Efficacité vaccinale chez la personne âgée
Vaccine efficiency in the elderly

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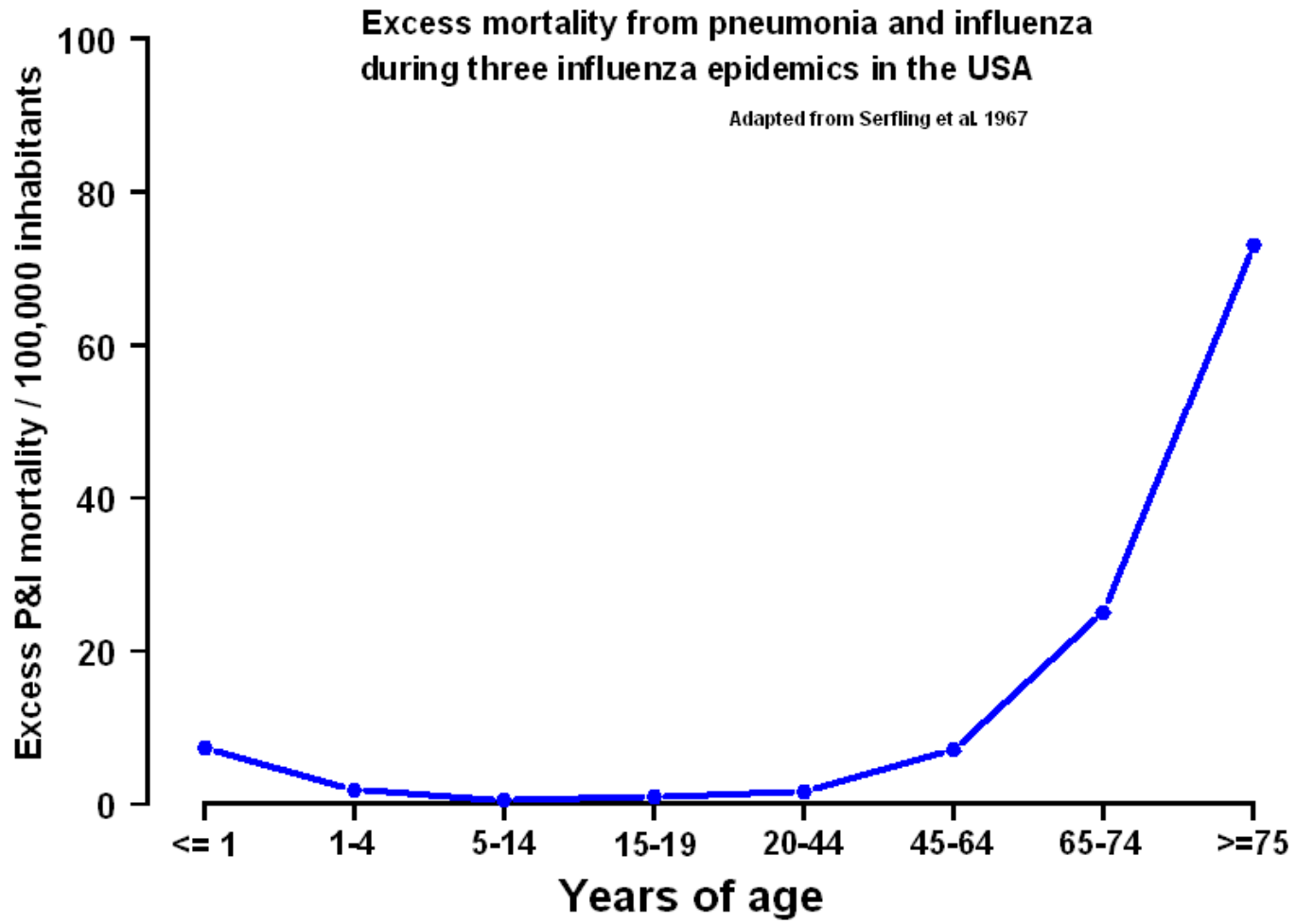
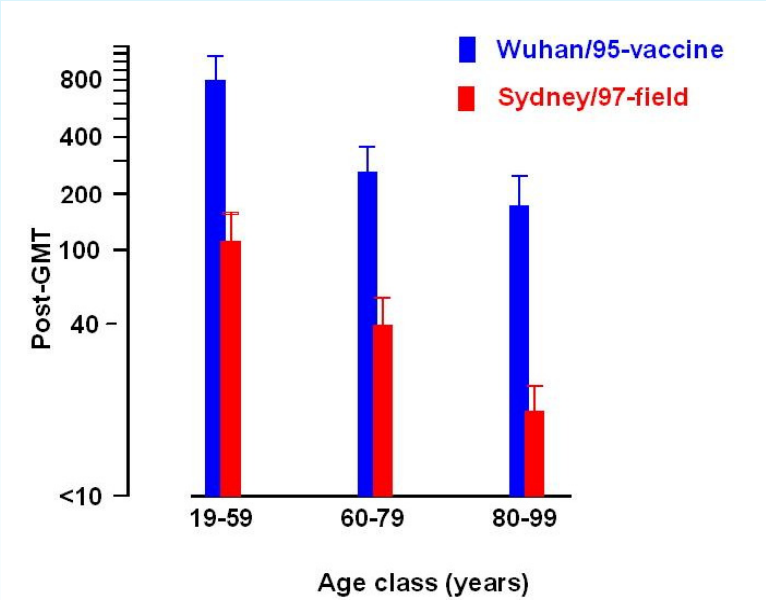
Age as risk factor for influenza mortality

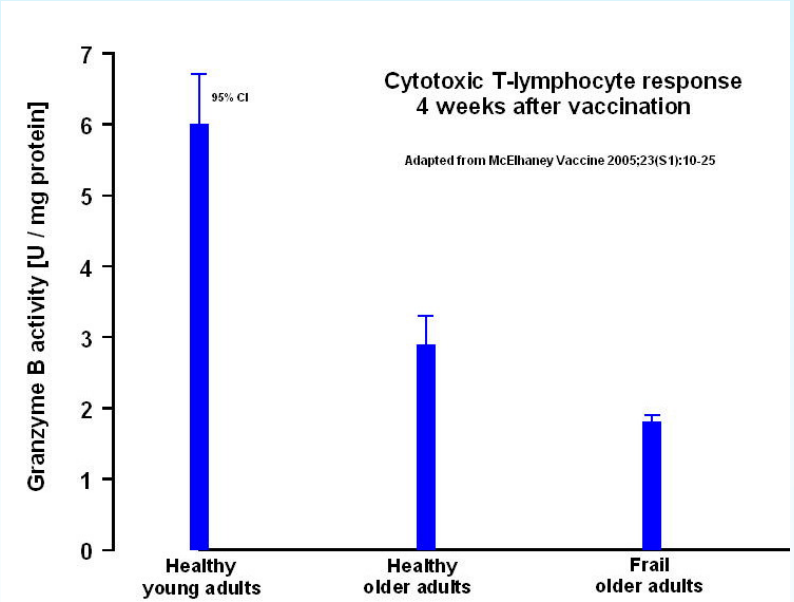


Effects of immunosenescence

- **Vaccination induces lower humoral and cellular immunity in the elderly compared to other ages.**

