Insights from 26 Years in Immunization

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Comparison of Current and 20th Century Annual Morbidity, Vaccine-Preventable Diseases

Disease	20th Century Annual Morbidity†	2003*	Percent Decrease
Diphtheria	175,885	1	99.99%
Measles	503,282	42	99.99%
Mumps	152,209	197	99.87%
Pertussis	147,271	8,483	94.24%
Polio (paralytic)	16,316	0	100%
Rubella	47,745	7	99.99%
Congenital Rubella Syndrome	823	0	100%
Tetanus	1,314	14	98.93%
H. influenzae, type b and unknown (<5 yrs)	20,000‡	213	98.94%

† Source: CDC. *MMWR* 1999. 48: 242-64

* Source: *MMWR* January 9, 2004. 52, No 53(provisional data)

‡ Data are estimated

Numbers in yellow indicate record lows

Primary Strategy

- Vaccinating subgroups at greatest risk for serious disease or complications (i.e., lowering their susceptibility)
- Protects individuals and communities by reducing transmission

Rubella is an Exception

- Vaccinate children to
  - Interrupt transmission, and thereby reduce the risk of exposure among women of childbearing age, …
  - While avoiding inadvertent vaccination of pregnant women
- Concern about waning of immunity led others to adopt our primary strategy (for other diseases):
  - Post-partum mothers
  - Adolescent girls

Evolution of Vaccination Programs

1. FDA licenses vaccines, certifying them safe and efficacious
2. CDC decides how best to employ them, given limitations (e.g., temperature/light sensitivity, doses needed, adverse events, contraindications, …)
3. And ensures that policies have desired impact (despite any changes in epidemiology that might accompany vaccination)
4. Should goals not be attained, considers other promising strategies or tactics

Characteristics§ of Licensed Vaccines

1. Effectiveness
   - Immunogenicity, efficacy†
   - Impact on transmission (e.g., reduce carriage, …), duration of immunity‡
2. Safety†‡
3. Logistics†
   - Storage requirements (e.g., need for cold-chain, …)
   - Parenteral versus non-parenteral

