Yale SCHOOL *of* MANAGEMENT

YALE UNIVERSITY
School of Public Health

YALE UNIVERSITY
School of Engineering and
Applied Science

Vaccination Policy in the Large and in the Small(pox!)

Edward H. Kaplan, PhD

William N. and Marie A. Beach Professor

of Operations Research

Professor of Public Health

Professor of Engineering

Yale University

Today's Menu:

- Review *PNAS* model: formulation, sample results, policy implications

- Compare to other models (*Science*, Brookings, *NEJM*)

- Smallpox eradication revisited

CDC's Interim Response Plan

- CDC has interim policy in place
  - CDC Interim Smallpox Response Plan and Guidelines, Draft 2.0, November 21, 2001, Atlanta (Advisory Committee on Immunization Practices approved 6/20/02) (Note: Draft 3.0 appeared October 2002)
- Calls for targeted vaccination and case isolation:
  - symptomatic smallpox cases isolated
  - contacts of cases vaccinated
  - asymptomatic contacts monitored but not isolated
  - febrile contacts quarantined for 5 days
  - broader vaccination strategy if above fails
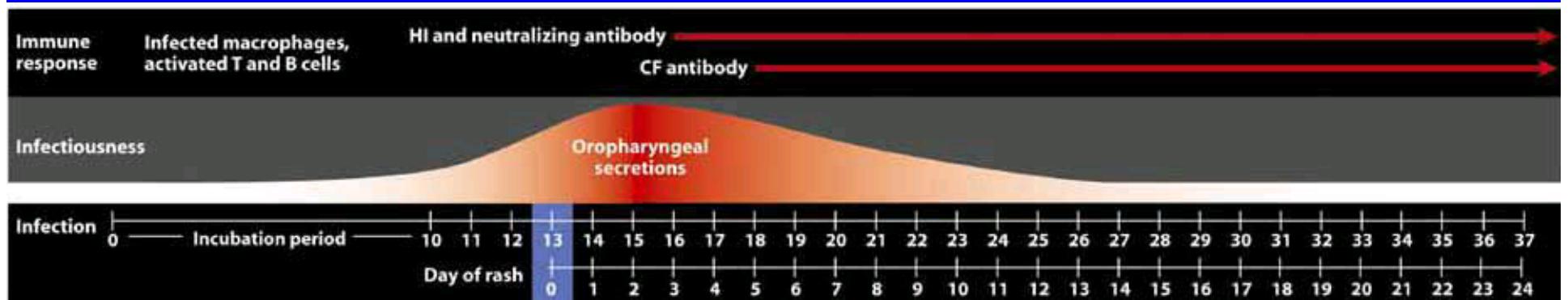   - Draft 3.0: clinic guide to vaccinate population in 10 days

Approach

- Focus on a large city (10,000,000)
- Construct "traced vaccination" (TV) model
- Contrast with "mass vaccination" (MV)
- Consider TV/MV switch if TV fails to control outbreak after 2 generations of cases
- Consider pre-attack vaccination

Model Features

- Disease transmission/progression: 4 disease stages (includes infected but vaccine sensitive), free mixing in population ("worst case"), imperfect vaccination and (low) vaccine-related mortality

- Response logistics: consistent tracing with disease transmission/progression linked to index case ("race to trace"), TV queues (finite TV capacity), MV rate higher than TV rate, quarantine capacity requirements

- State transitions governed by both disease transmission/progression and response logistics; *epidemic and response are on the same time scale*!
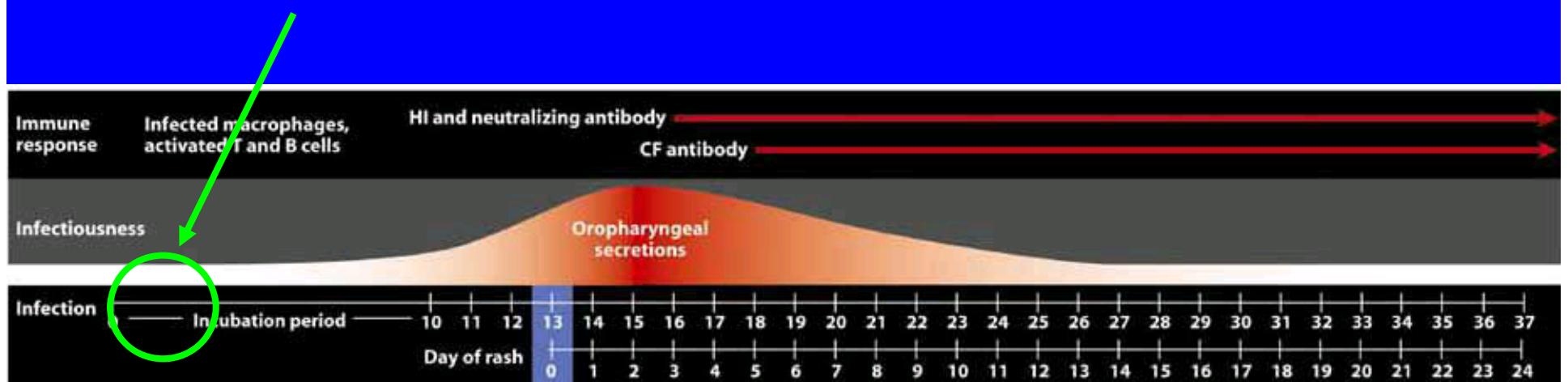
Clinical Course of Smallpox

Immune response — Infected macrophages, activated T and B cells — HI and neutralizing antibody — CF antibody

Infectiousness — Oropharyngeal secretions

Infection 0 — Incubation period — 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37

Day of rash 0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24

Source: Breman and Henderson, *NEJM* 346:1300-1308, 2002

Clinical Course of Smallpox

Mean duration of vaccine sensitive stage

Immune response	Infected macrophages, activated T and B cells	HI and neutralizing antibody
		CF antibody

Infectiousness — Oropharyngeal secretions

Infection	Incubation period	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37
Day of rash					0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24

