

Pandemic Influenza Readiness

Vaccine effectiveness

CIDER Summit

Roger Baxter

Kaiser Permanente Vaccine
Study Center



KAISER
PERMANENTE.®

VACCINE STUDY CENTER

Conflicts of interest

- I receive research grants from the following manufacturers of flu vaccines:
 - Sanofi Pasteur
 - MedImmune
 - GSK
 - Novartis
 - Protein Sciences

Flu vaccines – pandemic and others

- ❑ Recommended since the 1960's in elderly
- ❑ Massive public health and health care efforts to vaccinate
- ❑ More recent expansion to other groups
 - Those with medical illnesses
 - Over 50
 - 6 months to 5 years
 - Up to 18 years
 - Everyone!



H1N1 vaccines 2009 - successes

- Rapidly manufactured – less than 5 months after discovery of the virus
- Rapidly deployed – using an untried public health network
- Accurate – no change in viral antigens during the season

H1N1 vaccines 2009 - lessons

- ❑ Egg technology has time limitations
- ❑ We could work out a better system of delivery
- ❑ Need to cope with perceived favoritism
- ❑ Needs to be faster and more efficient

H1N1 vaccines special problems

Fear

- Safety
- GBS
- Pregnancy
- Kids

H1N1 turned out to be safe

- No good evidence to suspect H1N1 antigen to be dangerous
- No “signals” have been verified as showing an increase beyond seasonal flu vaccine
 - GBS: CEIP preliminary study showed possible 0.8 excess cases per 100,000-unconfirmed
 - Bell’s palsy AND Seizures – not verified
 - Methodologic issues with safety studies

2009-10 H1N1 vaccine

- **No** new technology
- **No** adjuvants
- All manufacturers of seasonal vaccine
- Basically, TIV with 1/3 the antigen

But...

how well do Flu vaccines really work?

- Demonstrated effectiveness in younger groups
 - Young adults: TIV
 - Children: LAIV > TIV
- Elderly: recommendations were based on studies in young adults. Only 1 RCT in elderly, little power to show effect

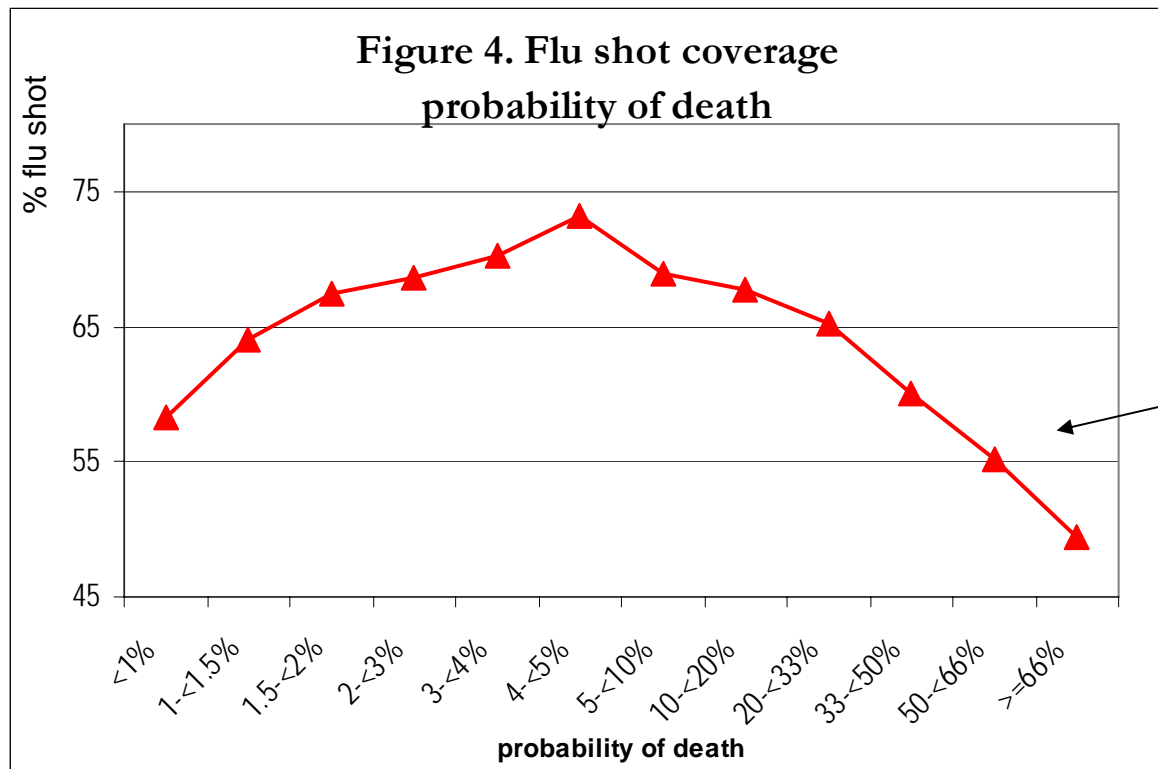
Bias in observational flu studies

Flu vaccines were shown to prevent 50% of all-cause mortality in patients over 65

2 problems:

1. The vaccine seemed to work even better before the flu season hit; and
 2. Only 10% of all deaths were calculated to be due to influenza
- So we decided to look at elderly flu vaccinees

