Influenza in high risk groups: Understanding the importance of frailty, function and immune aging

Melissa K. Andrew
Associate Professor of Medicine (Geriatrics) and Community Health & Epidemiology, Dalhousie University, Halifax, Canada

MENA Stakeholders Meeting
Cairo, Egypt
April 10-11, 2018

Disclosures

- Grant funding
  - Collaborative Research Agreements with GSK, Pfizer, Sanofi with the Canadian Institutes of Health Research, Public Health Agency of Canada and the Canadian Frailty Network
- No personal financial conflicts of interest

Overview

- Guidelines for high risk populations
- Let us take a step back and consider:
  - What makes people high risk for influenza?
  - Higher attack rates?
  - Poor immune responses (to vaccine and to illness)?
  - Sub-optimally recognized and treated illness
    - Atypical presentation of illness has implications for both surveillance and clinical practice
  - Poor outcomes (over short and long terms)?
    - Complications, persistent deficits
  - All of these?

  - Can we find a unified understanding?

Who is at high risk?
WHO Seasonal Influenza Fact Sheet

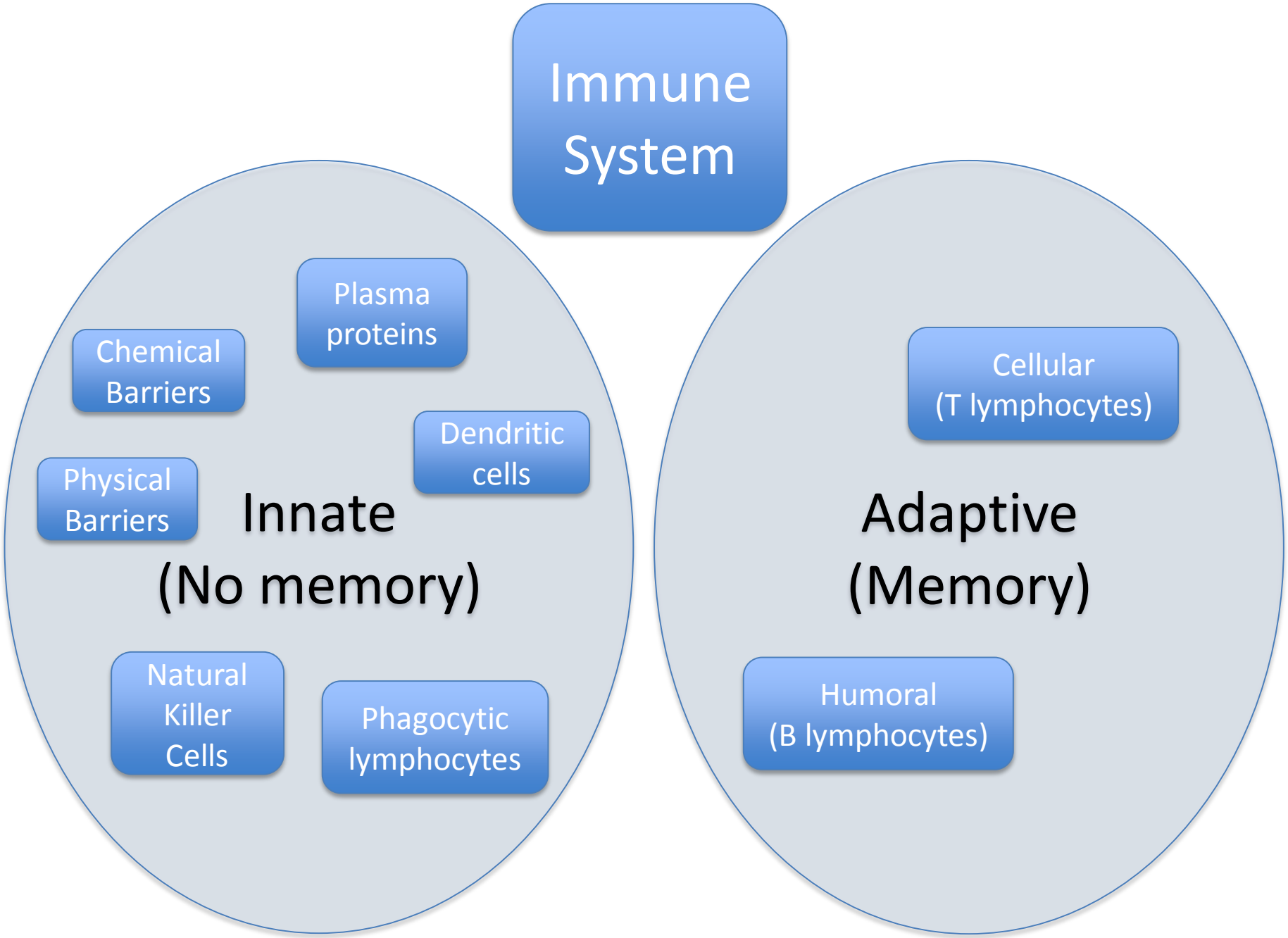
- All age groups can be affected but there are **groups that are more at risk** than others.
- People at greater risk of severe disease or complications when infected are:
  - pregnant women
  - children under 59 months
  - the elderly
  - individuals with chronic medical conditions (such as chronic cardiac, pulmonary, renal, metabolic, neurodevelopmental, liver or hematologic diseases)
  - individuals with immunosuppressive conditions (such as HIV/AIDS, receiving chemotherapy or steroids, or malignancy)
- Health care workers are at high risk acquiring influenza virus infection due to increased exposure to the patients and risk further spread particularly to vulnerable individuals

http://www.who.int/mediacentre/factsheets/fs211/en/

WHO recommends annual influenza vaccination for:

