

The Value of Vaccination the Elderly

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Simonsen - Conflict of Interest:

None at the time this work was undertaken and published

Key Points and Topics

- **~90% of Seasonal influenza Deaths are in Seniors**
 - Definitely a high risk group, but...
 - Are these deaths currently prevented with vaccination?
- **Problems with Vaccine Effectiveness (VE) measurements in Seniors**
 - Substantial overestimation in evidence base
 - Low VE when correcting for bias
- **The Need to increase vaccine protection**
 - Better vaccine formulations for seniors
 - Protect indirectly (herd immunity)
- **Pandemic-H1N1v 2009 pandemic**
 - Should seniors be a priority group for vaccination?

A bit of History.....

- **1940s: Influenza vaccine for military pop**
 - Goal: To protect the young, healthy
- **~1960s Policy: Vaccinate high risk populations**
 - Goal: reduce severe influenza outcomes, deaths
 - **Especially elderly >65 years**
- **1960-1994: Concern – was it working?**
 - Immune senescence?
- **mid-1990's: Concern gone**
 - “Electronic” cohorts studies report astonishing mortality benefits
- **Mid-1990's: Concern back again**
 - Influenza deaths rose despite 4-fold rise in senior vaccine coverage

How to Demonstrate Vaccine Effectiveness in Elderly

1. Randomized, controlled vaccine trials

- “Gold standard” evidence not available
- One Dutch study measured VE for mild illness in young healthy elderly

2. Observational studies (cohort, case-control)

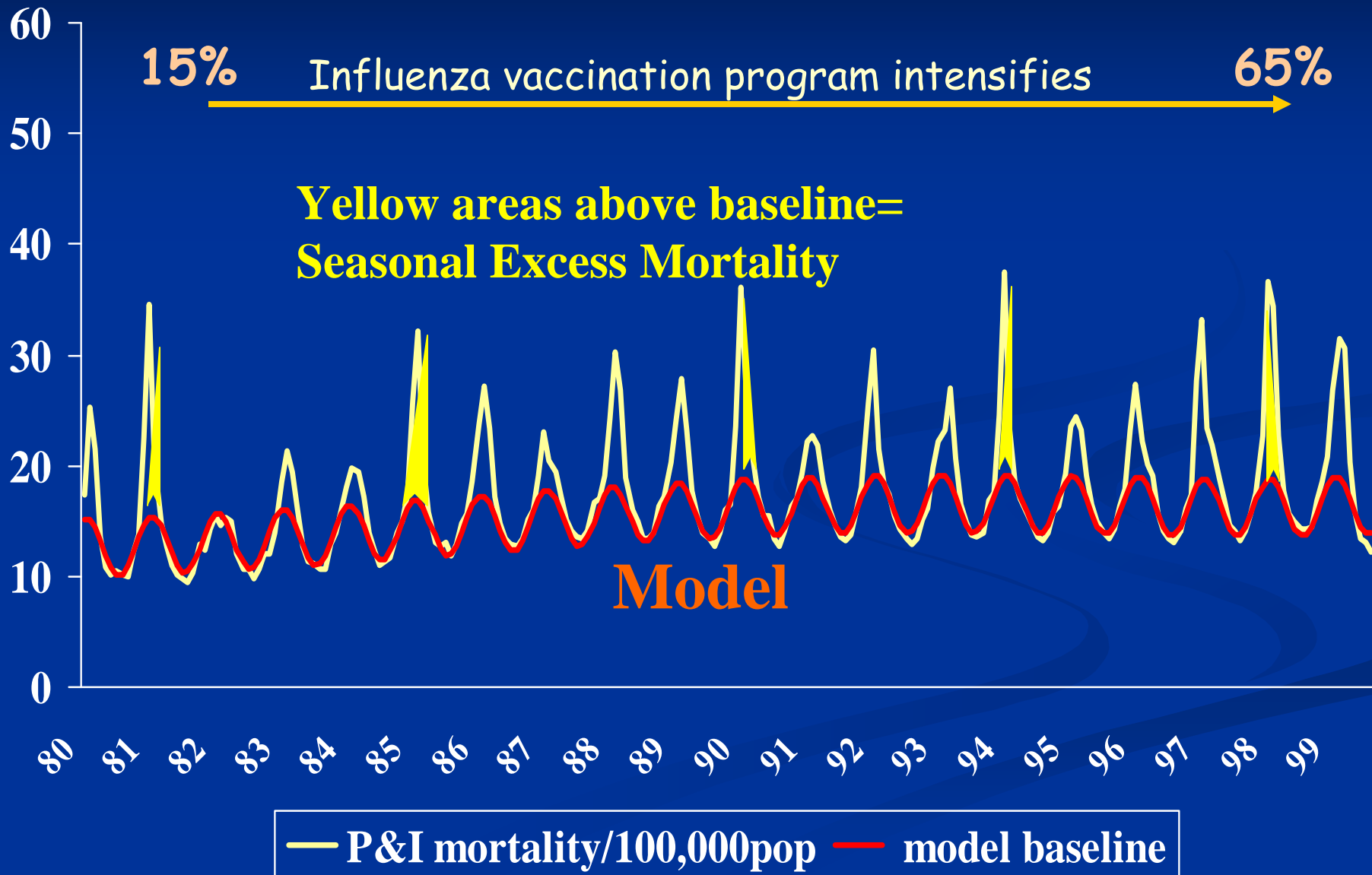
- Forms the evidence base
- Potential for selection bias

3. Trends in National excess mortality

- Mortality reduction achieved with vaccination
- Potential for “ecological fallacy”

Trends in US Excess Mortality:

