Antivirals and Vaccine Approaches to Pandemic Influenza

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James Hadler, MD, MPH
Connecticut Department of Public Health

Outline

- **Public antiviral and vaccine supplies**
- **Antivirals**
  - 3 strategies for use
  - Healthcare delivery challenges and possible models
- **Vaccines**
  - Priority groups
  - Healthcare delivery challenges

Public Antiviral Supplies

- Federal plan calls for stockpiles sufficient to treat 25% of U.S. population
  - 5 day course of Rx (=10 day course of prophylaxis)
  - ~80% oseltamivir (Tamiflu); ~20% zanamivir (Relenza)
- Federally purchased & centrally stockpiled
  - 15 % of the population
  - Remaining 10% up to states to purchase & locally stockpile Stockpiles completed by 2008
- Connecticut
  - 525,000 courses from federal sources
  - ~70,000 courses purchased with state funding

Public Vaccine Supplies

- Vaccine not in production until pandemic begins & have pandemic strain
- Current production technology:
  - 3-6 months for first courses to be produced
  - Production at rate sufficient for 1-2% of population per week
  - Pandemic may reach US before any vaccine available
- Current vaccination assumptions
  - Will require 2 doses, 1 month apart

Bottom line: *vaccine largely unavailable at beginning of pandemic*

Antivirals

Strategies for Use of Antivirals

Maintain critical workforce:

1. Use for Rx or prophylaxis of persons in selected priority groups; Rx severely ill or high risk patients
   - Little impact on overall morbidity

Dampen outbreak:

2. Prompt Rx of *all cases* to minimize illness severity, burden on healthcare system and to decrease duration of transmissibility
3. Rx all initial cases and give prophylaxis to all household contacts to slow transmission.

NVAC Priority Groups for Antiviral Use

1. Hospitalized patients with influenza
2. ***Symptomatic HCWs and EMS workers with direct patient contact***
3. Highest risk outpatients with influenza
4. ***Symptomatic pandemic health responders, public safety & key government decision makers***
5. Other high risk outpatients with influenza
6. Outbreak response (e.g., in nursing homes)
7. ***Prophylaxis HCWs in ER, ICU, EMS, dialysis***
8. ***Symptomatic pandemic societal responders & other HCWs***
9. Other outpatients
11. ***Prophylaxis for all HCW***

Healthcare Delivery Challenges Priority Group Strategy

Challenges

- Get antivirals to ill persons in priority groups within 6-24 hours of illness onset (when might have benefit)
- 7 day/week system needed
- How to distribute limited supply of antivirals to each healthcare provider to Rx staff and, possibly, high-priority patients

Healthcare Delivery Challenges
Priority Group Strategy

Proposed Systems

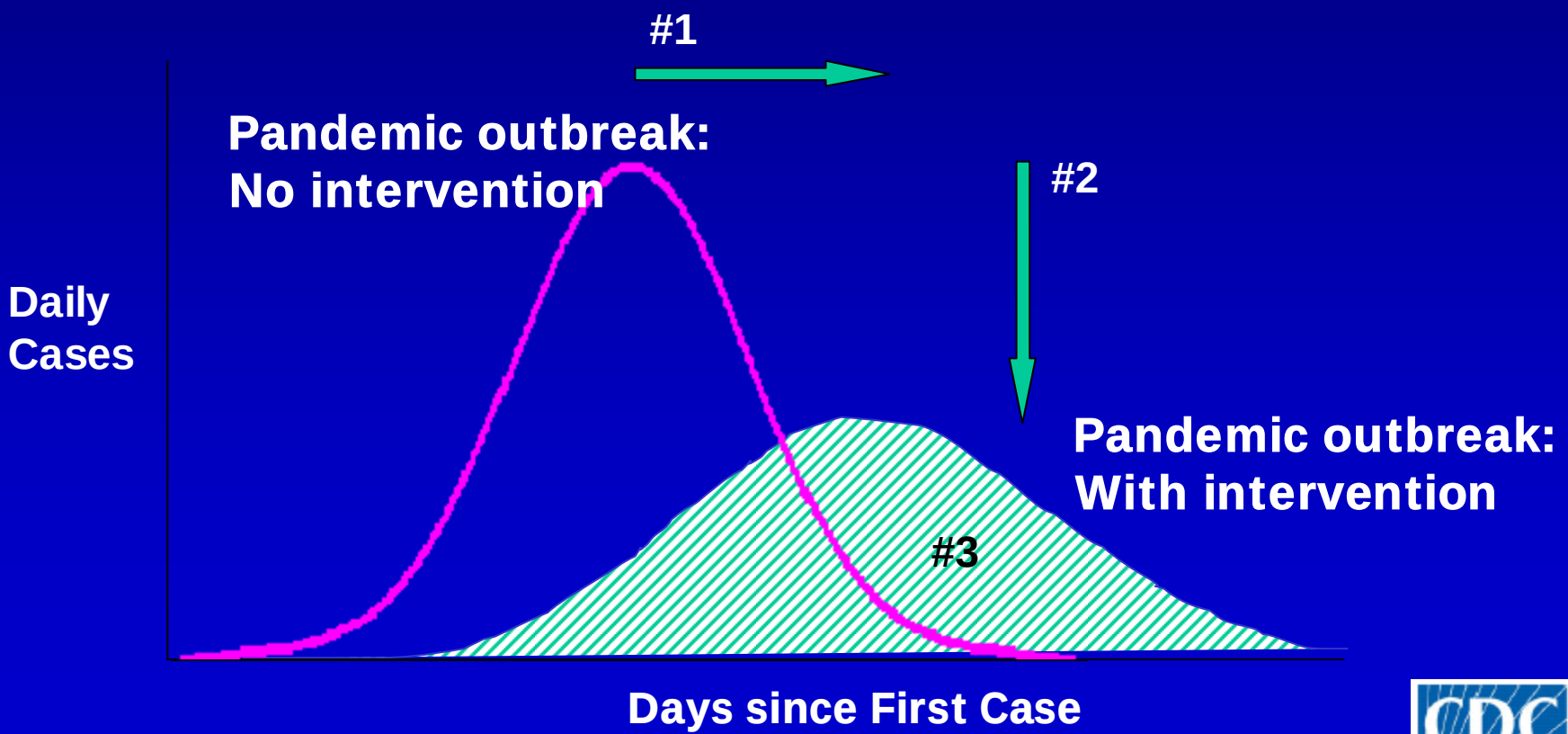
- ***Hospitals:*** distribute own – need sensitive system to monitor employee illness

- ***Primary care provider-based*** – each provider Dx & Rx's own staff and patients – fills own prescriptions
- ***Alternative*** – primary care providers make diagnoses, but write/phone prescriptions to special pharmacies which have public stores of antivirals.