†known at licensure

‡inferred or learned from experience

§may differ among sub-populations

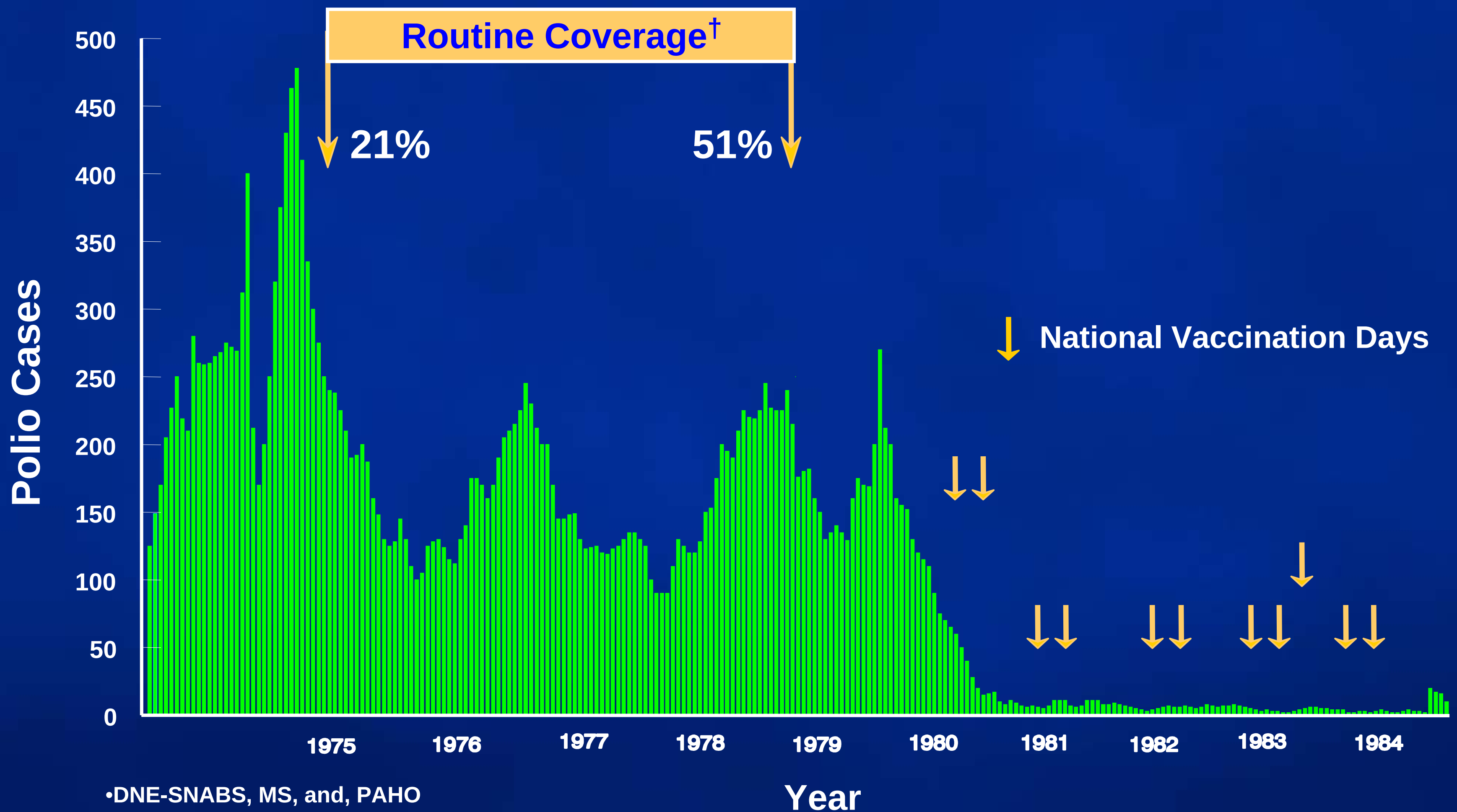
Policy Goal

Use available vaccines to maximize protection and minimize risk

Factors Affecting Policy Decision-Making

- Disease burden
- Transmission patterns
- Characteristics of vaccines
- Logistics
- Feasibility
- Public and provider acceptance
- Political will

Polio Cases by Four-Week Period Brazil, 1975-1984*



•DNE-SNABS, MS, and, PAHO

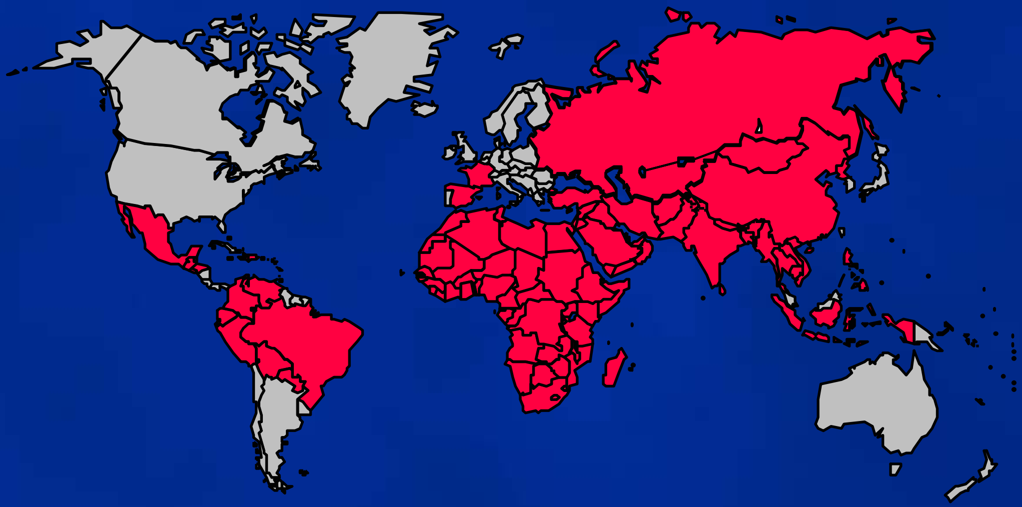
†*Rev Inf Dis* 1984;S400-S403

Polio Eradication Strategy

- Routine immunization
- National immunization days
- Careful surveillance
- Mop-up campaigns

Polio Eradication 1988 - 2003

1988
>350,000 cases
125 countries



2003
779 cases*
6 countries

*As of February 4, 2004

Modeling can Help to …

1. Modify vaccination programs if needs change (as well as if goals aren't being attained)
   - Switch to IPV or coordinated NIDs post-certification?
   - How should outbreaks be controlled?
   - Stockpile OPV or IPV?
   - If OPV, mono- or trivalent?