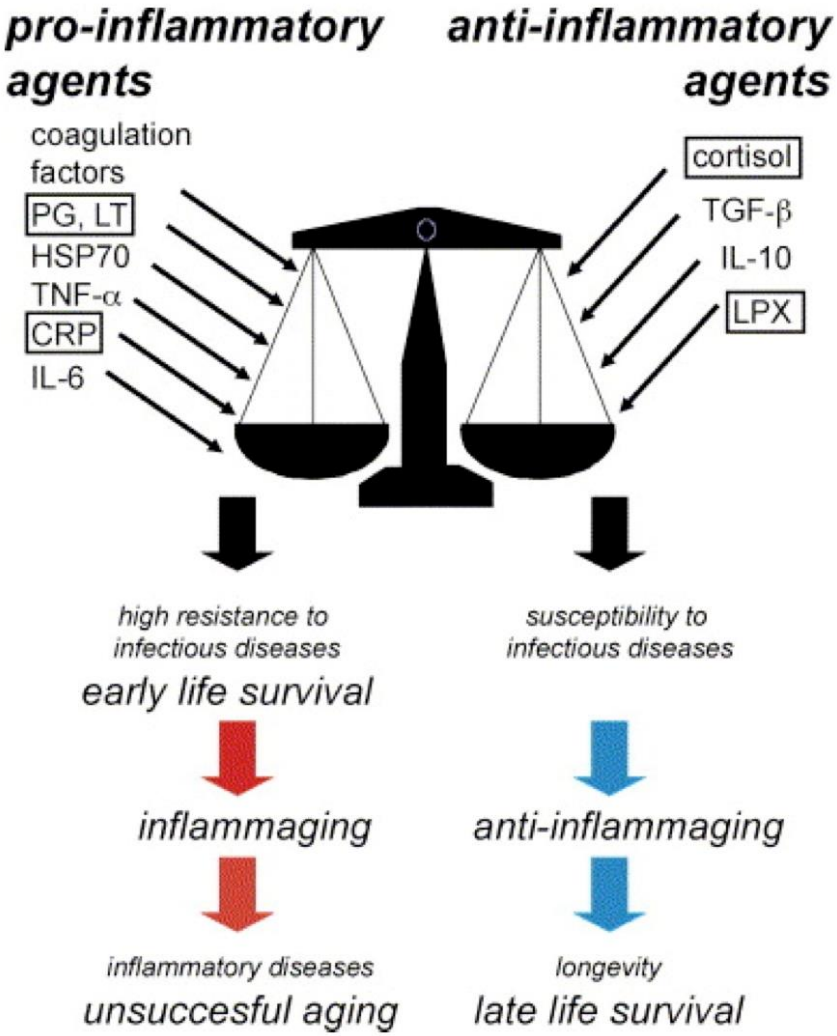
- pregnant women at any stage of pregnancy
- children aged between 6 months to 5 years
- elderly individuals (aged more than 65 years)
- individuals with chronic medical conditions
- health-care workers

http://www.who.int/mediacentre/factsheets/fs211/en/


Immune System
Plasma proteins
Chemical Barriers
Dendritic cells
Physical Barriers
Innate
(No memory)
Natural Killer Cells
Phagocytic lymphocytes
Cellular
(T lymphocytes)
Adaptive
(Memory)
Humoral
(B lymphocytes)

Vitality, frailty and immune aging

Th1



Th2

Franceschi C et al. Mech Age Dev 128: 92-105, 2007.

Frailty is a new way to think about vulnerability to influenza

- What do high-risk groups how have in common when it comes to influenza?
- The answer is vulnerability to worse outcomes than would be expected for a usual risk group
- One way we know quite a lot about measuring vulnerability is frailty

So what does frailty have to do with influenza?

Figure credit: Janet McElhaney

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 outcomes.

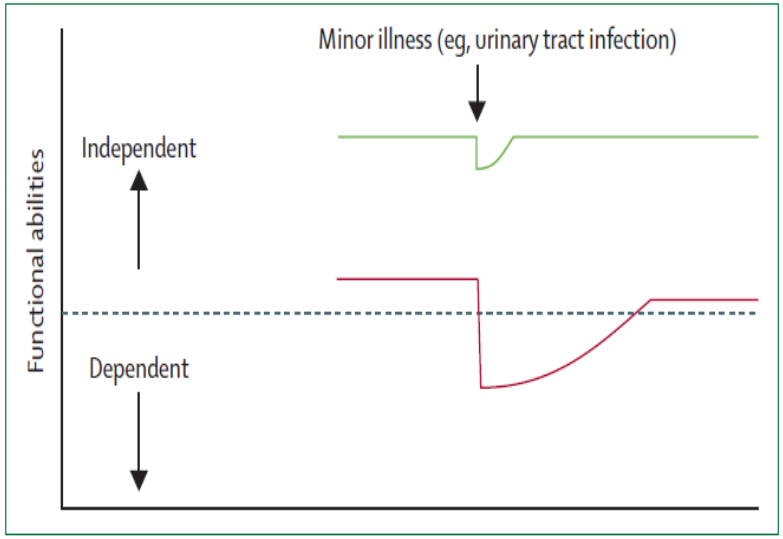
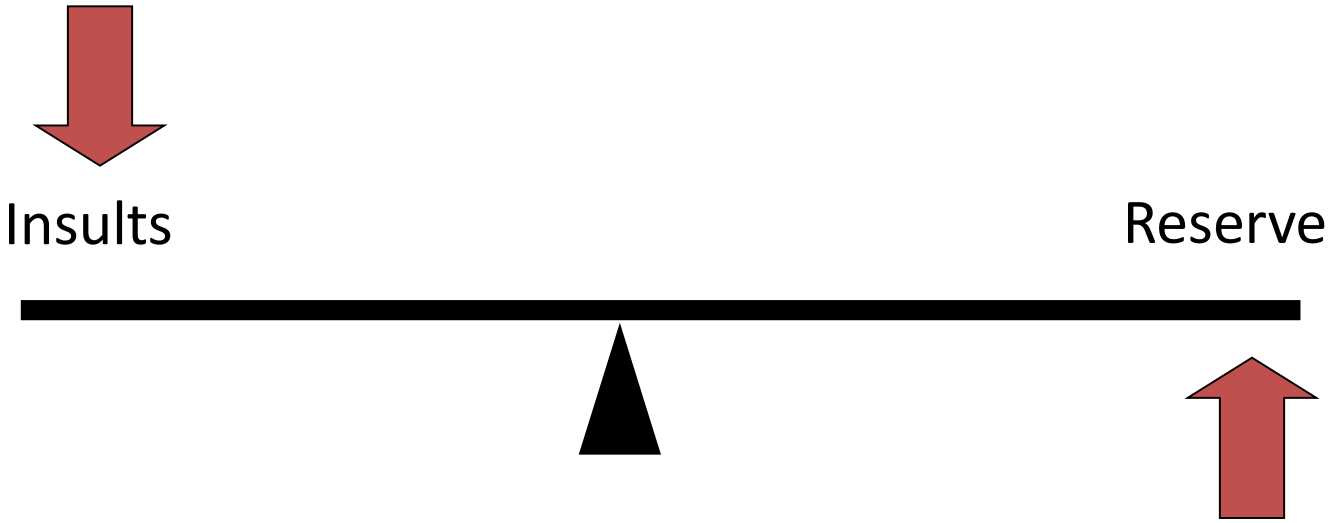


