onset of current illness), during admission, and 30 day post discharge.

- Assessment of independence in ADL.
- Score between 0-10 for each individual section: bowels, bladder, grooming, toilet use, feeding, transfer, mobility, dressing, stairs, and bathing, giving a score between 0-100 (100 indicating complete independence in ADL).

Distribution of hospital admissions by week and influenza strain (2011/12)





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Andrew MK et al. BMC Infect Dis. 2017;17(1):805

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Clinical Characteristic	Cases n=528 (%)	Controls n=835 (%)	p-value
Age mean (range)	67.1 (18-104)	69.2 (18-99)	0.73
Age ≥ 65y	**80.6 (65-104)**	**78.8 (65-99)**	**0.001**
Female	288 (54.5)	469 (56.2)	0.58
Obese (BMI >=30)	**103 (19.5)**	**229 (27.4)**	**0.016**
Pregnant **Mean gest wks**	**10 (1.9)** **27.94**	**1 (0.1)** **27.22**	**0.006**
Aboriginal	2 (0.4)	3 (0.4)	NS
Admitted from LTCF	**50 (9.5)**	**38(4.5)**	**<0.05**
Current smoker **Past smoker**	61 (29.3) **30 (14.4)**	83 (30.6) **70 (25.8)**	0.90 **0.004**
Cardiac disease **Pulmonary disease**	**210 (39.8)** **231 (43.8)**	**415 (49.7)** **426 (51.0)**	**0.005** **0.021**
Current season vaccine	**262 (49.6)**	**529 (63.4)**	**<0.001**
Prior season vaccine	**248/481 (51.6)**	**515/793 (64.9)**	**<0.001**
BL Frailty mean (SD)	**0.22 (0.13)**	**0.20 (0.11)**	**0.006**
Barthel Index mean (SD)	**81.7 (28.8)**	**88.1 (21.0)**	**0.003**

Clinical Characteristics (2011/12)

Variable	Vaccinated (n=792) %	Unvaccinated (n=602) %	p-value
Age mean (range)	**73.7 (18-104)**	**61.4 (18-98)**	**<0.001**
Age ≥ 65y mean **65-75** **>75**	**80.0 (65-104)** **32.4%** **67.6%**	**78.2 (65-98)** **39.6%** **60.4%**	**0.003** **0.041**
Gender			NS
Obese (BMI >30)			NS
Admitted fr LTCF	**9.0%**	**2.6%**	**<0.001**
Current or past smoker	**54.5%**	**49.2%**	**0.02**
BL Frailty mean (SD)	**0.20 (0.11)**	**0.17 (0.11)**	**<0.001**
≥ 1 comorbidity	**98.1%**	**87.9%**	**<0.001**
≥ 4 medications	**77.3%**	**49.4%**	**<0.001**

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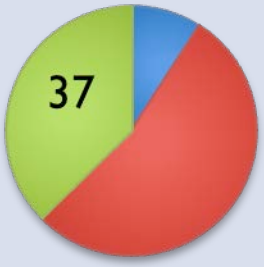
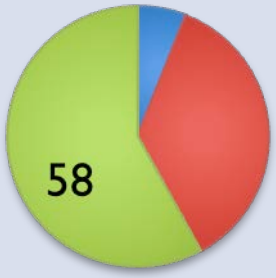
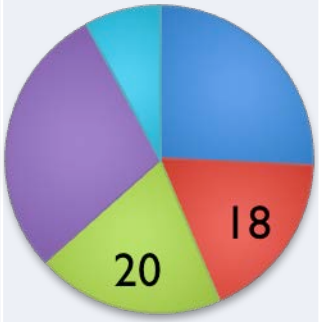
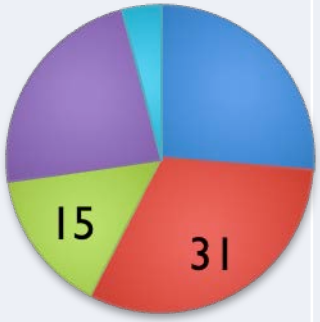
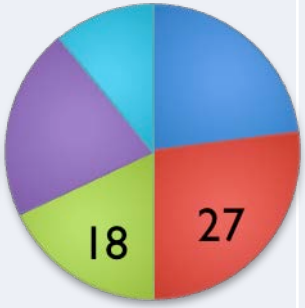
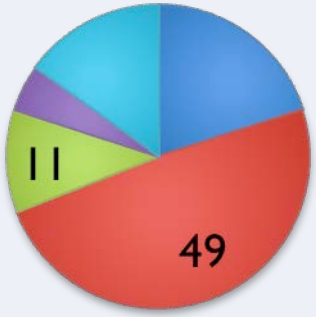
Age and Burden of Disease

	Age 16 – 49 N = 128	Age 50-64 N = 118	Age 65-75 N = 109	Age >75 N = 237
% vaccinated				
BOD by strain				
Death	1 (0.8%)	3 (2.5%)	6 (5.5%)	36 (15.2%)
ICU	16 (12.5%)	20 (16.9%)	17 (15.6%)	22 (9.3%)

Unk
No
Yes

Unk
Yam
Vic
H1
H3

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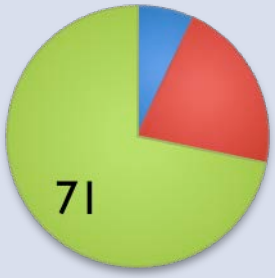
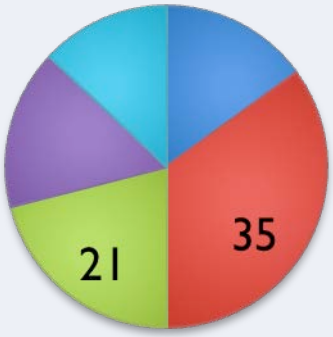
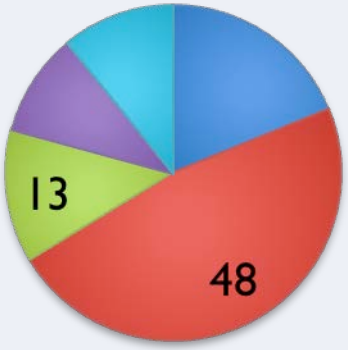
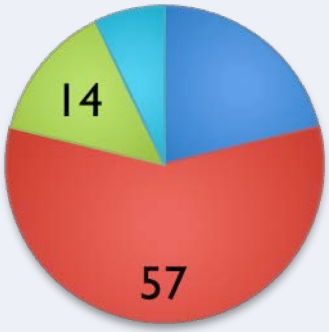
Frailty and Burden of Disease

	Low Frailty (FI < 0.2) N = 92	Med Frailty (FI 0.2-0.45) N = 84	High Frailty (FI >0.45) N = 14
% vaccinated			
BOD by strain			
Death	5 (5.4%)	11 (13.1%)	5 (35.7%)
ICU	7 (7.6%)	11 (13.1%)	1 (7.1%)

Unk
No
Yes

Unk
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Outcomes by type/subtype (2011/12)

Variable	Influenza A n = 161		Influenza B n = 299	
	A/H1N1 n=99	A/H3N2 n=61	B/Vic n=89	B/Yam n=204
Mean LOS (SD)	10.0 (10.4)		10.4 (11.9)	
	9.3 (9.1)	11.0 (12.4)	11.3 (13.2)	10.1 (11.4)
Admit to ICU	22 (13.7%)		30 (10.0%)	
	15 (15.2%)	7 (11.5%)	12 (13.5%)	18 (8.8%)
30d mortality	10 (6.2%)		23 (7.7%)	
	3 (3.0%)	**7 (11.5%)***	**3 (3.4%)**	**20 (9.8%)***

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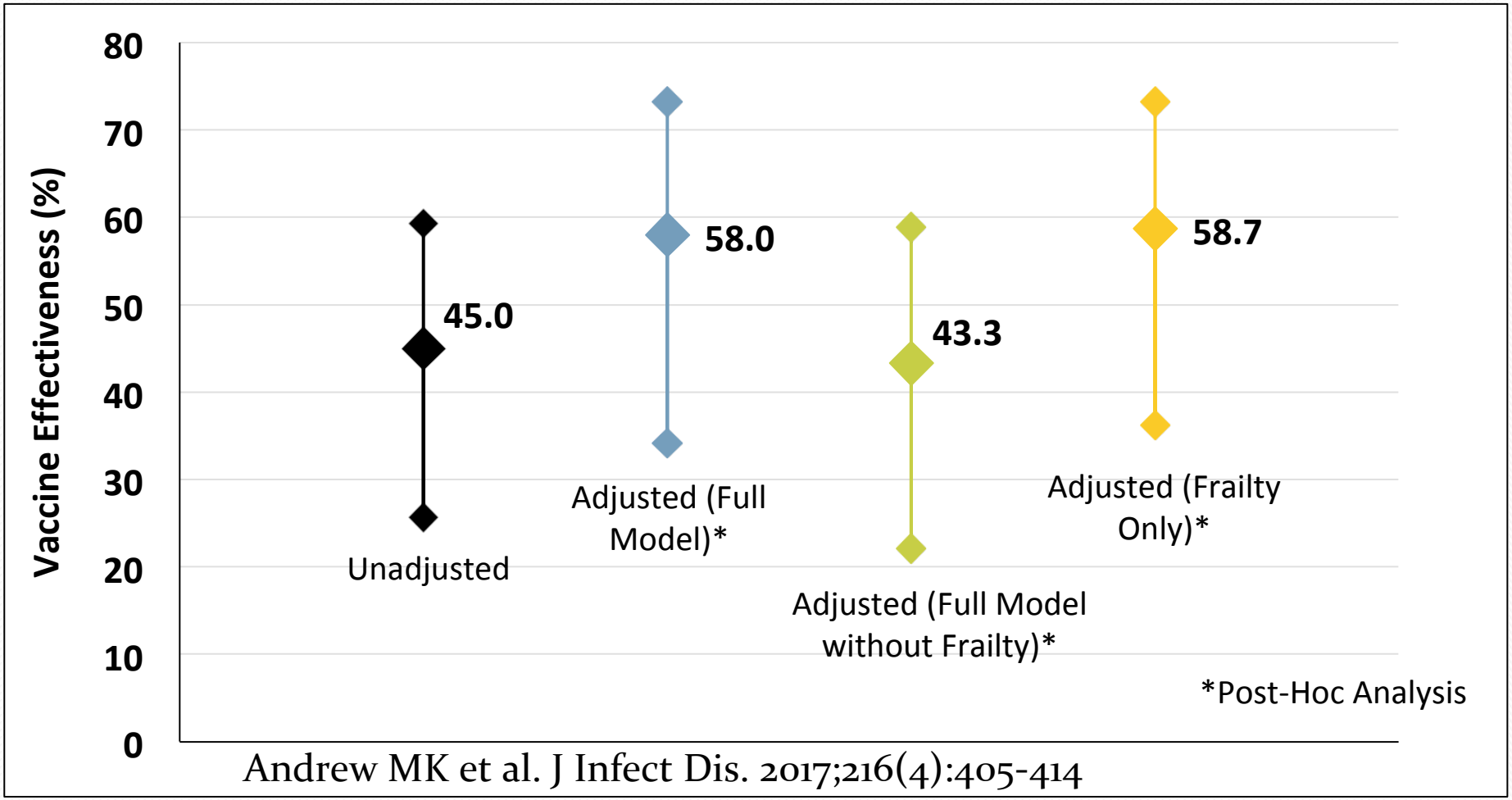
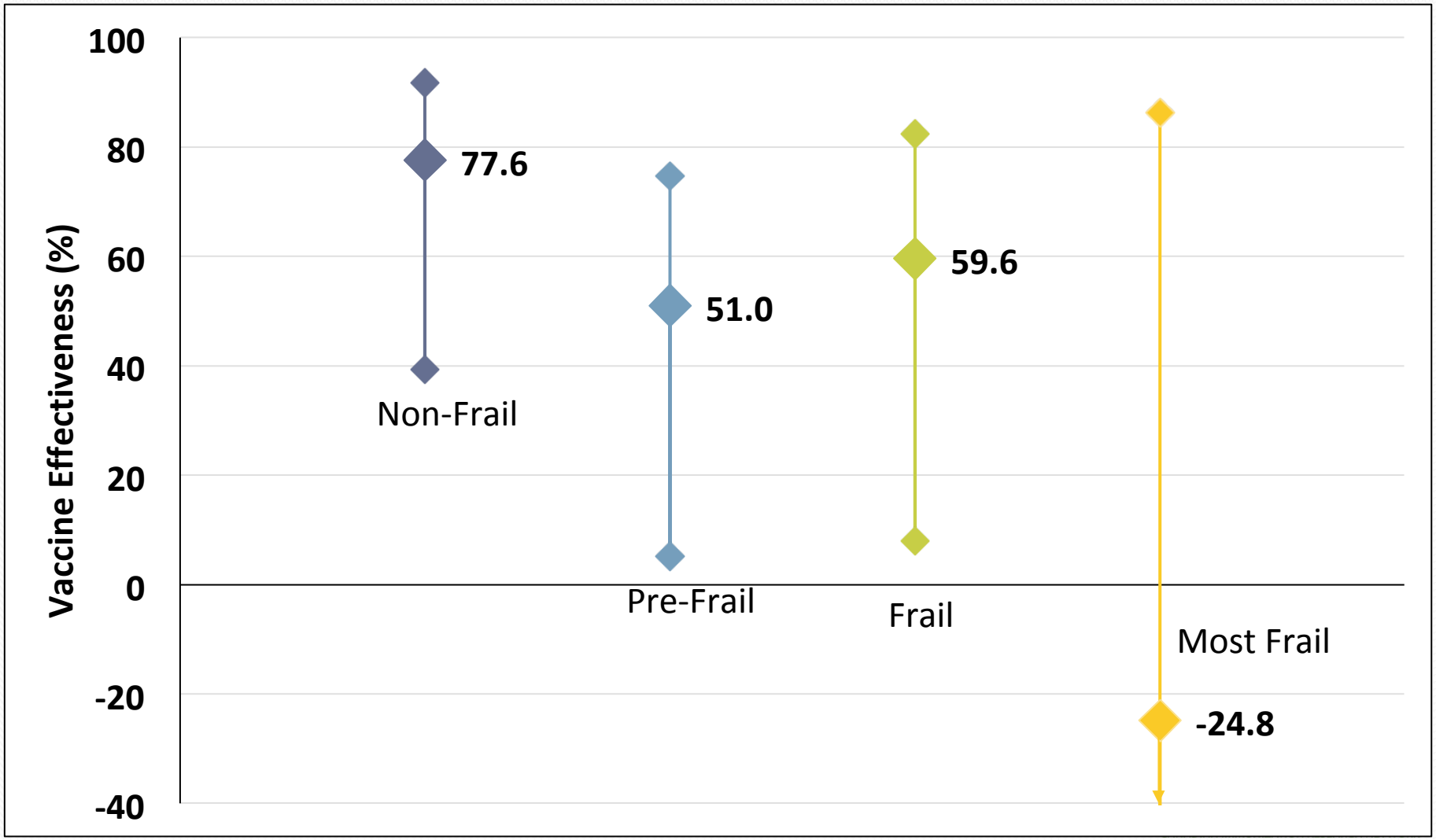
Unadjusted and Adjusted VE in Older Adults