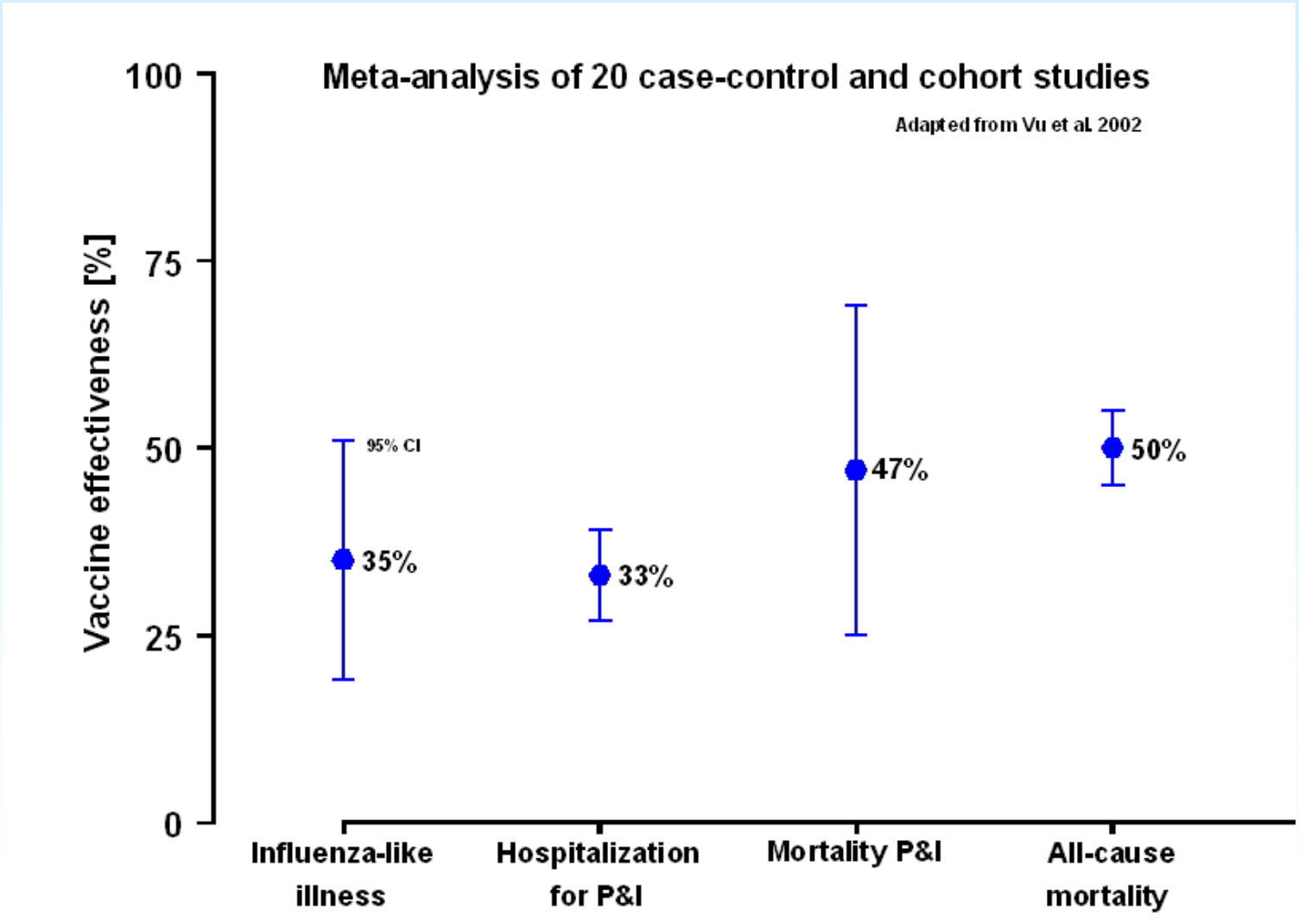


Adapted from de Jong et al. 2001



Adapted from McElhaney 2005

Observational studies in older adults



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Contradiction by Simonsen et al.

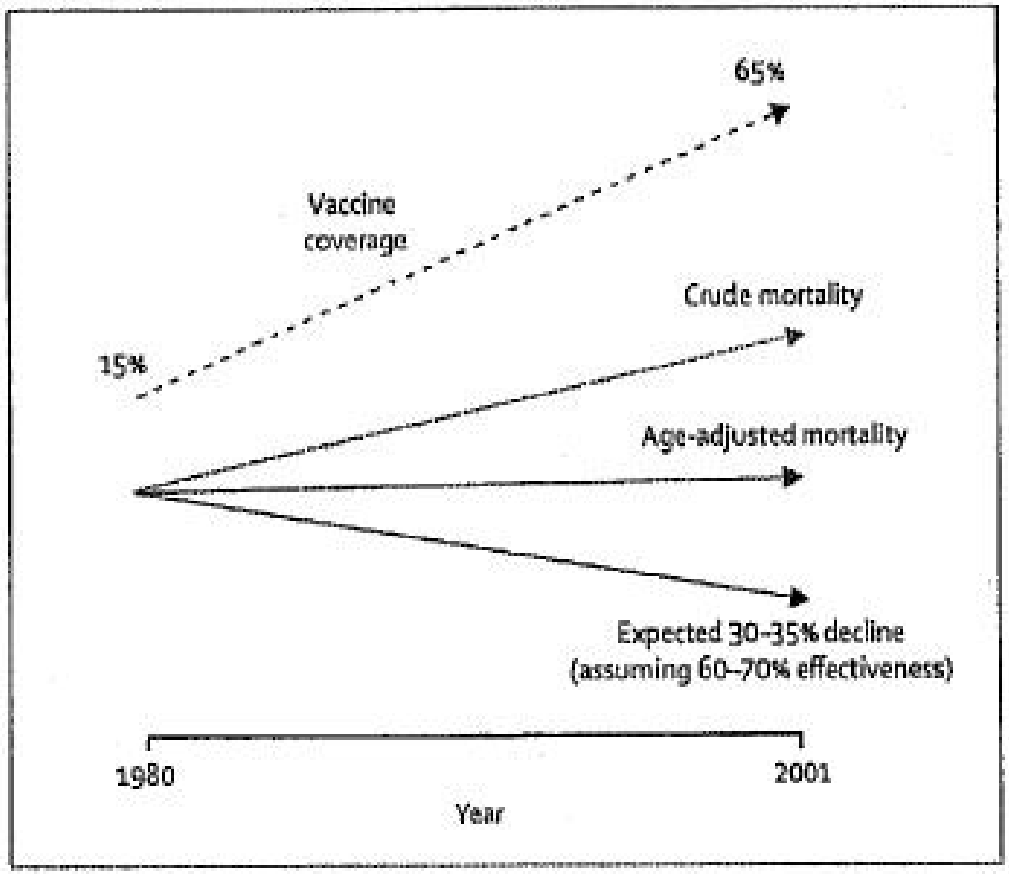

Figure 2: Crude and age-adjusted trends in vaccination and national excess pneumonia and influenza mortality in US elderly people aged 65 years or more

Simonsen et al., Lancet Infect.Dis. 2007;7:658-666

Controversy on vaccine effectiveness in older adults

"Inactivated vaccines have little or no effect…"

Yes	No
Simonsen L, Reichert TA et al. Impact of influenza vaccination on seasonal mortality in the US elderly population. Arch.Intern.Med. 2005;165:265-272.	Fedson DS, Nichol K. Should we question the benefits of influenza vaccination for the elderly? Infect.Dis.News 2005;18:6-8.
Rizzo C, Viboud C et al. Influenza-related mortality in the Italian elderly: No decline associated with increasing vaccination coverage. Vaccine 2006;24:6468-6475.	Nichol KL, Nordin JD et al. Effectiveness of influenza vaccine in the community-dwelling elderly. N.Engl.J.Med. 2007;357:1373-1381.
Jefferson T. Influenza vaccination: policy versus evidence. Br.Med.J. 2006;333:912-91.	Thijs C, Beyer WEP et al. Mortality benefits of influenza vaccination in elderly people. (Letter to the editor). Lancet Infect.Dis. 2008;8:460-461.
Simonsen L, Taylor RJ. Mortality benefits of influenza vaccination in elderly people: an ongoing controversy. Lancet Infect.Dis. 2007;7:658-666.	Hak E, Opstelten W et al. Influenza vaccination in the elderly: effectiveness not in doubt. Ned.Tijdschr.Geneeskd. 2008;152:1081-1083.

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Response of international press

The New York Times | Doubts Grow Over Flu Vaccine in Elderly

Sept. 1, 2008

FLU SHOT NOT WORTH THE BOTHER !

Indian Times 2006

Types of studies to assess vaccine efficacy / effectiveness

- **Randomised controlled trials (RCT) – gold standard**
  Random allocation of different interventions to subjects.
  Known and unknown confounding factors are evenly distributed between groups.
  Problem: Ethical issues, logistics, costs

- **Observational, cohort, case-control studies**
  Allocation to subjects is not ruled by chance.
  Problem: Biased conclusions when there are substantial differences between groups.

- **Ecological studies**
  Unit of analysis is a population rather than an individual.
  Problem: Ecological fallacy, Simpson's Paradox.

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Randomised controlled trials in older adults

Reference	Country	Population	Epidemic	Main outcome
Govaert et al. J.Am.Med.Ass. 1994	NL	1838 healthy persons ≥ 60 years-of-age	mild / medium	serologically confirmed ILI: 58% (26 to 77)
Allsup et al. Vaccine 2004	UK	729 healthy persons 65 to 74 years-of-age	mild	clinical ILI: 20% (n.s.)
Praditsuwan et al. J.Med.Assoc.Thai. 2005	Thailand	635 healthy persons ≥ 60 years-of-age	mild	clinical ILI: 44% (23 to 86)

Limitations: **no / few very old persons** **no chronically ill / frail persons**

no severe epidemics **no serious outcomes**

Observational vaccine effectiveness studies (cohort, case-control etc.)