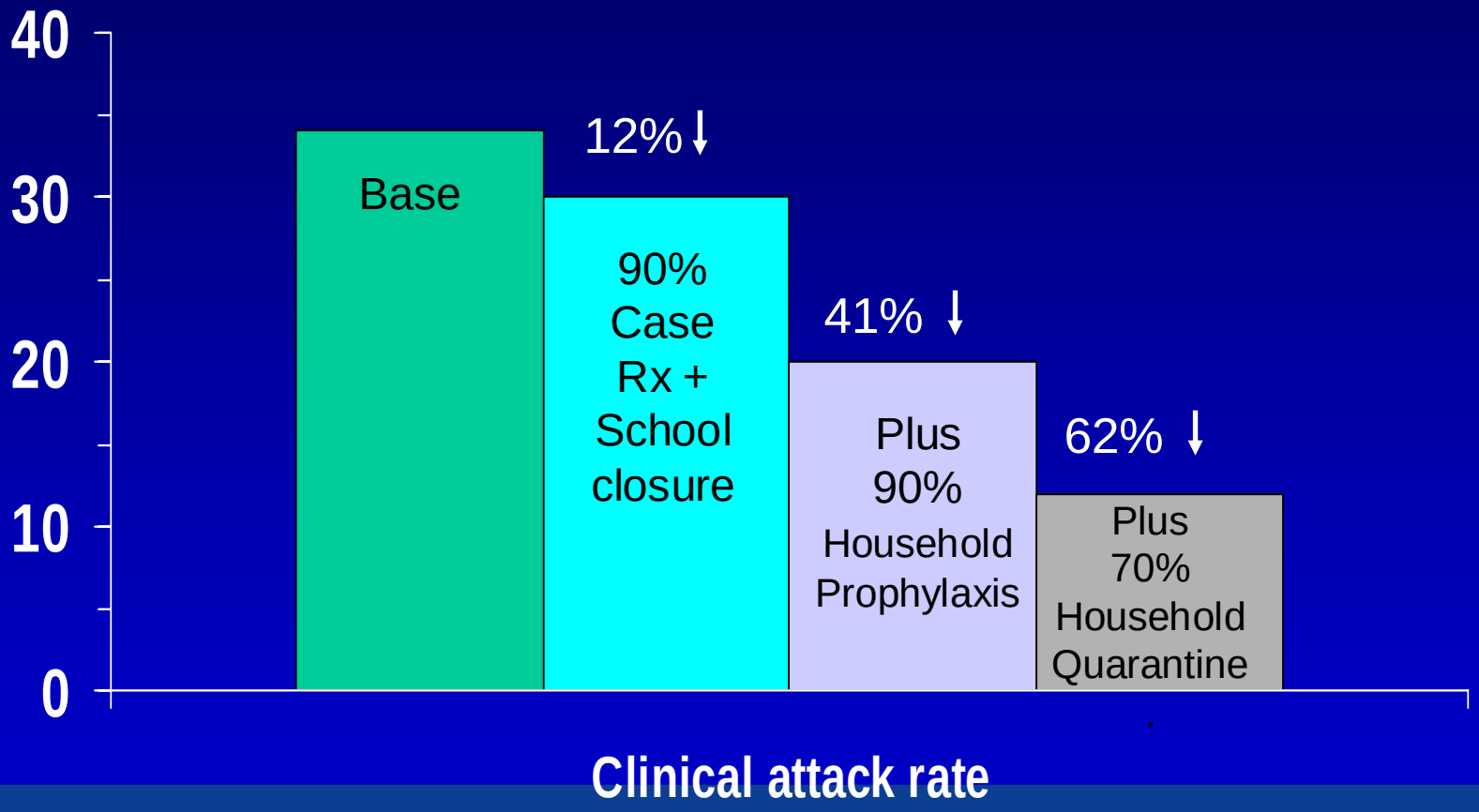
Use of Antivirals to Blunt a Pandemic

1. Delay disease transmission and outbreak peak
2. Decompress peak burden on healthcare infrastructure
3. Diminish overall cases and health impacts

Done in combination with non-drug interventions



Effect of Combining Antiviral and Social Distancing Strategies – Ferguson Model



Source: Ferguson N, Nature (online) April 26, 2006

Strategy 2: Prompt Treatment of All Influenza Cases

- **Studies of oseltamivir** show:
  - Reduces viral loads in upper respiratory tract
  - If Rx index case, reduces rates of secondary illness in household contacts
  - If Rx started shortly after symptom onset, will reduce probability of severe illness as well as duration. Reduction is greater the sooner after symptom onset Rx is started.
  - No effect if started >48 hrs after symptom onset.
  - Zanamivir Rx not effective in stopping transmission – just shortens illness duration.
- **Modeling**:
  - If give oseltamivir <24 hours after symptom onset to all ill, can slow spread and reduce incidence by as much as 10%; reduce hospitalization & mortality by potentially more

Healthcare Delivery Challenges
Strategy 2

Challenges

- Get antivirals to persons with pandemic flu within 6-24 hours of illness onset
- 7 day/week system needed
- Will use antivirals until they run out. Thus, best if accurately diagnose influenza & duration of symptoms.
- Who will diagnose influenza & how? Is there a role for rapid influenza tests other than very early on? Should there be a requirement that patients be seen and temperature confirmed?
- Who will dispense antivirals: Providers? Special clinics? Special pharmacies?