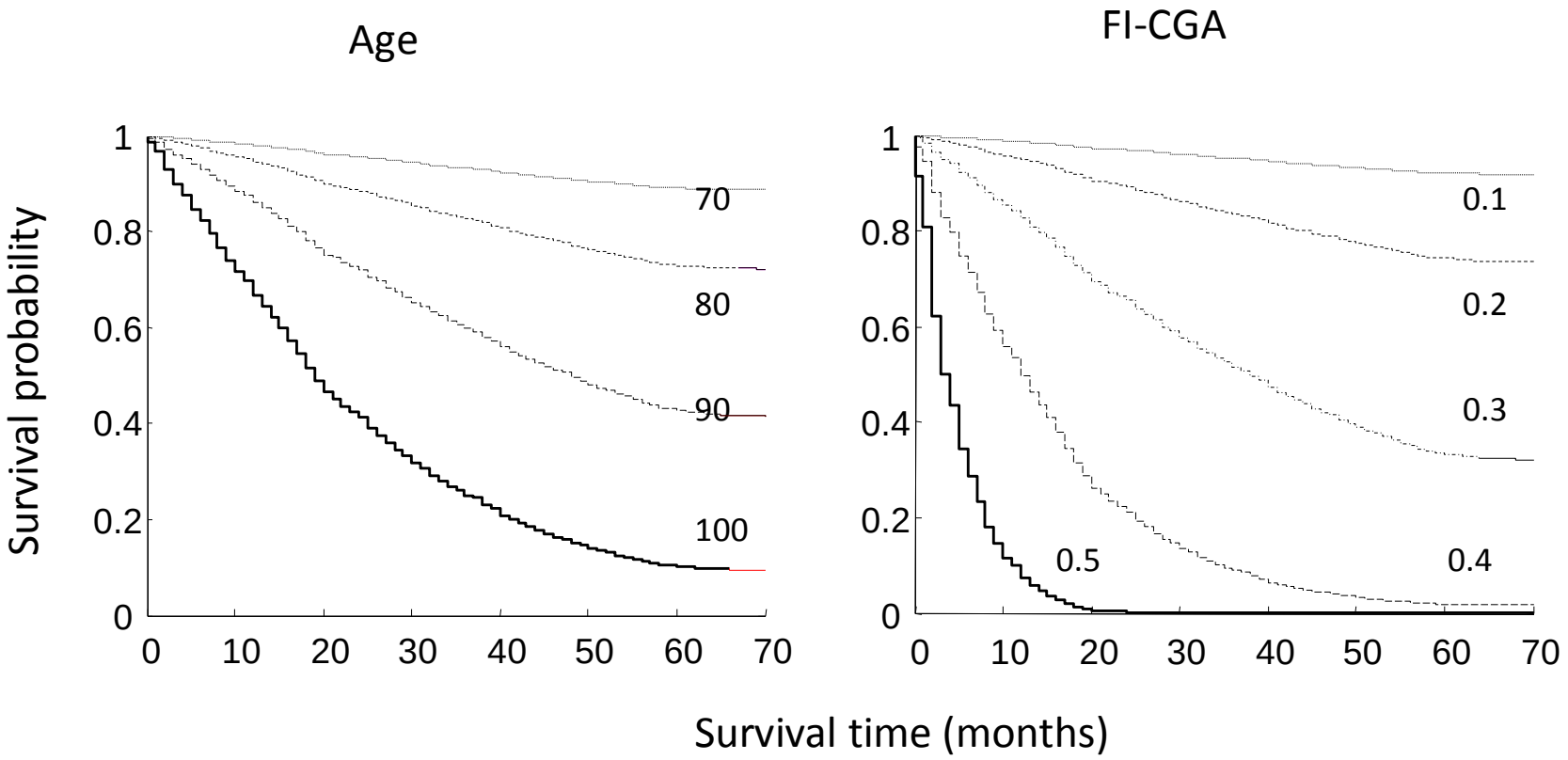
Figure 1: Vulnerability of frail elderly people to a sudden change in health status after a minor illness