Assignment of subjects to treatment or placebo is not ruled by chance.

Problem: Biased conclusions when there are substantial differences between groups (confounding).

Confounding factor	Treatment (vaccination)	Control (no vaccination)
Socio-economic position	high	low
Diet	healthy	not healthy
Exercise	yes	no
Frailty	few	much

Then, a difference in outcome is not (only) due to treatment, but (also) to confounding factors.

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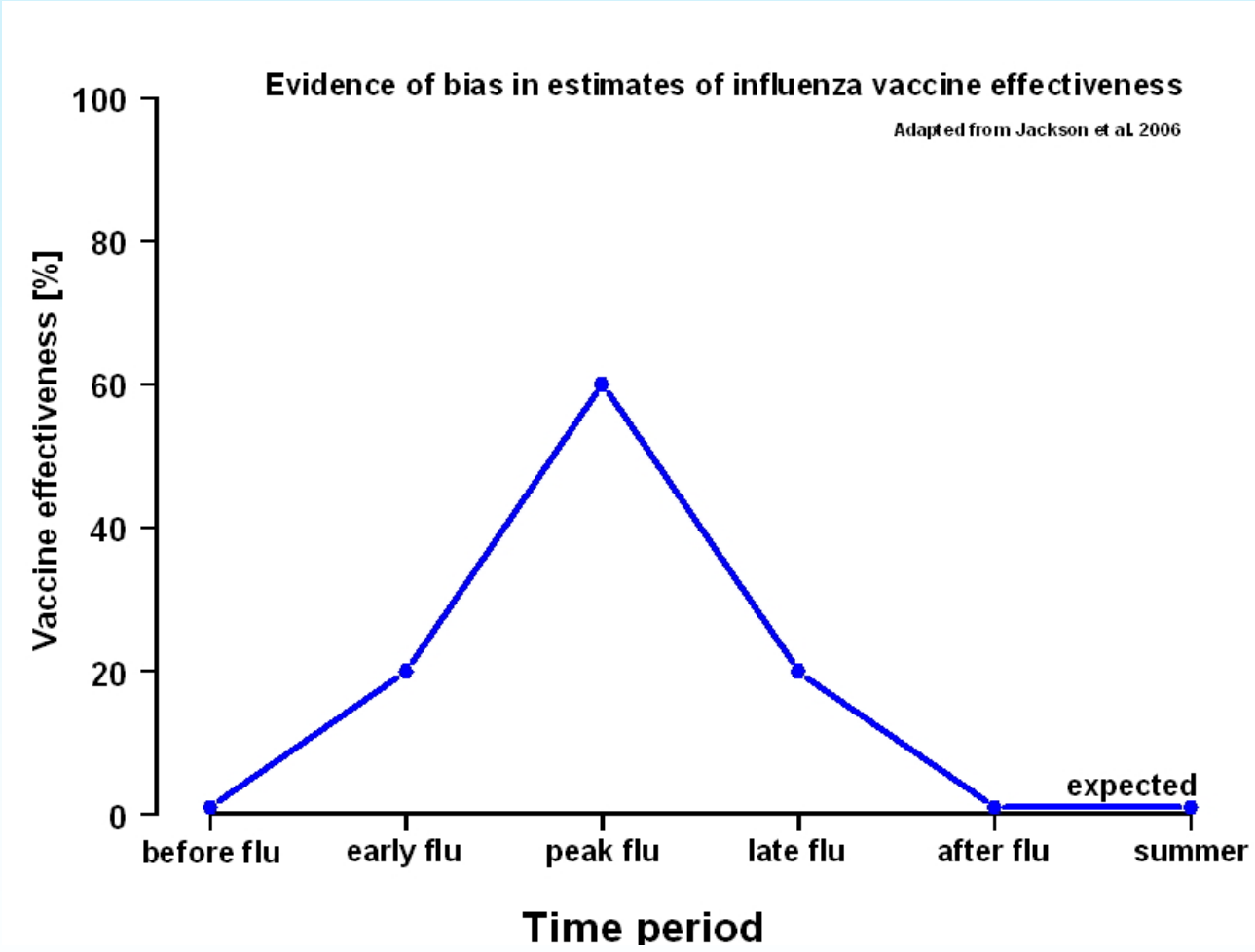
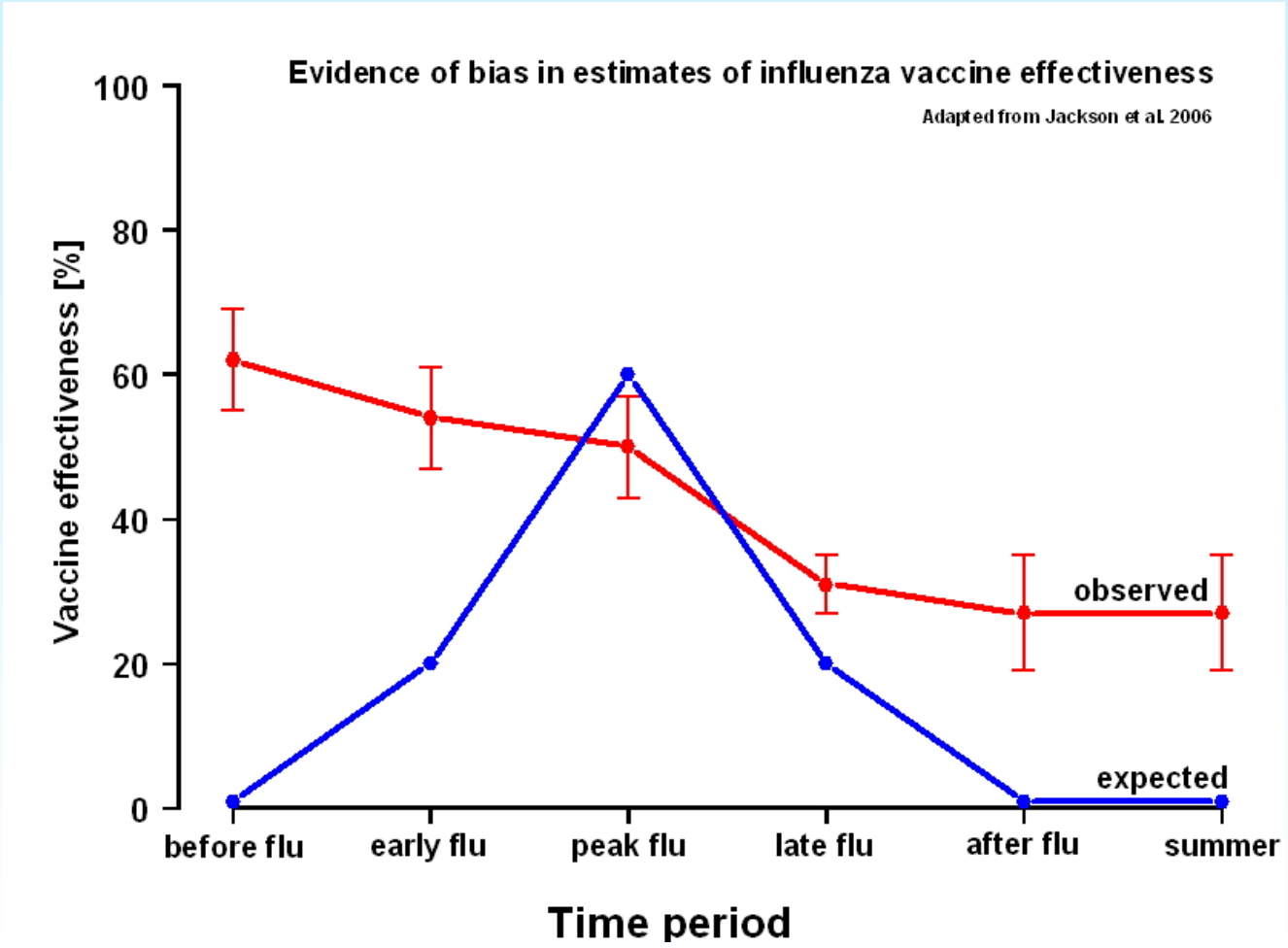
Bias in observational studies



Bias in observational studies



High quality observational studies

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 4, 2007 VOL. 357 NO. 14

Effectiveness of Influenza Vaccine in the Community-Dwelling Elderly

Kristin L. Nichol, M.D., M.P.H., M.B.A., James D. Nordin, M.D., M.P.H., David B. Nelson, Ph.D., John P. Mullooly, Ph.D., and Eelko Hak, Ph.D.