Source: Breman and Henderson, *NEJM* 346:1300-1308, 2002
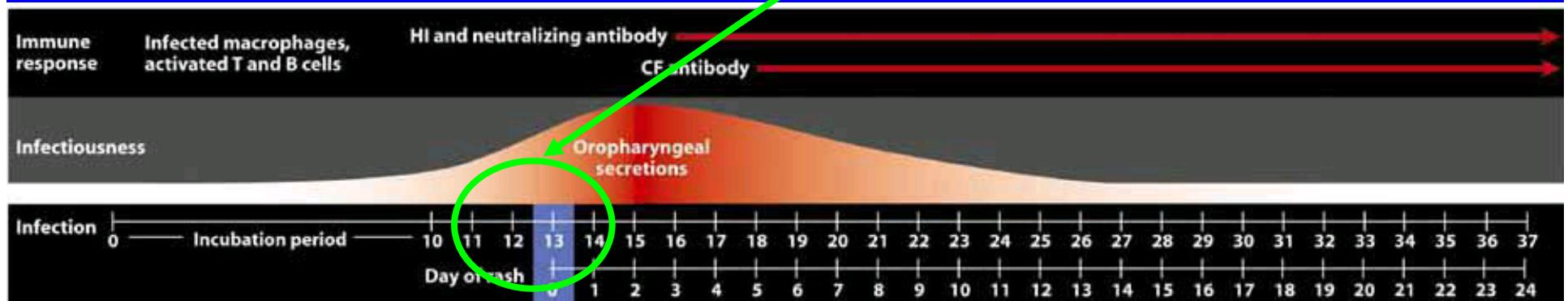
Clinical Course of Smallpox

Mean duration of asymptomatic vaccine
insensitive stage
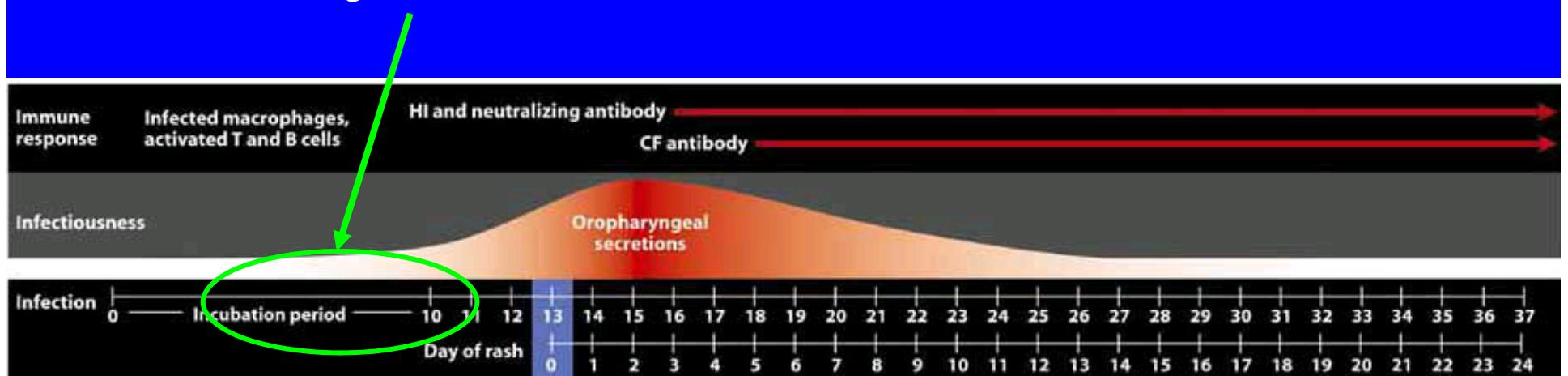
Source: Breman and Henderson, *NEJM*
346:1300-1308, 2002
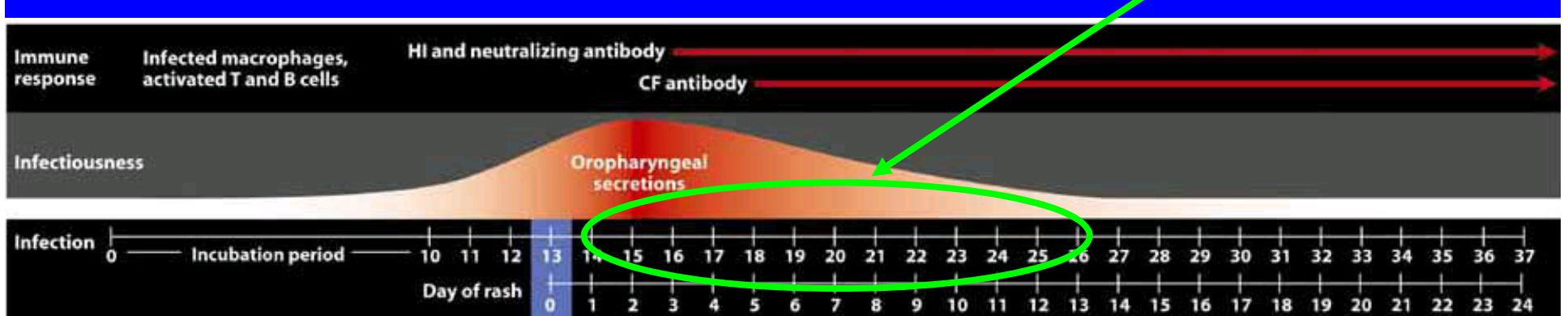
Clinical Course of Smallpox

Mean duration of infectiousness before detection/isolation

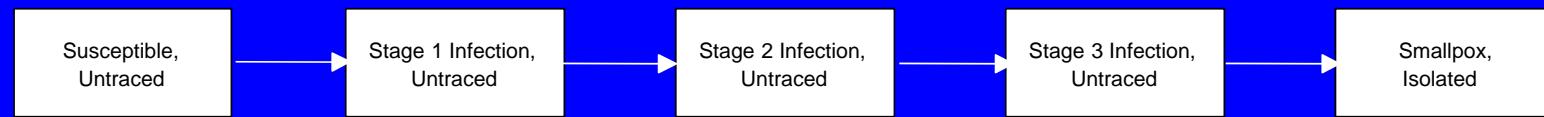Source: Breman and Henderson, *NEJM* 346:1300-1308, 2002

