Modeling influenza threats to aid pandemic preparedness

Cécile Viboud, Fogarty International Center, NIH
Lone Simonsen (NIAID, NIH)
Mark Miller (FIC, NIH)
Bryan Grenfell (Pennsylvania State University)

AAAS Forum on Policy & Technology, Apr 20, 2006

Outline

- Brief introduction of influenza epidemiology
- Lessons from historical pandemics
- Predicting the possible spread of future pandemics and the impact of interventions
- Conclusion

Seasonal influenza epidemics

- Wintertime epidemics
- Impact
  - 5-15% of the population infected every winter;
  - ~48,000 deaths in the US each year (1990-present), mostly in the elderly.
- Cycling of strains
  - 3 influenza (sub-)type co-circulate today : A/H3N2, A/H1N1, B
  - The virus constantly mutates (antigenic variants emerge every 2-5 years)
  - Mortality impact (and transmissibility) related to circulating subtype: A/H3N2 > B > A/H1N1

Simonsen et al, Arch Intern Med, 2005; Cox et at, Lancet, 2000

Influenza pandemics

- 16 influenza subtypes in birds; 3 routinely infect humans. Influenza viruses in other mammals (pigs).
- Emergence of a new subtype in humans (reassortment between avian and human viruses or gradual mutations of an avian virus)
- Rare event; the new virus must be transmissible from human to human (receptor differences in birds and humans)
- No or low pre-existing immunity => high incidence rate (30% and over), high death rate
- 3 well documented events

  1918 [A/H1N1], 1957 [A/H2N2] et 1968 [A/H3N2]
- Recent threat: A/H5N1 avian flu, 2003-2005, 196 human cases, 110 deaths in 9 countries*. Limited evidence of human-to-human transmission.