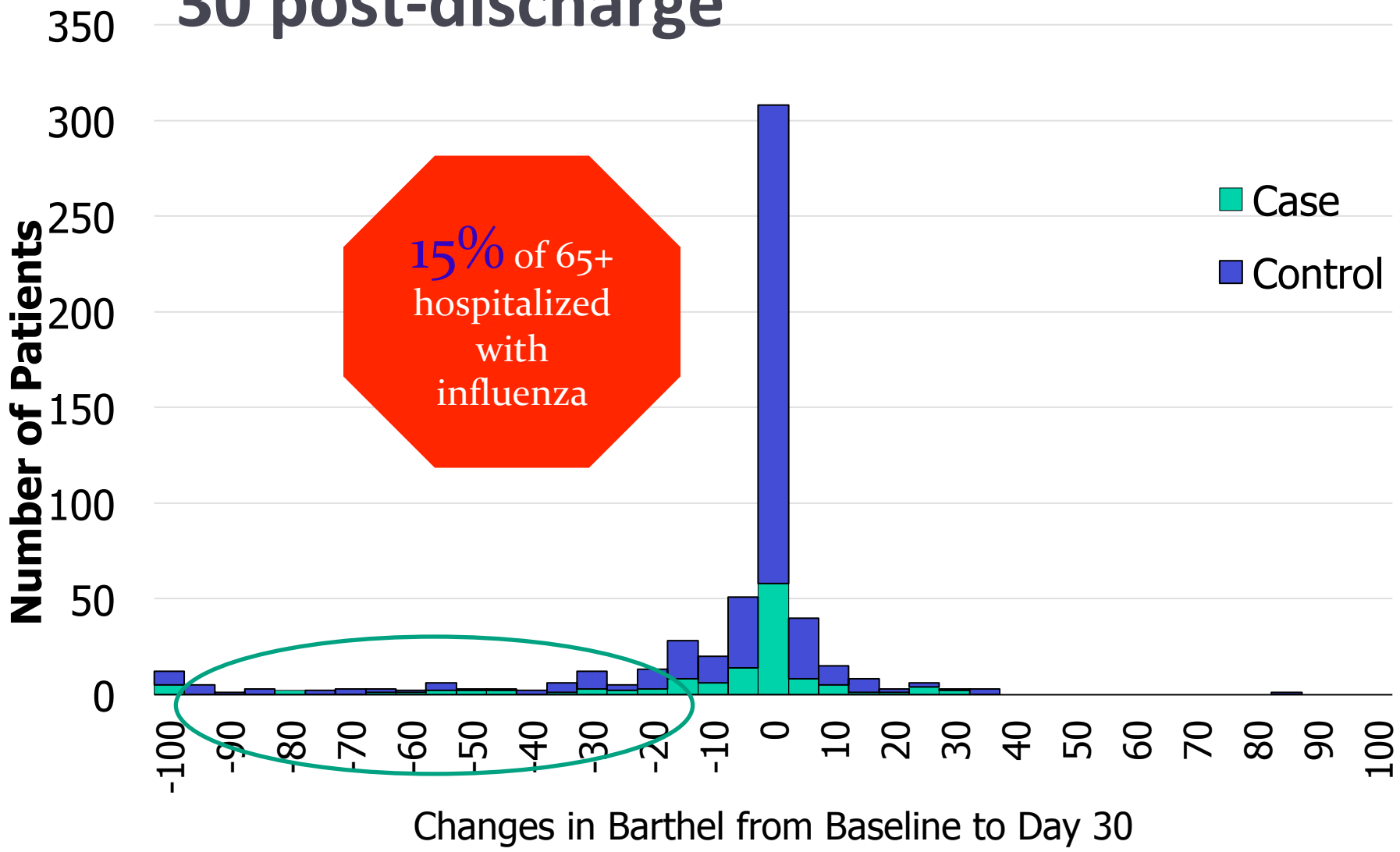
Andrew MK et al. J Infect Dis. 2017;216(4):405-414

Adjusted VE estimates by frailty level- Not all older adults are alike!*

*Post-Hoc Analysis



Barthel changes from baseline to Day 30 post-discharge



Summary

- TIV demonstrated moderate yet significant protection against influenza-related hospitalizations in older adults ≥65y (VE: 58.0%).
- Frailty was the most significant contributor in the fully adjusted VE model. Not adjusting for frailty may **underestimate** true VE estimates.
- **VE demonstrates a trend of decreasing as level of frailty increases. Given most older adults are not frail (frailty prevalence estimated at ~24% in community-dwelling older adults), the benefit of the vaccine in non-frail older adults should not be underestimated.**
- **14.6%** of patients lost between 20 and 100 points on the Barthel Index, indicating **catastrophic disability** following hospitalization.

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Conclusions

- Evaluating the impact of frailty on VE and serious outcomes is critically important for fully understanding the health benefits of the influenza vaccine in older adults

- The TIV remains an effective tool for preventing influenza-related hospitalizations in an older adult population and should be continued to be used to prevent serious outcomes associated with influenza

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Conclusions

- Understanding the impact of influenza on frailty (and of frailty on influenza) is critical to understanding its true burden
- Our data suggests a **frailty bias** in observational studies of VE
  - Indication bias (rather than healthy user bias)
- Observational studies which do not quantify and adjust for frailty will systematically **UNDERESTIMATE** the estimated vaccine effectiveness in this population
- VE estimates tend to increase when adjusted for frailty; this has important implications for targeting vaccination campaigns and understanding the true benefits of vaccination

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A Comparative Evaluation of the Burden of Disease Caused by Influenza A and Influenza B during the 2011/2012, 2012/2013 and 2013/2014 Influenza Seasons in Canada

Caoimhe McParland, BScH, MD Candidate
on behalf of the SOS Network of the
Canadian Immunization Research Network

Canadian Center for Vaccinology
Dalhousie University
IWK Health Centre
NS Health Authority

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Season Overview

Season	# of influenza A Cases	# of influenza B cases	Dominant circulating strain(s)
2011/2012	209	383	Influenza B (Yamagata)
2012/2013	1891	148	H3N2
2013/2014	1384	844	H1N1/ Influenza B (Yamagata)
Total	3484	1375	

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Results: Demographics

	Influenza A	Influenza B	p-value
Age (mean)	65.8	71.2	<0.01
Gender (male)	48.7%	46.0%	0.12
Admission from long-term care	5.5%	12.1%	<0.01
Number of medications (>4)	59%	64.6%	<0.01
Prior medical comorbidities (Yes)	88.3%	90.2%	0.05

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Results: Frailty

	Influenza A	Influenza B	p-value
Prior to illness onset	0.21	0.22	0.02
Worst between admission and enrolment	0.28	0.29	0.11
30-days post discharge	0.20	0.21	0.12

*Frailty Index is on a scale of increasing frailty from 0 to 1

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Results: Clinical Outcomes

	Influenza A	Influenza B	p-value
Duration of hospitalization	11.1 days	10.27 days	0.07
ICU admission	18.05%	12.22%	<0.01
Mechanical ventilation	11.77%	7.27%	<0.01
Antiviral use prior to admission	11.45%	12.80%	0.19
Antiviral use during admission	94.32%	91.49%	<0.01
Mortality 30 days post-discharge	9.01%	9.45%	0.63

Conclusion

- Current perception considers influenza A to be of more significance than influenza B
  - Influenza A is significantly more likely to be admitted to the ICU or require mechanical ventilation
- However, there is no difference in duration of hospitalization or mortality rates
- Influenza B has a more significant effect on the frail elderly, particularly those coming from a long-term care facility
  - Careful consideration should be given to the development of high-dose and adjuvanted QIV to enhance influenza B protection

Pooled VE: An assessment of average benefit of vaccination over time

- Influenza vaccine remains our best method of protection from influenza infection and associated serious outcomes
- Seasonal influenza vaccine effectiveness (VE) varies year to year depending on vaccine-strain mismatch, circulating strains, and host factors and is generally not predictable
- Influenza VE in older adults, likely due to a combination of factors including immunosenescence, increased comorbidities, and frailty, is generally shown to be lower than VE in working-age adults

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Nichols MK et al Vaccine 36(16);2018: 2166-2175