Frailty: it comes down to

Vulnerability



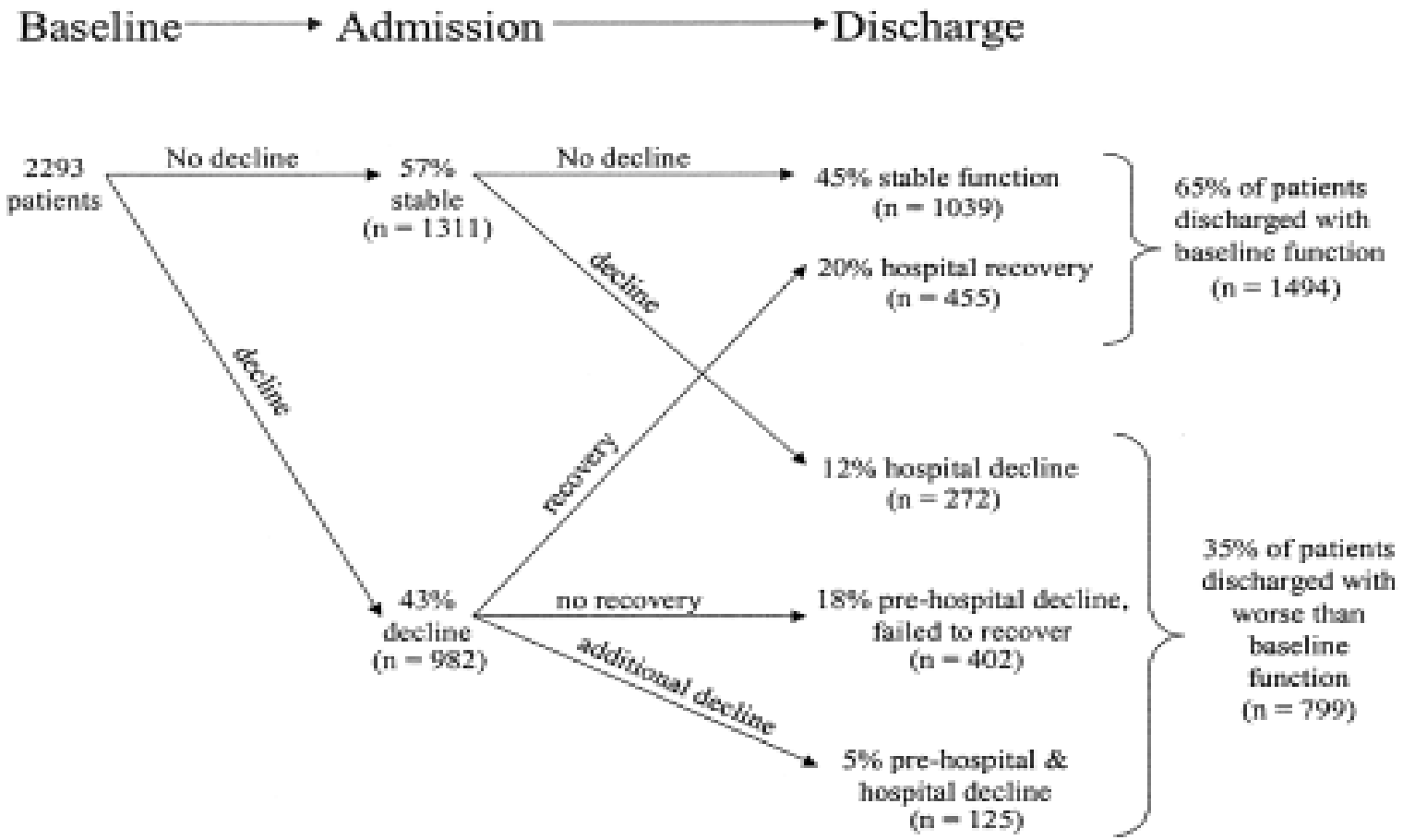
A frailty index based on a Comprehensive Geriatric Assessment (FI-CGA) better stratifies 70-month survival than does age



DALHOUSIE UNIVERSITY
Inspiring Minds

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

Functional loss is common when older people are in hospital



Covinsky JAGS 2003

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

Can influenza vaccines be improved for high risk groups?

- Adjuvanted
- High Dose
- Recombinant

For a recent review, see: Mohammad Bosaeed & Deepali Kumar (2018): Seasonal influenza vaccine in immunocompromised persons.
Human Vaccines & Immunotherapeutics, DOI: 10.1080/21645515.2018.1445446

Adjuvanted subunit vaccine

- MF59 adjuvant (oil-in-water emulsion of squalene) designed to potentiate immune response
- Greater immune response in older adults, including frail Nursing Home residents
- No RCTs comparing adjuvanted with standard vaccine, though meta-analysis of observational studies found increased effectiveness in preventing:
  - Lab-confirmed influenza (OR 0.37, 95% CI, 0.14-0.96)
  - Hospitalization (risk ratio 0.75, 95% CI 0.57-0.98)
  - Influenza-like-illness in LTCF (VE 94%, 95% CI: 35-97%)
  - Especially with underlying cardio-resp comorbodities
  - Reduced admissions for acute coronary syndrome (VE 87%, 95% CI: 35-97%) and stroke (VE 93%, 95% CI: 52-99%)

Domnich, A et al. Vaccine 2017; 35(4):513-520.
PMID: 28024956

High dose vaccine

- Contains 4x the dose of each antigen
- Targeting a more robust immune response
- N=31,989 age 65+
  - relative efficacy 24.1, 95% CI 9.7-36.5 vs. std dose
- Meta-analysis in older people
  - RR 0.76, 95% CI 0.65-0.90
- Cluster RCT in Long Term Care found reduced hospital admission with respiratory illness
  - RR 0.873, 95% CI, 0.776-0988

DiazGranados CA, et al. N Engl J Med. 2014 Aug 14;371(7):635-45.
Wilkonsin K, et al. Vaccine. 2017 May 15;35(21):2775-2780.
Gravenstein S, et al. Lancet Respir Med. 2017 Sep;5(9):738-746.

High dose vaccine has been found to be cost saving vs. regular dose

Probabilistic sensitivity analysis: 93% likely to be cost saving

- Single payer perspective (USA)
- Standard dose was
  - $116 higher for all
  - $106 higher for >= 1 comorbidity
  - $12 higher for age 75+

- Societal perspective (USA)
- Standard dose was
  - $128 higher for all
  - $119 higher for >= 1 comorbidity
  - $22 higher for age 75+

Chit A, et al. Lancet Infect Dis. 2015 Dec;15(12):1459-66

Also cost saving in a Canadian study

Becker DL, **et al.** Hum Vaccin Immunother. 2016 Dec;12(12):3036-3042.