* WHO, as of Apr 19, 2006

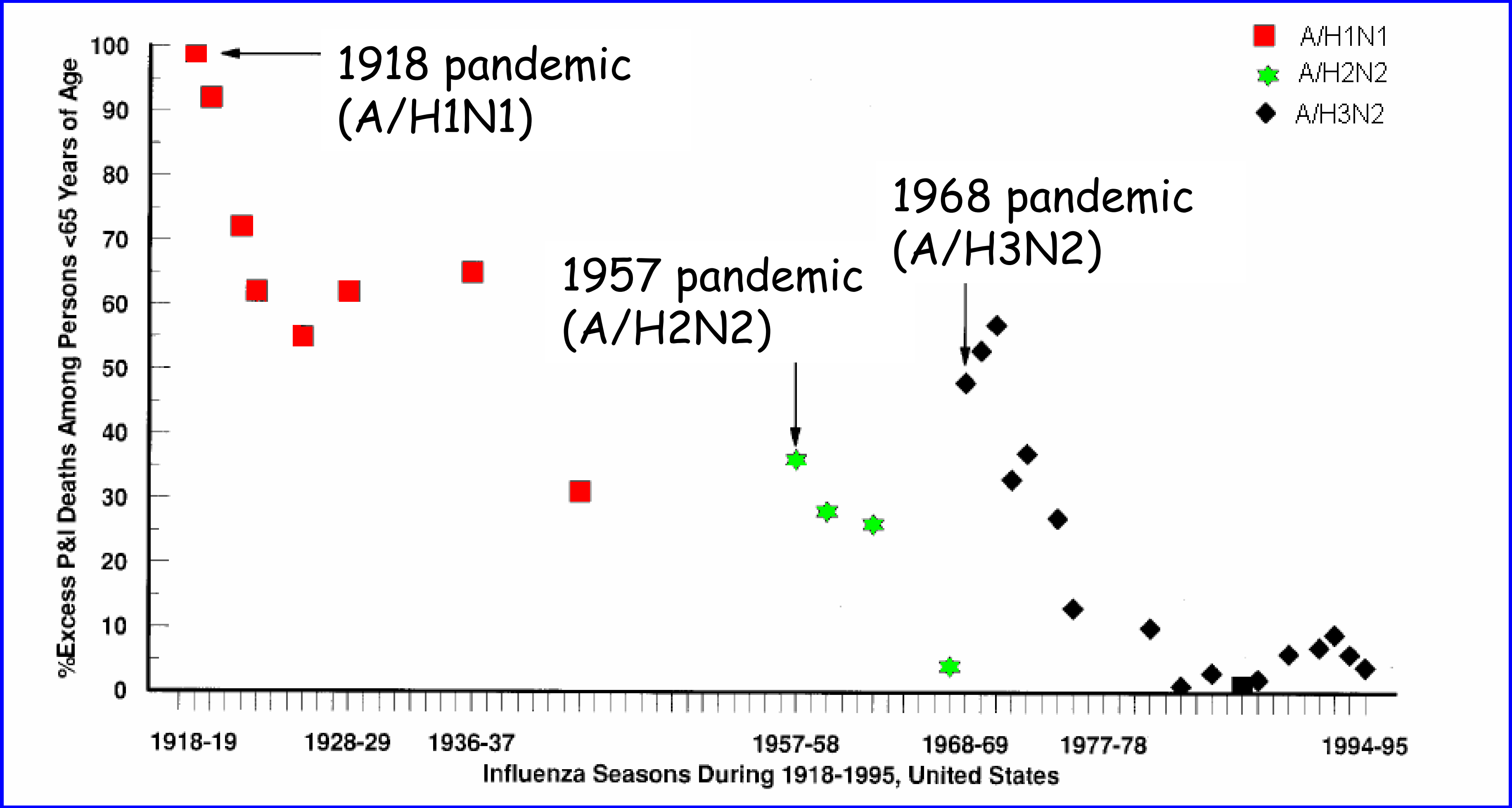
Influenza A evolution in humans

- 8 gene segments, two major surface antigens: hemagglutinin and neuraminidase
- Pandemic: new hemagglutinin

	Excess Deaths (US)	Excess Deaths per 100,000 population (US)
1918-19 A/H1N1	**~ 675,000**	**530**
1957-58 A/H2N2	**~ 60,000**	**40**
1968-69 A/H3N2	**~ 50,000**	**27**

Simonsen & al, IOM, 2004; Taubenberger et al, Nature, 2005

Age-shift: ~50% pandemic deaths in persons < 65 years After ~ 1 decade "epidemic" pattern is restored