Healthcare Delivery Challenges
Strategy 2

Proposed Outpatient Systems

- ***Primary-care provider-based*** – each provider Dx & Rx's own staff and patients – fills own prescriptions
- ***Alternative* 1**– primary care providers see patients or make telephone diagnoses: prescriptions filled at special pharmacies or local health dep't clinics.
- ***Alternative 2*** – primary care providers see only complex patients; special clinics set up to see uncomplicated patients with suspected influenza & dispense antivirals.
- ***Alternative 3*** – other, outside the box ideas?

Strategy 3: Rx of all flu cases, Prophylaxis of All Household Contacts

- **Studies of oseltamivir** show:
  - Can reduce clinical illness rate in household contacts by 67-89% if give prophylaxis to household contacts within 48 hours of index case symptom onset.
  - Rx contacts in addition to index case reduces illness by 68% over any reduction from Rx of index case alone.
  - Zanamivir has similar prophylaxis efficacy

- **Modeling**:
  - If can achieve high rates of household prophylaxis within 48 hours of symptom onset in index case, can reduce incidence of clinical illness in pandemic by ~40%

Healthcare Delivery Challenges Strategy 3

Challenges

- Get antivirals to households of persons with pandemic flu within 48 hours of illness onset in index case
- 7 day/week system needed.
- Will use antivirals until they run out – will run out most quickly with this strategy. Accurate diagnosis of influenza makes best use of limited supply.
- Who will diagnose influenza & how? Who will dispense antivirals to households?

Healthcare Delivery Challenges Strategy 3

Proposed Outpatient Systems

- ***All diagnosis primary-care provider-based*** / Distribution to households by local health departments

- ***Alternatives****:* Primary care providers see only complex patients & distribution to household by LHDs; special clinics set up to see uncomplicated patients with suspected influenza & dispense antivirals; telephone diagnosis of influenza with LHD distribution to home.
- ***"Out of the box" alternative***: If enough antivirals, over the counter distribution

Vaccines

NVAC Vaccine Priority Groups

Priority Group 1 – 45.7 million people **(16%)**

- ***Healthcare workers providing direct patient care and essential support personnel***
- Patients of any age with ≥2 underlying medical conditions
- Pregnant women and household contacts of infants, immunosuppressed
- *Key government leaders and critical public health responders*

Priority Group 2 – 67.5 million people (**24.1%)**

- All seniors and 6-23 month olds; anyone with 1 chronic condition
- Other public health emergency responders, critical infrastructure (e.g., utility, food transport)

Vaccination Challenges

- How to prioritize among primary healthcare providers
- Who should vaccinate non-hospital based providers?
- Should some get 2nd dose before others get 1st dose?

Vaccine Delivery Possible Models

Hospital-based staff

- Hospitals vaccinate own staff

Providers who are not hospital-based

- Vaccinate selves and staff
- *Alternative* – special clinics set up by either hospitals or local health departments to vaccinate providers who are not hospital based.

Other high-priority workforce

- Special workplace clinics

High-priority patients

- vaccinated by primary care providers
- *Alternative*: special vaccination clinics run by local health departments

Summary

Supplies

- Antiviral supplies sufficient to initiate dampening strategies for at least 3-4 weeks, but not to maintain them throughout if have >10-15% attack rate
- Don’t count on vaccine supplies

Antivirals

- May be able to be used to dampen an outbreak – next step is to develop healthcare delivery plans.