Attributing winter-seasonal deaths to influenza, elderly ≥ 65



A Paradox from Trends Studies:

Influenza-related mortality increased in US elderly while vaccine coverage rose from 15% to 65%

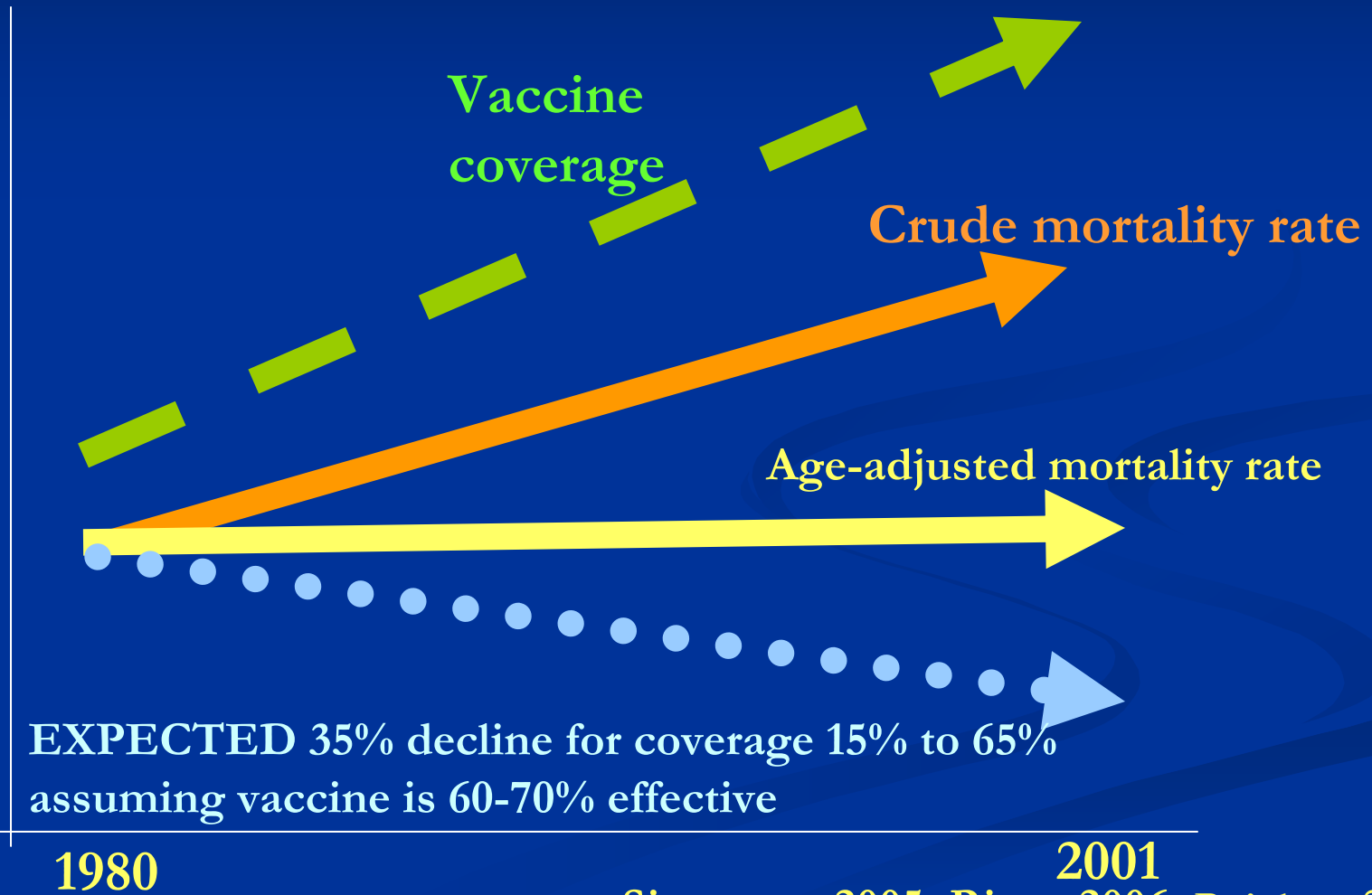


Seasons during 1968 to 2000

Simonsen et al 2005

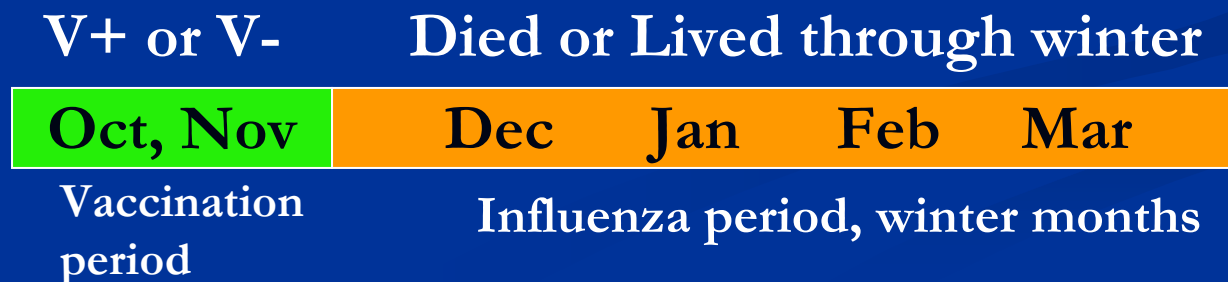
Disappointing Age-Adjusted Mortality Trends

- no reduction found in several countries, despite large gains in elderly vaccination coverage



Typical Design of a Vaccine Effectiveness (VE) Cohort Study

- Set in large managed care populations of seniors
 - **Exposure:** Influenza Vaccination
 - **Outcome:** Death, all causes, during Dec-March
 - **VE** = $1 - \text{Relative Risk (vaccinated vs unvaccinated)}$
- Adjustment for bias: does it work?
 - ICD-9 adjustments typically used to account for differences in co-morbidities.