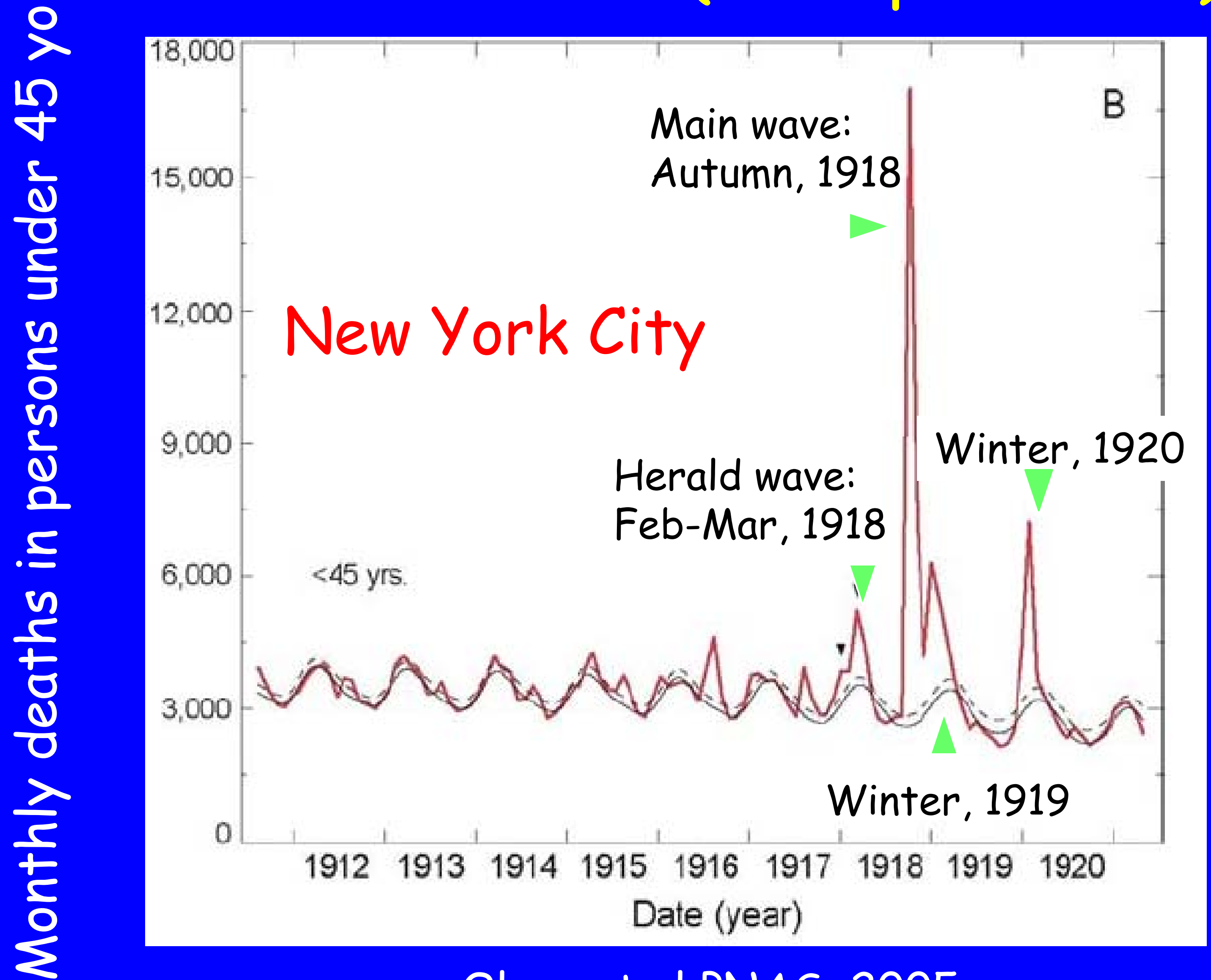
Adapted from Simonsen & al, JID, 1998

Predictive models of influenza

- Genetic and antigenic evolution of the virus
- Timing and mortality - morbidity impact
- Geographical spread
- Effectiveness of intervention strategies for controlling outbreaks