Flu vaccine uptake in the elderly is NOT linear



Most of the
deaths
occurred out
here

Mortality-vaccination association reflecting bias

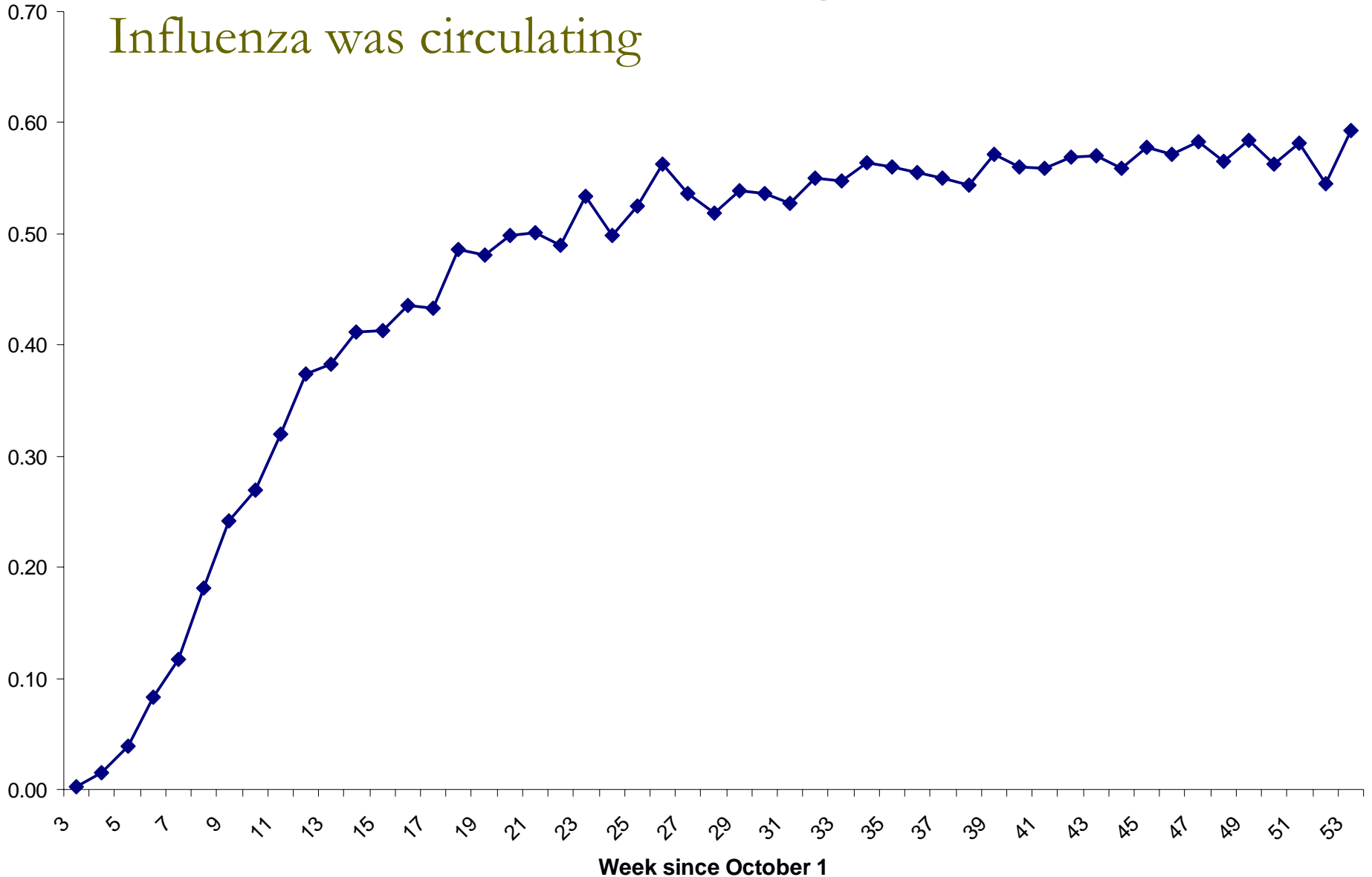
Odds of death, outside flu season, in relation to flu vaccination, in people 75 and over, adjusted for age, sex, 4 chronic diseases, year, and prior pneumonia vaccine.

Vaccines in prior 5 yrs	Population	Deaths	Odds Ratio: Unvaccinated vs. Vaccinated	95% CI	p-value
0	69,060	1,304	0.67	0.57- 0.80	<0.001
5	218,892	2,759	2.17	1.99 - 2.38	<0.001

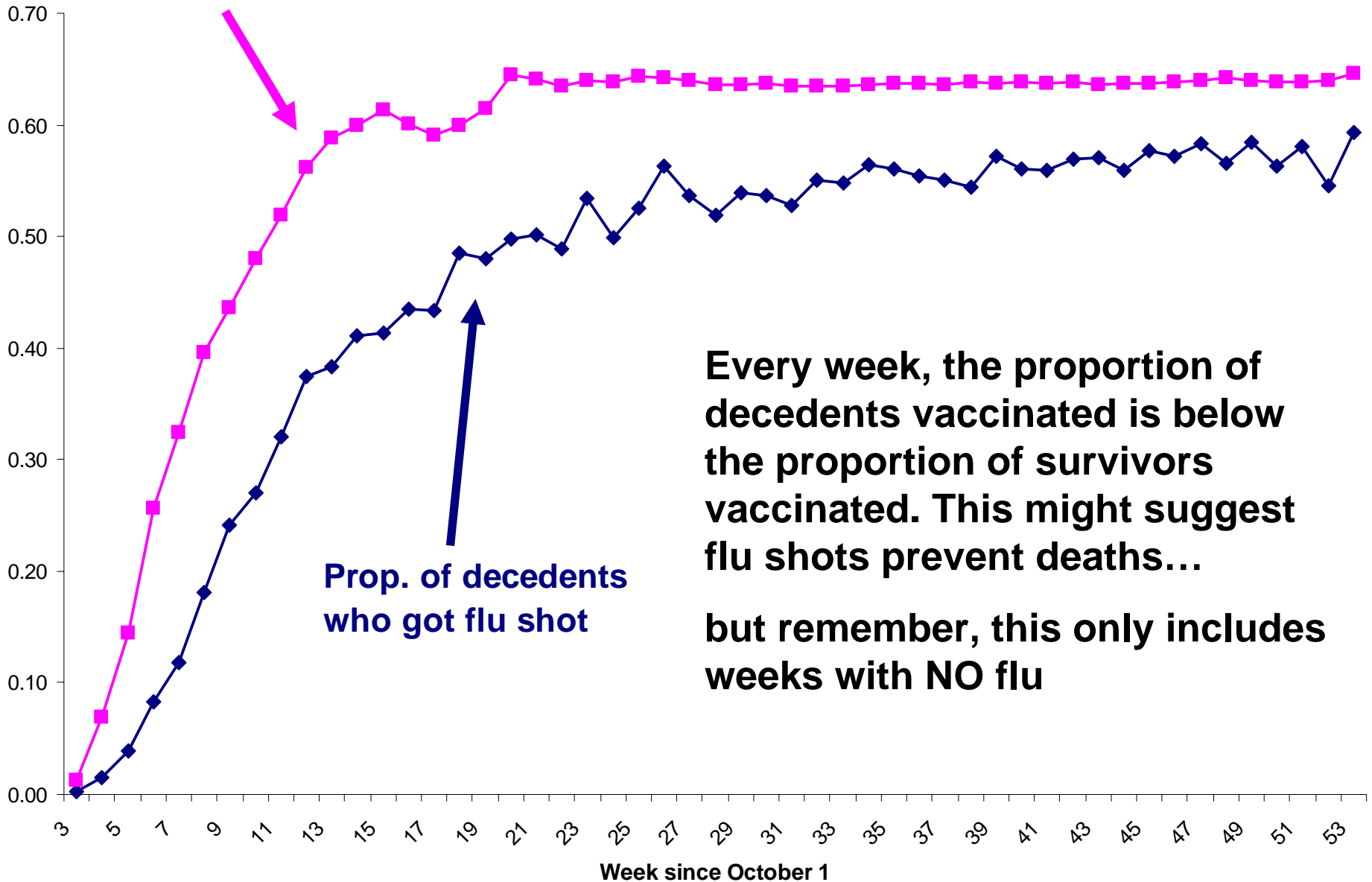
Confounding is powerful and unmeasured in flu vaccine studies

- ❑ It's probably not possible to adjust for this confounding
- ❑ It may be possible to "sidestep" the problem
- ❑ Here's what we did...