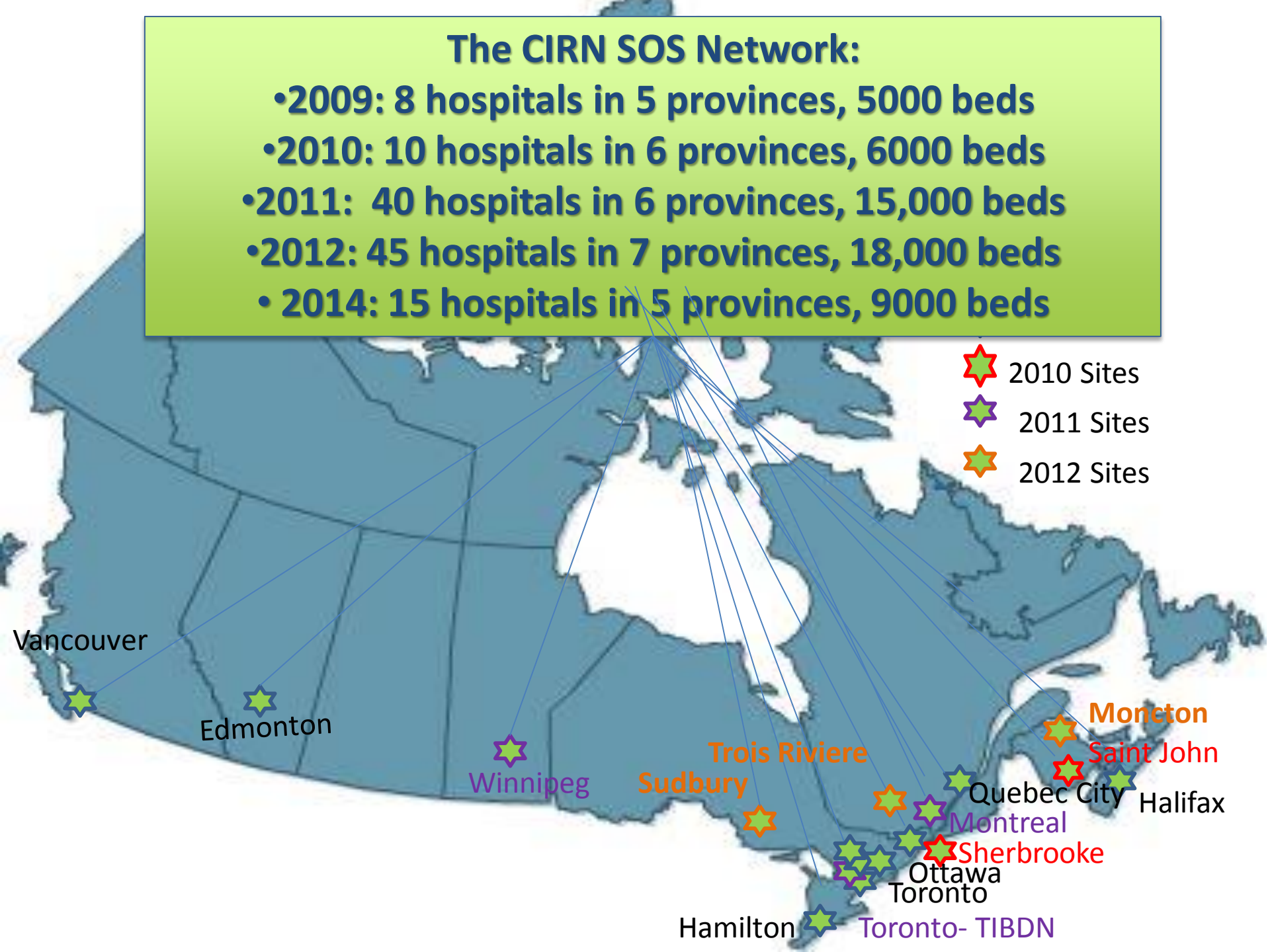
Recombinant influenza vaccine

- Using DNA recombinant technology, hemagglutinin protein is produced in cell culture vs. eggs
- Recently approved for age 50+
- Contains 3x the dose of antigen
- Subgroup analysis for adults 65+ suggests relative efficacy of 42% (95% CI: 9-65) against ILI (vs. QIV)

Dunkle LM, et al Efficacy of Recombinant Influenza Vaccine in Adults 50 Years of Age or Older N Engl J Med. 2017 Jun 22;376(25):2427-2436.

Back to thinking about why high risk groups are at high risk…

- Higher attack rates?
- Poor immune responses (to vaccine and to illness)?
- Sub-optimally recognized and treated illness
  - Atypical presentation of illness has implications for both surveillance and clinical practice
- Poor outcomes (over short and long terms)?
  - Complications, persistent deficits


The 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
• 2014: 15 hospitals in 5 provinces, 9000 beds
2010 Sites
2011 Sites
2012 Sites
Vancouver
Edmonton
Winnipeg
Trois Riviere
Sudbury
Moncton
Saint John
Quebec City
Halifax
Montreal
Sherbrooke
Ottawa
Toronto
Hamilton
Toronto- TIBDN

SOS Methods

- Up to 45 sentinel teaching hospitals across Canada
- active surveillance for influenza infection in adults (≥ 16 years of age)
  - NP swab obtained from all patients with an admitting diagnosis of CAP, exacerbation of COPD/asthma, unexplained sepsis, any respiratory diagnosis or symptom OR acute coronary syndrome, stroke or any other cardiac diagnosis with fever (≥37.5˚C)
  - All NP swabs tested for influenza A & B by PCR

VE calculation in a test-negative case control design

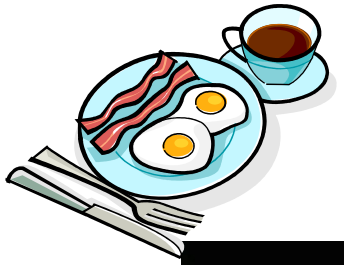
- VE estimated as:

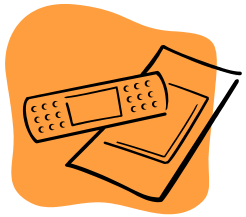
(1-OR of vaccination in cases vs controls)*100

  - Assuming protection from vaccine from 14 days post vaccination
  - Unadjusted & Adjusted (conditional logistic regression with backward stepwise selection; p≤ 0.1)
  - Overall VE and VE in age subgroups (16-49y, 50-64y, 65-75y, and >75y)
  - VE by influenza type/subtype

CIRN
CANADIAN IMMUNIZATION RESEARCH NETWORK

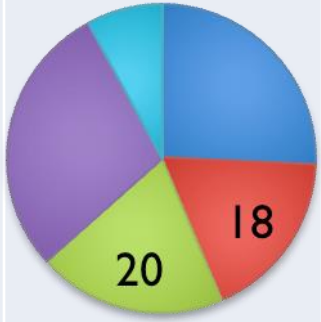
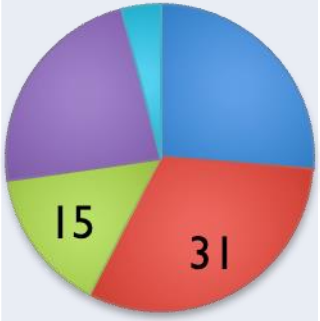
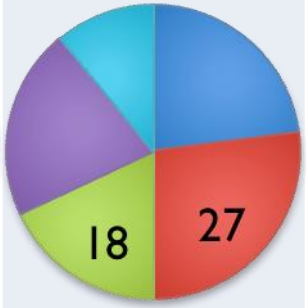
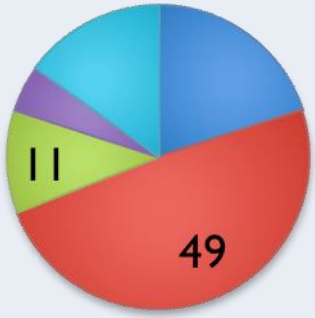
APPENDIX 6: Frailty Index and Frail Scale