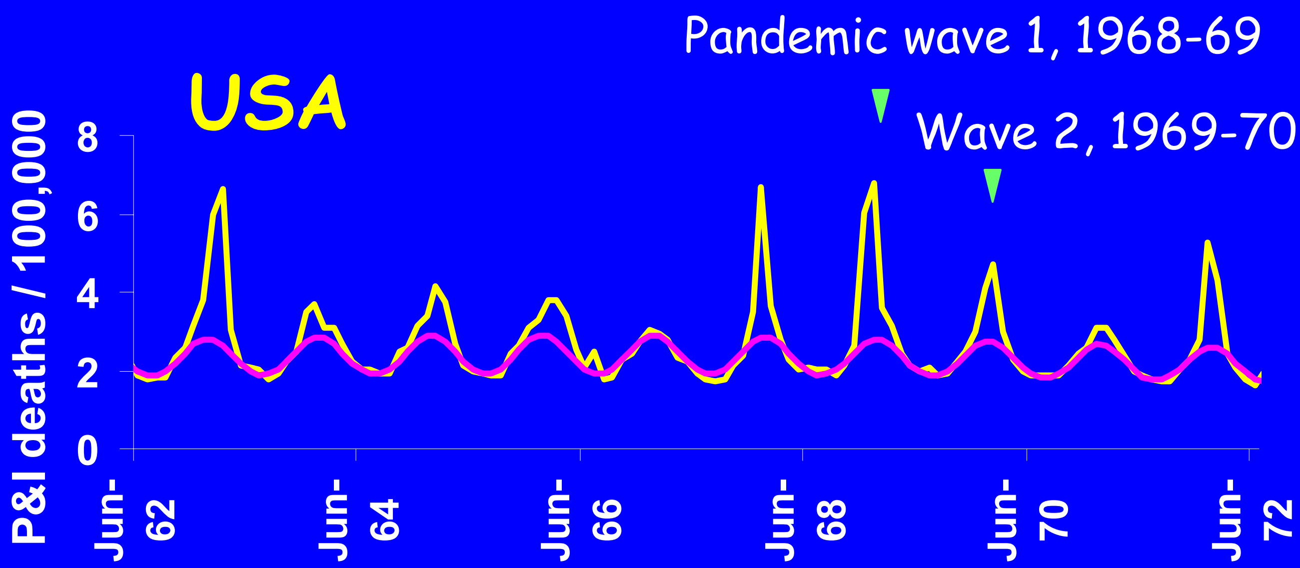
Lessons from past pandemics

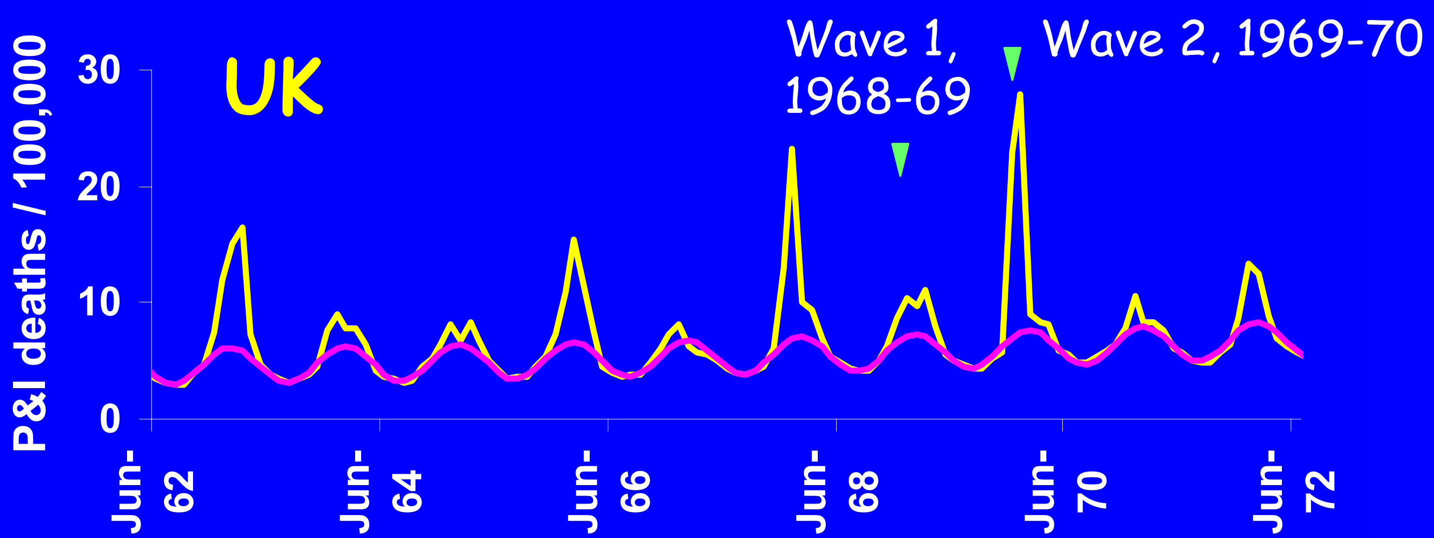
Early warning: pandemics come in several waves (1918 pandemic)



Olson et al PNAS, 2005

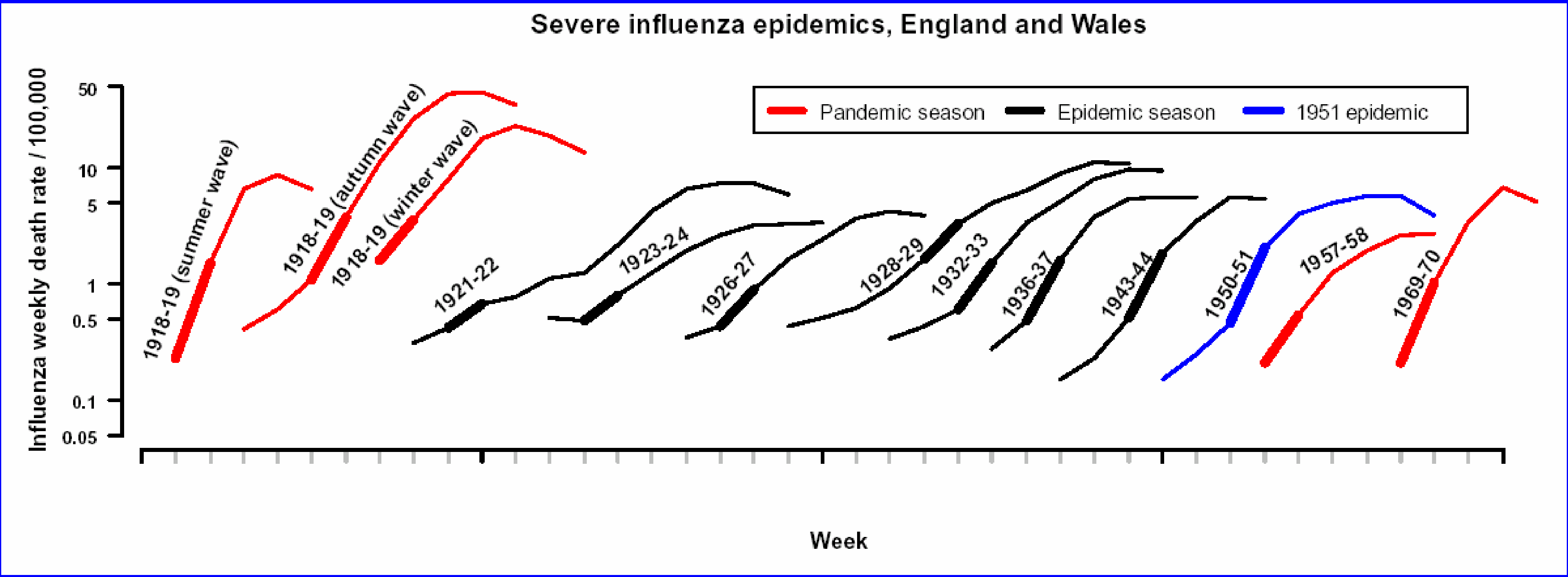
1968 pandemic: "mild" pandemic; major impact delayed by one year in Europe and Asia