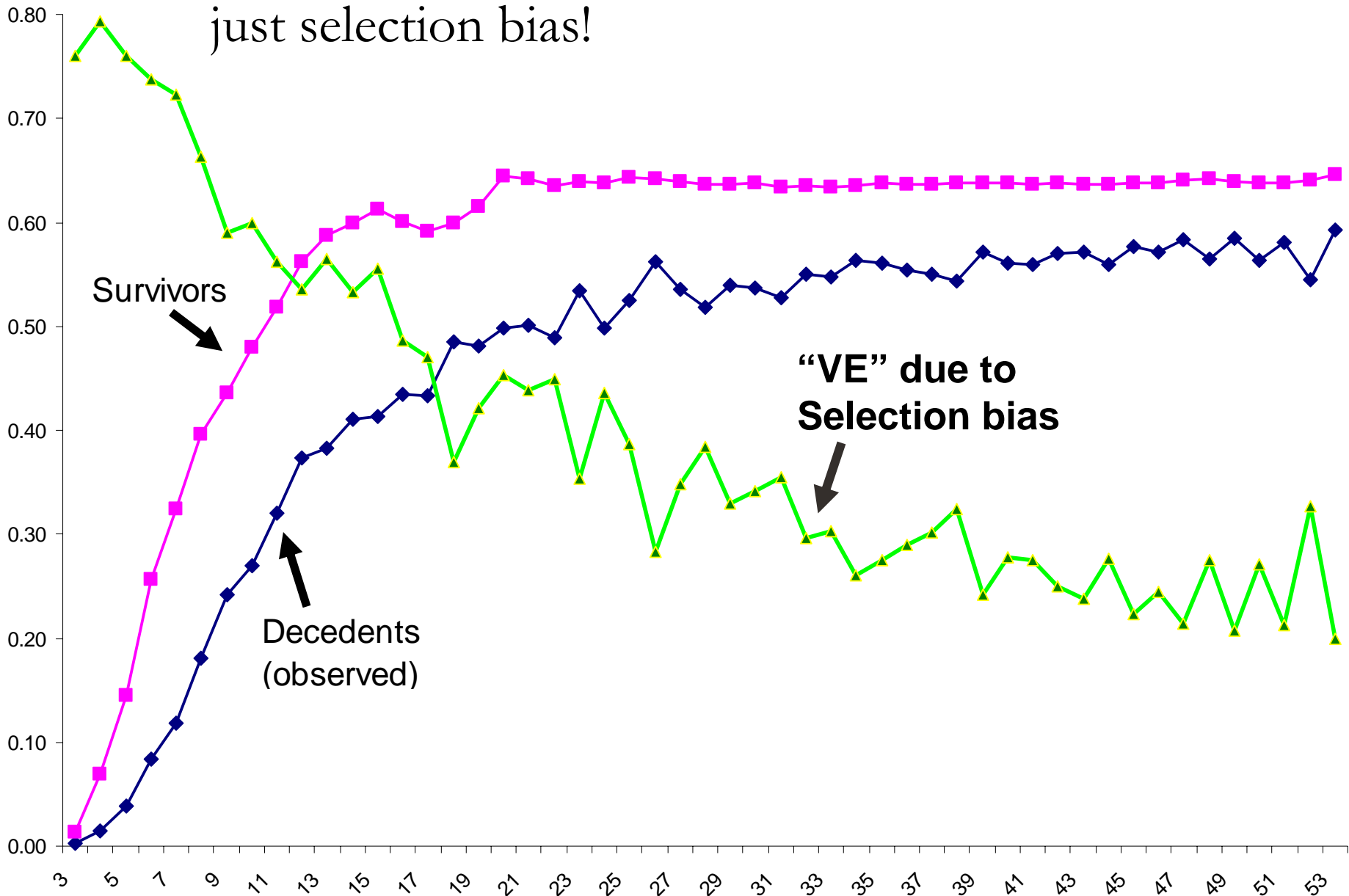
Proportion of decedents who were vaccinated
by week after October 1, omitting the deaths when
Influenza was circulating