Influenza Vaccine Effectiveness

- **Determinants**
  - age and immune status
  - vaccine match
- **Effectiveness by age and status**

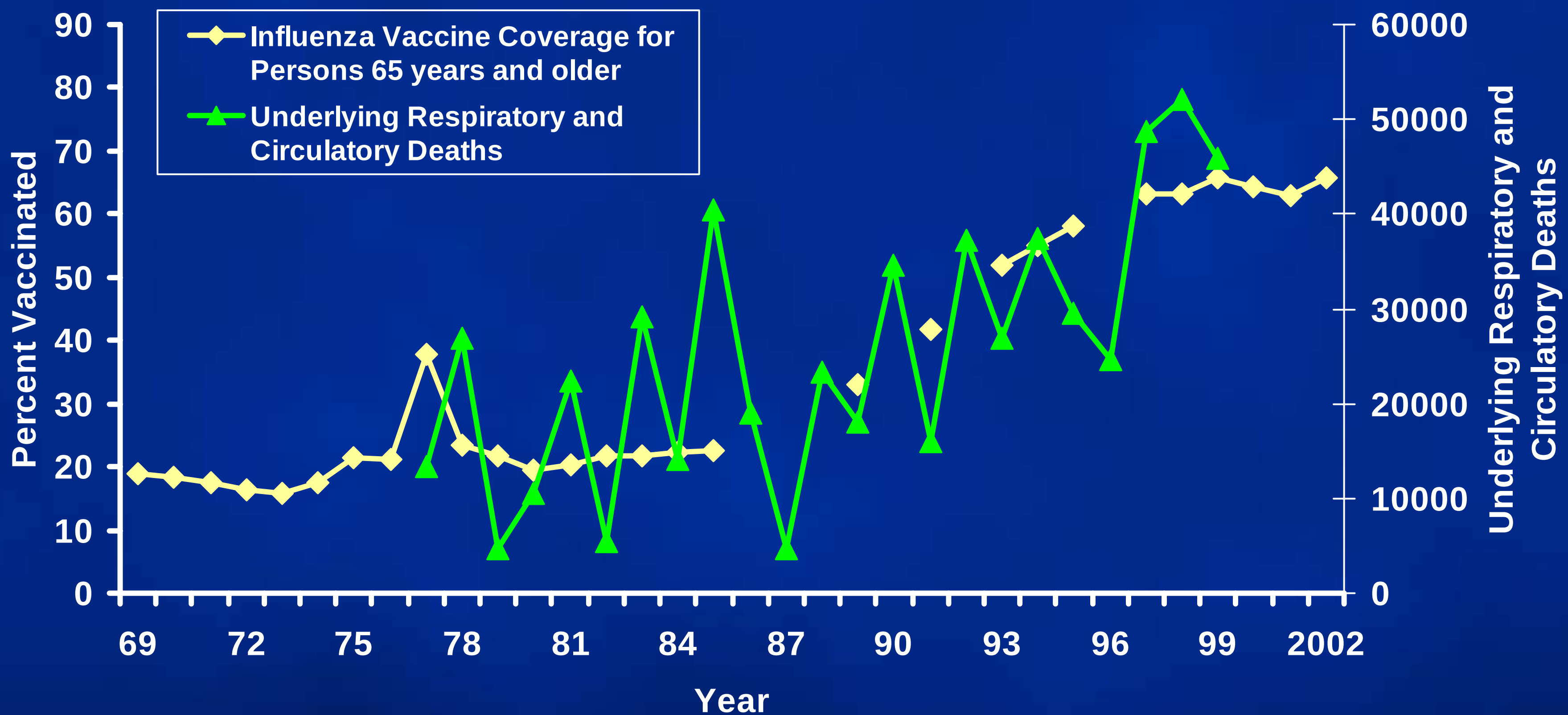
- < 65 years, healthy	70-90% influenza
- 65 years, community	30-70% influenza
- 65 years, nursing home	30-40% influenza
	50-60% hospital
	80% death

E-mail from Nancy Cox, 3/13/04

Differences Between Influenza and Other Vaccine Preventable Diseases

1. Year-to-year variation in viruses with differences in
   - Virulence
   - Transmissibility
   - Host susceptibility
2. Year-to-year variation in vaccine effectiveness