Multiple Cohort Studies found astonishing reduction in ALL WINTER DEATHS in vaccinated seniors

Meta-analyses	Study Population	%VE (reduction in All-Cause deaths)
Gross 1995	Nursing home seniors ≥ 65 years	68%
Vu & Kelly 2004	Community-living seniors ≥ 65 years	50%
Cochrane review Jefferson 2005	Community-living seniors ≥ 65 years	47% *

* Cochrane review, however, concluded bias, see later slide

Clinical Inf Dis, 2002

If You Could Halve the Mortality Rate, Would You Do It?

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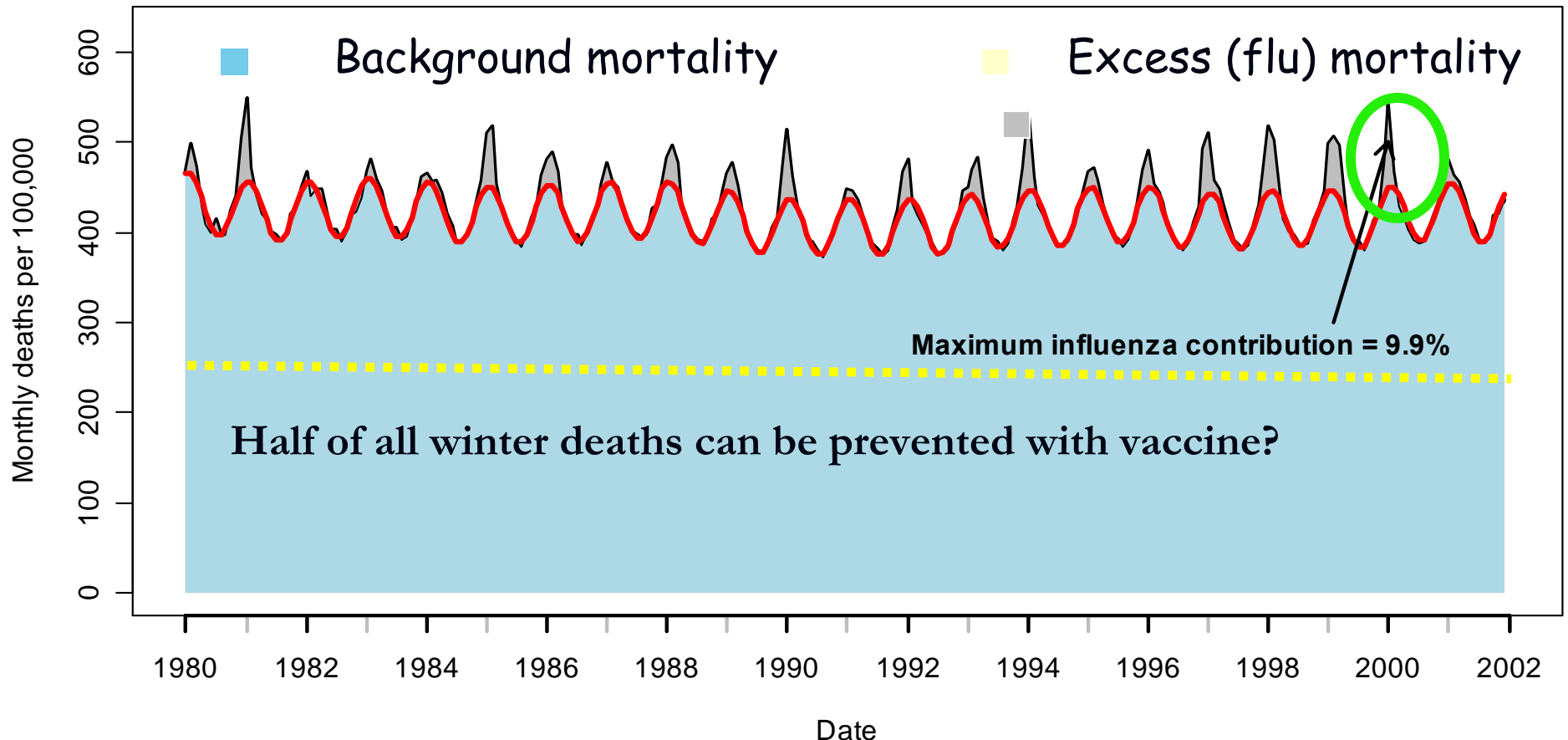
(See the article by Hak et al. on pages 370–7)

A Paradox:

- **No mortality decline in elderly as vaccine coverage rose**
- **Yet vaccine reduced half of ALL winter deaths in cohort studies**

Ocean of Deaths with Influenza “Foam”