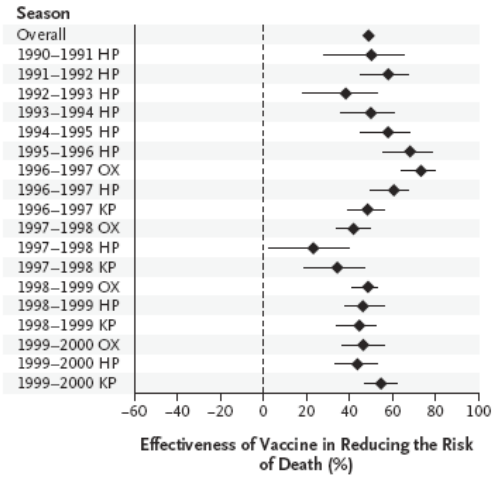


Table 2. Sensitivity Analysis to Quantify the Effects of a Hypothetical Unmeasured Confounder on the Study Results.*

Increase in the Risk of Outcome on Account of the Confounder	Prevalence of Confounder	Death	
		Vaccine Effectiveness	Adjusted Odds Ratio (95% CI)
	%	%	
—	0	48	0.52 (0.50–0.55)
Doubled	20	43	0.57 (0.55–0.60)
Doubled	40	40	0.60 (0.58–0.63)
Doubled	60	39	0.61 (0.59–0.65)
Tripled	20	38	0.62 (0.59–0.64)
Tripled	40	35	0.65 (0.63–0.69)
Tripled	60	33	0.67 (0.64–0.70)

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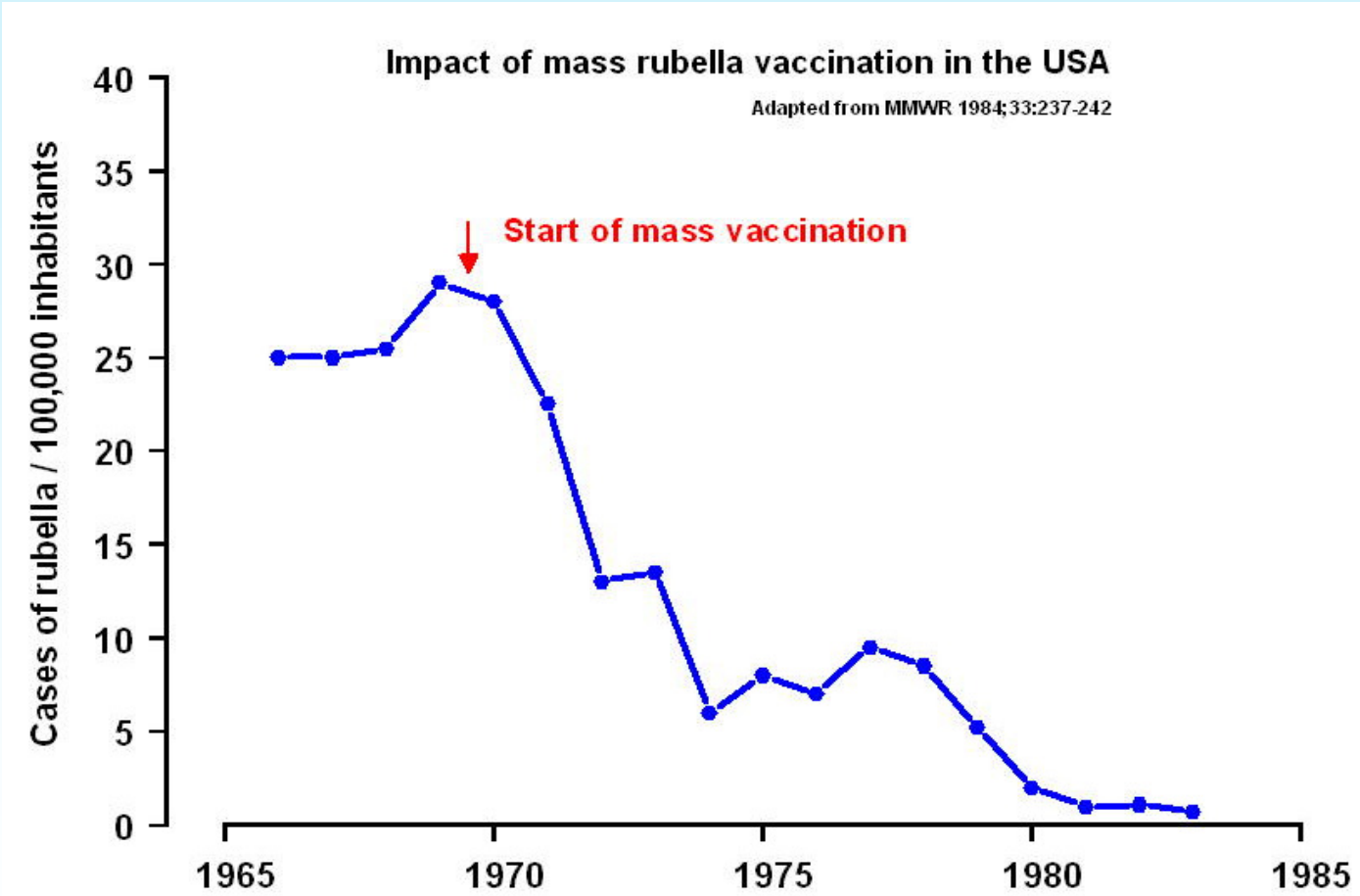
Ecological studies

Unit of analysis is a population rather than an individual



Can we do this for influenza vaccine as well?

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Ecological study: Impact of influenza vaccination on all-cause death in the USA

Influenza-related mortality in persons 65 years or older in the USA 1968 – 2001 (Simonsen et al. 2005).

Collected data (per winter season):

- **Predominant influenza virus (sub)type: A-H3N2, A-H1N1, B**
- **Influenza vaccination coverage**
- **Total number of all-cause winter deaths**
- **Number of all-cause excess deaths**

Season	(Sub)type	Coverage	Total deaths	Excess deaths	Excess mortality
1972-73	A-H3N2	16%	451 754	10 327	2.3%

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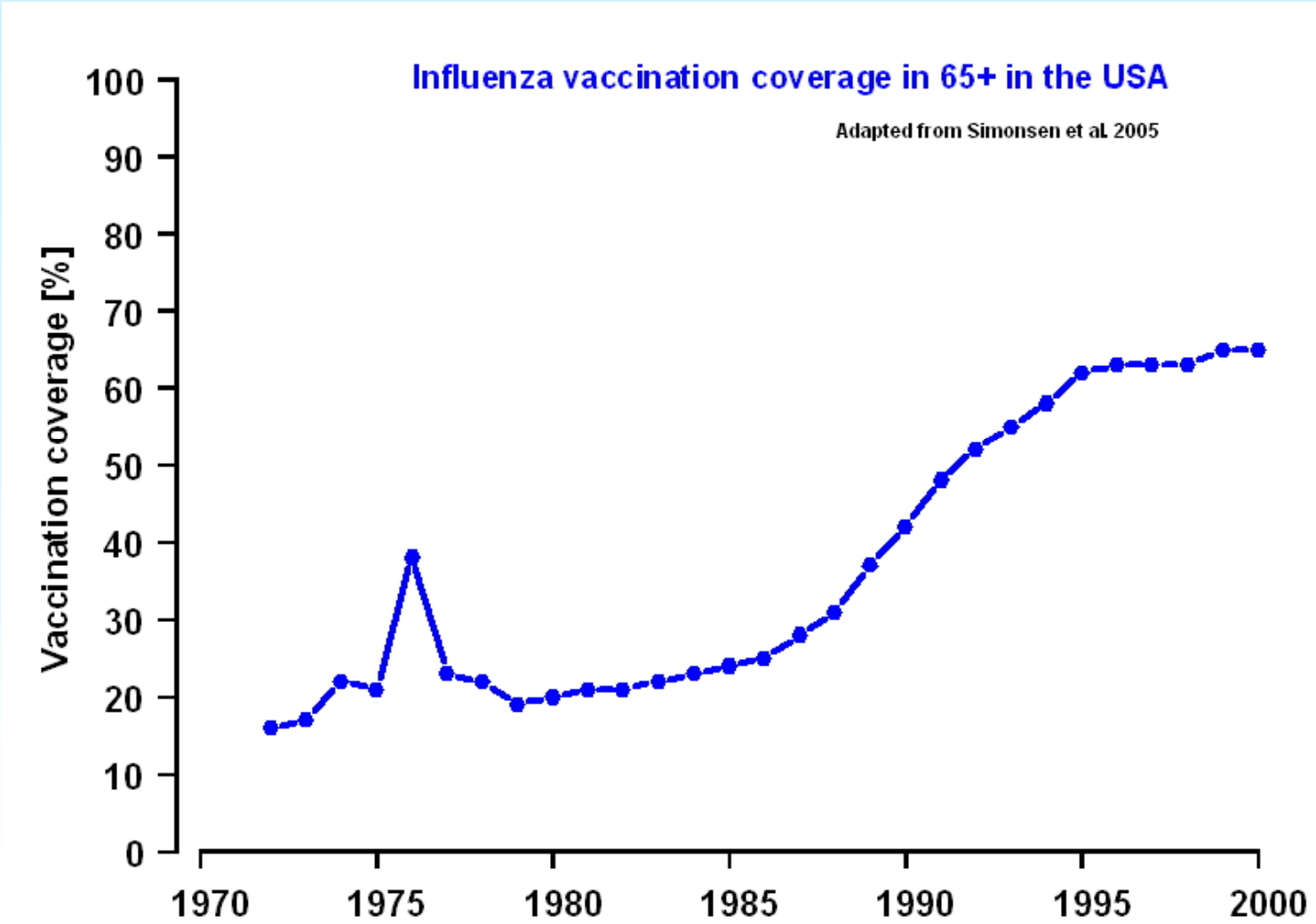
Influenza vaccination coverage in persons ≥65 years in the USA