Viboud et al, JID, 2005

Transmissibility of epidemic and pandemic influenza, England & Wales, 1918-1970



R for seasonal influenza ~ 1.3-1.5
R for pandemic influenza ~ 1.9-2.2

Viboud et al, Vaccine, 2006; Mills et al, Nature, 2004

Summary of lessons from past pandemics

- Mortality impact vary variable (differences >1 order of magnitude)
- More deaths and infections to be expected in the younger age groups, as compared with seasonal flu epidemics
- Lead time of 6 months to a year before full-blown peak impact (seasonality, virus evolution and population immunity)
- Transmissibility higher for pandemics than for seasonal epidemics (more susceptible hosts in the population)

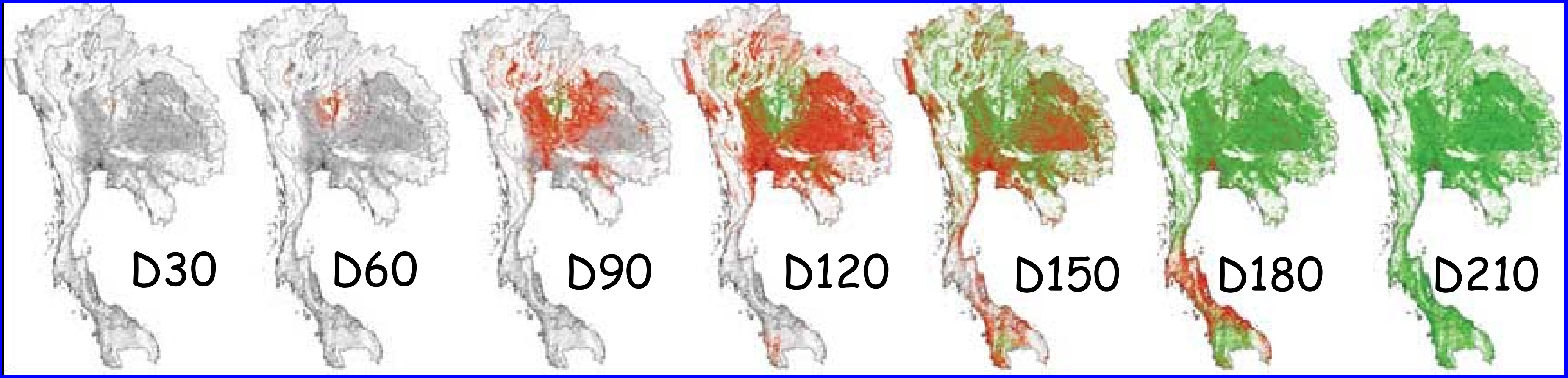
Modeling the spread of pandemic influenza and intervention strategies

Policy options

- Medical measures
  - vaccine (priority groups)
  - antivirals (prophylaxis, treatment)
- Non-medical measures (social distancing)
  - school closure
  - travel restrictions
  - isolation of cases and their contacts
  - masks