Estimated Annual Influenza-Associated Deaths and Influenza Coverage for Persons Aged $\geq$65 Years†



†Deaths taken from *JAMA* 2003; 289: 179-86
Coverage taken from U.S. Immunization Survey 1969-85
National Health Interview Survey (NHIS) 1989-2002
Influenza: 1997-2000 preliminary NHIS data based on January - June interviews only

Possible Explanations for Increasing Deaths and Coverage

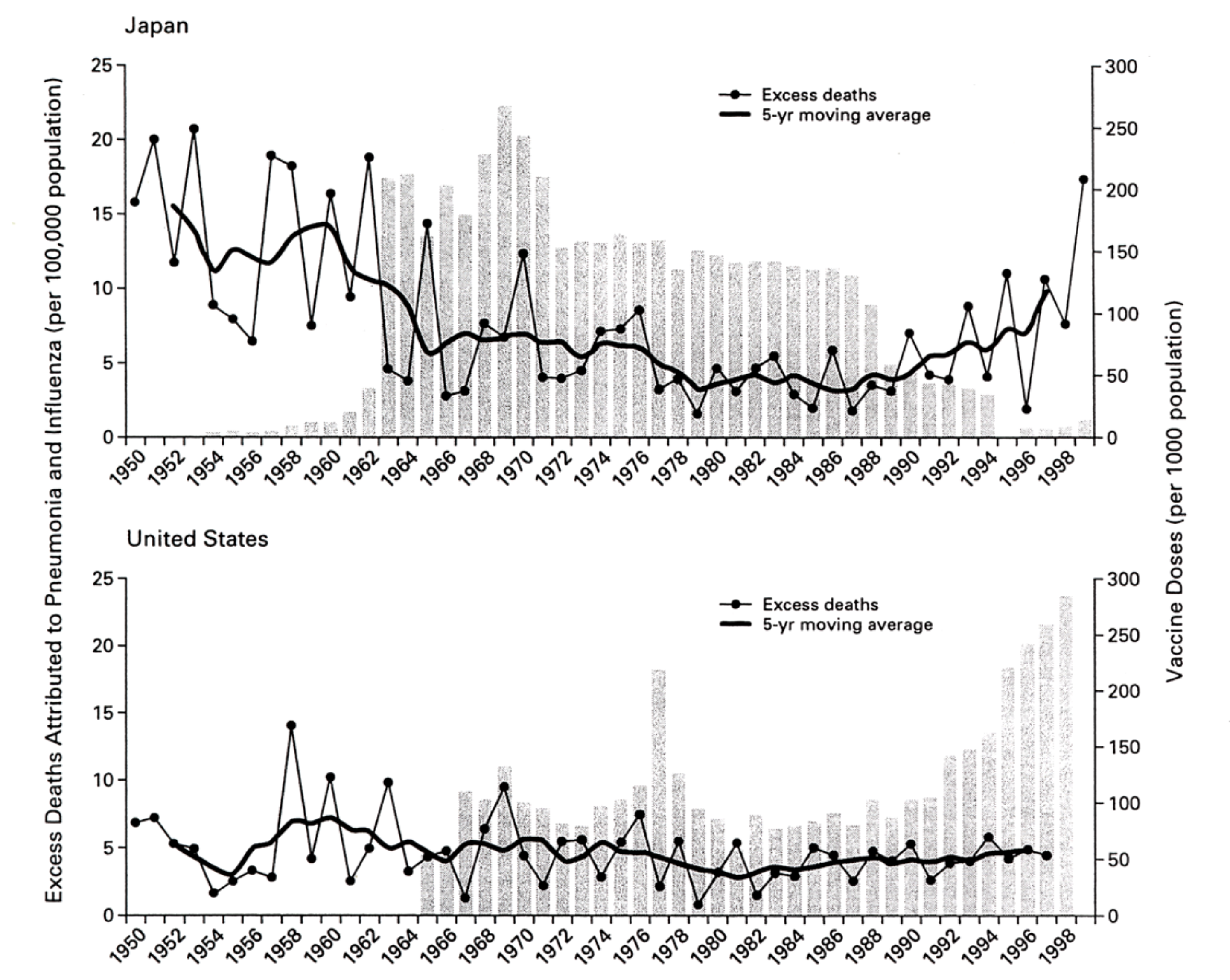
- Aging population
- Sicker population
- More H3N2 outbreaks in the 1990's
- Lower efficacy in elderly
- Non-influenza deaths