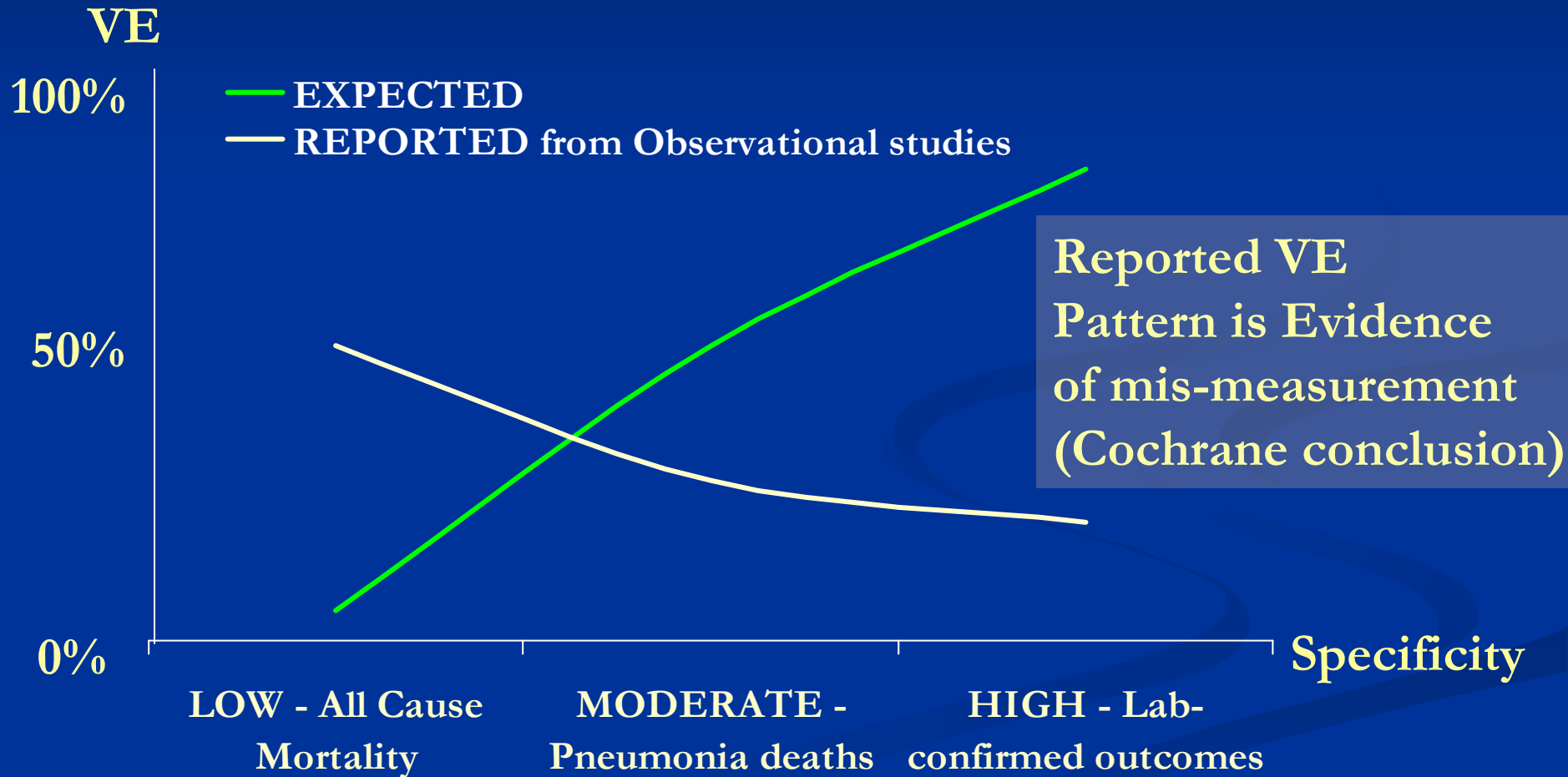
Monthly deaths in elderly ≥ 65 , all causes, US, 1980-2001



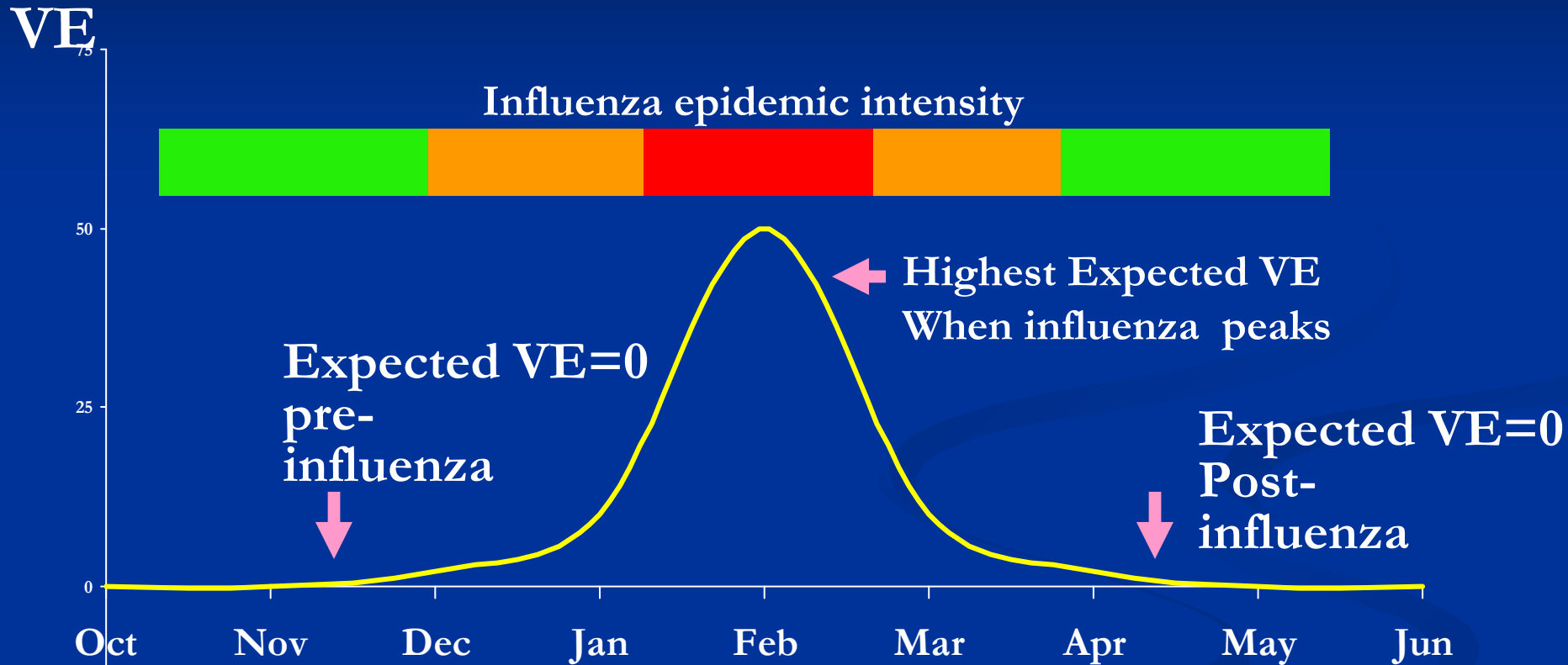
Nationally, influenza explained 5-10% of all winter deaths, even in 1968 pandemic, and seasons with vaccine mis-match