Controlling pandemic influenza at the source in South-East Asia

Simulated uncontrolled pandemic in Thailand



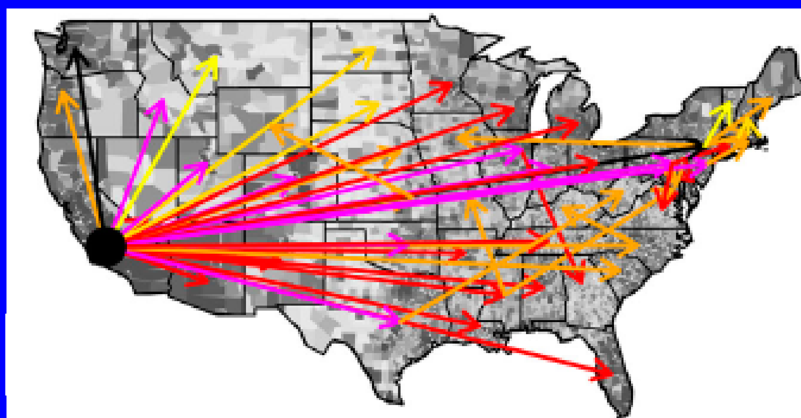
- influenza infections
- recovered or dead

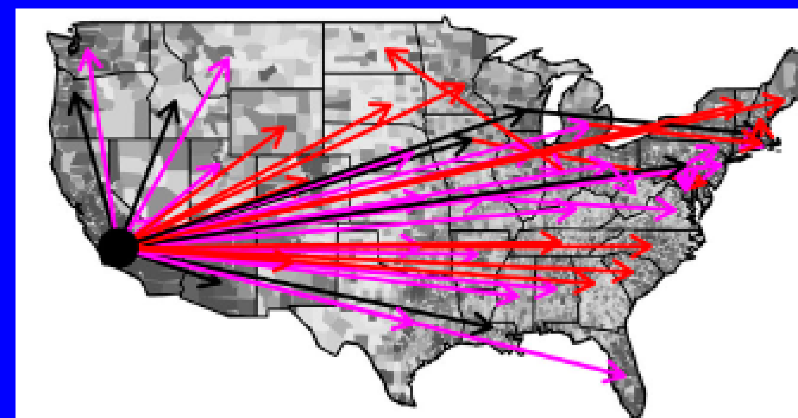
-Earliness of intervention
-Transmissibility of virus
-Size of stockpile of antivirals

Ferguson et al, Nature, 2005; Longini et al, Science, 2005

Predicted transcontinental spread of epidemic and pandemic flu in the US

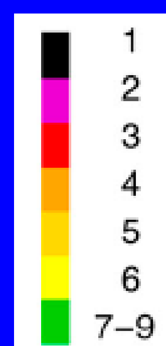
Initial case in California; spread via commutes to work