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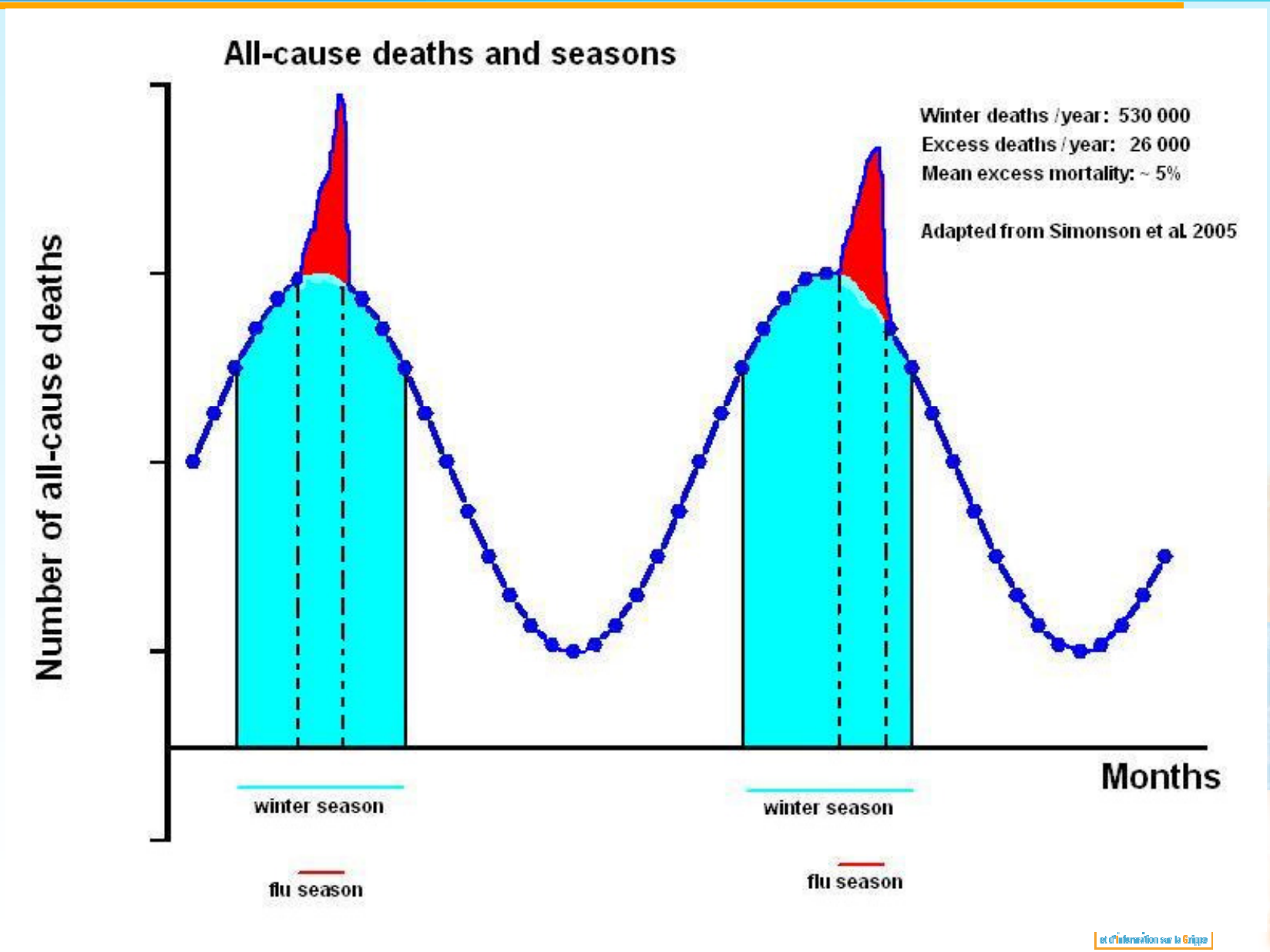
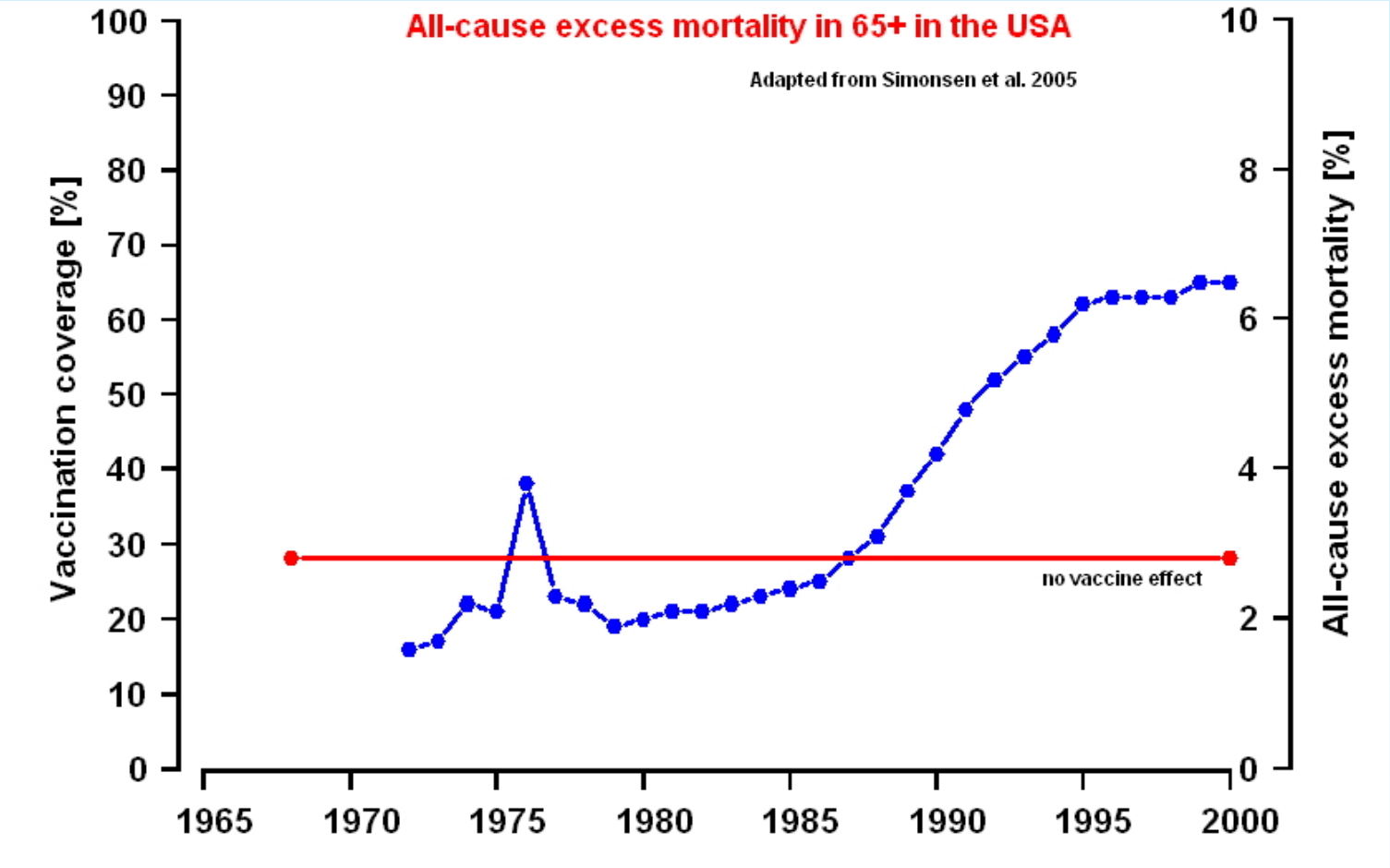
Excess all-cause mortality