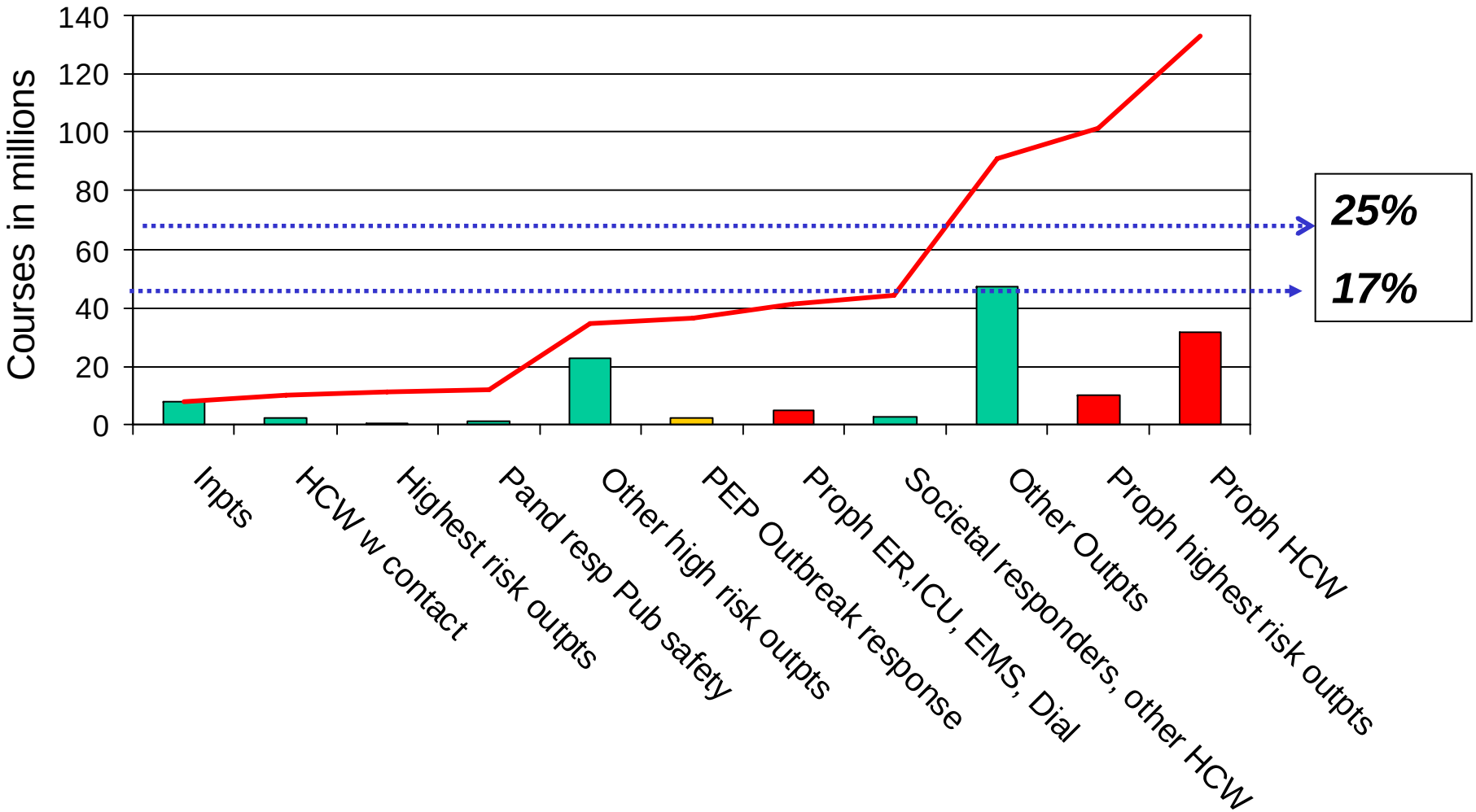
Vaccines

- Need to develop consensus priorities among HCW
- Promise of better production technology in 3 years.

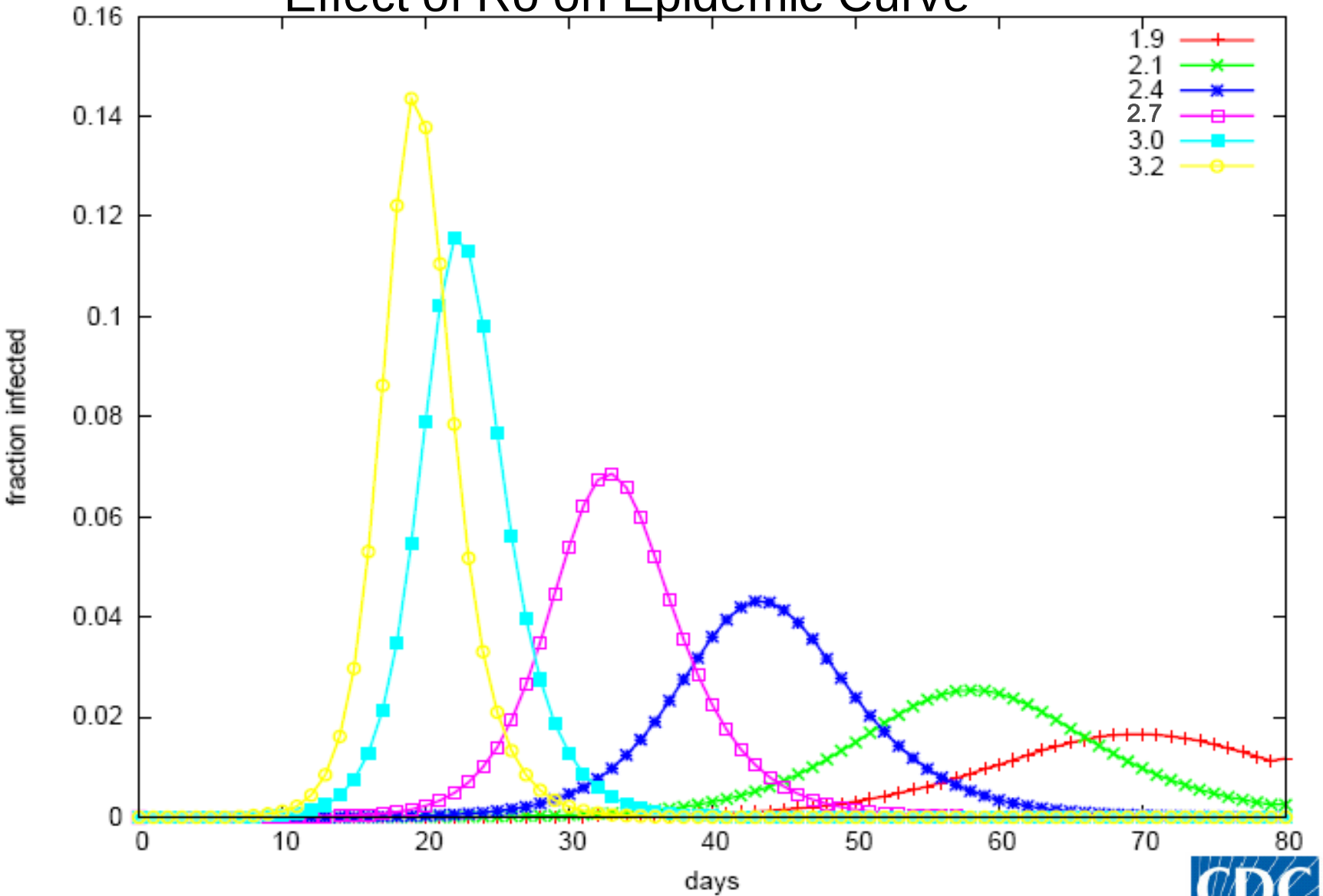
Extra Slides

Priority Groups			Approximate Number
Priority Group 1	A	Health care workers (HCWs) providing direct patient care, essential healthcare support personnel	9 million
		Key influenza vaccine and drug plant employees	40,000
	B	High-risk patients over age 65 with a chronic condition that increases the risk of a severe influenza infection, patients aged 6 months to 64 years with two such chronic conditions, and people hospitalized in the past year with influenza, pneumonia, or a chronic condition	25.8 million
	C	Pregnant women and people in a household with infants or severely immune-compromised patients	10.7 million
	D	Key government leaders and critical public health pandemic responders	151,000
Priority Group 2	A	All seniors, anyone with a chronic condition, and children aged 6 to 23 months	59 million
	B	Other public health emergency responders and critical infrastructure personnel, including utility and some transportation workers	8.5 million
Priority Group 3		Key government health decision-makers and funeral home workers	500,000
Priority Group 4		Healthy individuals aged 2 to 64 years	180 million