Therefore, 50% mortality savings (cohort studies) just not possible

VE estimates depend critically on specificity of outcome studied



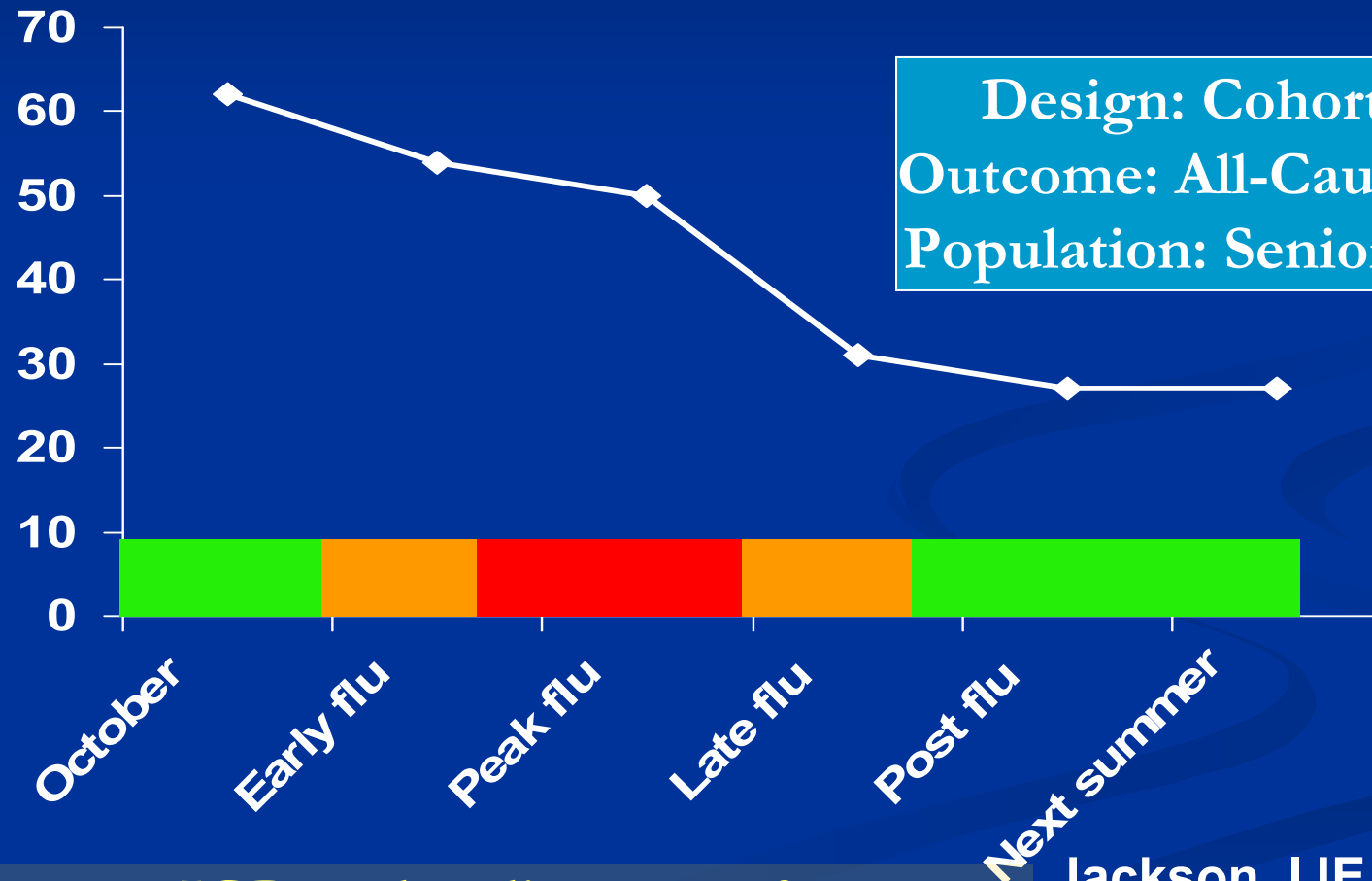
An Elegant Demonstration of Profound Bias in Cohort Studies using Seasonality



EXPECTATION: Vaccine Benefits should ONLY occur DURING influenza epidemics, NOT before

But expected pattern was NOT confirmed: highest “VE” measured in pre-influenza period