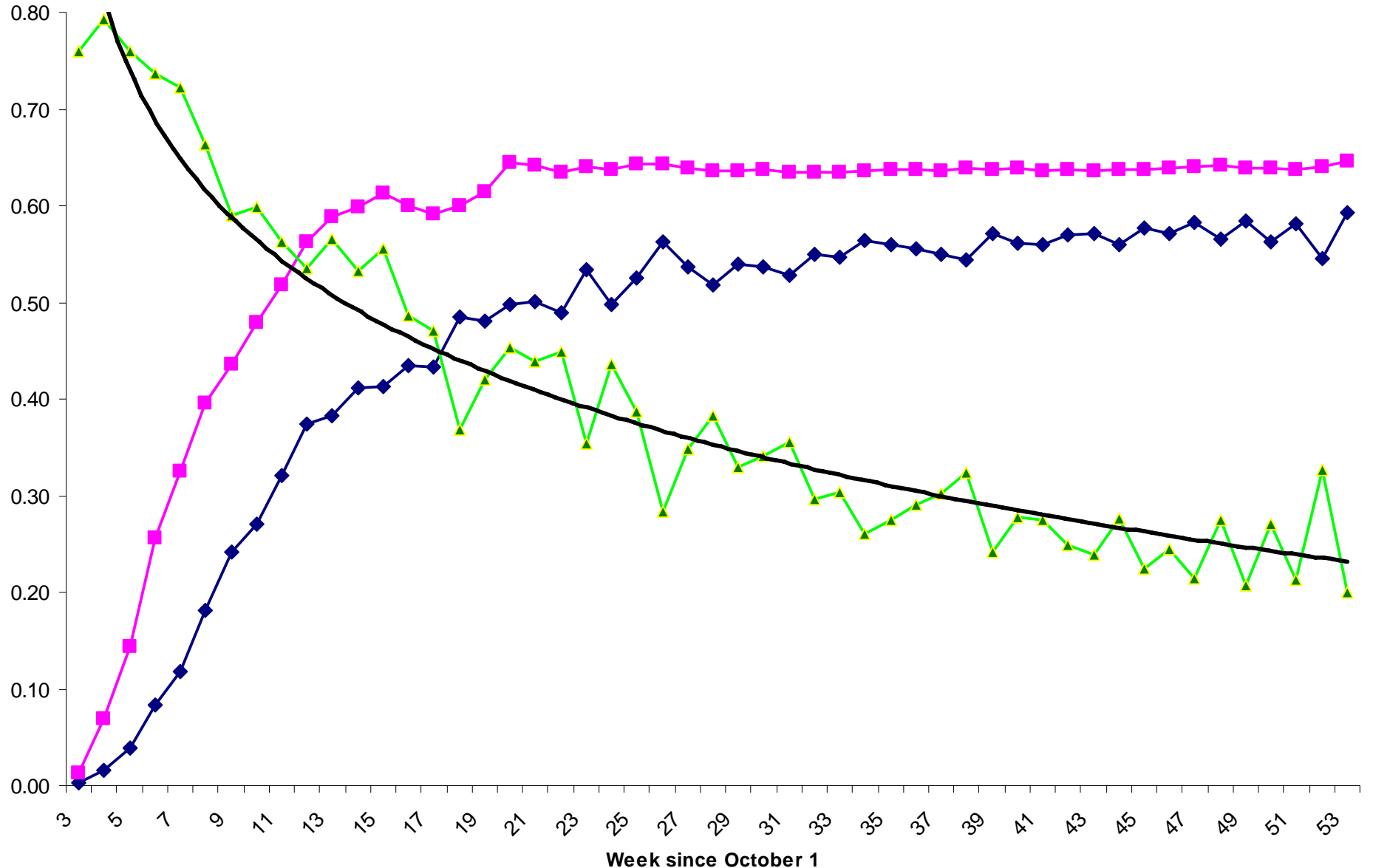
Proportion of age-sex matched survivors who were vaccinated



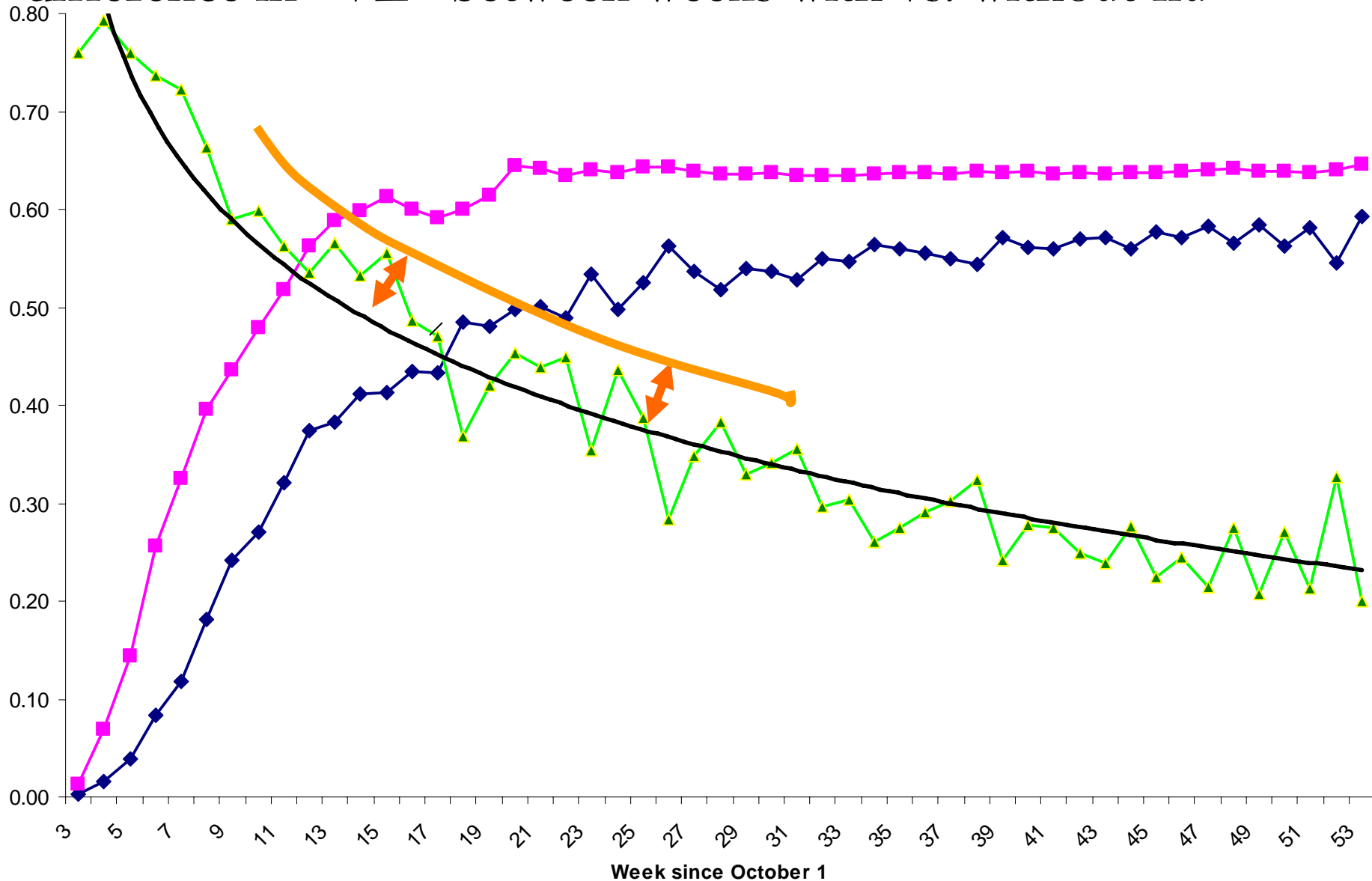
Green curve shows “VE” = 1- OR. This is actually just selection bias!