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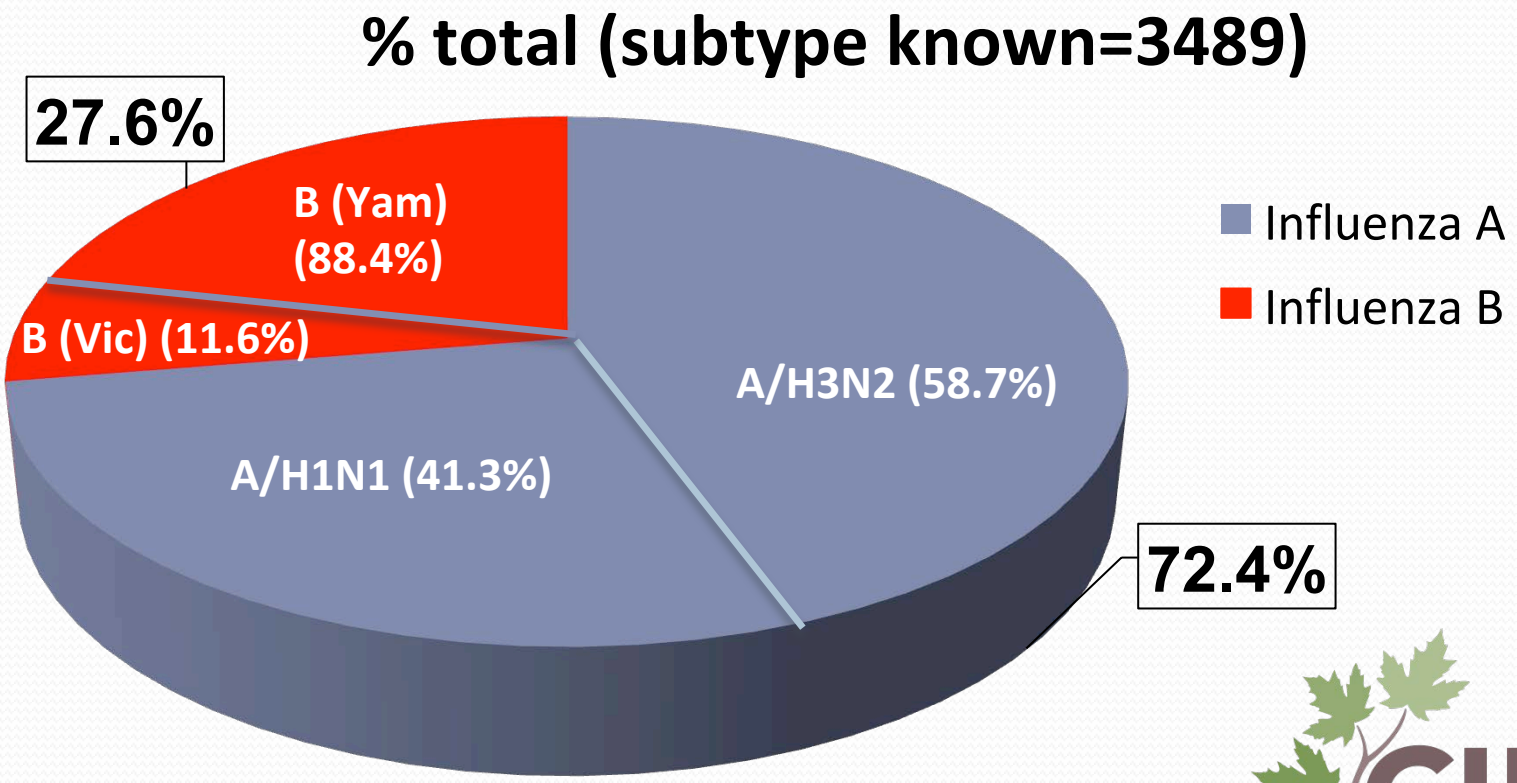
Clinical characteristics of cases and controls (11/12, 12/13, 13/14 pooled)

Characteristics	Cases (n=3394) n (%)	Controls (n=4560) n (%)	p value
Age mean (range)	67.6 (16-105)	68.8 (16-104)	0.193
16-49y	611 (18.0)	626 (13.7)	
50-64y	705 (20.8)	995 (21.8)	
65-75y	674 (19.9)	1063 (23.3)	
>75 y	1404 (41.4)	1876 (41.1)	
Female	1805 (53.2)	2436 (53.4)	0.94
≥1 comorbidities	3025 (89.1)	4234 (92.9)	0.00
Pregnant	87 (2.6)	13 (0.3)	0.00
Smoker	1669 (49.2)	2702 (59.3)	0.00
Antiviral use PTA	33 (1.0)	32 (0.7)	0.33
Current season vaccine	1585 (46.7)	2806 (61.5)	0.00
Prior season vaccine	1588/2957 (53.7)	2360/3758 (62.8)	0.00

Overall strain distribution (11/12, 12/13, 13/14 pooled)



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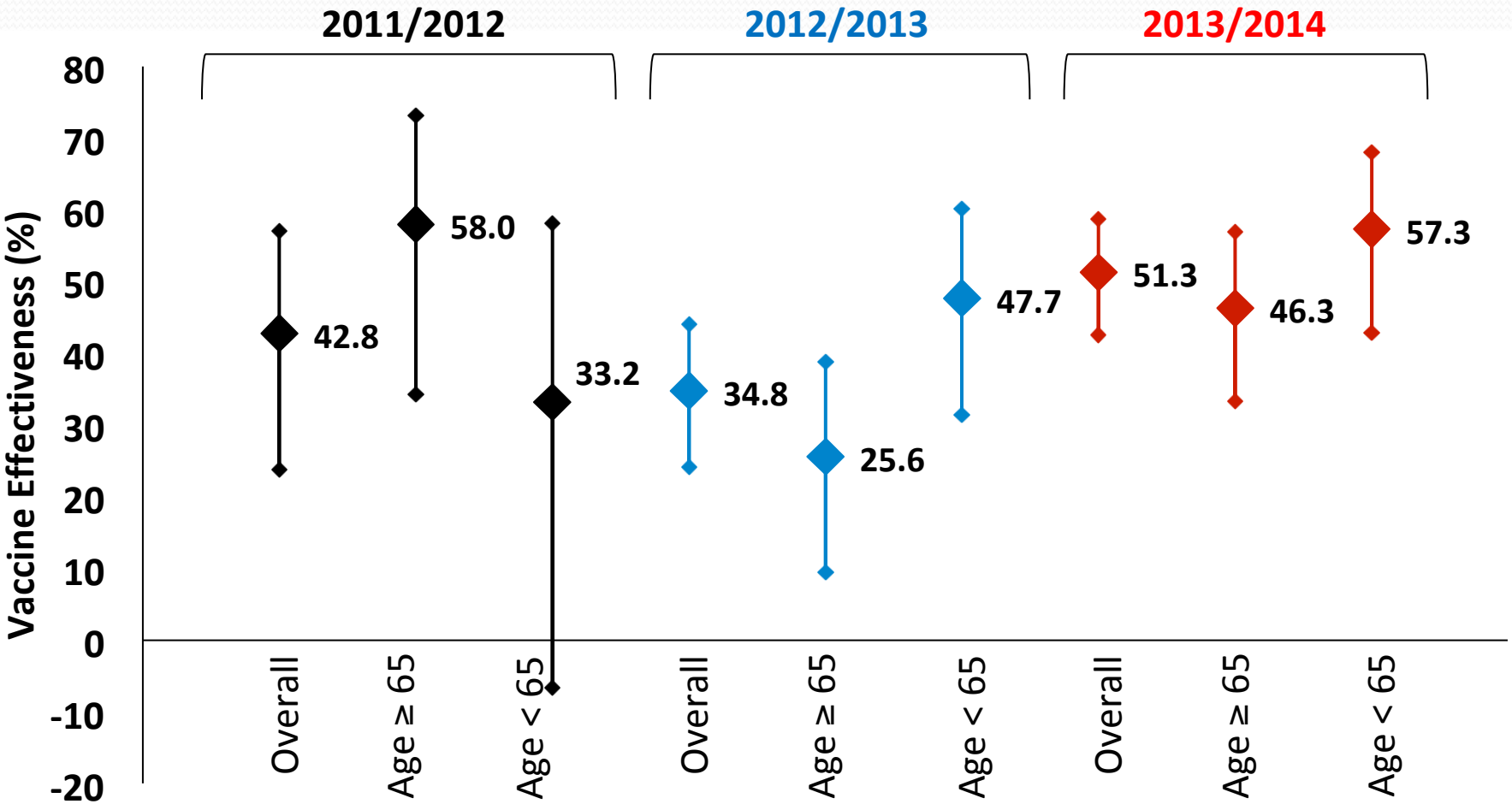
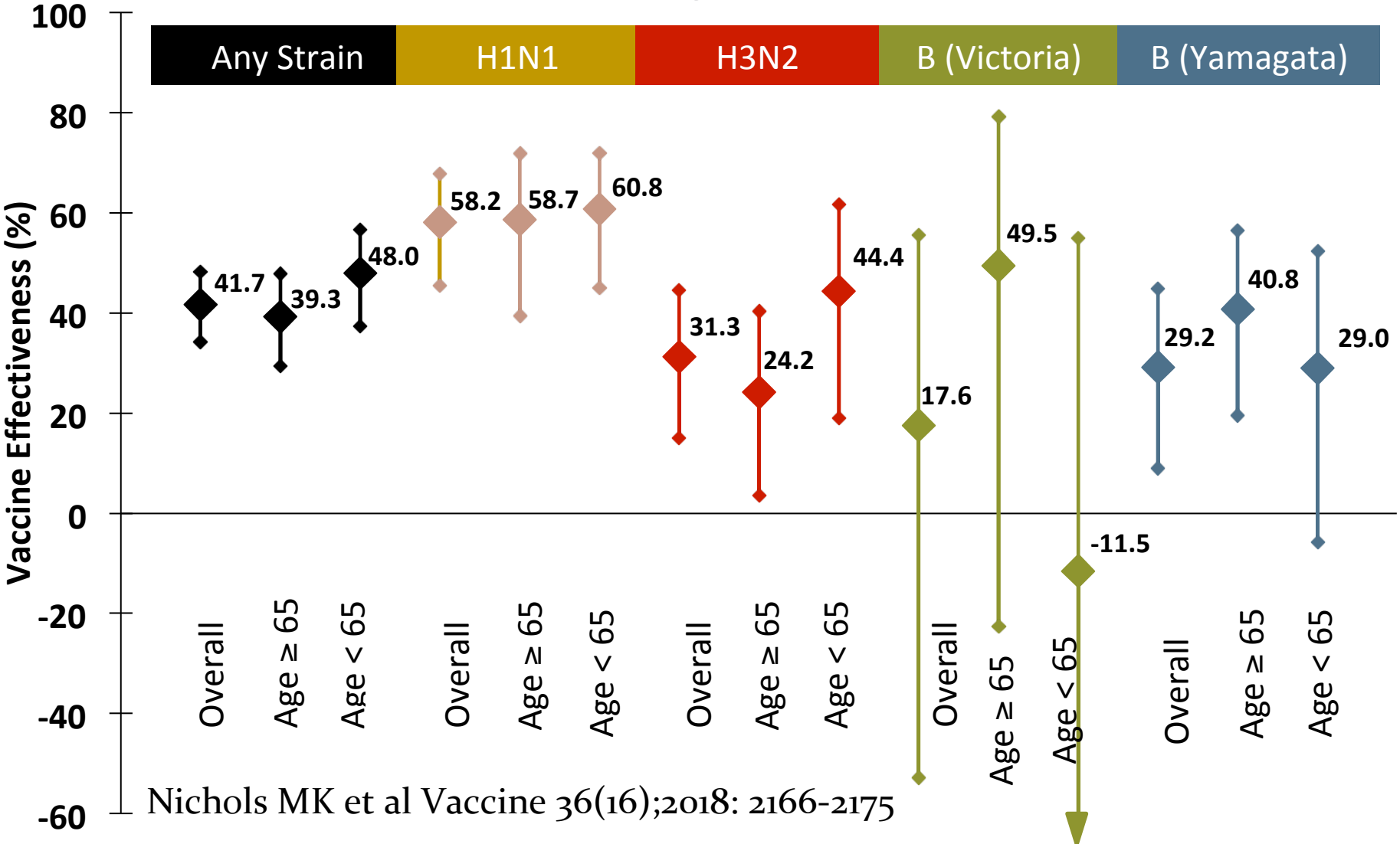
Adjusted VE estimate by influenza season