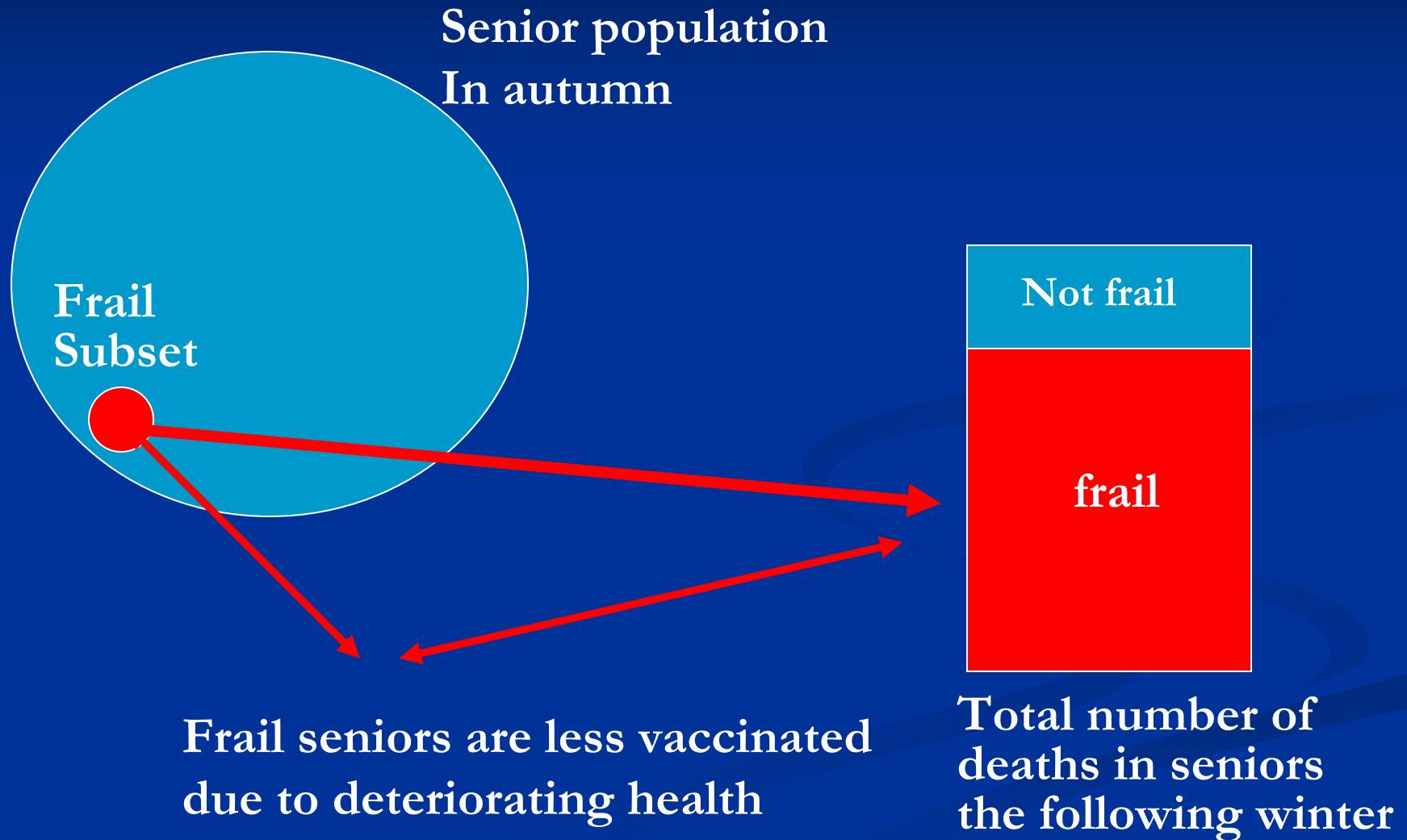
% “VE” (=1-RR)