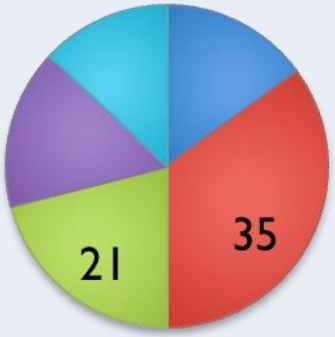
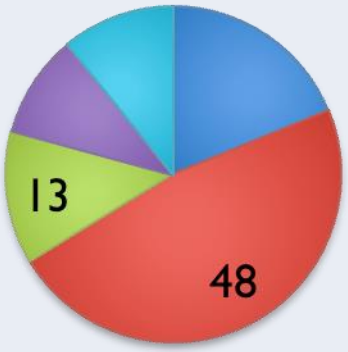
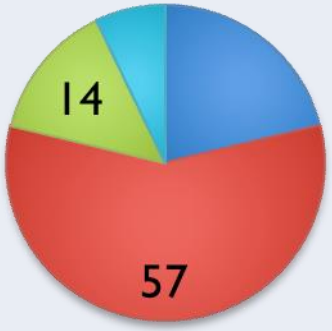


Frailty Index (for patients 65 years and older)		Check if Frailty Index was not done: ☐
	Two Weeks Prior to Admission	**On Admission**
A. Cognition	☐ WNL ☐ CIND ☐ Dementia ☐ Delirium due to illness? ☐ unk If dementia, type _____	☐ WNL ☐ CIND ☐ Dementia ☐ Delirium due to illness? ☐ unk If dementia, type _____
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 =Independent, 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 =Independent, 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: _____

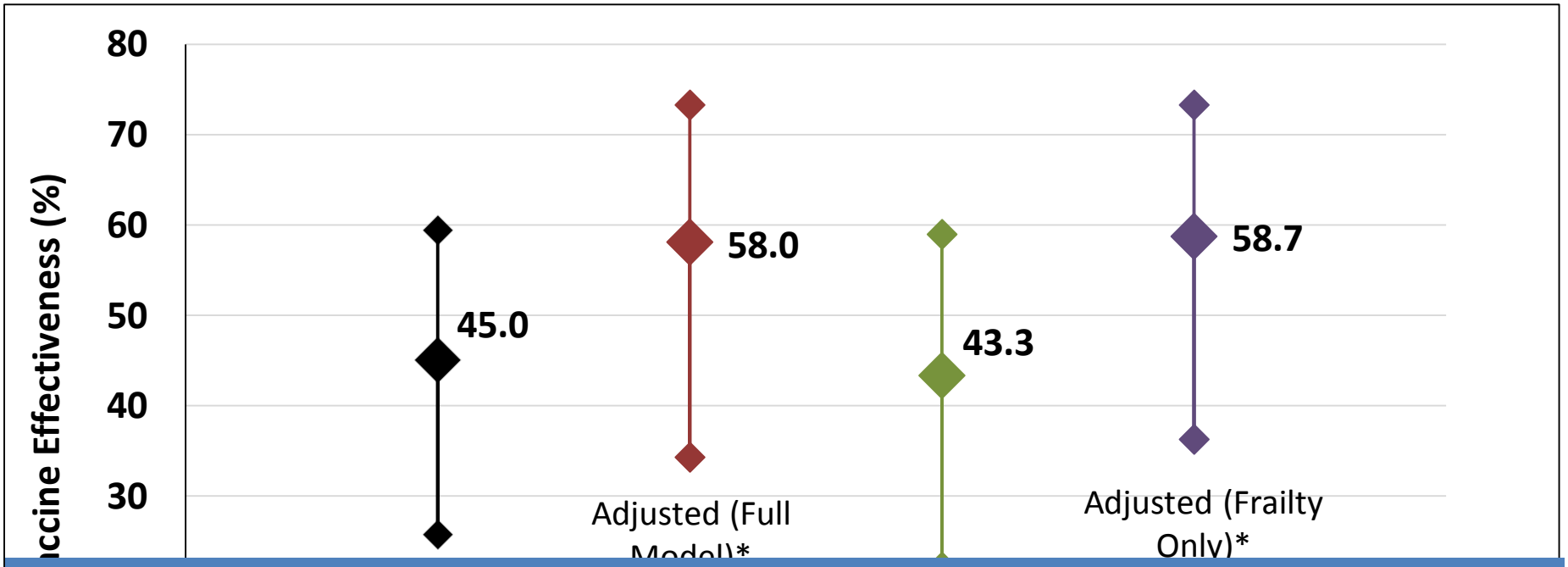
Age and Burden of Disease

	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%)

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%)

It is important to consider frailty when we think about VE in older adults



Adjusting for frailty alone very closely approximates the final fully adjusted model. Frailty is the most important confounder to take into account in adults 65+.

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

How well do ILI and SARI criteria perform?

- Influenza-Like Illness
- An acute respiratory Infection with:
  - Measured fever >=38.0 ^{o}C
  - And cough
  - With onset within the last 10 days

- SARI case definition
- An acute respiratory infection with:
  - History of fever or measured fever >=38.0 ^{o}C
  - And cough
  - With onset within the last 10 days
  - And requires hospitalization

ILI criteria do not perform very well

Relying on fever and cough will miss more than half of hospitalized influenza cases, yet false positives remain an issue.

This is especially true for older adults.

* Data shown at the meeting are being submitted for publication

SARI criteria are not much better

SARI criteria (particularly “history of fever” or “feverishness” vs. measured fever) has somewhat improved sensitivity compared with ILI, but about 40% of cases will still be missed.

Again, this is most prominent for older adults.