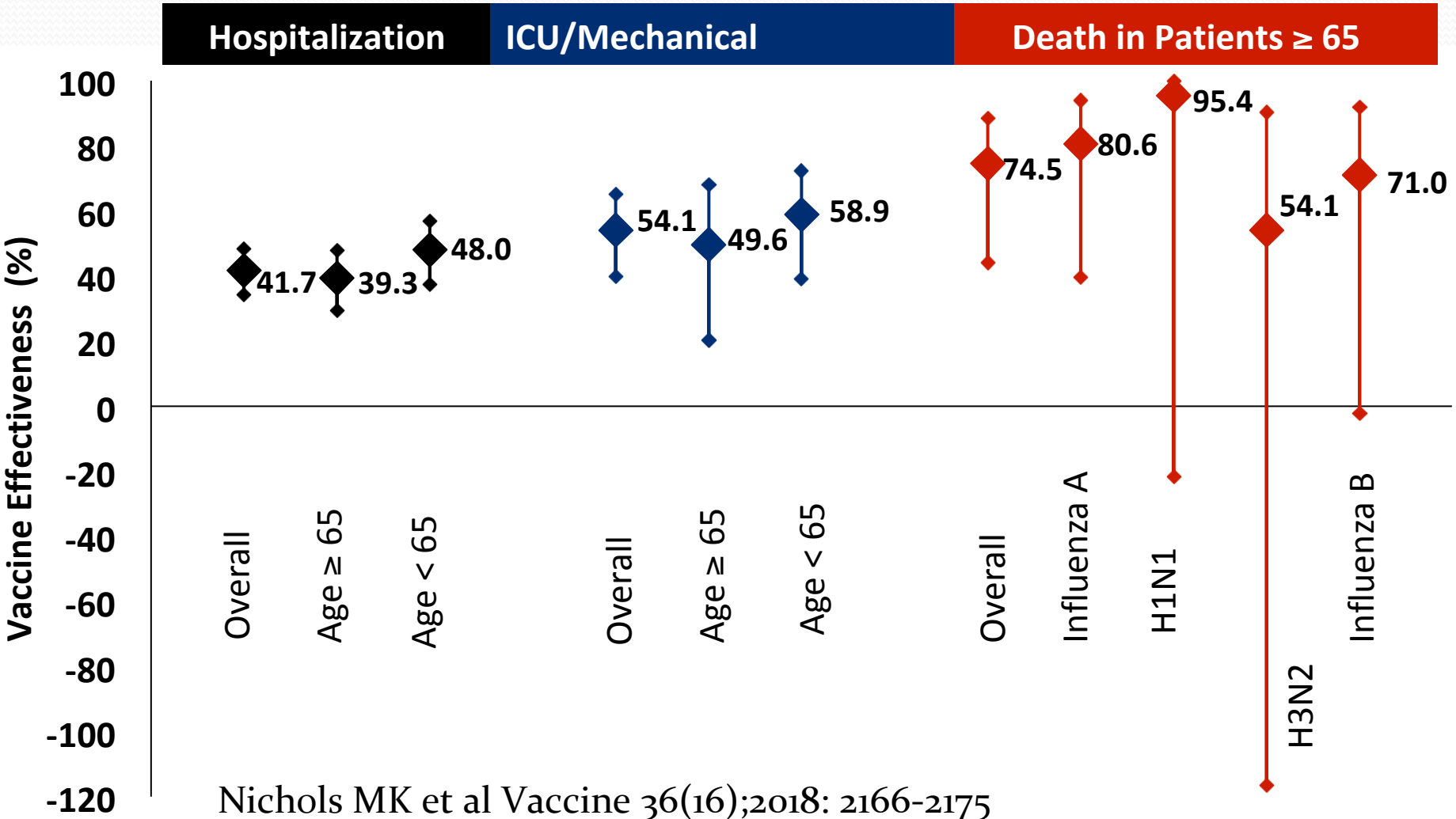


Adjusted VE estimate by influenza subtype (11/12, 12/13, 13/14 pooled)



Nichols MK et al Vaccine 36(16);2018: 2166-2175

Adjusted VE estimate by severity (11/12, 12/13, 13/14 pooled)



Nichols MK et al Vaccine 36(16);2018: 2166-2175

Summary

- While influenza vaccine effectiveness varies year-to-year due to factors such as virulence of the circulating strain and match between circulating and vaccine strains, we demonstrate a statistically and clinically important benefit of vaccination in adults spanning three influenza seasons (overall VE 42%)
- Over 3 seasons, TIV effectiveness for the prevention of hospitalization due to influenza A(H3N2) was 24% in older adults
- Statistically significant protection against severe outcomes including need for ICU admission or mechanical ventilation and death was demonstrated in older adults (VE estimate 54% and 75%, respectively), and this protection increased with the severity of the outcome

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Conclusion

- The individual and public health benefits of influenza vaccines should not be understated and public messaging should address overall benefits over time while acknowledging year-to-year variability

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Adjuvanted Vaccines

- Adj-influenza vaccine (Fluad®) was first approved for use in Canada in 2011 and was recommended for use in older adults by NACI
- Not all provinces/territories fund adj-influenza vaccine
- In clinical trials, adj-influenza vaccine has been shown to elicit a stronger immune response in older adults than non-adjuvanted influenza vaccines
- It is difficult to demonstrate adj-vaccine's benefit over non-adj vaccines in observational studies

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Why Evaluate Adj-Influenza VE?

- The bulk of serious outcomes associated with influenza (for example: hospitalization, ICU admission, functional decline or death) comes from older adults (≥65)
- Understanding if there is an additional benefit to vaccinating older adults with adjuvanted vaccines compared to non-adjuvanted vaccines is important to inform vaccine policy and potentially optimize use of influenza vaccination in older adults (≥65)

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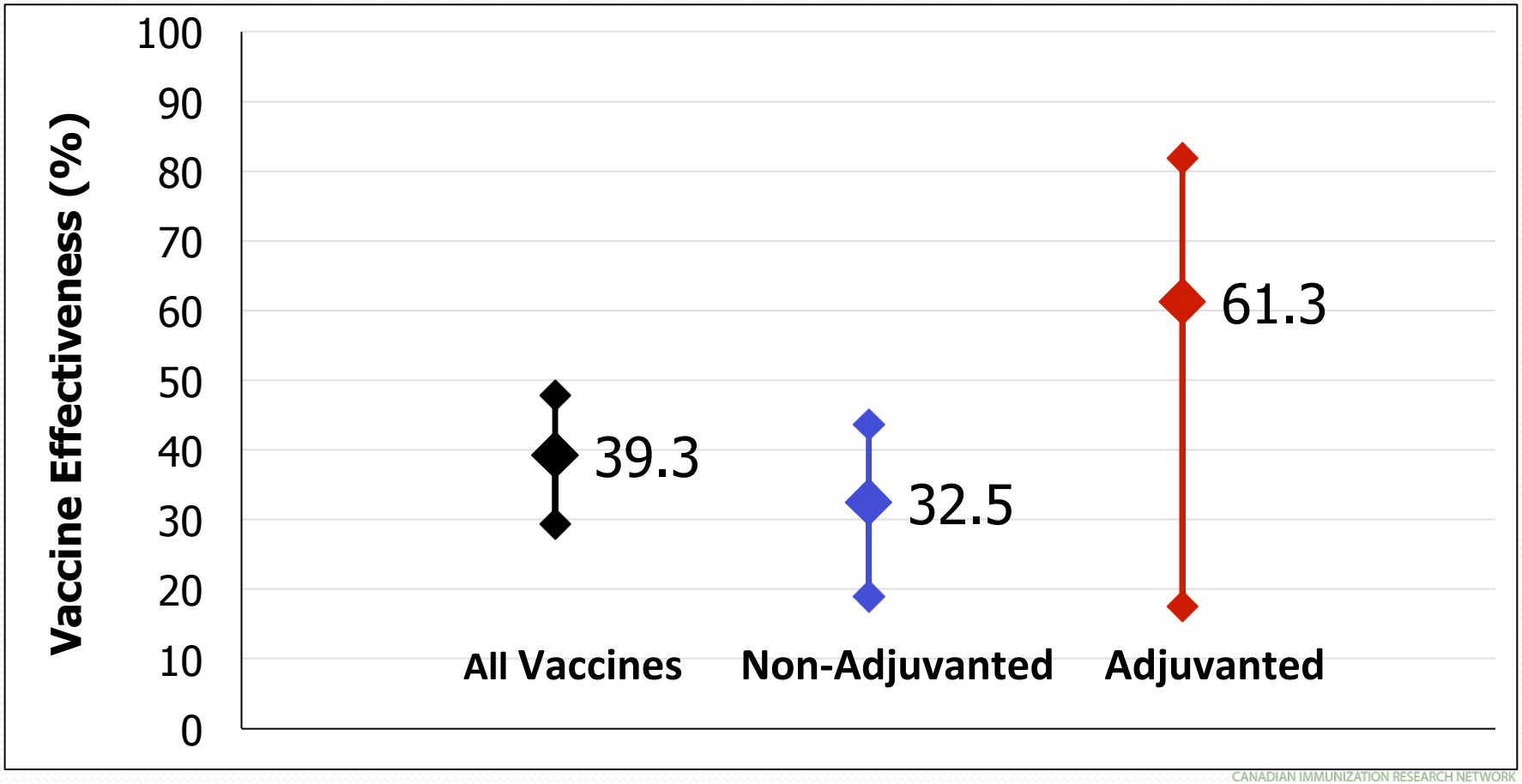
Clinical characteristics of cases and controls ≥65y (pooled 2011-2014)

Variable		Cases 2078 (41.42%)	Controls 2939 (58.58%)	P Value[1]
Sex	Male	1000 (48.12%)	1355 (46.10%)	0.15
Age	65-74 75 and older	674 (32.44%) 1404 (67.56%)	1063 (36.17%) 1876 (63.83%)	0.006*
Was vaccinated in current season	Yes	1244 (59.80%)	2126 (72.34%)	<0.001*
BMI[2]	Underweight <18.5	117 (5.63%)	190 (6.46%)	0.0006*
	Normal weight 18.5-24.99	740 (35.61%)	1073 (36.51%)	
	Overweight 25-29.99	598 (28.47%)	808 (27.49%)	
	Obese 30-40	327 (15.74%)	561 (19.09%)	
	Very obese >40	39 (1.88%)	108 (3.67%)	
Past or current smoker[2]	Yes	1029 (49.52%)	1744 (59.34%)	<0.001*
Medical comorbidities	Yes	2010 (96.73%)	2864 (97.45%)	0.13
# of medications prior to admission[2]	0-4	529 (25.46%)	506 (17.22%)	<0.001*