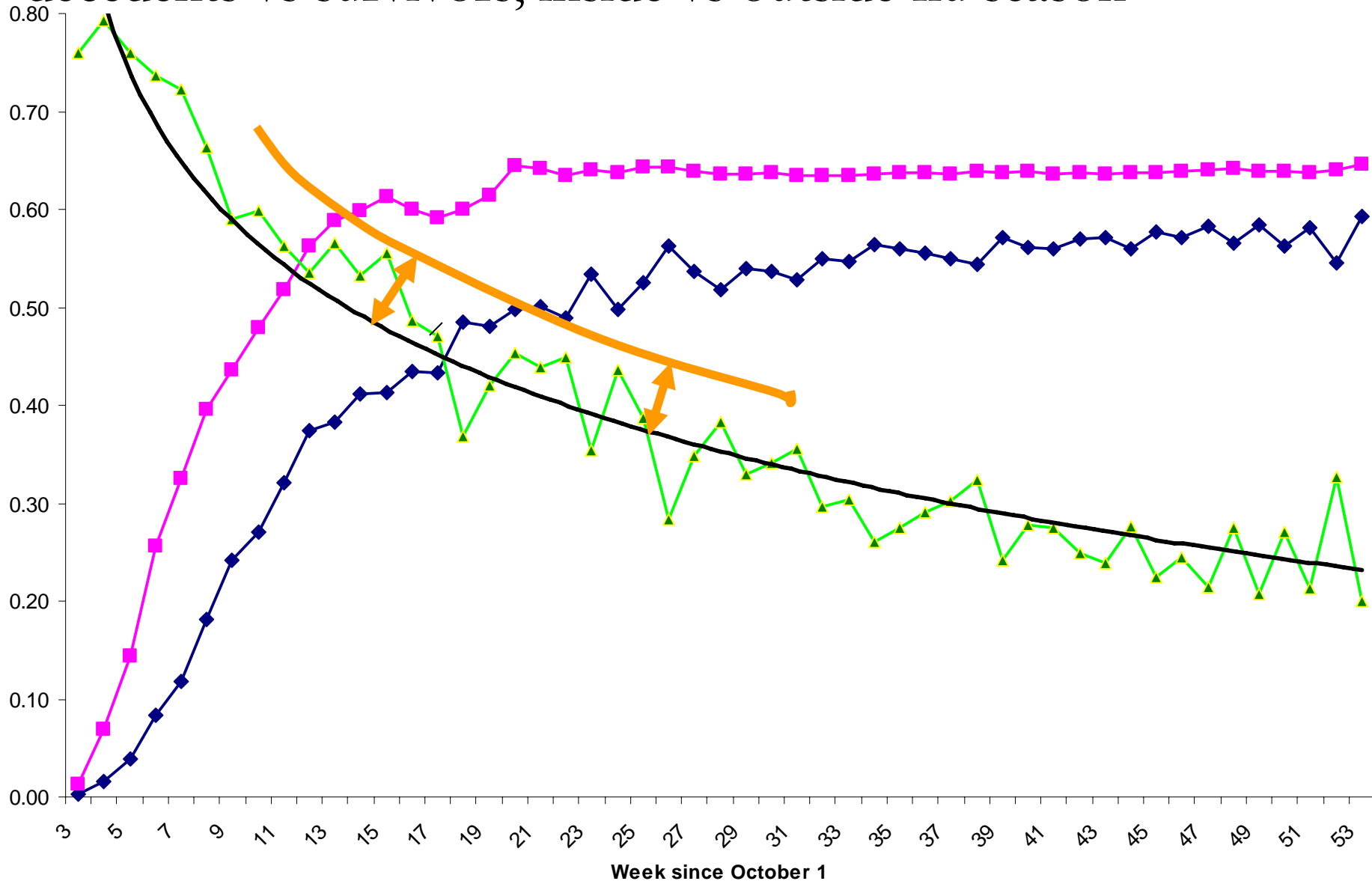
Smoothed trajectory of selection bias using case-centered logistic regression



Then we fit data from weeks WITH FLU, and found the difference in “VE” between weeks with vs. without flu



Thus, our VE estimate is the difference-in-differences:
decedents vs survivors, inside vs outside flu season



Vaccine Effectiveness (VE) in Preventing Mortality in the Elderly during 9 Flu Seasons, by Cause of Death and Age Group

Cause of death	Age Group	N of Deaths	VE (%)	95% CI for VE (%)	P value
All causes	65 & up	61,436	4.6	0.7, 8.3	0.0212
All causes	65-79	29,743	5.3	-0.3, 10.6	0.0641
All causes	80 & up	31,693	3.9	-1.6, 9.0	0.1606
CVD or Respiratory	65 & up	31,798	8.5	3.3, 13.4	0.0017
Other causes	65 & up	29,638	0.1	-5.9, 5.8	0.9632

Fireman, Baxter. Flu vaccination and mortality AJE 2009

Does 4.6% VE seem low?

- We estimated excess mortality due to flu in KP: 7.8%,
 - but we were vaccinating 63% of the population.
- If we weren't vaccinating anybody, then excess mortality would be about 9.8%.
- With an excess mortality of 9.8% , 4.6% VE means that flu shots prevent roughly 47% of all of the deaths that can be attributed to influenza.
- That's not so bad...

Effect of flu vaccine on hospitalizations

Effectiveness of Influenza Vaccination in Preventing Hospitalizations Among Persons Over 50 During Influenza Season. 1997-2007.

Cause of Hospitalization^{/a}	Age Group, years	Vaccine Effectiveness (%)	95% Confidence Interval	P value
Pneumonia and Influenza	50 to 64	12.4	1.6 to 22.0	0.03
	65+	8.5	3.3 to 13.5	<0.01
Congestive Heart Failure	50 to 64	-3.4	-18.8 to 10.0	0.63
	65+	-2.6	-9.5 to 3.9	0.44
Cerebrovascular Disease	50 to 64	4.9	-8.7 to 16.6	0.46
	65+	2.8	-3.9 to 9.0	0.40
Ischemic Heart Disease	50 to 64	-2.5	-9.7 to 4.3	0.49
	65+	1.4	-3.8 to 6.4	0.59

Flu Vaccines – can we make them better?