Size of Priority Groups and Cumulative Need for Antivirals



Effect of Ro on Epidemic Curve



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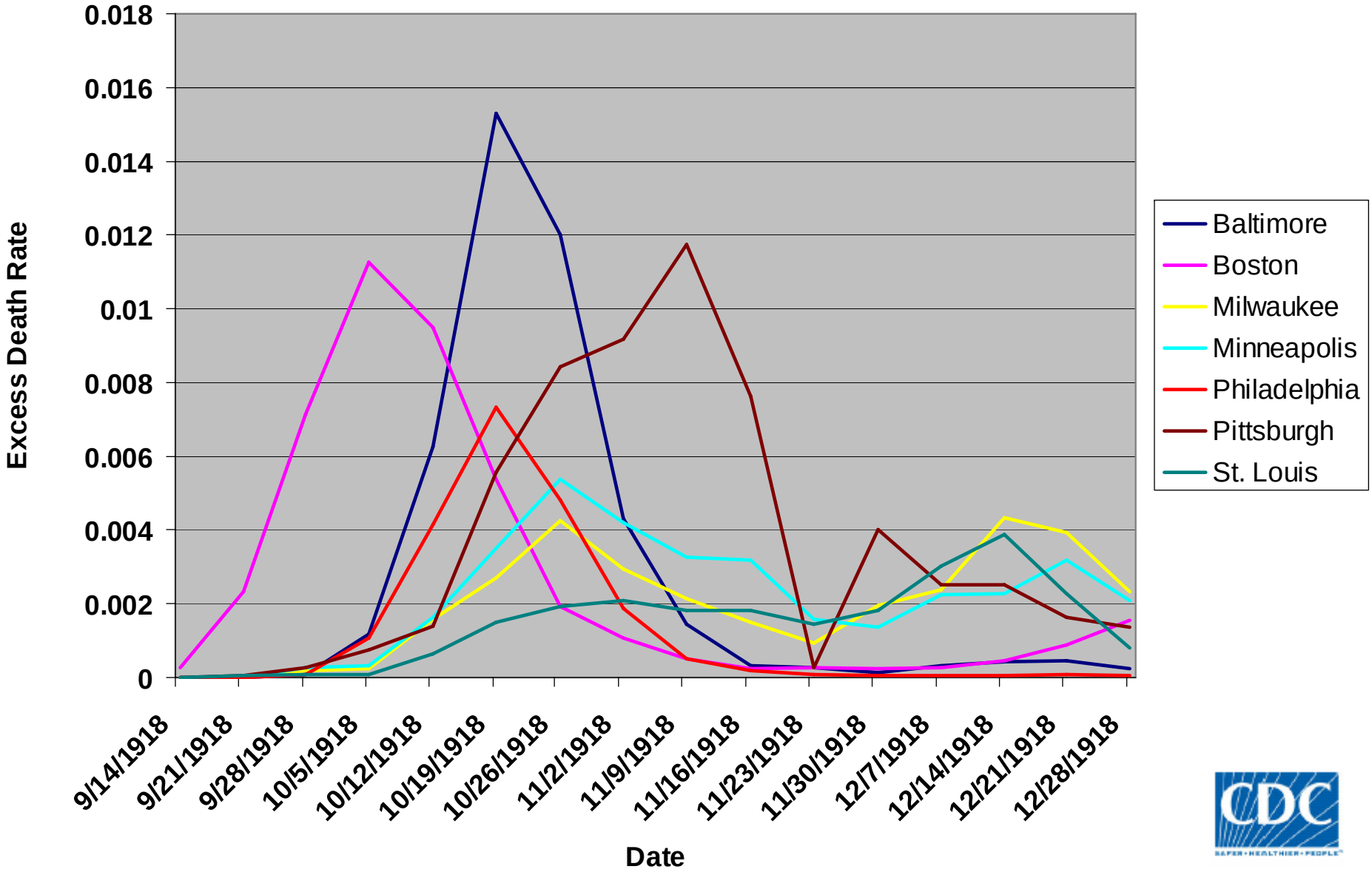
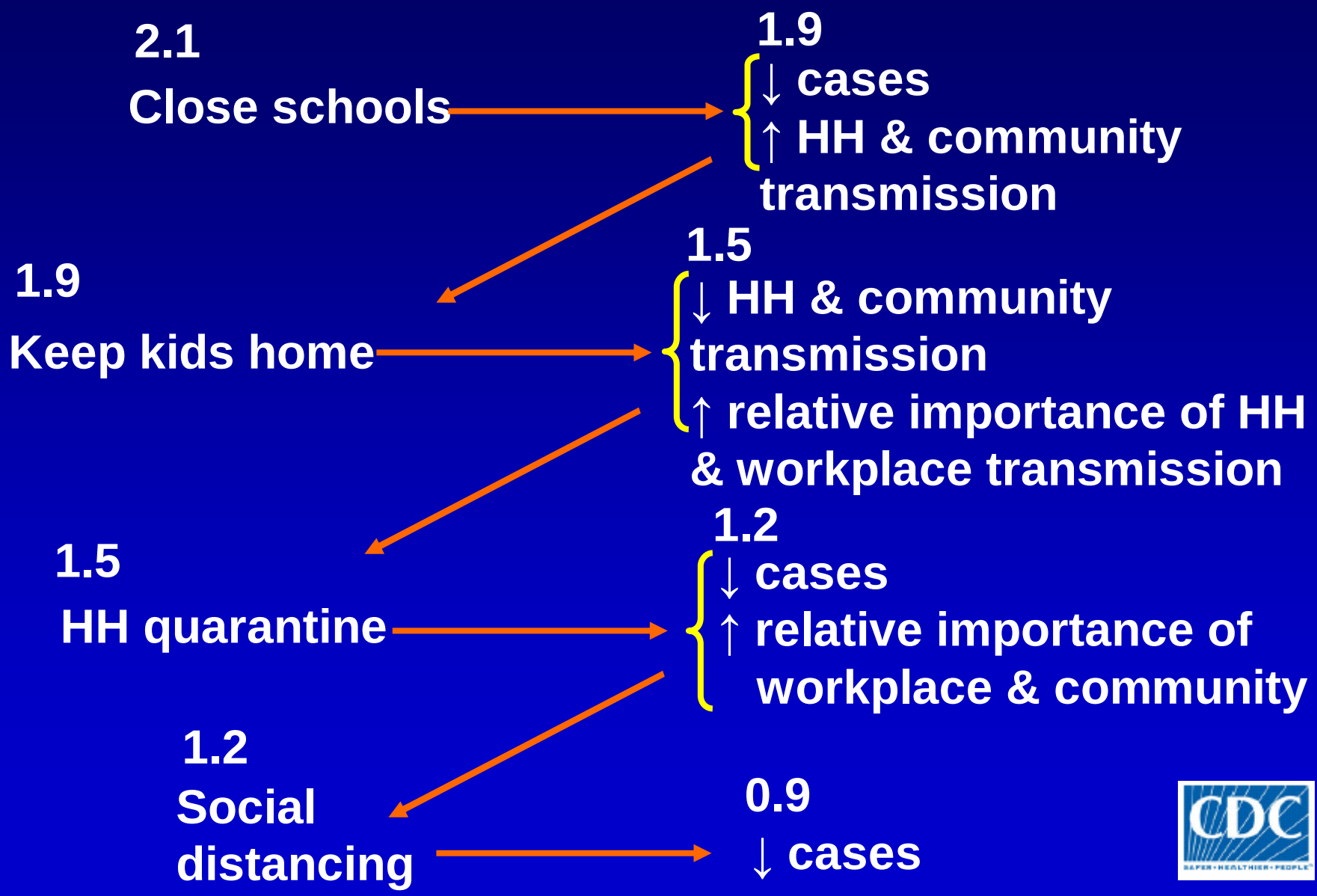
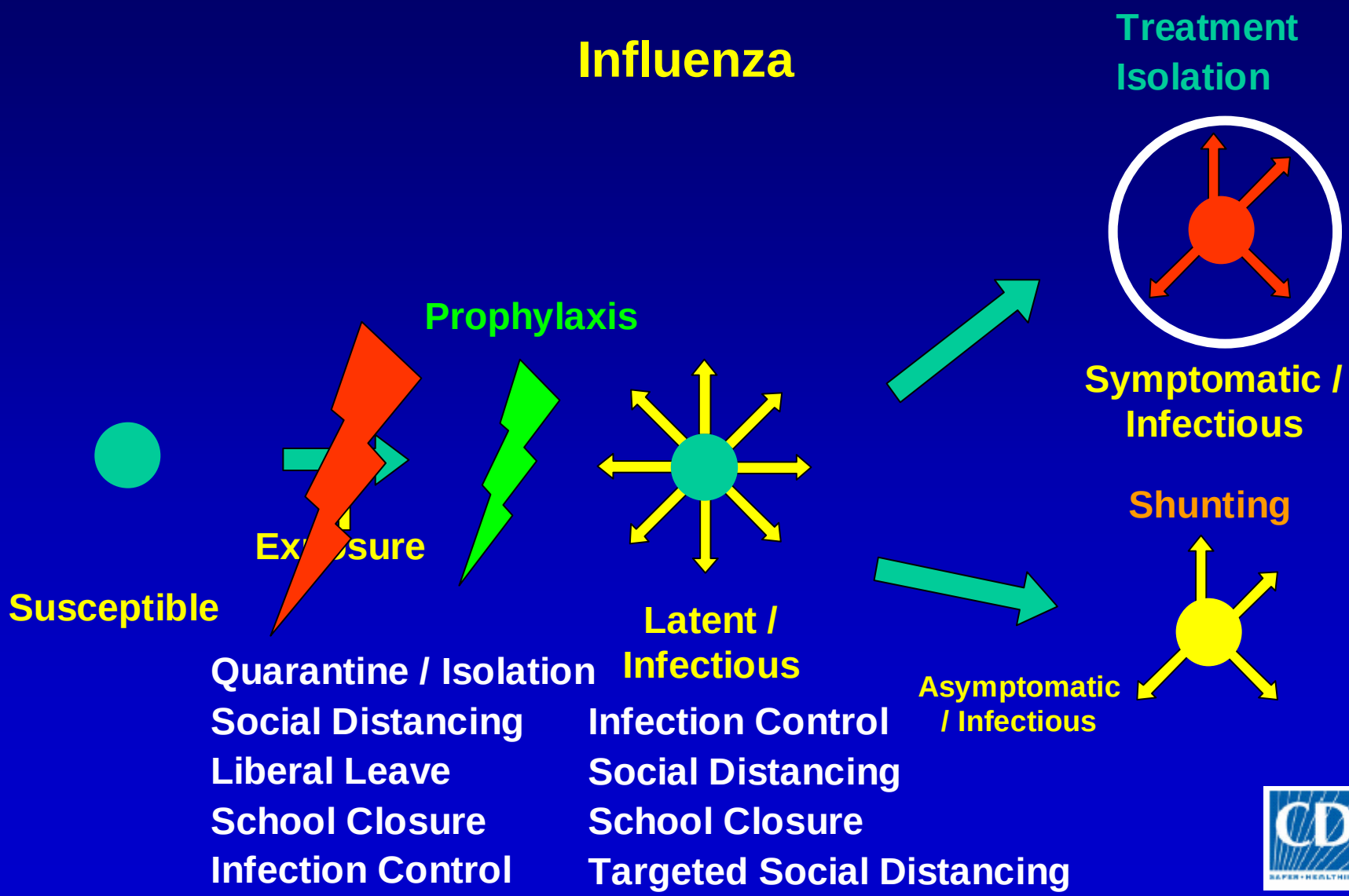
1918 Weekly Excess Death Rate by City