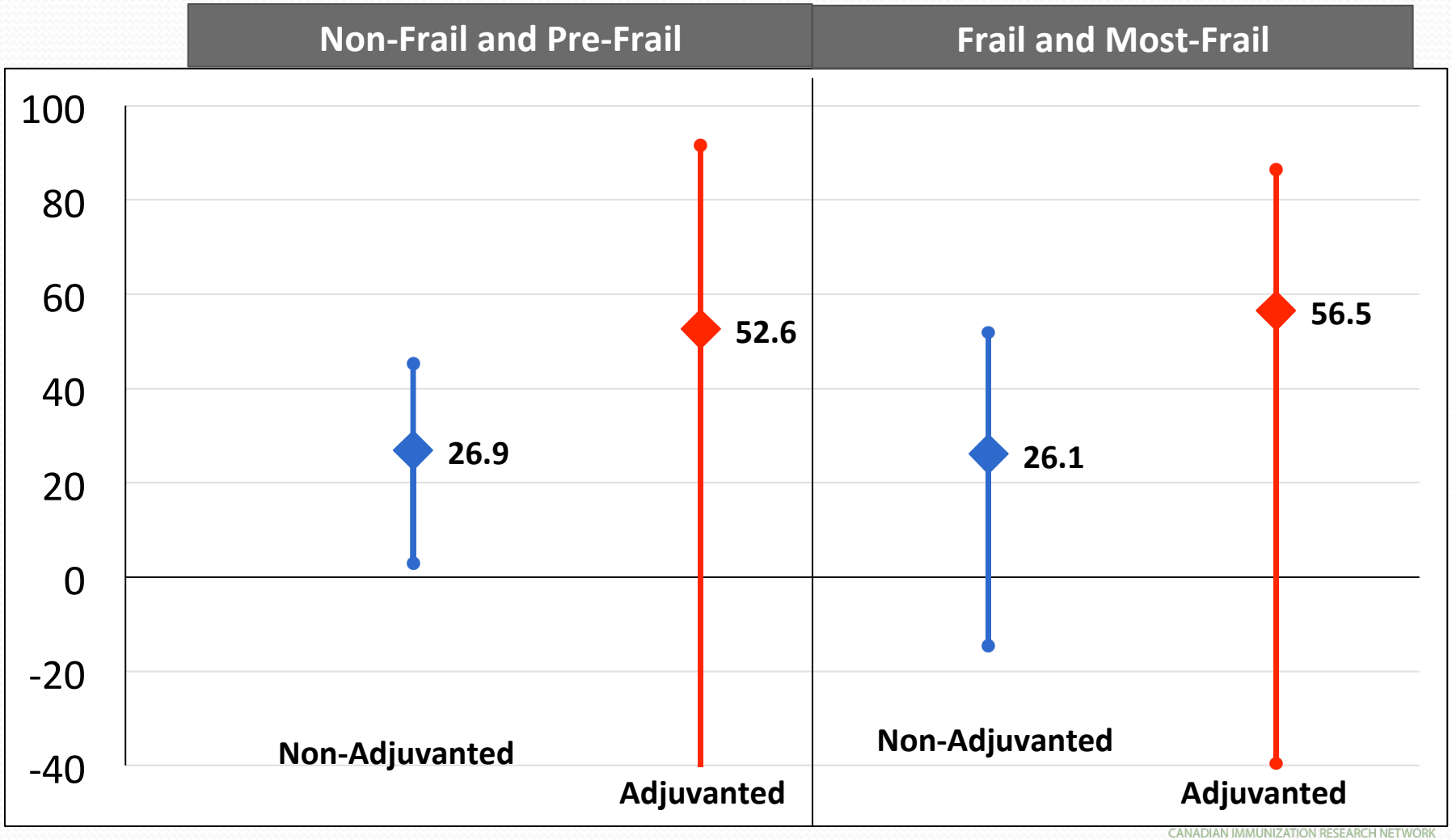
Clinical characteristics of patients ≥65y who received non-adj TIV vs adj TIV (2011-2014)

Variable		Adjuvanted (Fluad®)[1] N=284	Non-Adjuvanted [1] N=2049	P Value[2]
Sex	Male	127 (44.72)	1002 (48.90%)	0.18
Age	Mean Age Median Range	83.58 85.0 65-105	79.85 80.0 65-102	<0.0001*
Was vaccinated in previous season[3]	Yes	197 (69.37%)	1646 (80.33%)	0.17
Past or current smoker[3]	Yes	133 (46.83%)	1205 (58.81%)	0.002*
Medical comorbidities	Yes	277 (97.54%)	2007 (97.95%)	0.64
Antiviral use prior to admission	Yes	11 (3.87%)	17 (0.83%)	<0.0001*
Number of medications prior to admission[3]	0-4 4+	45 (15.85%) 237 (83.45%)	332 (16.20%) 1704 (83.16%)	0.88
Admission from a long-term care facility[3]	Yes	163 (57.39%)	116 (5.66%)	<0.0001*
Frailty index prior to admission[3]	Non-Frail	11 (3.87%)	311 (15.18%)	<0.0001*
	Pre-Frail	43 (15.14%)	857 (41.83%)	
	Frail	126 (44.37%)	716 (34.94%)	
	Most Frail	56 (19.72%)	55 (2.68%)	

VE of vaccine types for preventing influenza-related hospitalizations in patients ≥65y, 2011-2014



VE of vaccine types for preventing influenza-related hospitalizations by level of frailty



Summary

- Overall VE of all influenza vaccines was ~39% for preventing influenza-related hospitalizations in patients ≥65y enrolled in the SOS Network between 2011-2014
- VE of adj-influenza vaccine was 61.3% in patients ≥65y; representing an increase of ~30% over non-adj influenza vaccine (difference was not statistically significant)
- VE of adj-influenza vaccine for preventing influenza-related hospitalizations was good (61.3%) in this elderly, frail population, with a large proportion of patients admitted from long-term care
- Appears to be a trend of increased protection from adj-influenza vaccine but should be interpreted cautiously- 95% CIs were wide and overlapped the non-adj and all-vaccines VE estimates

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Conclusions

- Our findings demonstrate a possible trend of increased VE of adjuvanted influenza vaccine relative to non-adjuvanted vaccines in an elderly, hospitalized, and frail population

- Continued monitoring of VE for adjuvanted as well as high dose influenza vaccines in future study years is necessary to inform influenza immunization policy in Canada

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Impact of prior season influenza vaccination on vaccine effectiveness

Michaela Nichols-Evans, MSc
Epidemiologist, CIRN SOS Network

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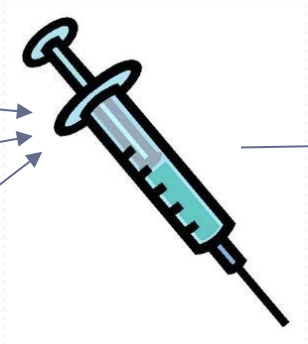
Overview

Human Factors (Age, Comorbidities)

Influenza Strain Factors (Mismatch)

Vaccine Factors (immunogenicity)



Vaccine Effectiveness

- Variability in influenza vaccine effectiveness (VE) estimates between seasons and strains may not be fully explained by these factors
- Prior vaccination has emerged as a factor that may impact subsequent VE
- **Antigenic Distance Hypothesis (1)**: Could be negative interference from prior immunization when the antigenic distance is small between successive vaccine components but large between vaccine and circulating strains

(1)Smith, D. J., Forrest, S., Ackley, D. H., & Perelson, A. S. (1999). Variable efficacy of repeated annual influenza vaccination. *Proceedings of the National Academy of Sciences of the United States of America*,*96*(24), 14001–14006.

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Overview

- Several recent observational studies (2,3,4) have shown an impact of prior seasonal influenza vaccination on subsequent influenza vaccine effectiveness
- There was a need to assess if this impact was present within Canada's influenza hospitalization network
- We looked at this impact over 4 influenza seasons in Canada, which enabled seasonal comparisons

2. Skowronski DM, Chambers C, Sabaiduc S, De Serres G, Winter AL, Dickinson JA, et al. A perfect storm: Impact of genomic variation and serial vaccination on low influenza vaccine effectiveness during the 2014-15 season. Clin Infect Dis. 2016 Mar 29.
3. Skowronski DM, de Serres G, Crowcroft NS, Janjua NZ, Boulianne N, Hottes TS, et al. Association between the 2008-09 seasonal influenza vaccine and pandemic H1N1 illness during spring-summer 2009: Four observational studies from Canada. PLoS Med. 2010 /;7(4).
4. McLean HQ, Thompson MG, Sundaram ME, Meece JK, McClure DL, Friedrich TC, et al. Impact of repeated vaccination on vaccine effectiveness against influenza A(H3N2) and B during 8 seasons. Clin Infect Dis. 2014 Nov 15;59(10):1375-85.

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VE calculations

- Cases and controls were then divided into 4 categories of vaccination status:
  - (1) Vaccinated in neither season (REFERENT)
  - (2) Vaccinated in current season only
  - (3) Vaccinated in both current and prior season
  - (4) Vaccinated in prior season only

- VE = 1-OR x 100%
  - Unadjusted & Adjusted (conditional logistic regression with backward stepwise selection; $p \leq 0.1$)
  - VE point estimates and 95% CI presented