Influenza vaccines – current technology

USA

- All vaccines are egg-based
- TIV
- LAIV
- MIV (H1N1)

- 15 mcg Hemagglutinin
- No adjuvants

Influenza vaccines - solutions

- High dose: approximately 60 mcg H
 - Improved antibody response in elderly
- Intradermal: 9 mcg H
 - Equal to TIV

Influenza vaccines – other solutions

- ❑ Adjuvants
- ❑ Vaccinate groups other than old people



Adjuvants

- Adjuvants strengthen the immune response; they do not confer immunogenicity.
- Live vaccines generally do not need adjuvants



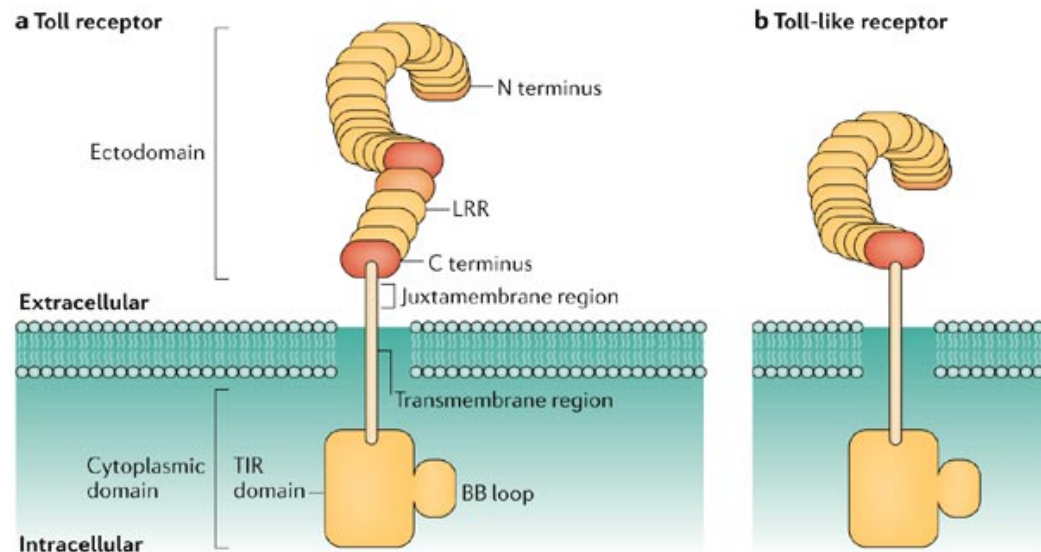
Adjuvants may have other actions:

- ❑ Create a depot effect, maintaining antigen in an appropriate site for continual immune stimulation
- ❑ Enhance stability of antigen
- ❑ Adjuvants may target specific TLRs



Toll-like Receptors (TLRs)

- Signaling proteins expressed by mammalian cells
- Highly specific binding to pathogen-associated molecular patterns (PAMPs)



Adjuvants for flu vaccines

- MF59
- MPL

MF59

- Squalene and two surfactants in an oil-in-water emulsion
 - from shark liver oil, rice bran, wheat germ, and olives
- Enhances the immunogenicity of recombinant vaccines.
- Used in Flud in Europe for years (Chiron)
 - Improves response in elderly



Squalene “controversy”

- ❑ Accused of being the cause of Gulf War Syndrome
- ❑ Later studies found no association, and similar levels of squalene in healthy volunteers.
- ❑ Still making the rounds of Internet and anti-vaccine groups



MPL-Monophosphoryl Lipid A

- ❑ Derivative of lipopolysaccharide (LPS) of Salmonella
 - Modified for reduced toxicity
- ❑ Used in GSK's Cervarix (HPV) vaccine
- ❑ Licensed in Europe for Hepatitis B (GSK-Fendrix®)

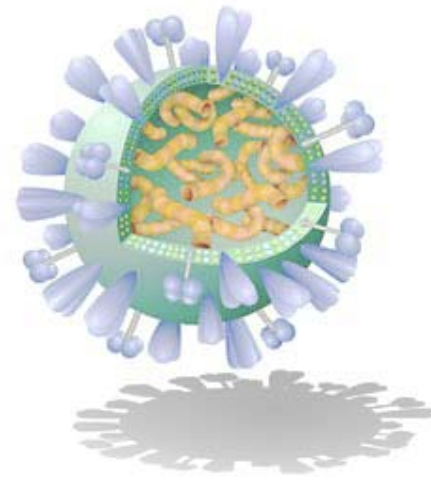
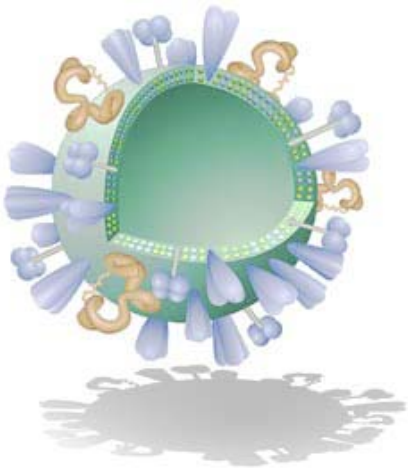


Influenza vaccines – other solutions

- Virosomes
- H1 replication using baculovirus expression vector system
 - Produces high titers H1

Virosomes

- ❑ Reconstituted empty influenza virus envelopes
- ❑ Contain hemagglutinin and neuraminidase which facilitate the uptake into antigen presenting cells.
- ❑ Mimic natural infection

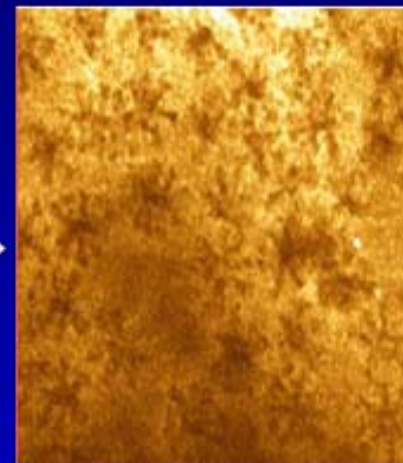
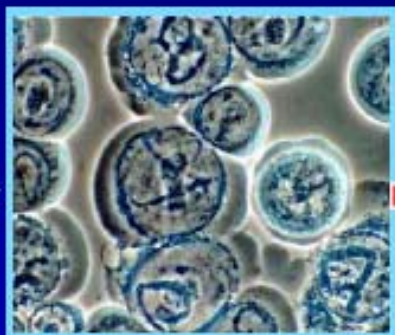
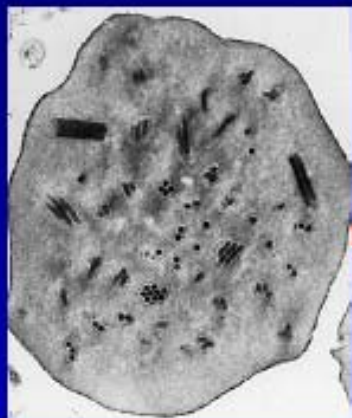