* Data shown at the meeting are being submitted for publication

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.

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

Use of antivirals prior to outcome reduced the odds of needing ICU/mechanical ventilation by 90%, with very tight confidence limits.

* Data shown at the meeting are being submitted for publication

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

Referent = No Antivirals

There was no statistically significant difference in outcomes when the timing of antiviral use after symptom onset was <2 days, 2-5 days, or >5 days.

* Data shown at the meeting are being submitted for publication

So what does frailty have to do with influenza?

Understanding frailty is important in identifying influenza illness and measuring influenza vaccine effectiveness

Understanding the impact of influenza on frailty is critical to understanding its true burden

Figure credit: Janet McElhaney

NOT Adding Life to Years

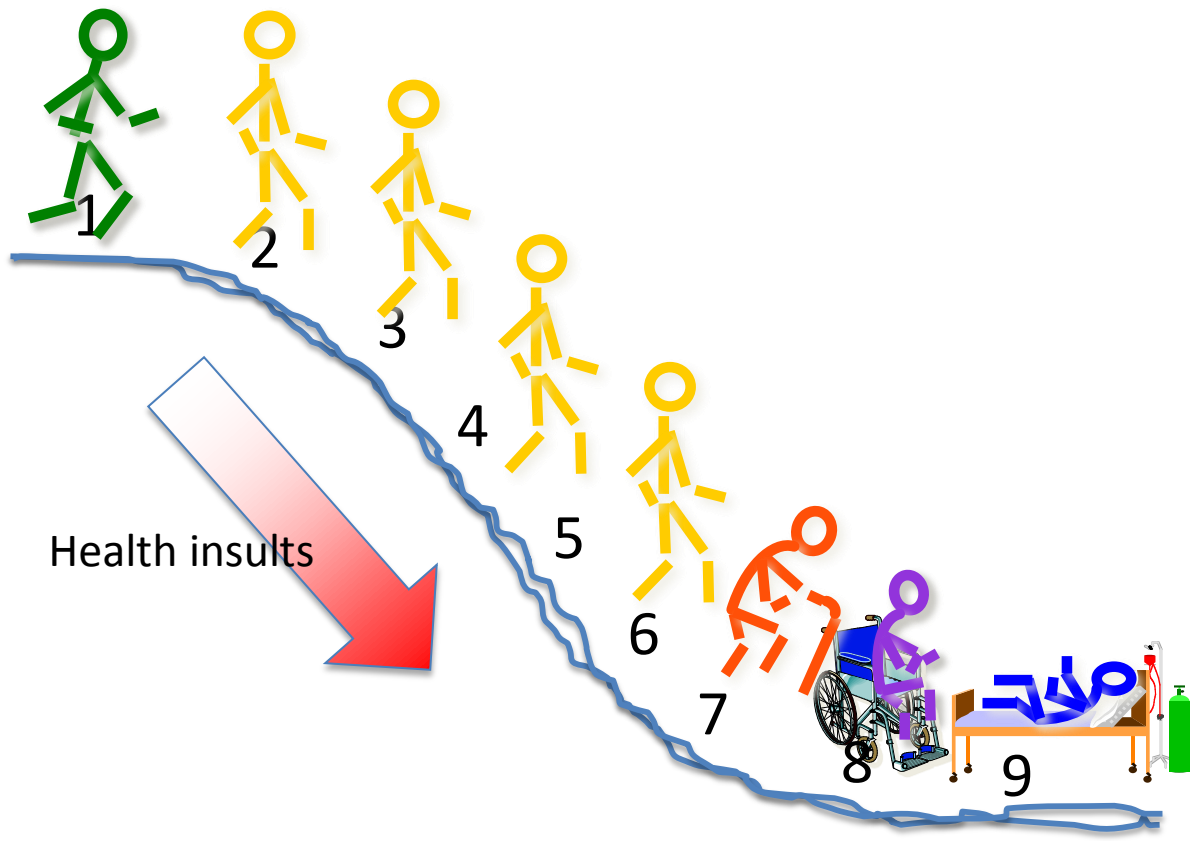
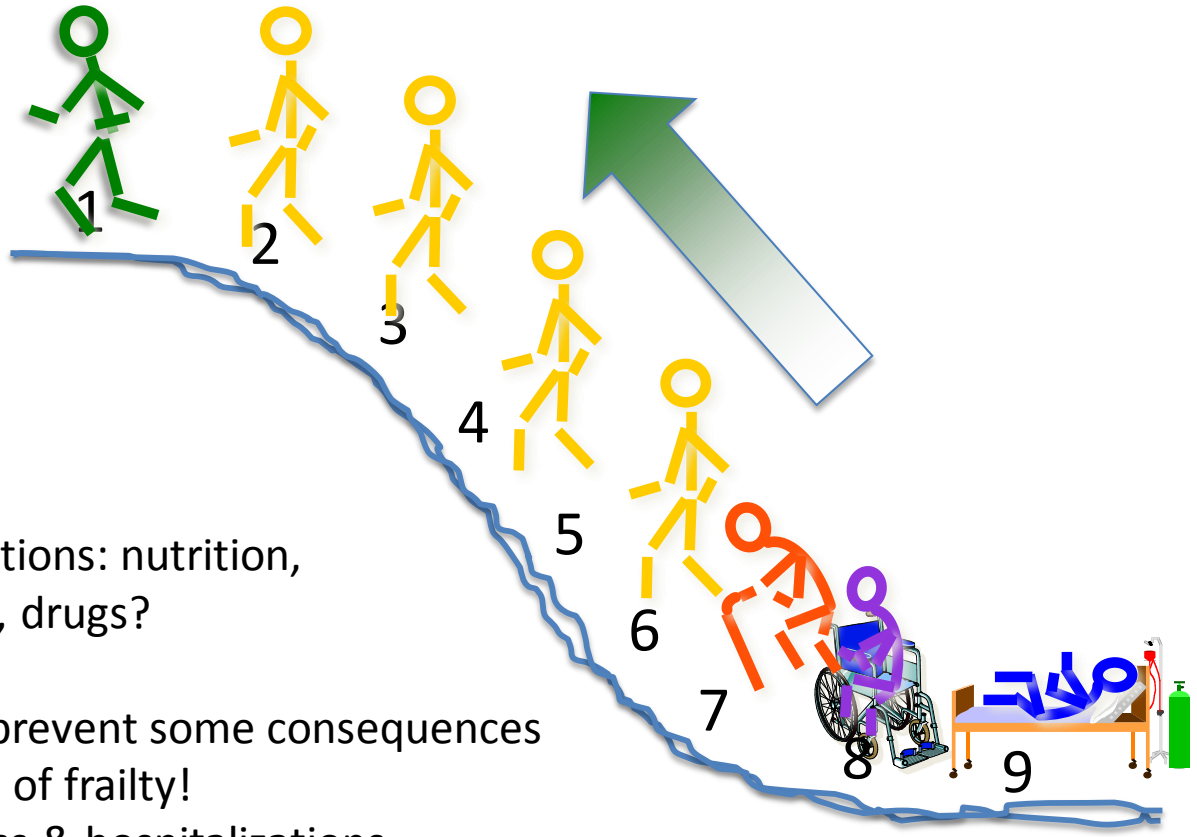