Influenza-related mortality in persons ≥65 years in the USA



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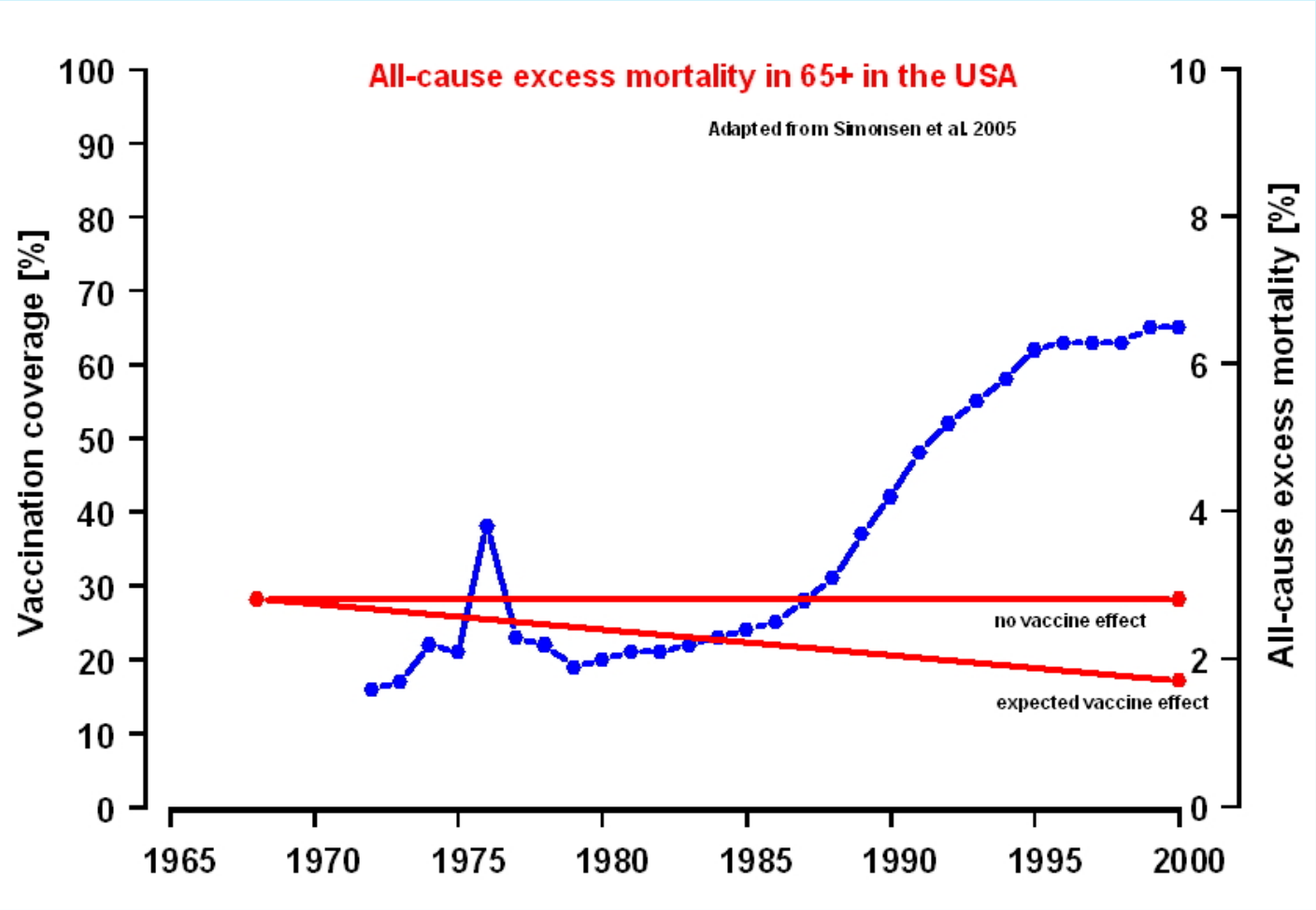

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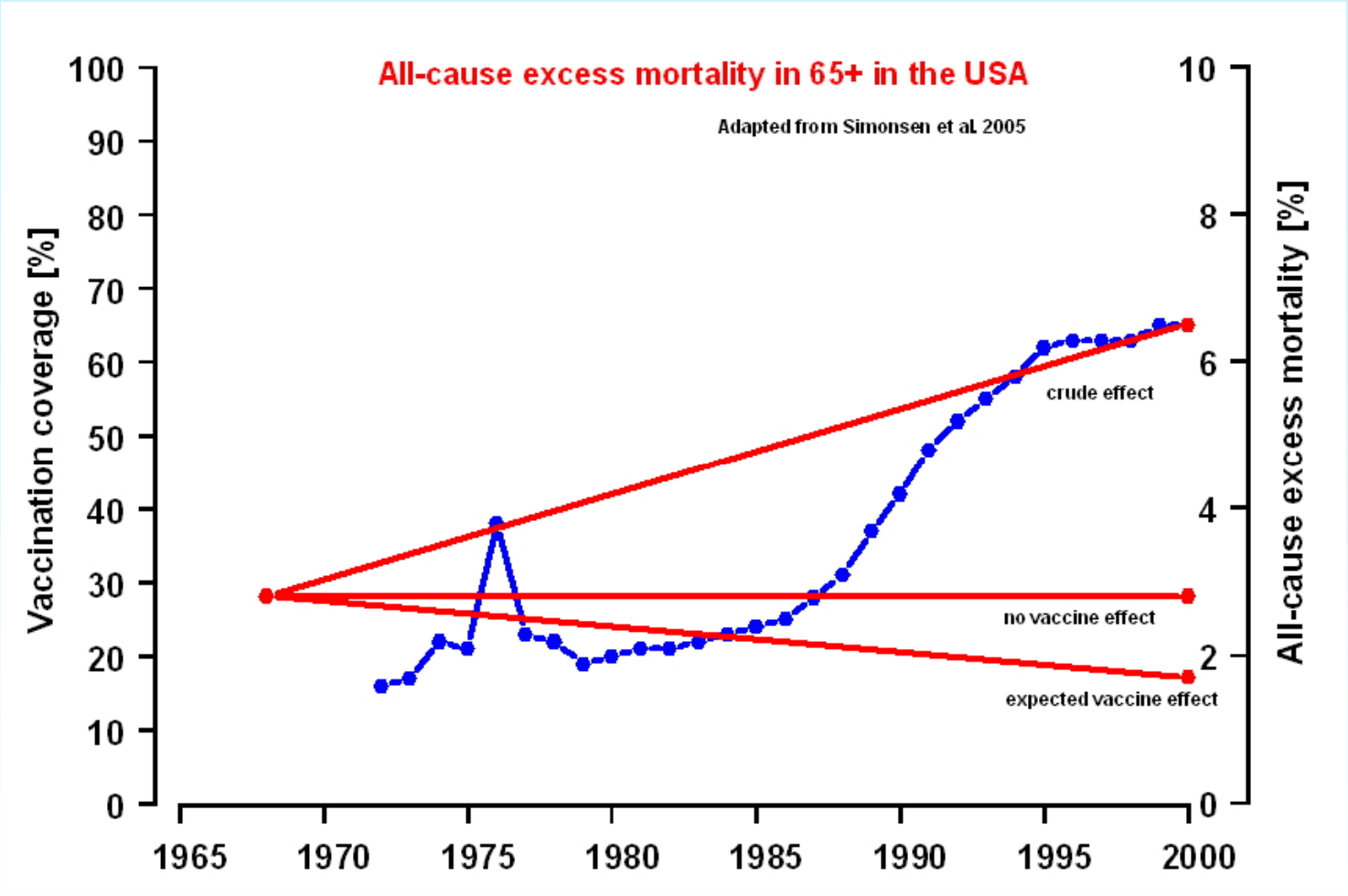