Layered Interventions



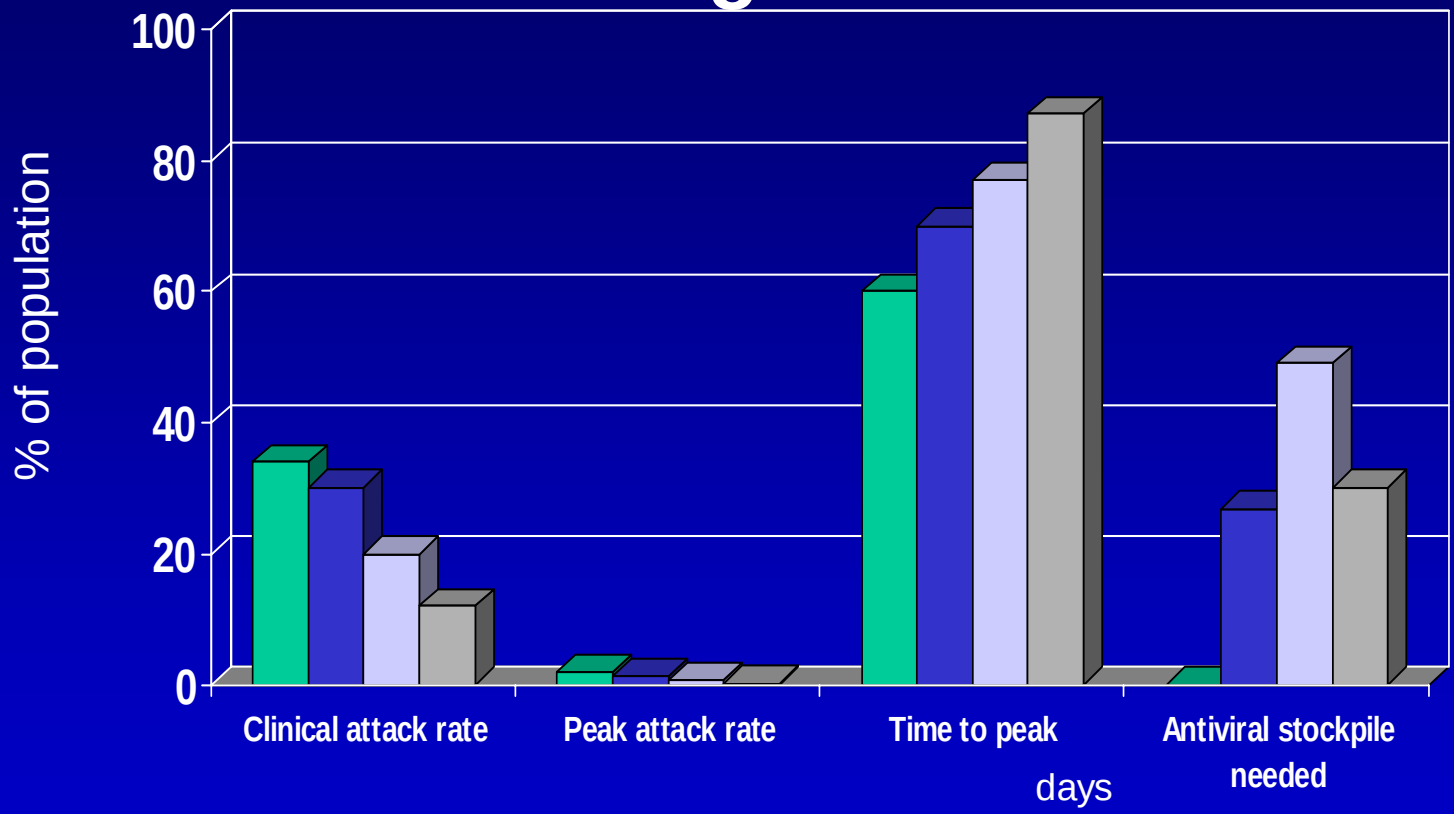
Population-based Containment



Community Mitigation of Influenza: Information Considered by Mathematical Modelers

- Population structure, dynamics, interactions
  - Age groups, social compartments (home, school, workplace)
- Transmission characteristics of influenza
- Who infects whom and where?
  - Estimates of transmission among age groups, and % of population in these groups; social compartments
  - Clinical trials of antiviral treatment and contact prophylaxis
    - Impact on transmission

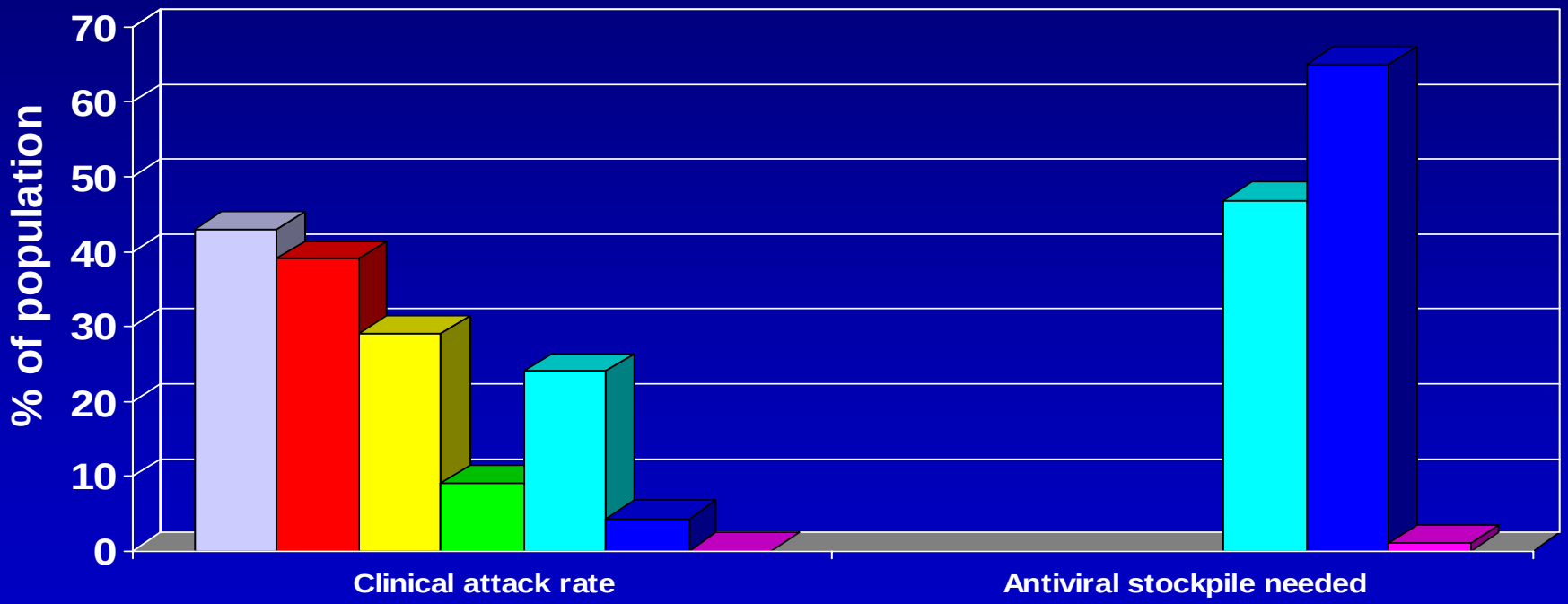
Value of Combining Strategies – Ferguson Model