Figure credit: Janet McElhaney

Adding Life to Years: Can frailty and disability be prevented?



Candidates:

- Exercise
- Social integration
- Physiological interventions: nutrition, inflammation, immune, drugs?
- Good care?

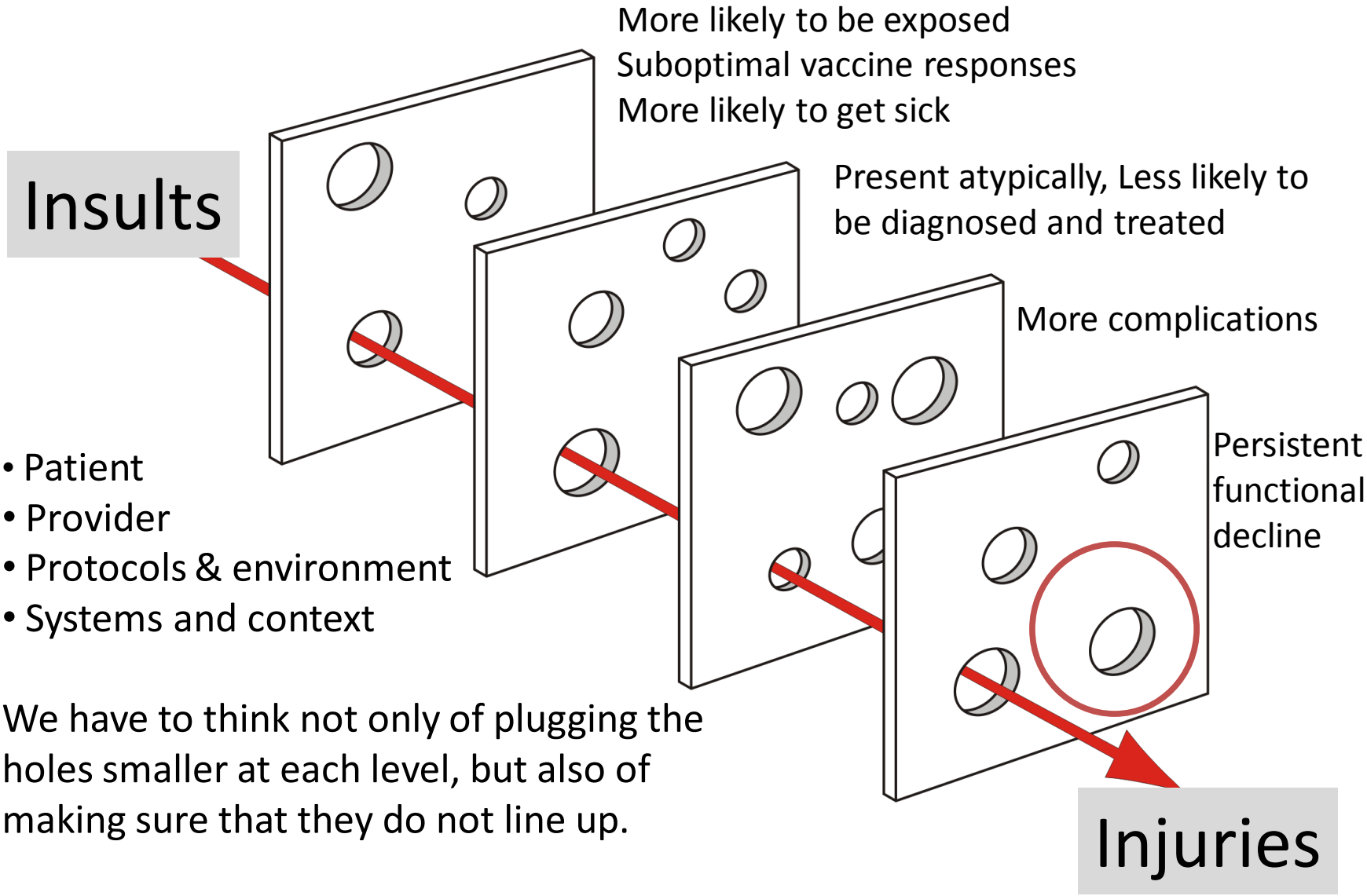
  * At least we can prevent some consequences and complications of frailty!
  - Avoidable illness & hospitalizations
  - Vaccine preventable illness and disability!

Figure credit: Janet McElhaney

How should this impact practice?

- Actively recommend vaccination for high risk groups, establish protocols
- Consider different vaccine products, depending on your setting
- Prevent influenza in those around them too
  - Vaccinate family, caregivers, health care professionals
  - Hand hygiene, self-isolate when ill…
- Broaden surveillance and clinical diagnosis and management
  - If we do not look for ‘flu, we will often miss it
- Consider frailty and function in research and clinical practice

Putting it all together – improving influenza prevention and care for high risk populations



Thank you for your interest!

Acknowledgements

Thanks to Jan McElhaney for sharing her slides and wisdom.
Special thanks to the SOS Network team: Shelly McNeil (PI) and the dedicated SOS Network surveillance monitors, Ardith Ambrose (SOS Network Project Manager) and Donna MacKinnon-Cameron, Peter Ye, Judith Godin, SOS trainees Zach Shaffelburg, Sarah MacDonald, Caitlin Lees