Clinical Course of Smallpox

Mean duration of symptomatic disease in isolation before death or recovery

| Immune response | Infected macrophages, activated T and B cells | HI and neutralizing antibody |
| CF antibody |
Infectiousness	Oropharyngeal secretions
Infection	0 — Incubation period — 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37
Day of rash	0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24

Source: Breman and Henderson, *NEJM* 346:1300-1308, 2002

Traced Vaccination Smallpox Response Model

| Susceptible, Untraced | → | Stage 1 Infection, Untraced | → | Stage 2 Infection, Untraced | → | Stage 3 Infection, Untraced | → | Smallpox, Isolated |

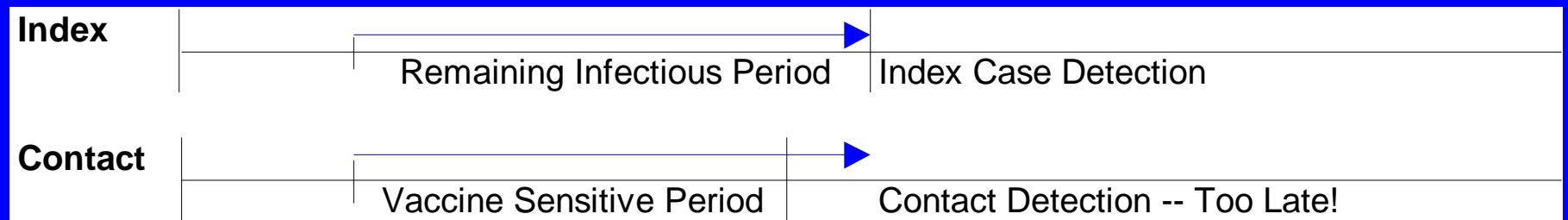## Disease Transmission, Progression, and Case Isolation

Traced Vaccination Smallpox Response Model
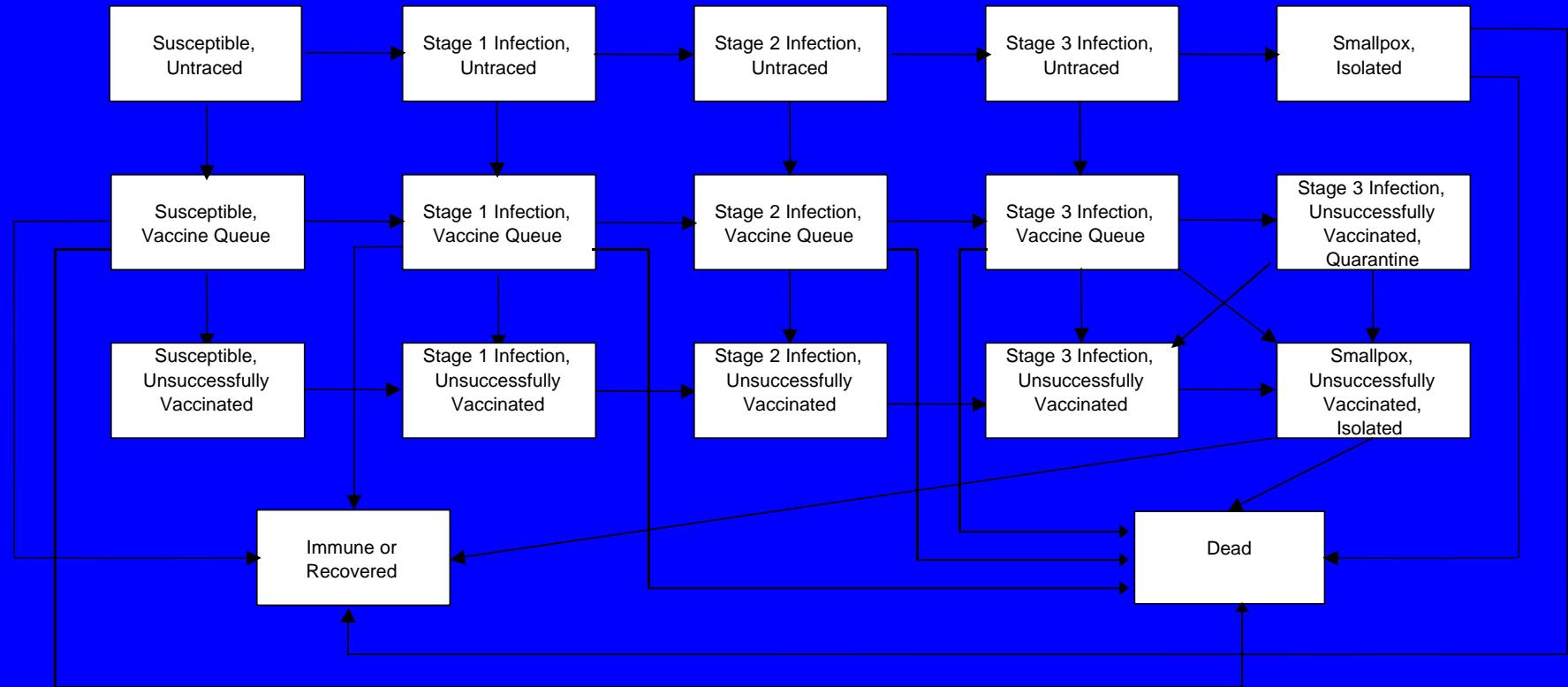
Complete Model

Contact Tracing: The Race To Trace!!