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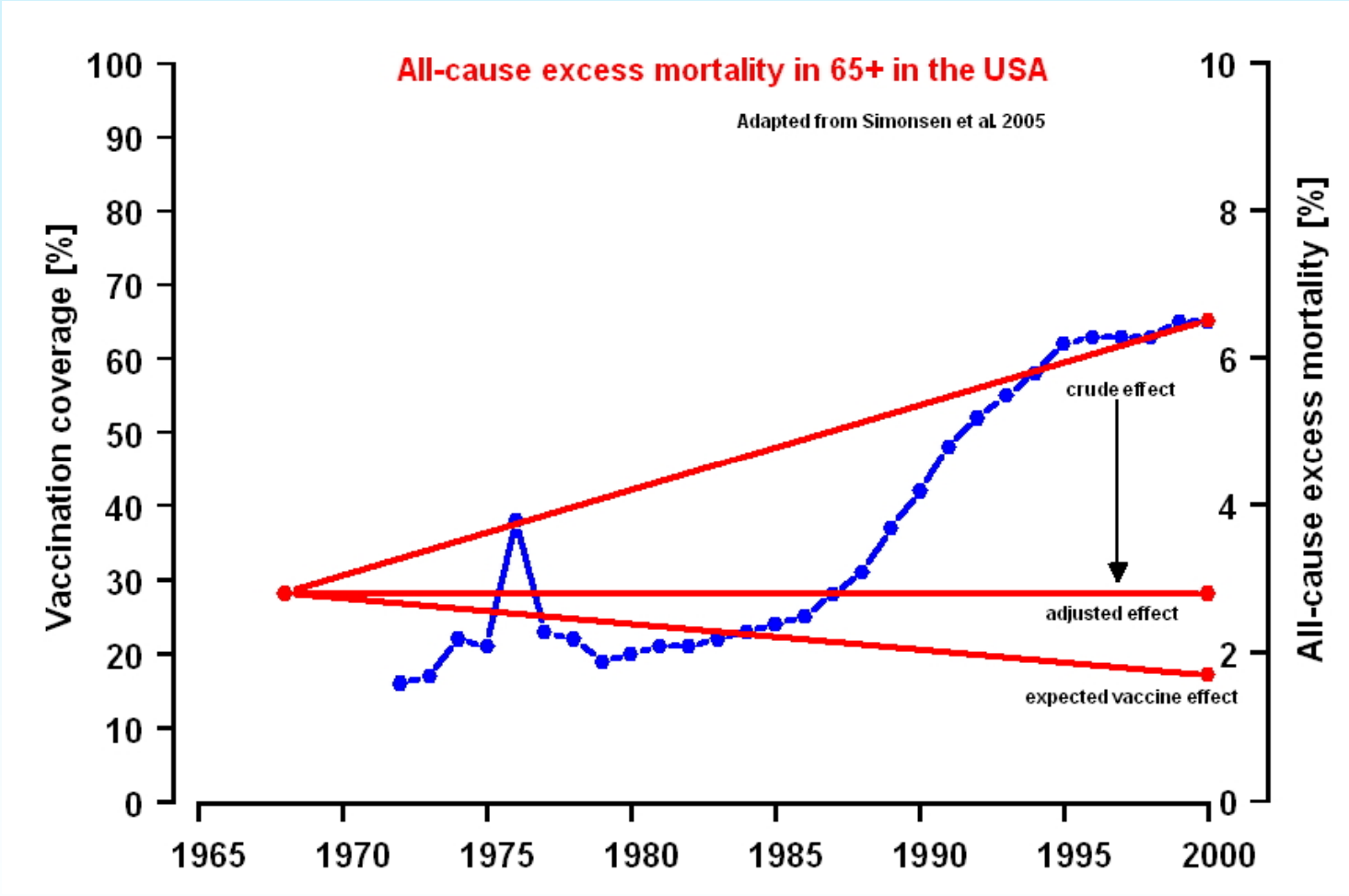

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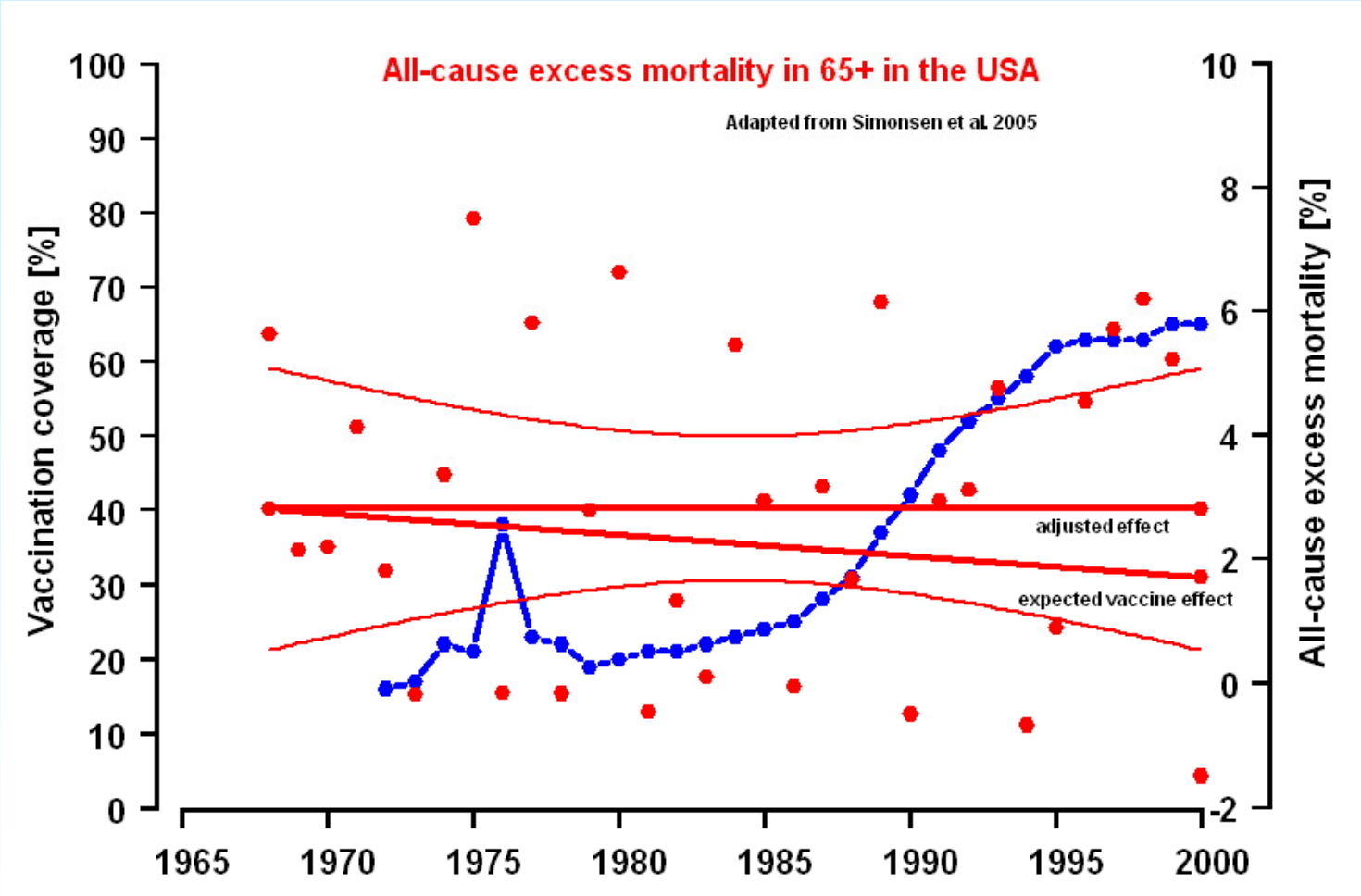
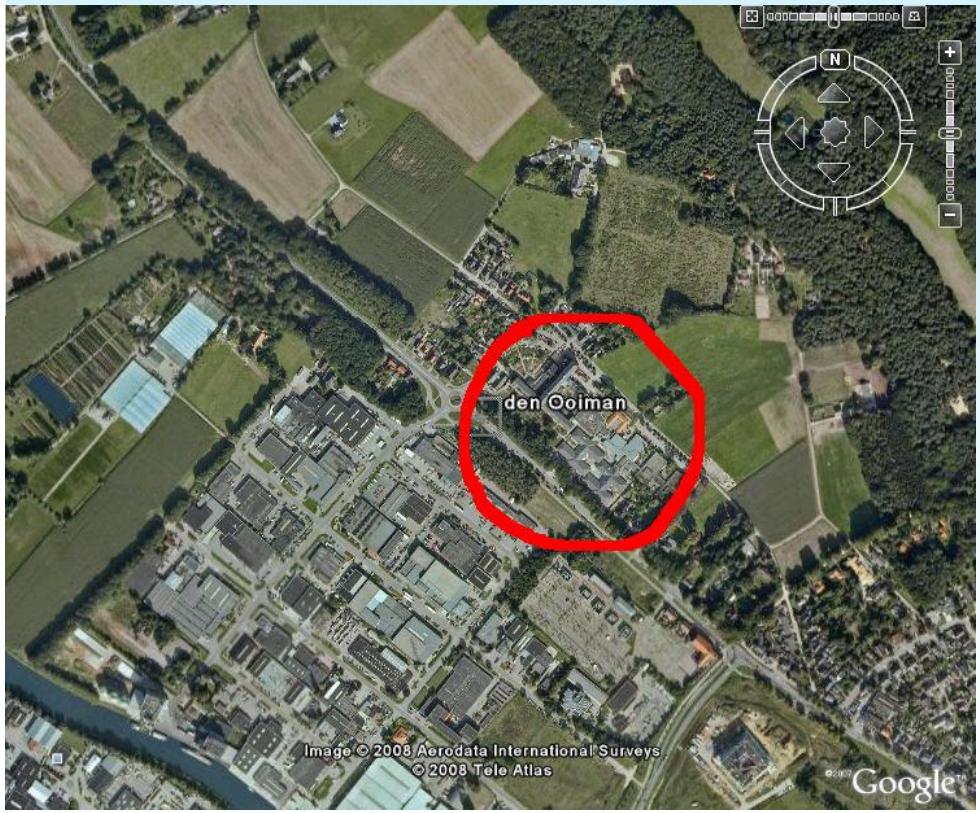