Virosome-based vaccines already licensed

- Influenza (Inflexal®)
- Hepatitis A (Epaxal®)
 - Together, these two vaccines are approved in over 45 countries
 - More than 10 million patients have been immunized to date.
 - Good safety and efficacy profile

Production of an influenza vaccine using BEVS Technology

Highly Efficient Protein Expression System: Baculovirus Expression Vector System (BEVS)



Engineer baculovirus with the gene of interest (e.g. Hemagglutinin)

Baculoviruses highly specific to insect cells

Powerful promoter generates high yield of protein of interest

- Culture expression of insect cells in a fermenter
- Infect cells with engineered virus
- Incubate infection for ~48 - 72 hours

- Protein forms rosettes
- Purify protein to > 95% into final product
- Formulate with PBS vaccine

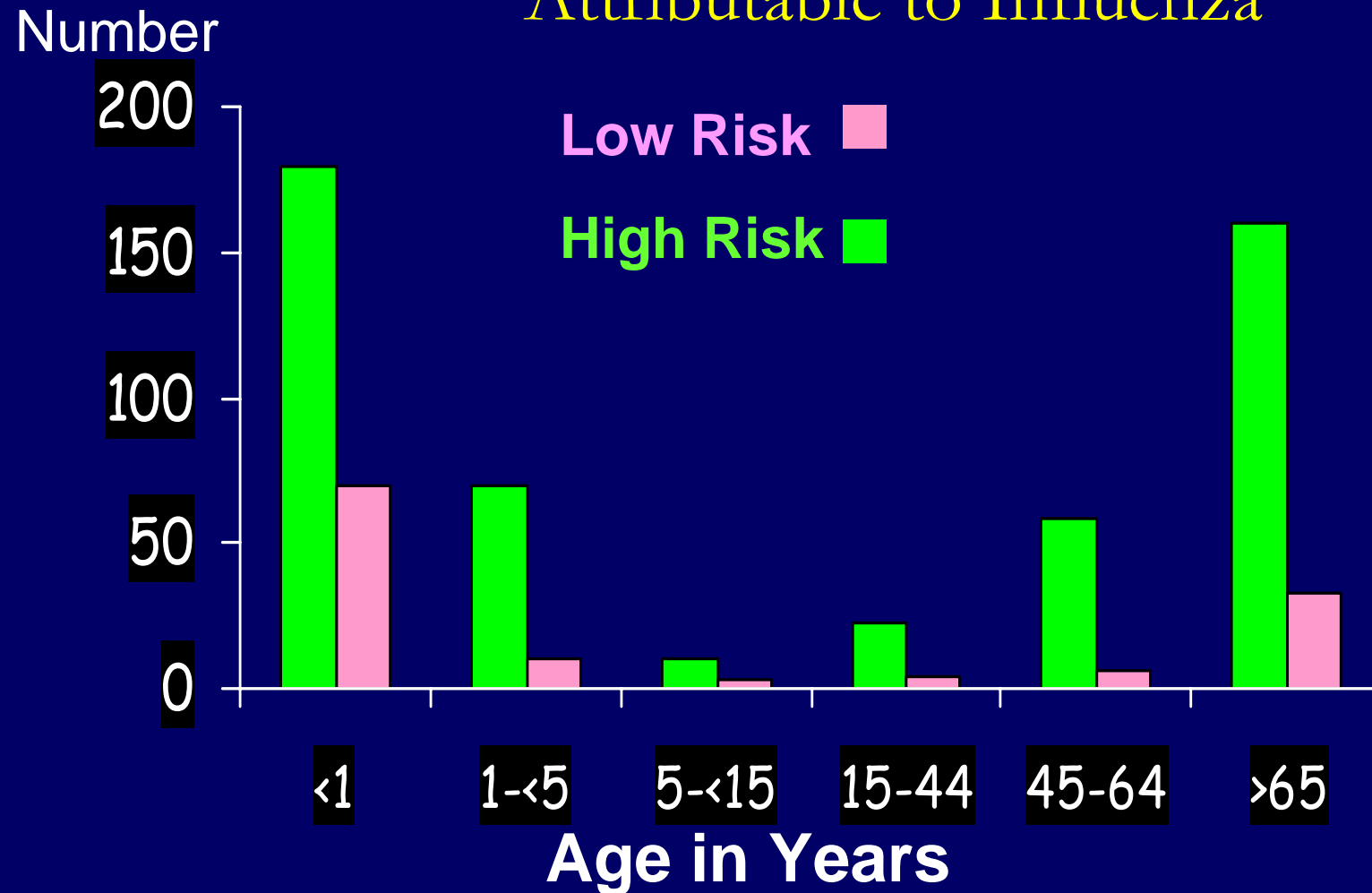
Vaccinating kids?

- ❑ Good response (after 6 months of age)
- ❑ Protects the most vulnerable
- ❑ Prevention of outbreaks
- ❑ Herd effect to protect the elderly



CHILDREN AS A HIGH RISK GROUP:

Hospitalizations Per 10,000 Persons
Attributable to Influenza



Glezen et al Am Rev Respir Dis 1987

Neuzil et al. NEJM 2000, J Peds 2000

Does vaccination of schoolchildren provide herd immunity?

- ❑ Talbot, et al. Vaccine 2009: Hospitalizations for adults 50-64 were reduced in a county with flu vaccination of school children compared to another county.
- ❑ Monto, et al. JID 1970: An unvaccinated community had 3 times more flu-like illness in all ages than an unvaccinated community.