*All VE analyses are post-hoc

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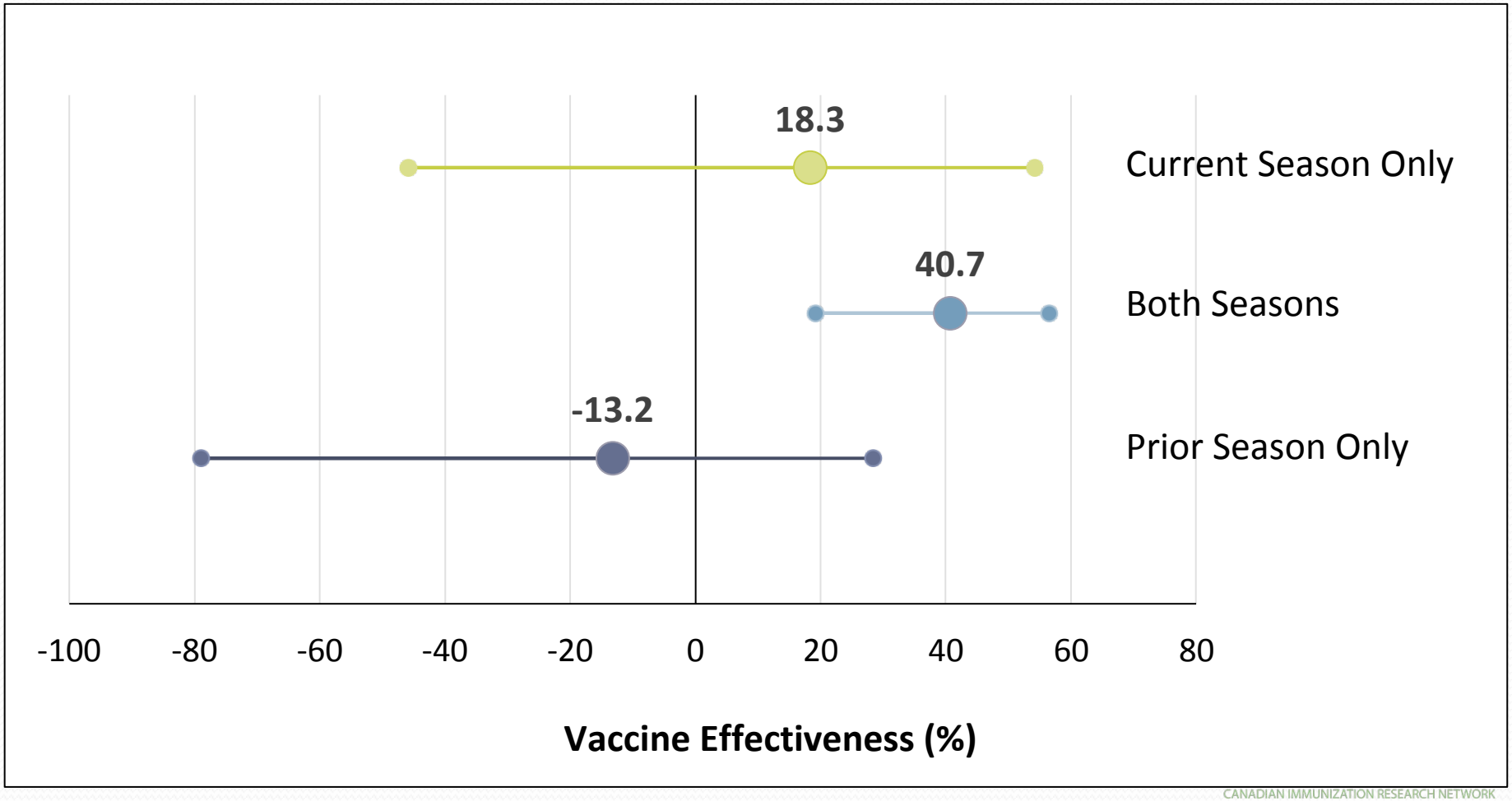
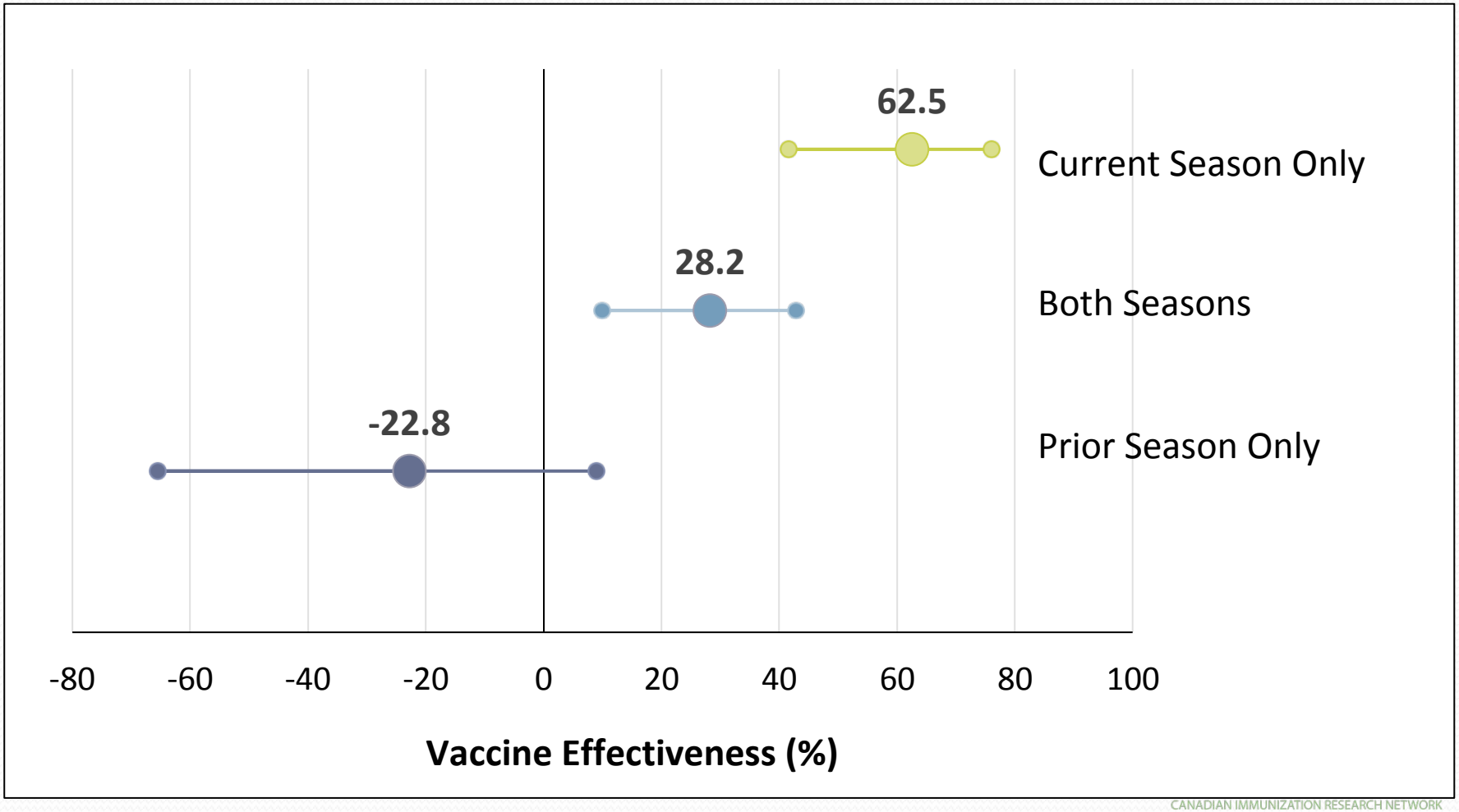
Cases and Controls per season in SOS Network

Season	# of Cases	# of Controls	Dominant circulating strain(s)	Notes on Season/Vaccine
2011/2012	528	835	Influenza B (Yamagata)	B-lineage strain included in the TIV did not matching the B strain circulating
2012/2013	1292	1573	H3N2	Dominant H3N2 season (73% of SOS subtyped cases)
2013/2014	1574	2152	H1N1/ Influenza B (Yamagata)	Mixed H1N1, influenza B season
2014/2015	1262	1538	H3N2	Mismatch of H3N2 included in TIV to H3N2 strain circulating