Worse: ICD-code adjustment for
co-morbidities was counter-productive

Jackson IJE 2006
See also Fireman AJE 2009

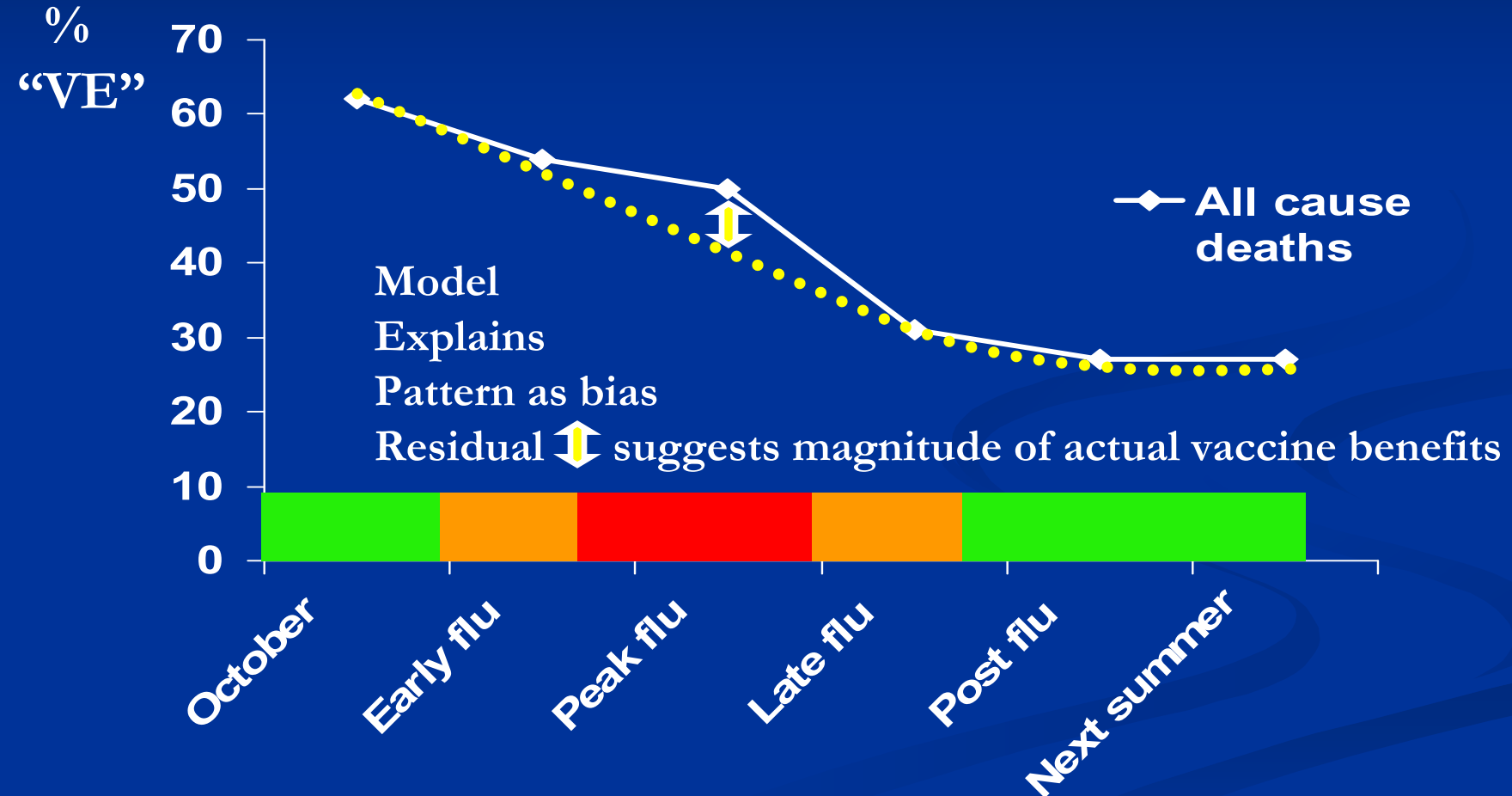
Explaining profound bias and VE overestimation: Frailty selection bias



Frailty Selection Bias Explains Pattern

Assumptions: 5% frail seniors, with $\frac{1}{2}$ the vaccine coverage and 20-fold the mortality risk of other seniors

SIR model simulation (dotted line) assumes NO vaccine benefits



Simonsen and Viboud, unpublished

Mortality benefits of influenza vaccination in elderly people: an ongoing controversy

Lone Simonsen, Robert J Taylor, Cecile Viboud, Mark A Miller, Lisa A Jackson

detecting such residual bias. We conclude that frailty selection bias and use of non-specific endpoints such as all-cause mortality have led cohort studies to greatly exaggerate vaccine benefits. The remaining evidence base is currently insufficient to indicate the magnitude of the mortality benefit, if any, that elderly people derive from the vaccination programme.

Simonsen et al, Lancet Inf Dis 2007

A handful of bias-adjusted cohort studies with more specific outcomes during influenza periods provide improved VE estimates for elderly

	Design	Outcome	VE [95% CI] Seniors
Mangtani JID 2004	GP databases Cohort	Pneumonia deaths All cause deaths	12% 0%
Jackson LANCET 2008	HMO data + chart review Case-Control	X-ray confirmed Pneumonia hosp All cause deaths	8% (-4% in peak) Low; no est possible
Fireman AJE 2009	HMO data + chart review Cohort	Resp/circ hosp All cause deaths	9% 4.6% [0.7 to 8.3%]

Prevention of Inf Dis in seniors through immunization: the challenge of the senescent immune response.

- A decline in immune function with aging increases the risk of many infectious diseases
- Influenza remains a significant problem in older adults despite widespread influenza vaccination programs
- There are major challenges to developing new or more effective vaccines against influenza and the many other virus and bacterial illnesses that commonly affect elderly

A Moment of Opportunity

- If we know it is broken, then we can fix it !

- **Conduct more appropriate VE studies**
 - **Good:** Chart reviewed studies with more specific outcomes + bias adjustment
 - **Better :** Lab-confirmed case-control studies
 - **Best :** Randomized placebo-controlled trials (?)
- **Develop more immunogenic formulations for seniors:**
 - Higher antigen dose, adjuvants, intradermal delivery, whole virus formulations, combined flushot/live attenuated, pro-biotics?
- **Protect seniors indirectly**
 - Increase vaccine coverage in children/contacts to achieve lower influenza transmission to high risk pop

**Should Elderly be given priority for
pandemic-H1N1 vaccination?**

Sparing of Elderly in the 1918 pandemic

Monthly NY city All Cause Mortality, by age, 1910-19

Deaths
Per
10,000



≥65

25-44

1918/19

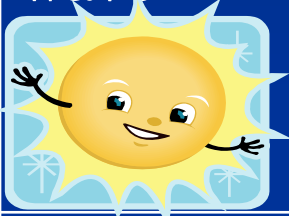

Olson et al, PNAS 2005

Also in Scandinavia (Andreasen et al JID 2008)

See also Lee V et al, EID 2007 and Ann Acad Med Singapore 2008

Excess Mortality Rates by Age:

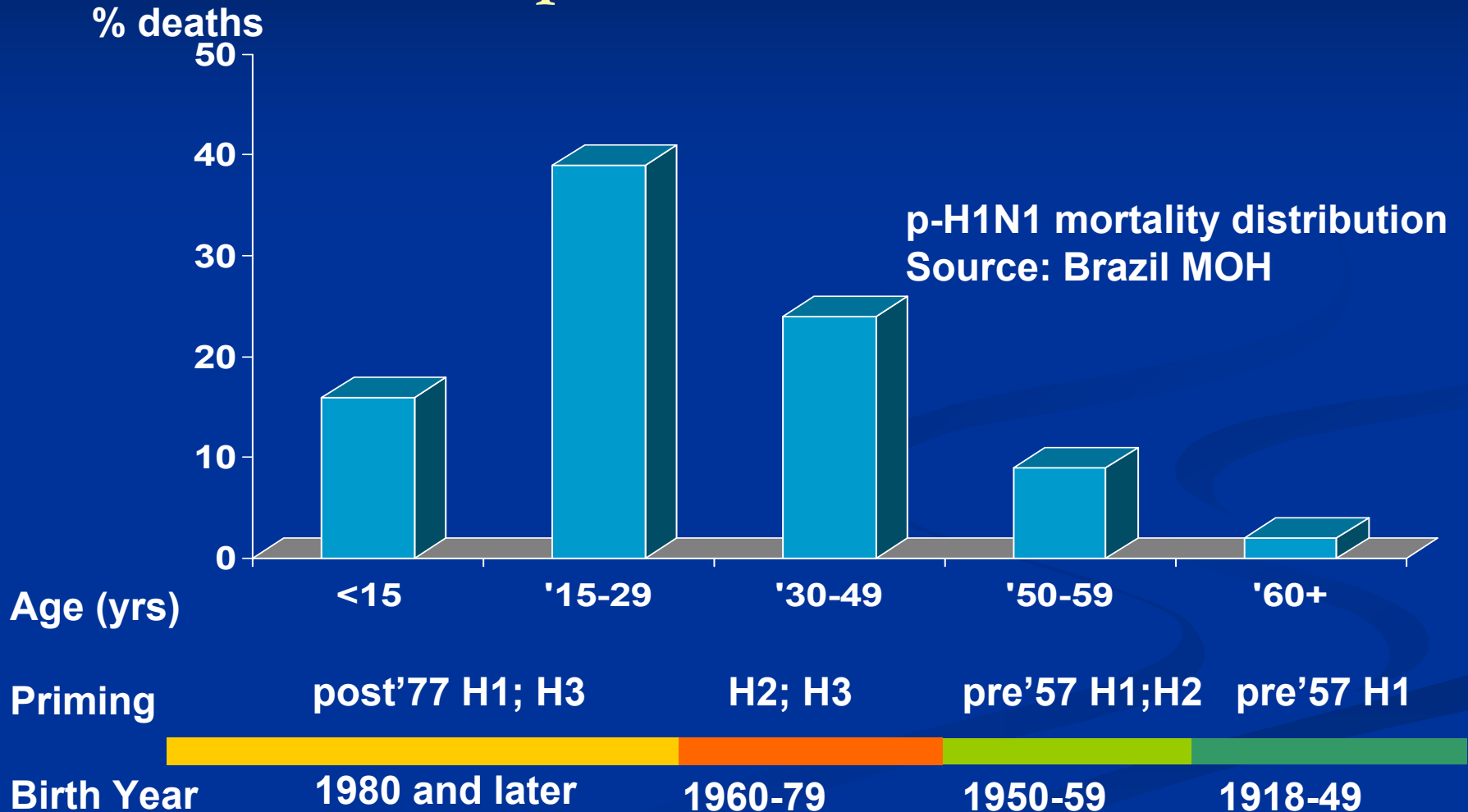
Summer wave had “1918 pandemic signature” age pattern like autumn wave (highest risk in young adults, elderly spared)

Age Group (years)	1918 summer wave 	1918 autumn wave 
<15	0.2	12
15-44	3.1	47
45-64	0.3	8
≥65	0	0.5

Data from Copenhagen, Andreasen et al, JID 2008

2009 Pandemic H1N1 Situation

Are the elderly protected by pre-1957 H1N1 virus exposure in childhood?



Should Elderly be given priority for pandemic-H1N1 vaccination?

■ Pandemics – not business as usual

- Elderly may or may not be at elevated risk
 - 1918 - elderly were spared - immune protection from childhood exp?
 - 1957 and 1968 – elderly were at high risk
 - P-H1N1 2009 resembles summer 1918 mild 1st wave – 2nd wave?

■ Considerations for decision making

- Magnitude of p-H1N1 burden?
 - Will elderly be at high mortality risk relative to other age groups?
 - Or, will elderly be filling up ICUs ?
- Can the p-H1N1 vaccine protect seniors?
 - Trials pending; adjuvanted vaccines? No. of doses ?
- How many Life Years may be saved? (Miller et al, JID 2008)

Mortality impact of Pandemic influenza

Highly variable; shift towards younger ages

<i>Pandemic and virus sub-type</i>	<i>Global mortality impact</i>	<i>% deaths in younger persons <65</i>	<i>Age grp at highest risk</i>
<i>1918-19</i>	<i>~50 M</i>	<i>~95%</i>	<i>20-40 yrs</i>
<i>1957-58</i>	<i>~2M</i>	<i>~40%</i>	<i>>65 yrs</i>
<i>1968/69</i>	<i>~1M</i>	<i>~50%</i>	<i>>65 yrs</i>
<i>Avg seasonal H3N2 epidemic</i>	<i>~0.5M</i>	<i>~10%</i>	<i>>65 yrs</i>
<i>Pandemic-H1N1-2009</i>			
<i>- 1st wave</i>	<i><0.5M?</i>	<i>~95%?*</i>	<i>20-50 yrs?*</i>
<i>- Autumn wave</i>	<i>Higher?</i>	<i>same?</i>	<i>same?</i>

* Australia study report more p-H1N1 2009 elderly deaths than Brazil, US, Mexico