- "Contact identification is the most urgent task when investigating smallpox cases since vaccination of close contacts as soon as possible following exposure but preferably within 3-4 days may prevent or modify disease. This was the successful strategy used for the global eradication of smallpox." -CDC Interim Plan, Guide A, p. A-10

Index		
	Remaining Infectious Period	Index Case Detection
Contact		
	Vaccine Sensitive Period	Contact Detection -- Too Late!

- Our model estimates the probability of finding a contact in time; for contact tracing to be effective, the race to trace must be won repeatedly!
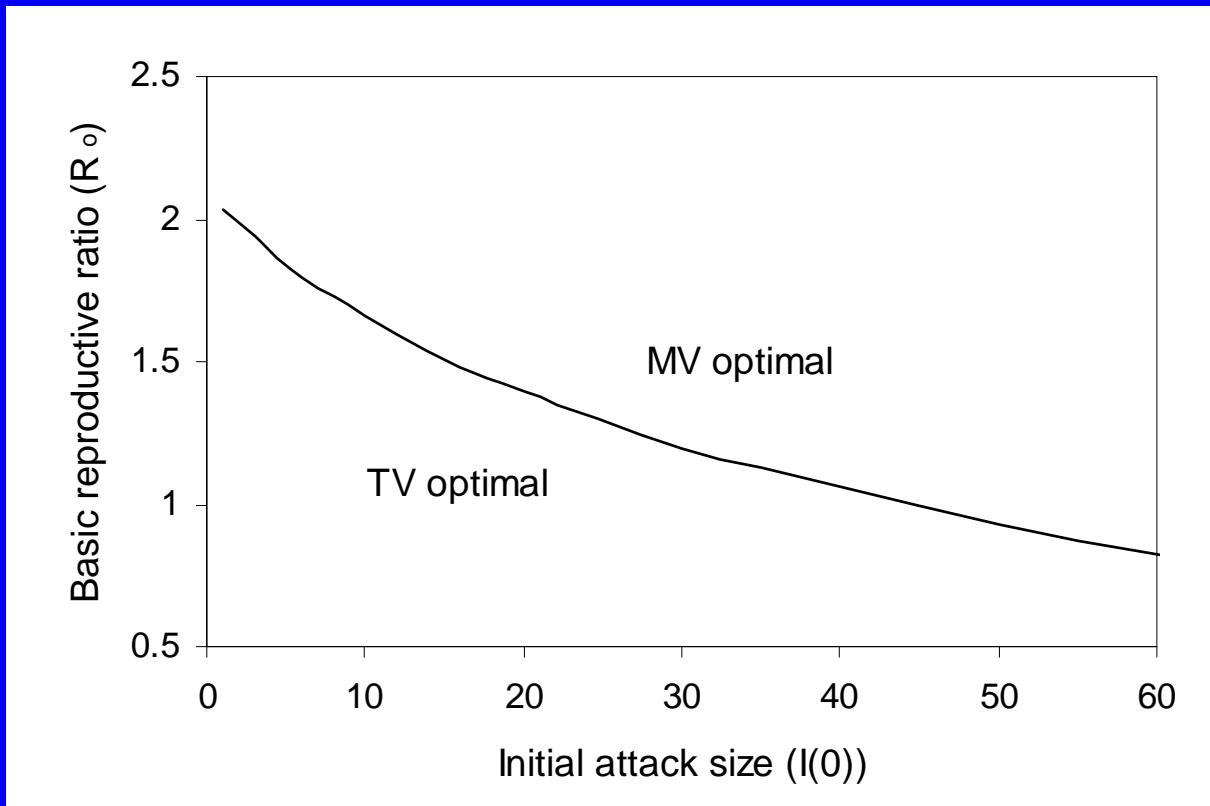
Vaccination Logistics: Queueing!!

Mass protection. Vaccination quickly curbs smallpox epidemics, as New York City learned during a scare in 1947.

The Most Important Result: TV or MV?
(100% Tracing Accuracy)

- Favor MV for any $R_0 > 2$

What is the Trade-Off?

- Tracing leads to *slower* overall vaccination, but with focus on *higher-yield* subjects (i.e. household contacts most likely to be infected)

- For large attack, quickly building immunity in community is more important than specificity