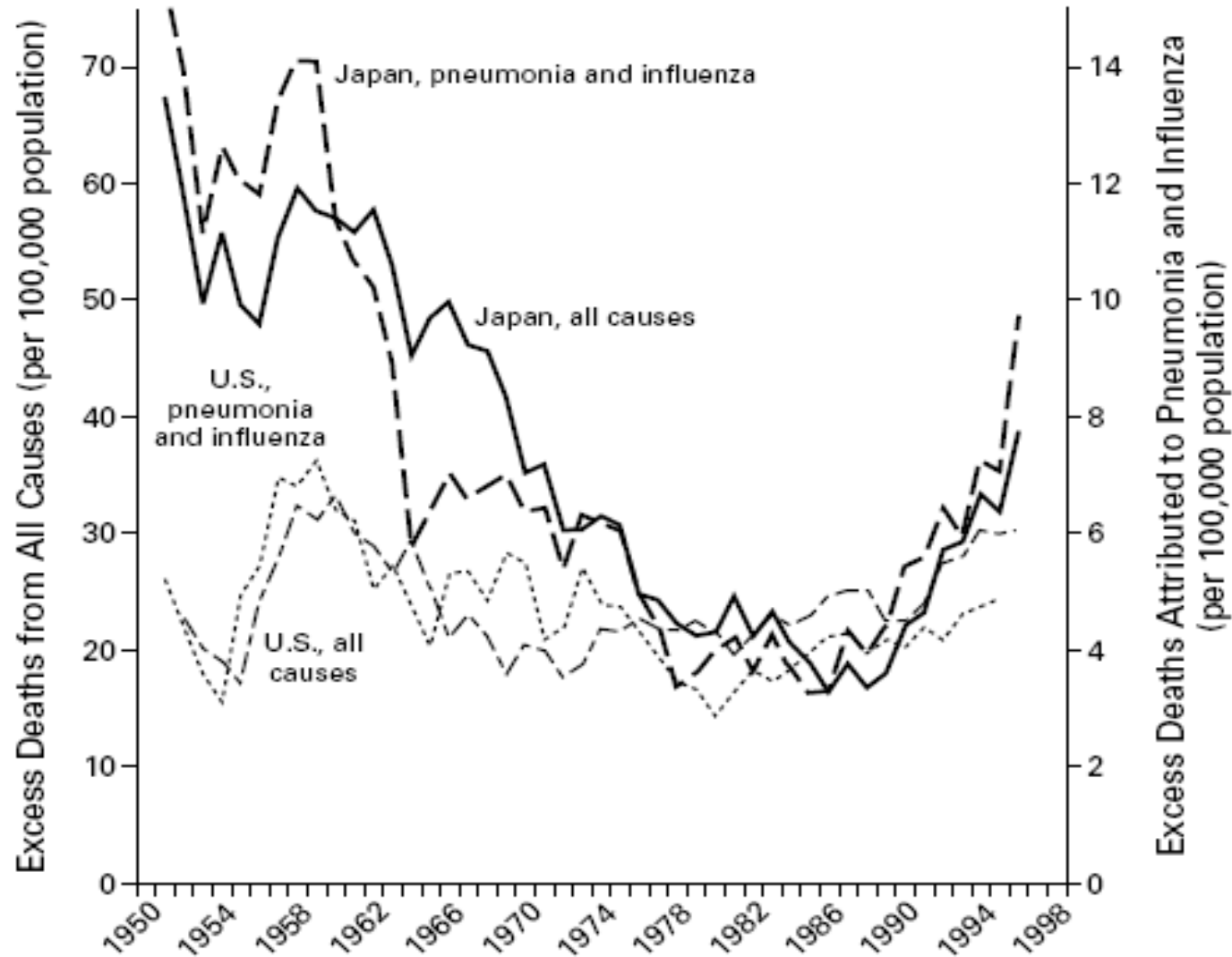


Figure 3. The Five-Year Moving Average of Excess Deaths Attributed to Both Pneumonia and Influenza and All Causes, for Japan and the United States.

Tick marks represent the beginning of the years indicated.

Why vaccinate pregnant women?

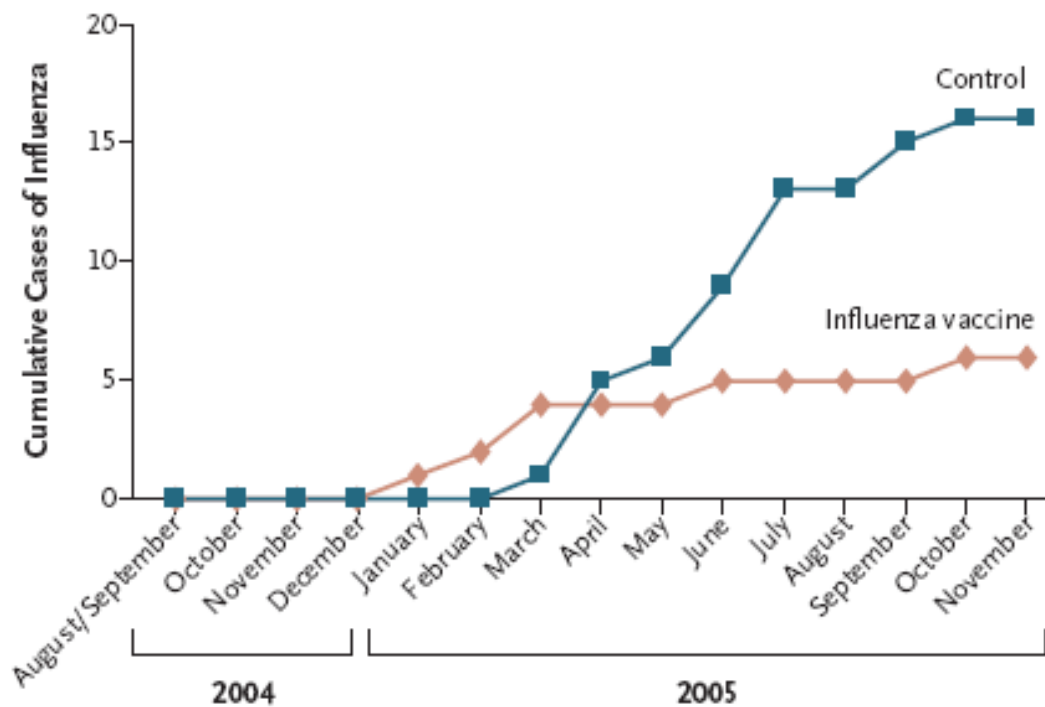


Figure 2. Cumulative Cases of Laboratory-Proven Influenza in Infants Whose Mothers Received Influenza Vaccine, as Compared with Control Subjects.

Testing for influenza antigen was performed from December 2004 to November 2005.

Seasonal Flu

- ❑ 63% reduction in confirmed flu in babies
- ❑ 29% reduction in fever and respiratory illness in the infants
- ❑ 36% reduction in fever and respiratory illness in the moms

Zaman et al. NEJM 2008

H1N1 Deaths among Pregnant Women

- Pregnant women constitute only about 1% of the general population
- 5% of deaths in US from pandemic (H1N1) 2009 Influenza were among pregnant women (CDC)

Pregnancy – vaccine concerns

- ❑ No good studies on effectiveness
- ❑ Not enough data to be convincing on safety
- ❑ Little knowledge on differences in immunity in pregnancy

Conclusions:

- ❑ H1N1 is just another flu vaccine
- ❑ Flu vaccines offer protection, but could be better
- ❑ New solutions may be necessary for the elderly
- ❑ Kids are people too
- ❑ Pregnancy is a big issue

THE END