Japan Influenza†

- 1962 – mass vaccination of school children
- 1977 – vaccination obligatory
- Mid 1970’s to late 80’s – coverage 50-85%
- 1984 – law to opt out
- 1994 – program ended

† *N Eng J Med* 2001; 344: 889-96

Excess Deaths Attributed to Pneumonia and Influenza Over a 50-Year Period in Japan and the United States



Bars are vaccine doses/1,000 popluation

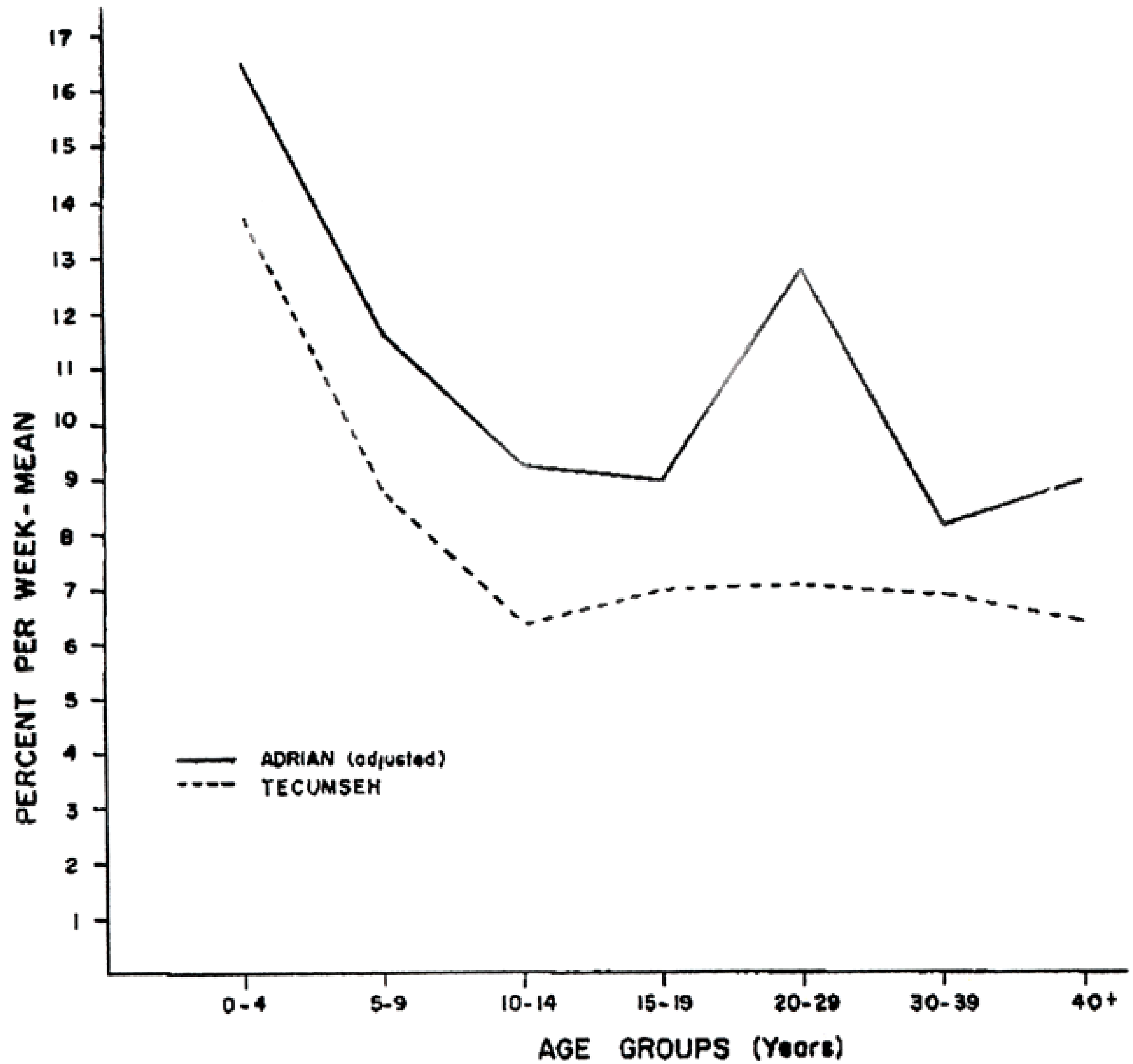
N Engl J Med 2001; 344: 889-96

Concerns Raised about Japanese Data[†]