- Note: can still prioritize household contacts within a mass vaccination program – just don't sacrifice overall vaccination rate at expense of searching!
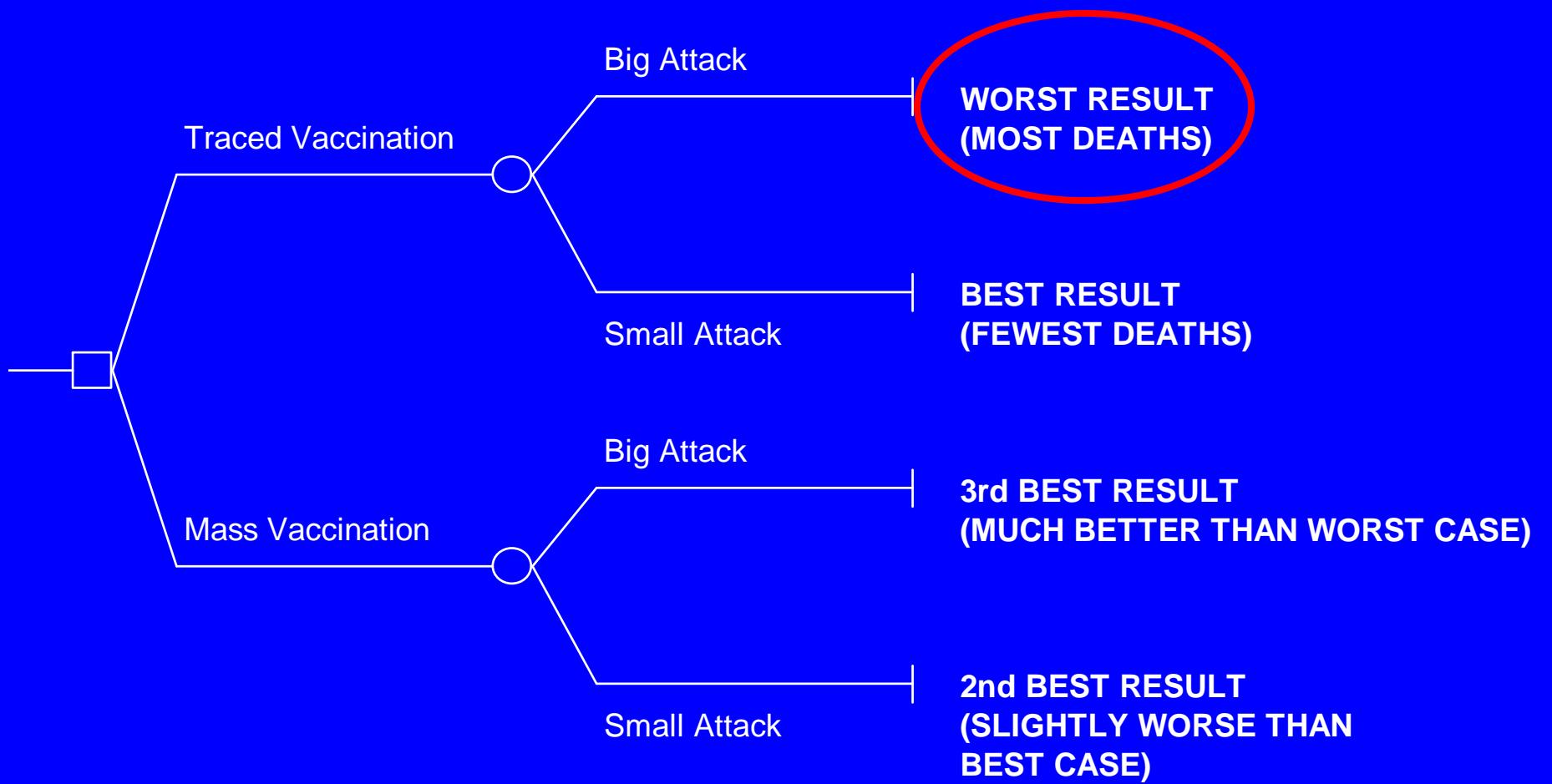
Consequences of choosing the wrong policy are not symmetric!!

- If TV is optimal, choosing MV would lead to few incremental deaths
- If MV is optimal, choosing TV could lead to a disaster with many incremental deaths
- Would therefore suggest choosing TV only if extremely confident (i.e. highly certain) that initial attack size and R_0 fall on the TV-favorable side of the tradeoff curve

But "Small Attack" is More Likely Scenario!!

- *Common error in decision-making*: determine "most-likely scenario" and plan for that

- Better approach: identify options, consider possible scenarios, pick death-minimizing option

- *Even if "big attack" scenario has only a very small chance of occurring, still optimal to prepare for that eventuality!*

- *Key intelligence question:* is a major attack possible (i.e. is the risk non-zero)? If the answer is yes, *actual risk of attack loses its importance – it is optimal to prepare for the worst case!*

The Post-Attack Decision

Traced Vaccination

Big Attack — **WORST RESULT (MOST DEATHS)**

Small Attack — **BEST RESULT (FEWEST DEATHS)**

Mass Vaccination

Big Attack — **3rd BEST RESULT (MUCH BETTER THAN WORST CASE)**

Small Attack — **2nd BEST RESULT (SLIGHTLY WORSE THAN BEST CASE)**

Why Not Start Small, Go To Mass Only If Needed?

Build Button Now

Attack
Vaccine complications among first responders and population and smallpox cases/fatalities from immediate response
3rd BEST RESULT

No Attack
Vaccine complications among first responders
2nd BEST RESULT

Wait For Attack

Attack
Vaccine complications among first responders and population and smallpox cases/fatalities from **delayed** response
WORST RESULT

No Attack
No morbidity/mortality since no attack
BEST RESULT

Think like a terrorist!

An attack is less likely if you prepare.

Advertising lack of preparedness (e.g. hospital or health district opt-out) might invite attack.