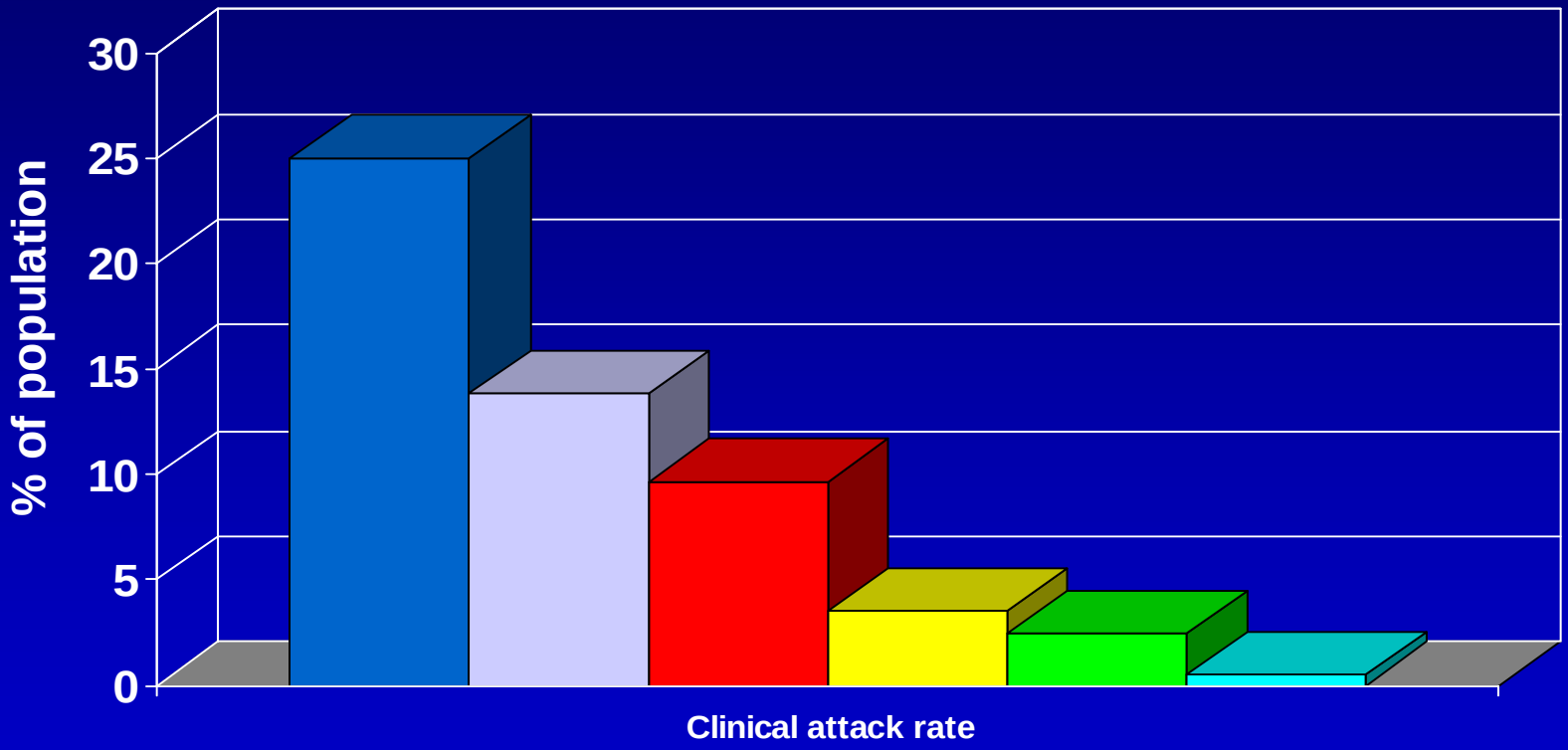
Source: Ferguson N, Nature (online) April 26, 2006

Value of Combining Strategies –Longini Model

Source: German TC. PNAS (online) April 11, 2006



Combining strategies – Glass model: Targeted Social Distancing



Evidence to Support School Closure

- Children are thought to be the main introducers of influenza into households.
- Children appear to be more susceptible to influenza and more infectious than adults in well-designed prospective studies of risk factors of influenza transmission in households.
- Nationwide school closure in Israel during an influenza epidemic resulted in significant decreases in the diagnoses of respiratory infections (42%), visits to physicians (28%) and emergency departments (28%), and medication purchases (35%).

What do the Modeling Results Mean?

- Not proof of efficacy or effectiveness, BUT offer *reason for optimism* regarding non-pharmaceutical interventions
- Suggest that maximal effectiveness will be achieved by appropriate layering and timing
- Need to be evaluated based upon assumptions and validated against experience