Epidemic scenario: R=1.4
Spreads in 4-7 weeks

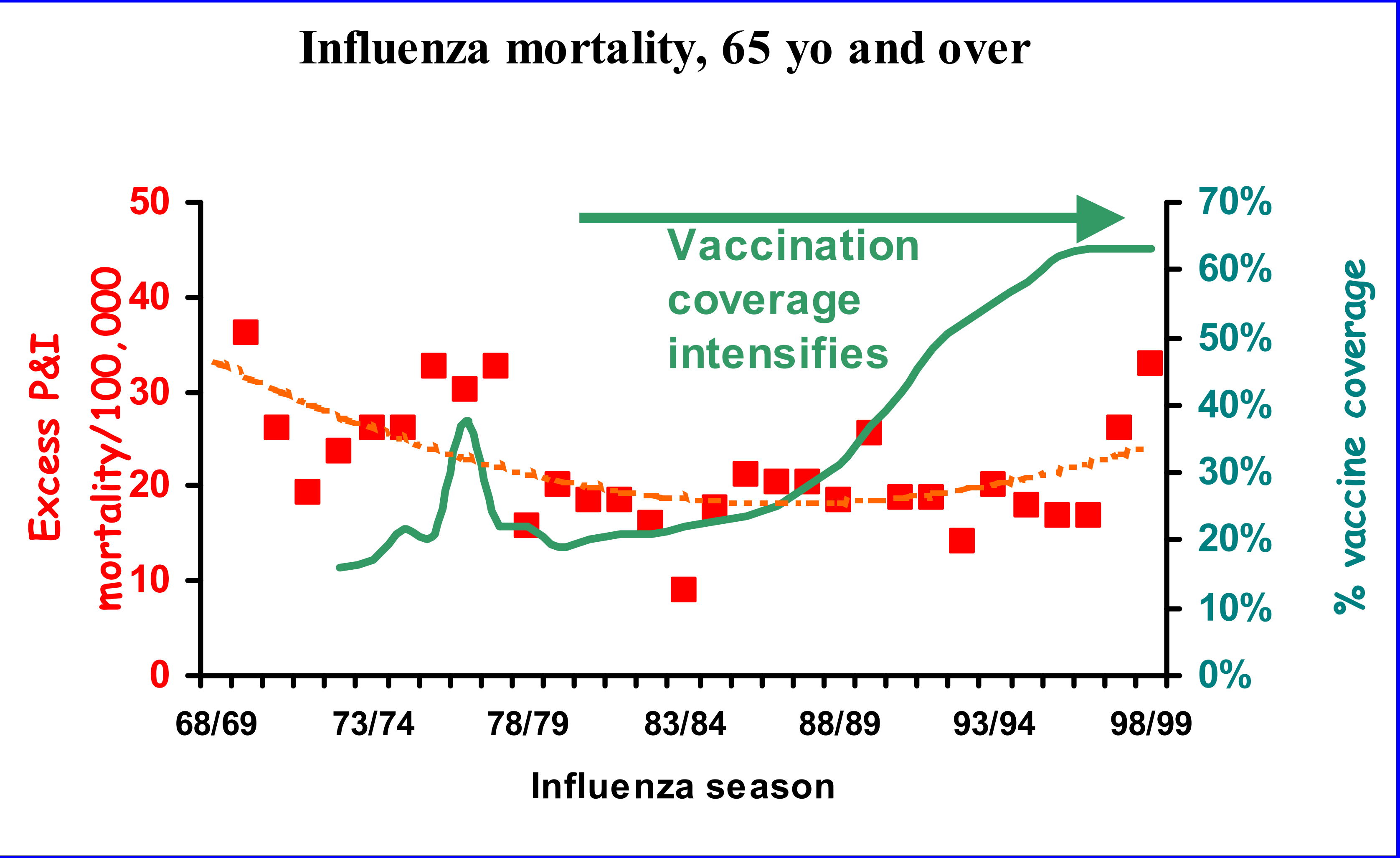
Pandemic scenario: R=1. 9
Spreads in 2-4 weeks