Percentage of Second Generation Infections Prevented
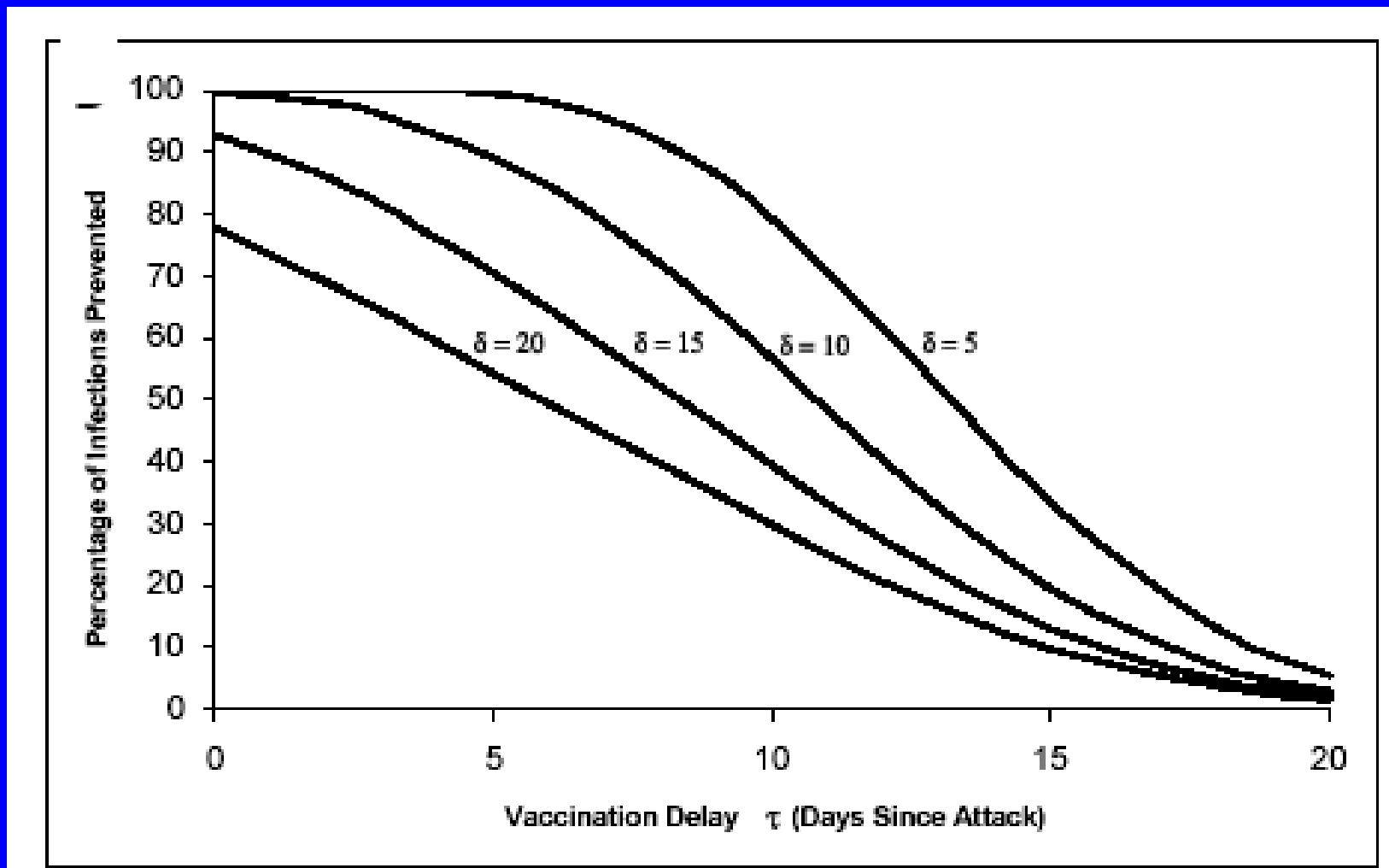
Economic Costs Mount
With Duration of Response

The New York Times — **Health** — October 13, 2002

SEARCH ▸ Go to Advanced Search/Archive

Past 30 Days

SEARCH SPONSORED BY **Twin treats hair loss!**

▸ GO TO **MEMBER CENTER** ▸ LOG OUT

Welcome, kaplaneh

☒ E-Mail This Article
🖨 Printer-Friendly Format
📧 Most E-Mailed Articles
© Reprints

SBC — **Infinite possibilities.**

A LIVING WEAPON

White House Debate on Smallpox Slows Plan for Wide Vaccination

By WILLIAM J. BROAD

ARTICLE TOOLS SPONSORED BY **STARBUCKS.COM**

This article was reported by Lawrence K. Altman, William J. Broad and Denise Grady and was written by Mr. Broad.

Intense debates in the Bush administration over smallpox vaccinations have delayed critical decisions in the nation's program against germ terrorism for months, participants say.

Douglas Holtz-Eakin, chief economist at the White House Council of Economic Advisers, went so far as to argue that a major attack could virtually shut down the economy and cost $177 billion per week. At a public meeting in June, he asked if even truck drivers and airplane pilots should be vaccinated.

Associated Press

A hospital worker receiving a smallpox vaccination last month in Tel Aviv. In August, Israel became the first nation known to have started vaccinating emergency workers.

HOME
JOB MARKET
REAL ESTATE
AUTOMOBILES

NEWS
International
National
Washington
Campaigns
Business
Technology
Science
Health
- Aging
- Anatomy
- Children
- Fitness
- Genetics
- Men
- Nutrition
- Policy
- Psychology
- Women
- Columns
Sports
New York Region
Education
Weather
Obituaries
NYT Front Page
Corrections

OPINION
Editorials/Op-Ed
Readers' Opinions

Advertisement

Celebrity Cruises℠

MULTIMEDIA

Graphic: Preparing for Smallpox

Given Costs, Want *Fast* Control!

- Traced vaccination is *slow*: proceeds at the pace of the epidemic (need new cases to trigger tracing and vaccination)

- Mass vaccination is *fast*: limited only by available vaccination resources, independent of epidemic

Thinking About Vaccine Risks

- Vaccinia expected to kill at most 1 per million
- What are other death risks we face?
  - Annual road accident risk: 145 per million
  - Annual alcohol risk: 161 per million
  - Annual risk of drowning: 15.6 per million
  - Annual bicycle death risk: 2.7 per million
  - Death risk per airplane flight: 1 in 8 million (and at 10 flights per year, 1.25 per million, similar to vaccinia)
- Post-attack, vaccinia risks just don't matter relative to risk of smallpox