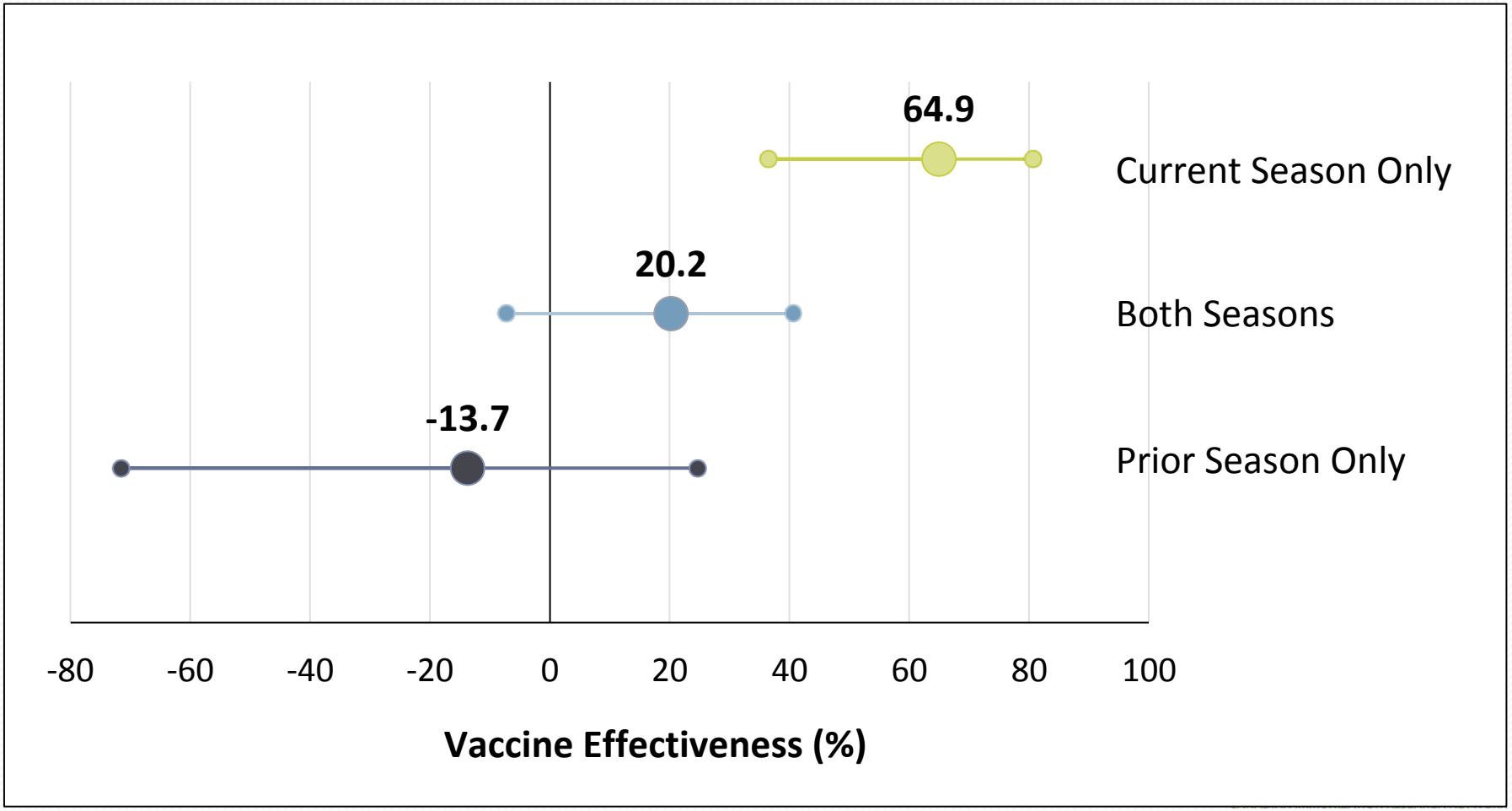
2011/2012 Season- Overall



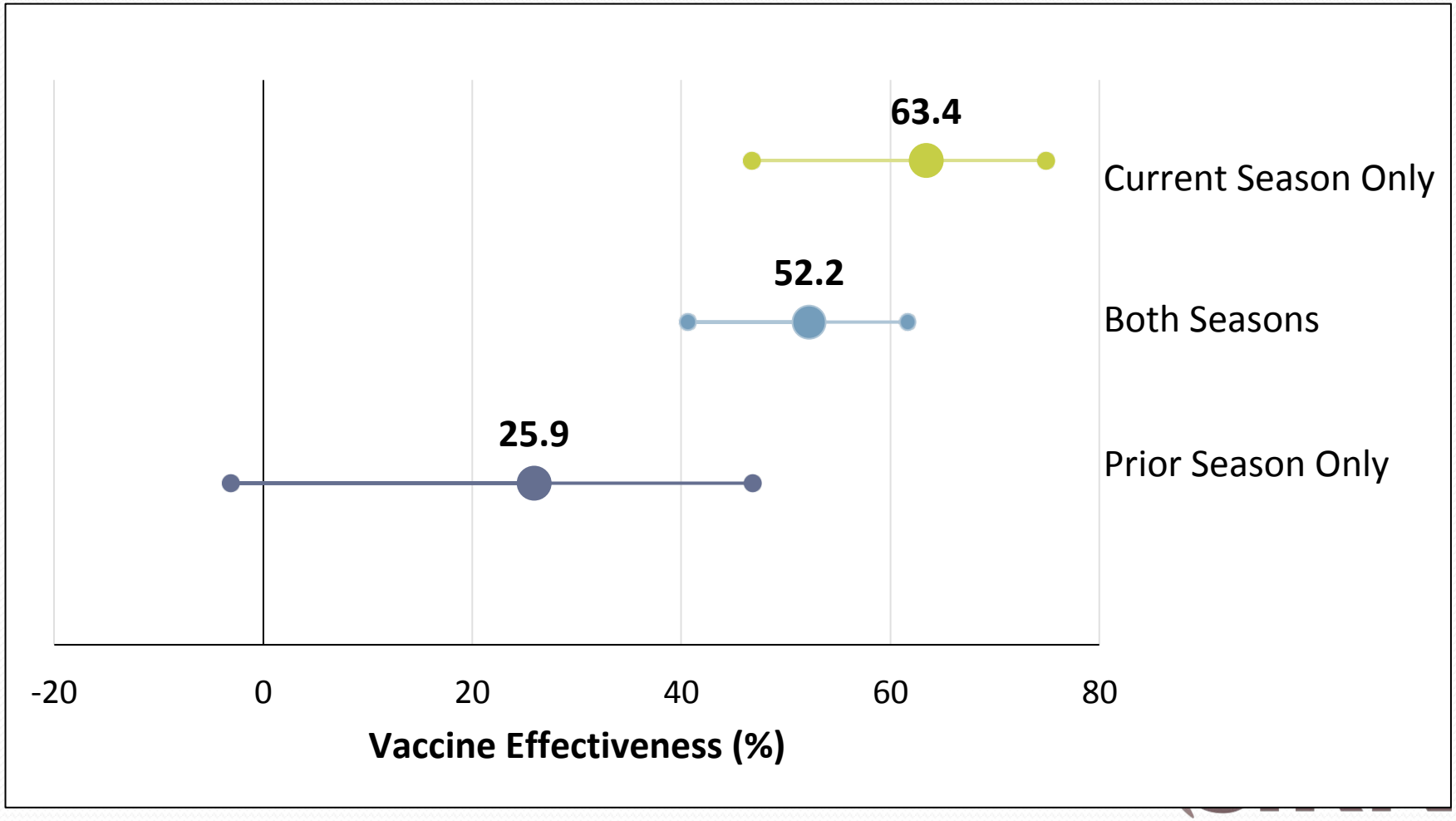
2012/2013 Season-Overall



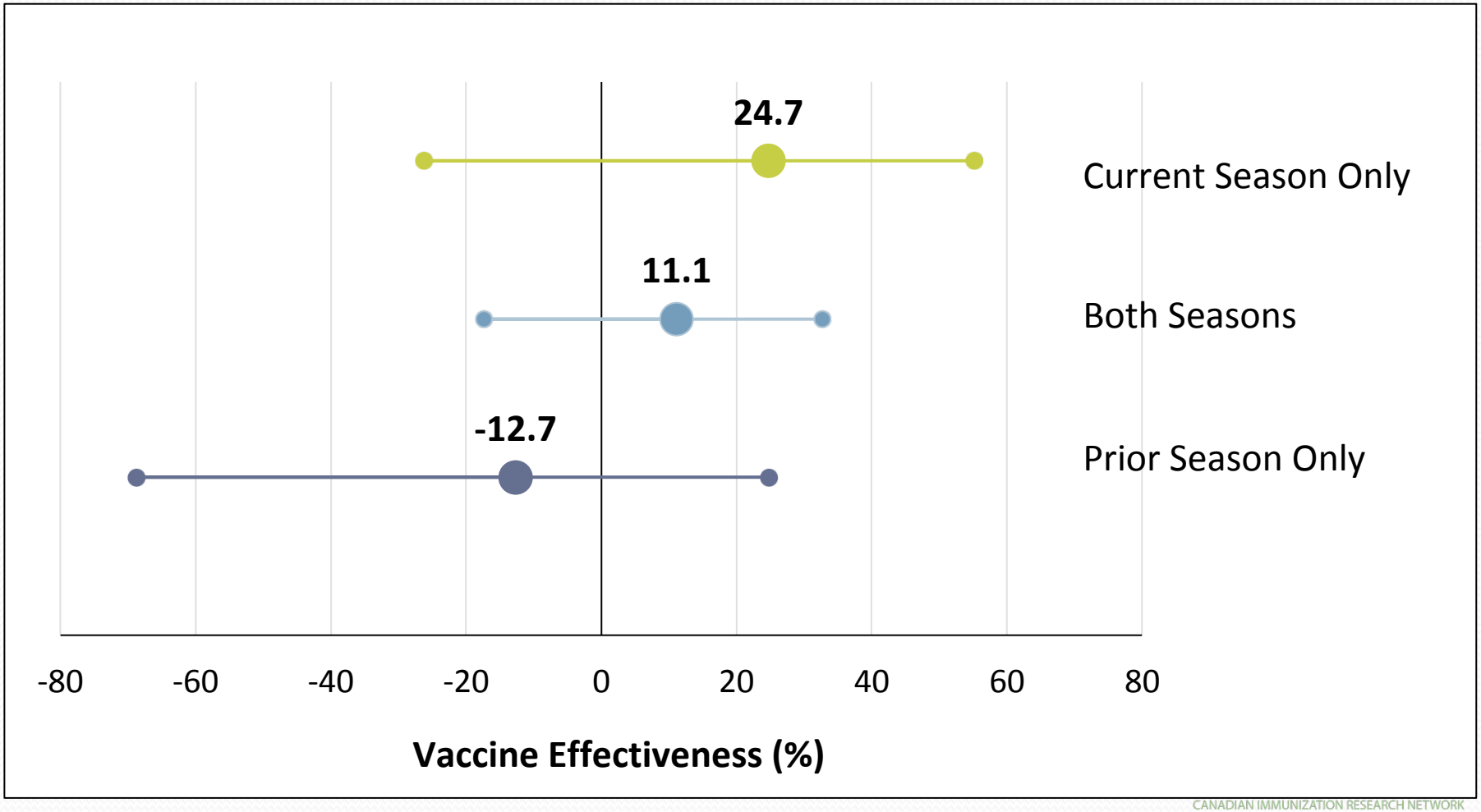
2012/2013 Season- Age ≥ 65



2013/2014 Season-Overall



2014/2015 Season-Overall



Summary

	2011/2012 Season	2012/2013 Season	2013/2014 Season	2014/2015 Season
Dominant Strain	Influenza B	H3N2	H1N1	H3N2
Vaccine Composition in relation to previous year	Same	Updated B Updated H3N2 Same H1N1	Updated B Updated H3N2 Same H1N1	Same
Mismatch	YES- B component	No	No	YES- H3N2 component
Effect	Non-signif Positive	**Negative**	Non-signif Negative	Non-signif Negative

Conclusions

- There was varied impact of prior vaccination on subsequent VE observed from season to season and between age groups
  - Largest impacts were seen in the 2012/2013 season where influenza A H3N2 was the dominant circulating strain
- Unmeasured bias by indication cannot be ruled out
- Current-only and both-seasons VE was always better than prior-only VE, indicating receiving annual influenza vaccination is still providing added protection over not receiving annual influenza vaccination

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What else can we do? The role of antivirals in the treatment of influenza

Zachary Shaffelburg, MD candidate 2018

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Does treatment with antivirals improve outcomes?What about timing?

- WHO and others recommend that treatment with neuraminidase inhibitors should be initiated as early as possible for any patient with confirmed or suspected influenza who is hospitalized, has severe illness, or among the risk groups targeted for vaccination.
- Clinicians often hesitate to use antivirals, especially >2 days after symptom onset.

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Clinical characteristics of hospitalized patients with laboratory-confirmed influenza (11/12, 12/13, 13/14 pooled)

Clinical Characteristics	
Characteristics	**All patients (n=4862) n (%)**
Age median (range)	70 (16-105)
16-49y	892 (18)
50-64y	1061 (22)
65-75y	928 (19)
>75 y	1981 (41)
Female	2535 (52)
≥1 comorbidities	4319 (89)
Pregnant	118 (2)
Smoker	2318 (48)
Antiviral use prior to outcome (PTO)	2642 (54)
Time from symptom onset to antiviral start	Mean: 4.21d, Range: 0-21d
Current season vaccine	1850 (38)
Influenza A	3484 (72)
Influenza B	1375(28)

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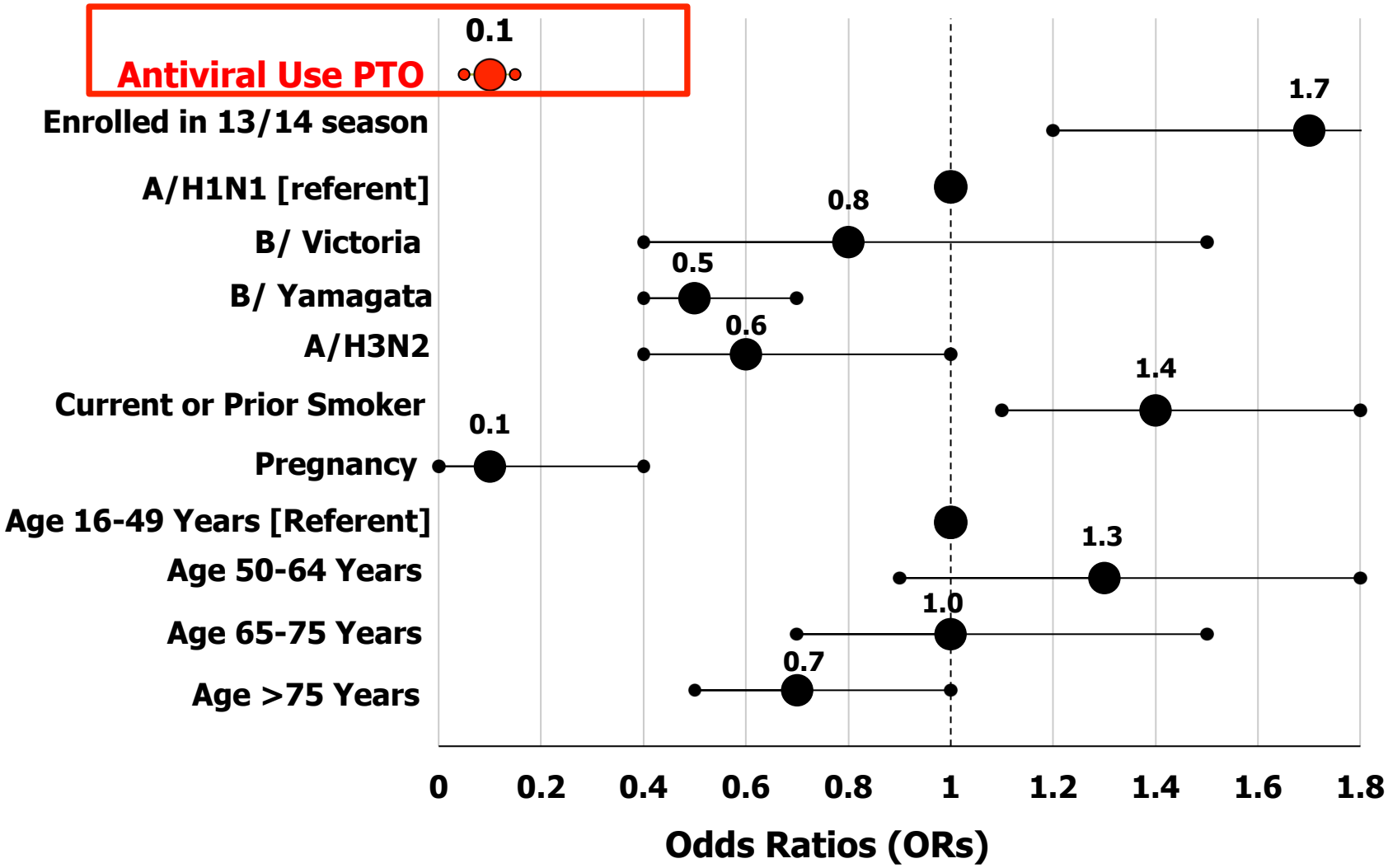
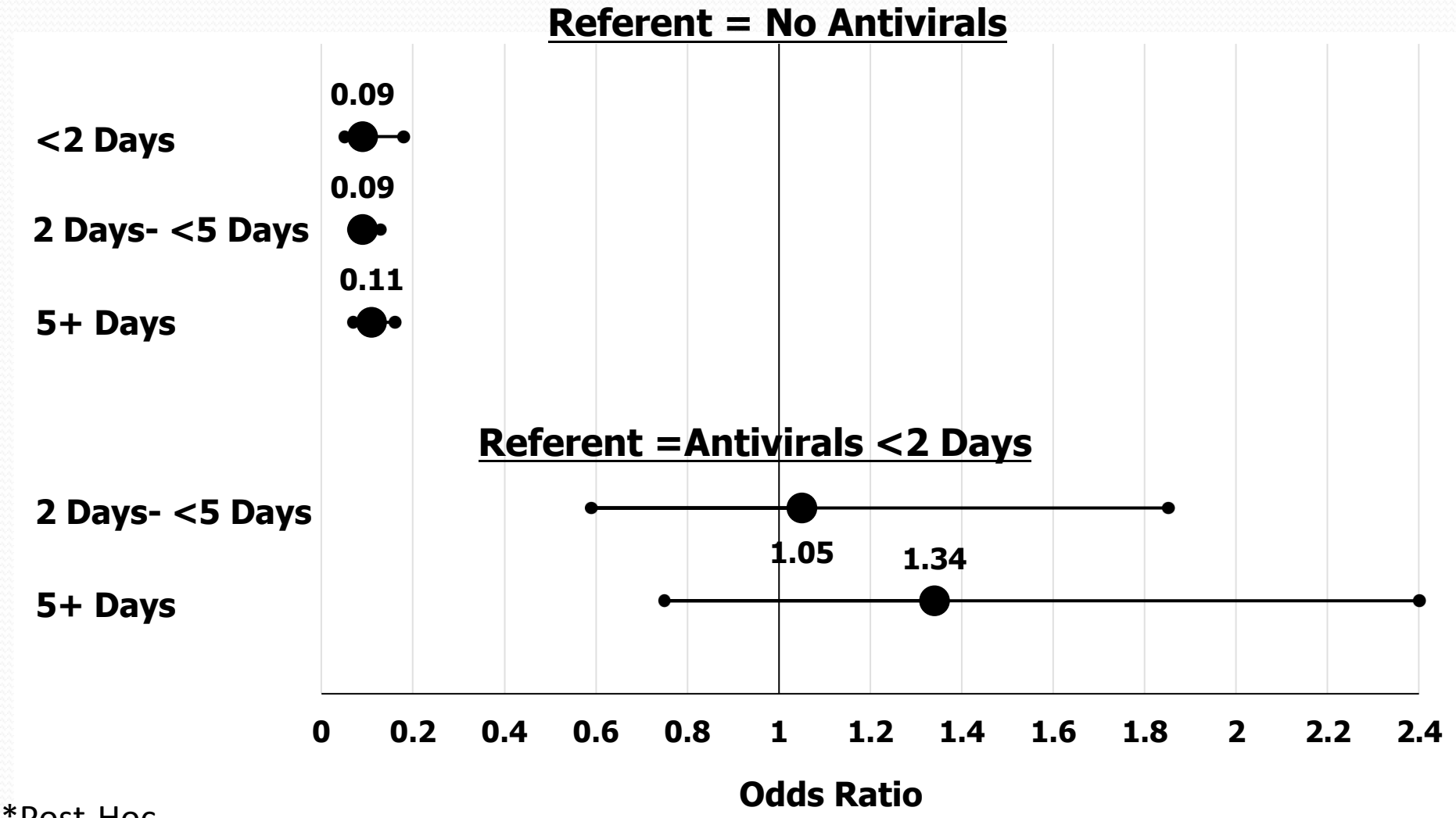
ORs of risk factors for an outcome of ICU admission or mechanical ventilation in hospitalized patients with laboratory-confirmed influenza