- Aging of Japanese population
  - 10% $\geq$65 years in 1985
  - 16% in 1998
- Exaggerated influenza season – 6 months
- Lack of age-specific data
- 10-fold increase in nursing homes, convalescent facilities, etc

[†] *N Engl J Med* 2001; 344: 1946-48

Age-Specific Rates of Respiratory Illness in Tecumseh and Adrian, Michigan, during the Influenza Season



Bull WHO 1969; 41: 537-42

85.8% of students vaccinated against H2 Hong Kong in Tecumseh

Issues that Must be Addressed

- Would universal vaccination of children and young adults protect high risk adults?
- Would children benefit, and do their benefits outweigh their risks?
- Would this program be cost-effective?
- Is it feasible?

Modeling can Help to …

2. Explore protecting target sub-populations by vaccinating others (largely a secondary strategy so far)
   - Modelers cautioned that high coverage must be sustained to avoid increasing susceptibility among WCBA by vaccinating children against rubella
   - Considering this strategy for pneumococcal disease as well as influenza among the elderly and pertussis among infants, but altruism is a hard sell

Modeling can Help to …

3. Design optimal vaccination programs for new vaccines
   - HPV: adolescent girls?
   - HSV2 (beneficial among those negative for HSV1): ?
   - Meningococcal conjugate: adolescents, coverage?
   - Rotavirus: optimal age, coverage?
   - Zoster: age, interval?

Modeling can Help to …

4. Respond to, if not anticipate changes in epidemiology that may accompany vaccination
   - Increased pertussis among adolescents and young infants
   - Vaccine-strain poliomyelitis during peri-eradication period
   - Increased zoster among middle-aged persons infected as children

Modeling can Help to …

5. Ensure that goals are appropriate, or assist in revising them (e.g., varicella)
    - At coverage ~ 80%, outbreaks are occurring among vaccinated populations
    - Can we anticipate more of this given our current strategy?
    - If so, does it justify changing the goal (from control to elimination)?
    - Would this require another dose? When?
    - Impact of zoster?

Modeling can Help to …

6. Design composite strategies: given a program in which … % of children are vaccinated against …
   - rubella, what proportion of adolescent girls or mothers should be vaccinated post-partum?
   - measles, how frequently should NIDs be conducted, what age range targeted and coverage attained?

Modeling can Help to …

7. Decide which drugs/vaccines to stockpile, and how many doses, in preparation for
   - Post-eradication polio outbreaks (earlier slide)
   - Pandemic influenza – while vaccine is being manufactured
   - Large-scale anthrax attack – drugs for use while immunity is developing, vaccine
   - Smallpox attack – contacts post-exposure, if not members of the general population

Modeling can Help to …

8. Determine additional disease burdens that might be ameliorated via combination vaccines, given

- Benefits (increased coverage):
  - Fewer visits or injections per visit
  - Means of introducing new antigens
- Costs (reduced resilience):
  - Product may dominate marketplace, eliminating manufacturers
  - Product may be less reliable, as ensemble is only as strong as weakest constituent

Policymakers will Appreciate Modeling More if Modelers Will

1. Explain which features are based on observation and which on expert opinion
2. Validate predictions insofar as possible, evaluate otherwise
3. Identify influential features (i.e., functions or parameters) via sensitivity analyses
4. If their bases are equivocal, help to design the requisite studies

EXTRA SLIDES (other issues to consider in modeling)

Besides Epidemiology I

- Logistics – what is practical?
  - Hepatitis B infections occur among adolescents and young adults, who however are relatively inaccessible
  - Together with earlier infection increasing risk of carriage ➔ childhood vaccination
- Economics – what are the likely costs?
  - Attaining the goal via alternative strategies, tactics
  - Opportunity costs too

Besides Epidemiology II

- Social factors – is behavior rational?
  - Single re-introduction of smallpox increases prospect of others ➔ widespread vaccination
  - Provider and public acceptance of vaccines or vaccination strategies
- Ethics – individual or societal perspective?
  - If there are risks, always better to let others bear them
  - Who should be vaccinated first, … (e.g., during influenza pandemics)?