Pre-Attack Vaccination

- Reduces degree of susceptibility in the population

- Effect is to reduce R_0 and initial attack size

- Pre-attack vaccination makes post-attack TV more attractive as a result

TV with Pre-Attack Vaccination
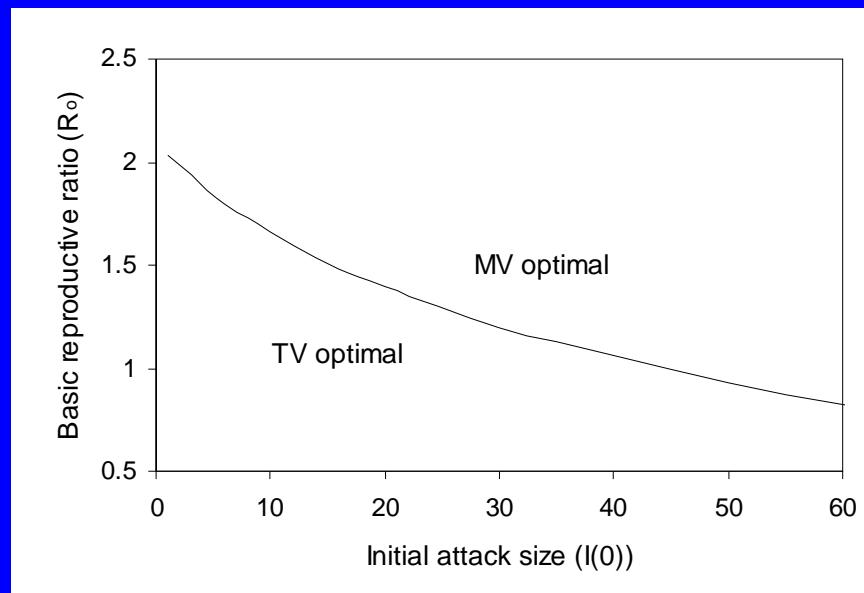
TV Deaths with Pre-Attack Vaccination
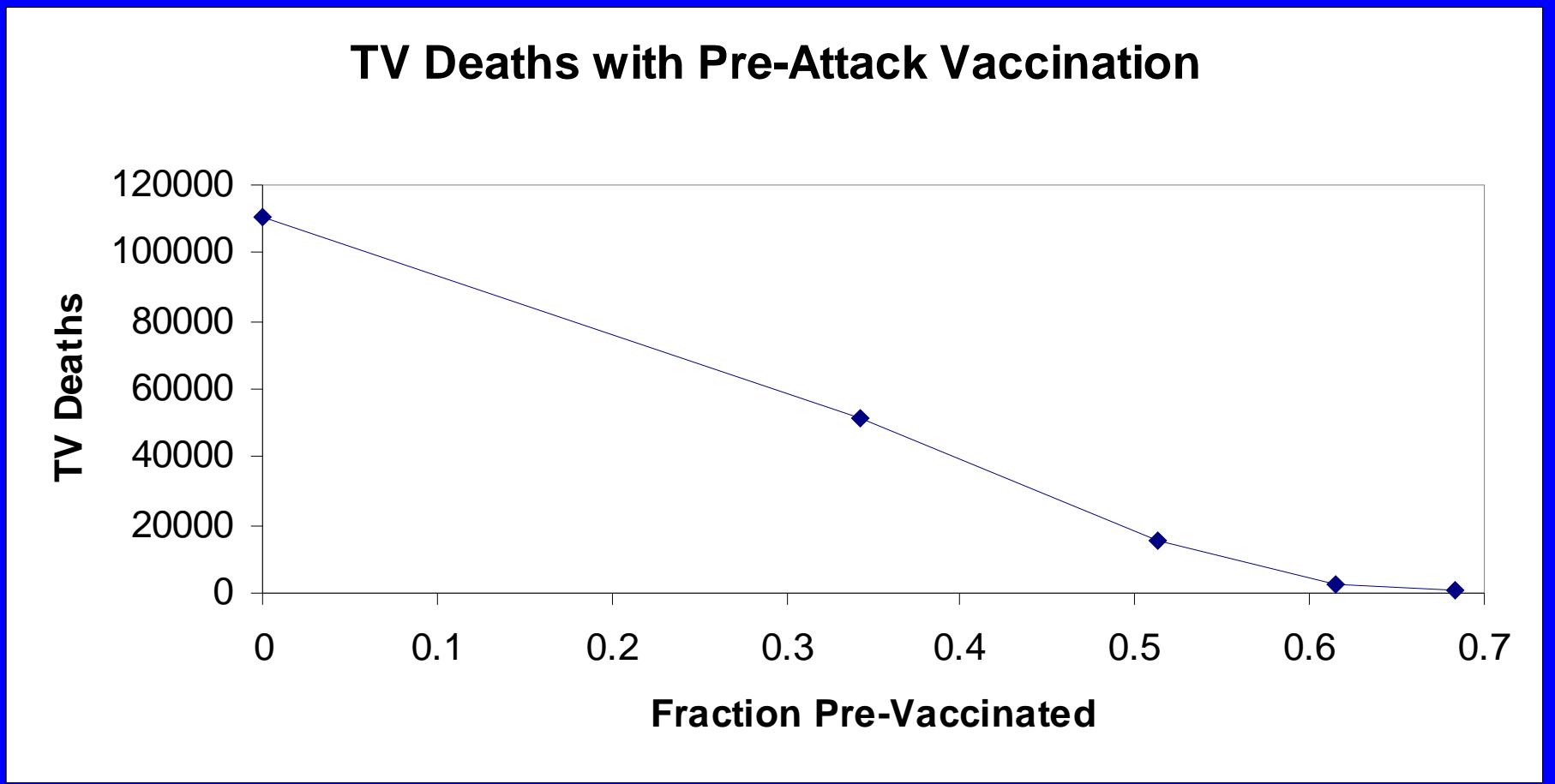
Pre-Attack Vaccination?

- Suppose 100% successful pre-attack vaccination – expect 10 vaccine-related deaths
- Let α = Pr{Smallpox Attack}, $d(\pi)$ = deaths post attack from response policy π
  - Note: think of attack risk over 5-10 year time frame
- Solve $10 = \alpha\, d(\pi)$ for α; consider pre-attack vaccination if *perceived* attack risk exceeds α
- Base case results:
  - for π = TV, α = 9 in 100,000
  - for π = MV, α = 1.8% (!!)
  - for π = TV/MV (CDC policy), α = 2 in 1,000

Pre-Attack Mass Vaccination?

- Take home message: decision to vaccinate pre-attack should depend not only on the risk of vaccine and attack, but also on the response policy

- If one does not have confidence in the response policy, one is much more likely to favor pre-attack vaccination

- If one is confident that the response policy could contain an attack, desire for pre-attack vaccination lessens

Thought Experiment: Smallpox Detected in NYC. You Are Mayor of Los Angeles. Do You Opt for Mass Vaccination?

- Yes. What is my estimate of the risk of attack in LA, given an observed attack in NYC? *Somewhat increased!!*

- Yes. My citizens would demand vaccine!

- And who knows ... maybe an infected New Yorker has landed in Los Angeles by now ... so ... *yes!*

Conclusions: Why Mass Vaccination?