Week of onset

Viboud et al, Science, 2006; Germann et al, PNAS, 2006

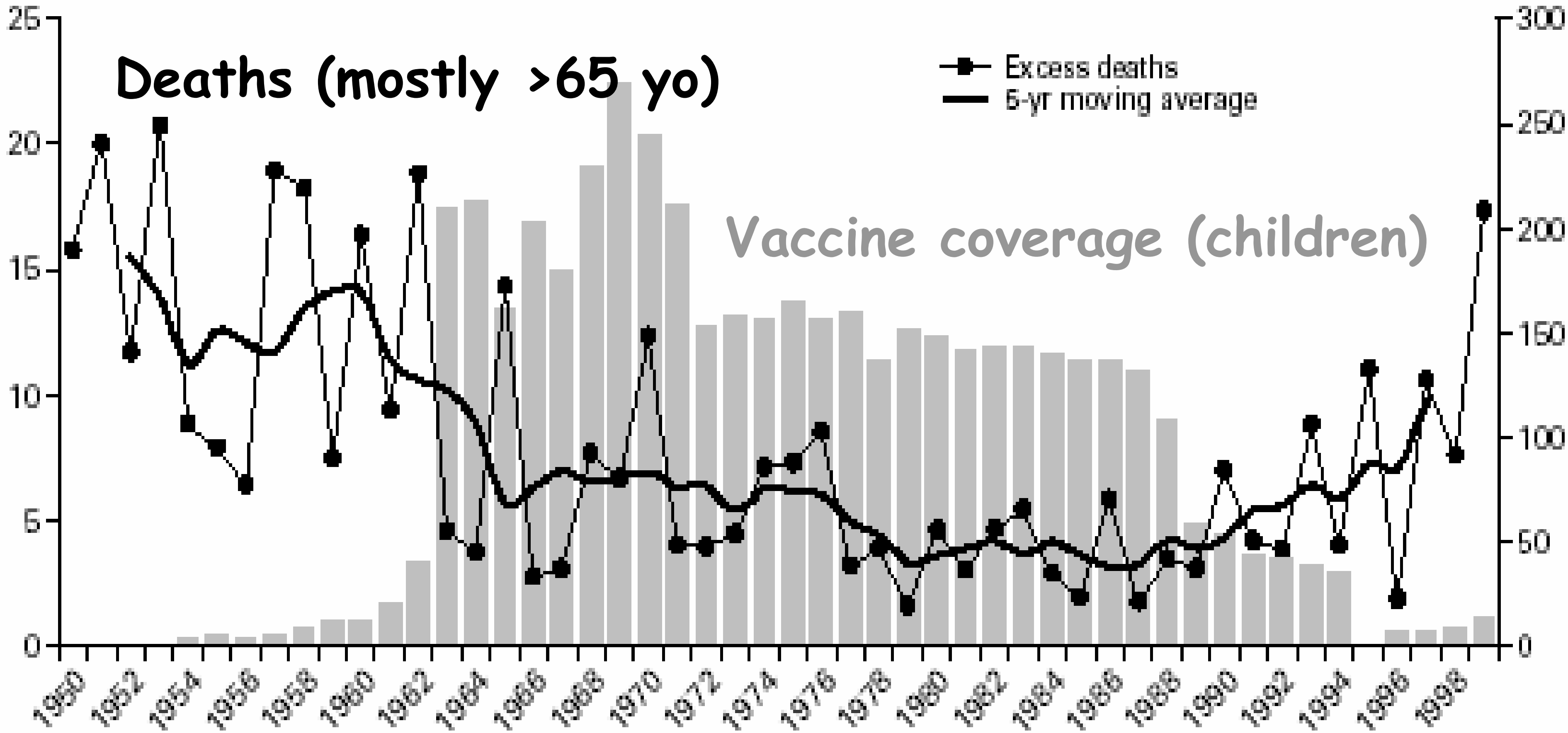
Priority groups for vaccine: US influenza vaccination program: no mortality reduction among elderly



Simonsen et al, Arch Intern Med, 2005

Vaccinating schoolchildren to reduce influenza-related mortality among the elderly (herd immunity)

Japan



Reichert et al, N Engl J Med, 2001

Priority groups for pandemic vaccination: younger population

- Possible to induce herd immunity by vaccinating school children and high-transmitter groups, and indirectly protect the elderly/feeble
- Immune senescence: low vaccine efficacy among the very elderly *
- Younger pandemic deaths occur earlier
- If objective is to prevent "years of life lost", more cost-effective to vaccinate younger age groups

*Goodwin K et al, Vaccine, 2006

Planning pandemic interventions: summary

- Pre-pandemic vaccine +++
- Combination of intervention strategies could work for a range of pandemic scenarios, where targeted prophylaxis and social distancing are applied early in the epidemic
- Would not necessarily reduce the overall number of infected but would spread out the epidemic = slower influx of sick people; more time to organize health care response
- Little health benefits expected in closing borders or limiting transcontinental air travels, balance economic costs.

Uncertainties and remaining questions

- Major uncertainties regarding the pandemic virus:
  - subtype (A/H5N1 most likely today, A/H9 or A/H7 possible)
  - subtype variant (Vietnamese or Indonesia variant of A/H5N1)
- Who to vaccinate in priority (modeling: transmitter groups, traditional vaccine strategy: elderly and high risk)
- Natural history of disease: length of infectious period, incubation period (longer in early human cases of H5N1), clinical signs (GI vs entirely resp disease).
- Likelihood of successful containment if repeated introductions ?*

*Mills et al, Plos Med, 2006

Conclusions

- Prediction in epidemiology is recent, while it is well established for other natural biological physical phenomenon.
- Like weather forecasts, epidemiologic predictions come with uncertainty
- Examples of useful epidemiologic predictions :
  - HIV/AIDS, CJDv, Foot and mouth disease, SARS
- Models are useful guide for policymakers
  - Highlight the conditions necessary to control an outbreak
  - Sensitivity of results to underlying assumptions