Disparity of influenza attack rates: Nursing home Den Ooiman (NL)

Influenza January 1986



	# total	# ILI	attack rate
all	276	103	37%
ER	30	0	0%
JA	31	0	0%
OL	33	6	18%
KA	32	13	41%
CL	31	13	42%
FO	27	14	52%
MI	30	17	57%
MA	31	18	58%
WI	31	22	71%

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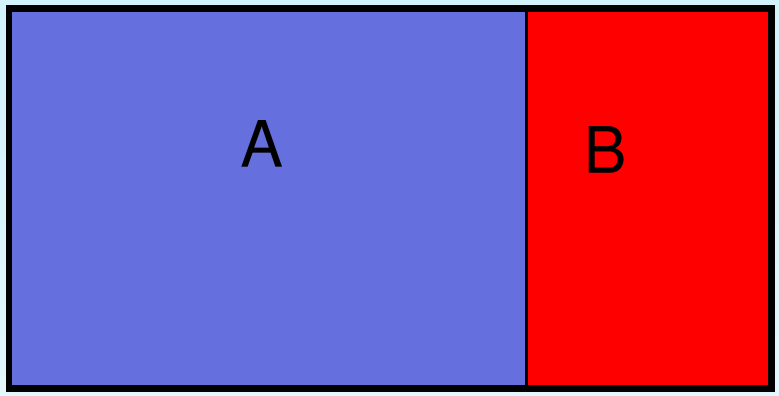
Disparity of vaccination coverage rates

Ecological study: Unit of analysis is a population rather than an individual

Two populations



# total	200	100
vacc.coverage	0%	100%
attack rate	20%	20%
# cases	40	0

Ecological approach

# total	300	(200+100)
vacc. cov.	33%	(100/300)
# cases	40	(40+0)
attack rate	13%	(40/300)

Simpson's Paradox

Vaccination state	City A			City B		
	N total	N infection	infection rate	N total	N infection	infection rate
vaccinated	49,000	10,000	20.4%	580,000	170,000	29.3%
not vaccinated	411,000	104,000	25.3%	140,000	45,000	32.1%
Vaccine efficacy	+19.3%			+8.8%		

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Simpson's Paradox

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not vaccinated	411,000	104,000	25.3 %	140,000	45,000	32.1 %
Vaccine efficacy	+19.3 %			+8.8 %		

Vaccination state	City A + City B		
	N total	N infection	infection rate
vaccinated	49,000 + 580,000	10,000+ 170,000	28.6 %
not vaccinated	411,000+ 140,000	104,000+ 45,000	27.0 %
Vaccine efficacy	-5.8 %		

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Influenza-related mortality in persons ≥65 years in the USA 1968 – 2001

- The ecological excess mortality study of Simonsen et al. (2005) does not suffer from selection bias.
- But it can suffer from ecological fallacy and Simpson's Paradox.
- An ecological study cannot prove causality between two factors (here: vaccination and mortality).
- Precision of estimates may be low.

"… a mortality reduction corresponding to 30% vaccine effectiveness would not have been detected…"

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No confidence intervals

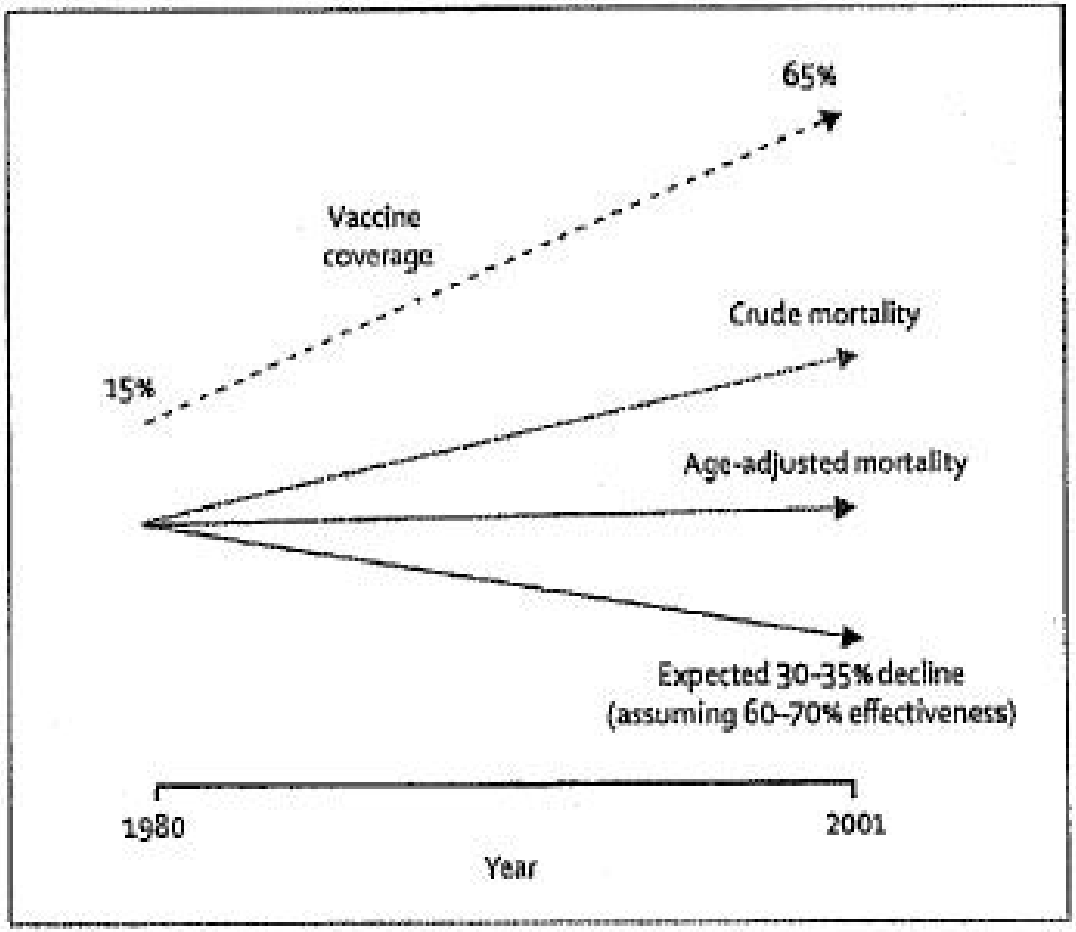

Figure 2: Crude and age-adjusted trends in vaccination and national excess pneumonia and influenza mortality in US elderly people aged 65 years or more

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General conclusions

- **Critical evaluation of all available evidence:**

  Influenza vaccination is effective in preventing serious influenza-related illness and death in the elderly.

- **However, the quantitative degree of vaccine efficacy / effectiveness may be lower than previously thought, particularly in the very old and very frail.**

- **Awaiting better influenza vaccines for older people, we should continue to vaccinate.**

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