Even after 5+ days, antiviral use is still beneficial in reducing ICU/mechanical ventilation



*Post-Hoc

ORs of risk factors for an outcome of ICU and/or Mech Ventilation in hospitalized patients with laboratory-confirmed influenza A

Variable	OR (95% CI)	P value
Pregnant	0.1 (0.0-0.4)	0.006
Smoker	1.4 (1.1-1.8)	0.018
Antiviral use PTO	0.10 (0.08-0.14)	<0.001
Hospitalized in 13/14 Season	1.9 (1.1-3.4)	0.020

ORs of risk factors for an outcome of ICU and/or Mech ventilation in hospitalized patients with laboratory-confirmed influenza B

Variable	OR (95% CI)	P value
Smoker	1.8 (1.1-2.7)	0.012
Antiviral use PTO	0.14 (0.1-0.2)	<0.001

So what does frailty have to do with influenza?

Figure credit: Janet McElhaney

Adjusting for frailty is important in measuring influenza vaccine effectiveness (Frailty Bias)

Understanding the relationship between influenza and frailty is critical to understanding the true burden of influenza

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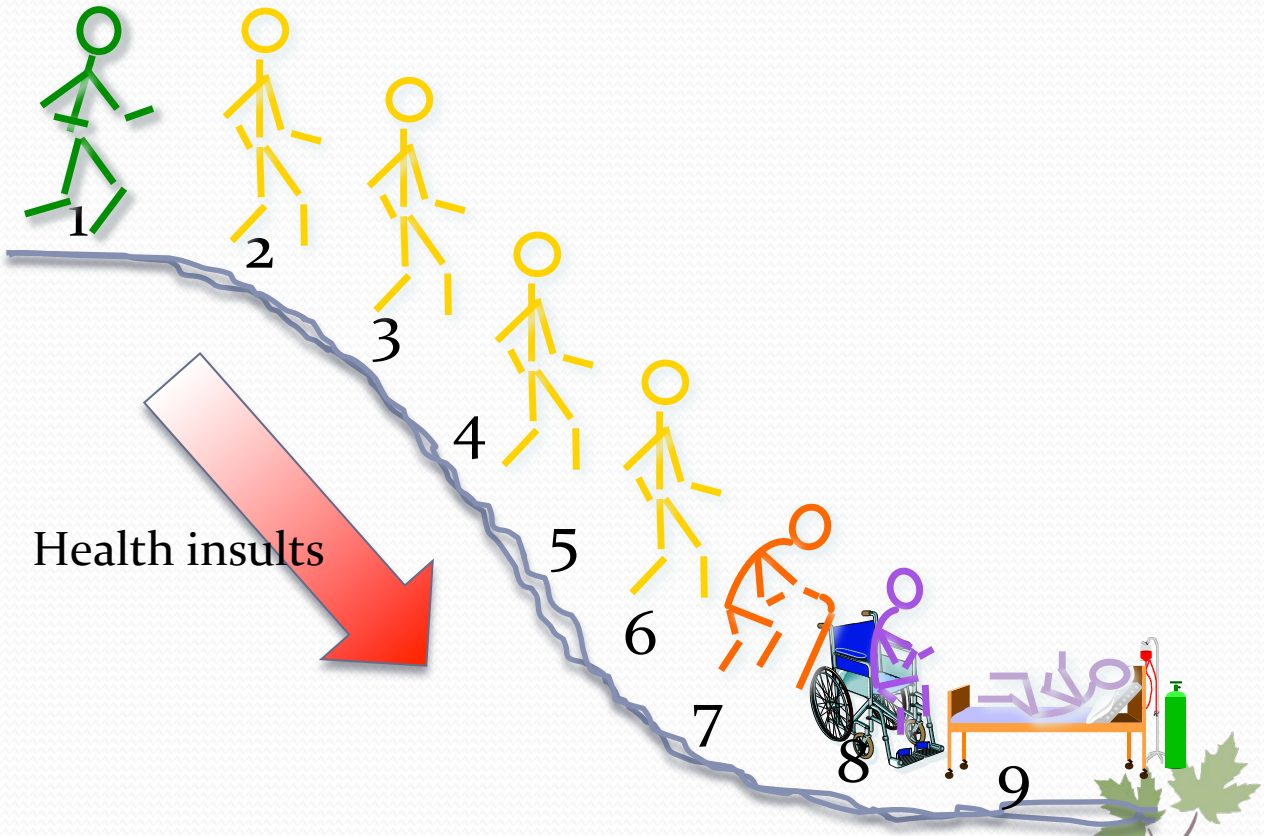
NOT Adding Life to Years



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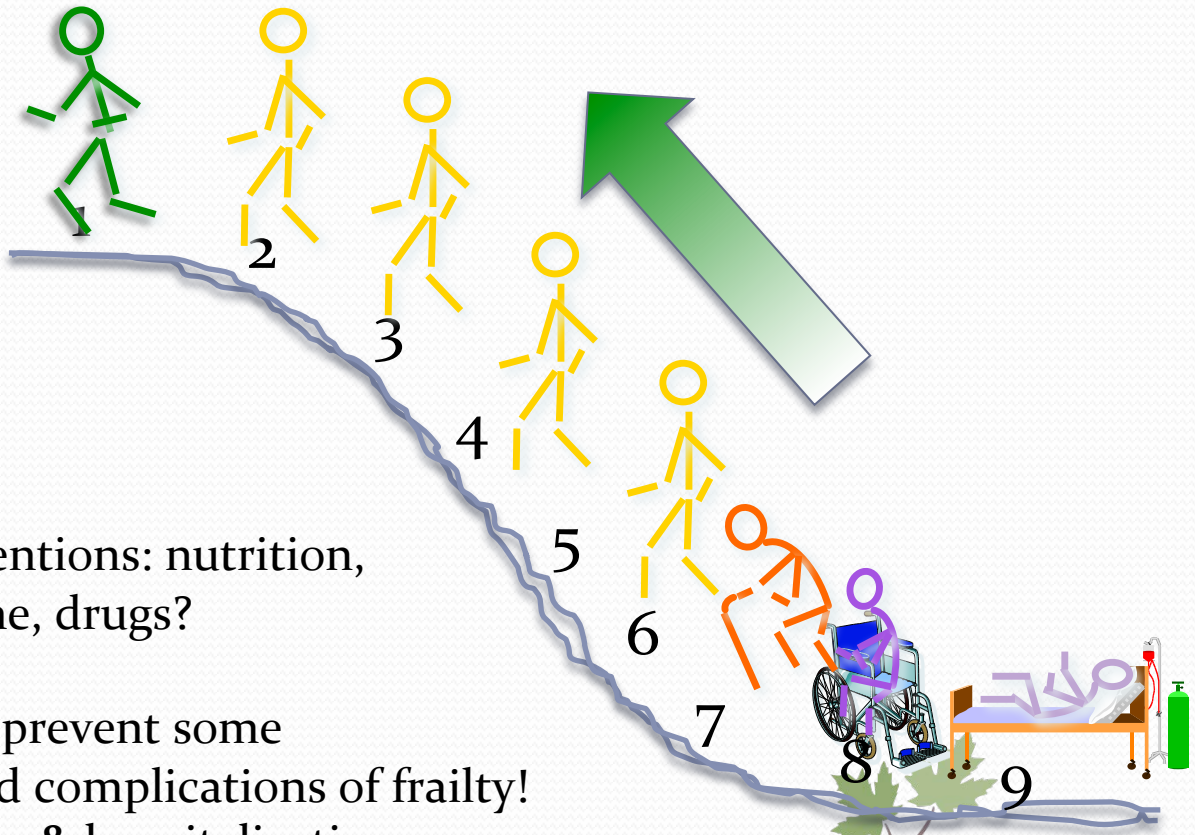
Adding Life to Years: can frailty be prevented?



Candidates:

- Exercise
- Social integration
- Physiological interventions: nutrition, inflammation, immune, drugs?
- Good care?
    - * At least we can prevent some consequences and complications of frailty!
    - * Avoidable illness & hospitalizations

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Acknowledgements

Many thanks to the SOS Network team!
Melissa Andrew, Janet McElhaney, Ardith Ambrose, Donna MacKinnon-Cameron, Christina Wang, Peter Ye & the dedicated SOS Network surveillance monitors

QUESTIONS & DISCUSSION

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