- Models suggest fewer deaths from mass vaccination

- Principles of decision-making

- Cost of delay

- Vaccine risks don't matter post-attack

- Post-attack, the risk of further attack is somewhat increased!!

What Happened

- June 2002: Advisory Committee in Immunization Practices approves CDC ring vaccination policy and vaccination of 15,000 workers

- July 2002: Paper appears at www.pnas.org

  - Meetings in Israel with IDF Surgeon General, head of ICDC, etc.

  - 3-hour talk at White House

  - Op-eds in NYT, WSJ, etc.

- Gov't announces plans for vaccination of 500,000 workers

- August 2002: Visit and presentation to CDC

- October 2002: Detailed MV guidelines appear (CDC plan 3.0)

- Dec. 13, 2002: President Bush announces his policy

  - Phase I: 510,000 first responders; Phase II: 10 million; Phase III: Public

  - Plan stalls: only about 40,000 first responders vaccinated to date (11/04)

- Jan. 16-17, 2003: Consultation with Health Canada

Bioterrorism
Preparedness and Response
A Call to Action

Smallpox Update

Joxel Garcia, MD, MBA
Commissioner

Connecticut Department of Public Health

WHY SMALLPOX PLANNING IS ON A FAST-TRACK

Generated by threat of war

- If war, ideally & potentially by February 2003
- If war, smallpox could be used against troops, others
- Threat of smallpox is deemed genuine

Major Issues Needing Detailed Planning

- Surveillance & diagnosis
- Hospital Planning
- Type C facility
- Pre-vaccination
- *Emergency Mass Vaccination*
- Quarantine

NATIONAL SMALLPOX PLANNING TIMETABLE

- Initial request for pre-vaccination recommendations from ACIP by mid-June

- Mass vaccination clinic guidelines: Sept 23

- Licensing of Dryvax vaccine; October 25

- Request made on October 28 for all states to have written response plans by December 1

- Pre-vaccination of military has begun

Other Smallpox Analyses

- Halloran *et al.* (*Science*, 11/02)

- Epstein *et al.* (*Brookings*, 12/02)

- Bozzette *et al.* (*NEJM*, 12/02)

"Containing of Bioterrorist Smallpox" (*Science* 11/15/02)

- Paper by Betz Halloran, Ira Longini *et al.* uses "structured stochastic simulator"

- Looks at 2,000 person "community" of four neighborhoods, one high school, one middle school, two elementary schools, play groups and day care centers

- Introduces 1-5 infected terrorists who mingle in population (claiming this is the "most likely method of attack")

Main Finding

- Absent residual immunity from vaccinations among adults 20+ years ago, deaths under TV only a factor of 2 higher than deaths under MV

- With residual immunity, TV does better

- Attributes difference from our "factor of 200" TV/MV death ratio to difference between "structured" and free mixing

An Alternative Interpretation...

- If we place the *Science* inputs into our *PNAS* model, look what happens! (*Science*, 300:1503, 2003)

	Deaths per 1000	
	Halloran *et al* (*1*)	Kaplan *et al* (*2*)
80% MV after:		
1 case	0.9	0.4
15th case	9.4	6.4
25th case	13.7	17.8
80% TV after:		
1 case	10.9	8.8
15th case	19.6	12.0
25th case	28.2	33.9

What Is Going On?

- Newly identified cases required to trigger contact tracing
  - TV proceeds with the pace of epidemic
  - Number of deaths scales with population size; independent of initial infections
- MV operates on its own timetable
  - 10 days in the examples above
  - Number of deaths depends on initial infections; independent of the population size
- Ratio of deaths from TV/MV grows with population size!

Brookings Model

- "Agent based" model; 1 initial infection
- 2 counties, each with 100 households, each household with 2 adults and 2 kids
- Similar to Halloran *et al*. with different transmission depending upon contact type, and different mixing places (e.g. schools, hospital, work)

From **Toward a Containment Strategy for Smallpox Bioterror: An Individual-Based Computational Approach**
Joshua M. Epstein , Derek A. T. Cummings,
Shubha Chakravarty, Ramesh M. Singa, and
Donald S. Burke
Center on Social and Economic Dynamics
Working Paper No. 31
December 2002

The horizontal axis is the percentage of the population vaccinated or immune prior to an attack, while the vertical axis is the number of smallpox cases in a population of 800. The tick marks on the vertical axes in both graphs are at intervals of 200.

b) 25% Family Contact Tracing
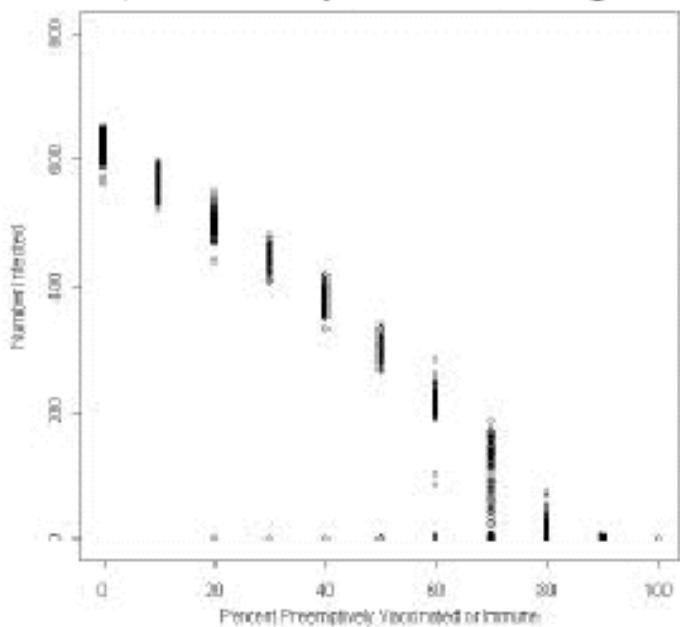
c) 50% Family Contact Tracing

We've Seen This Before!

TV Deaths with Pre-Attack Vaccination
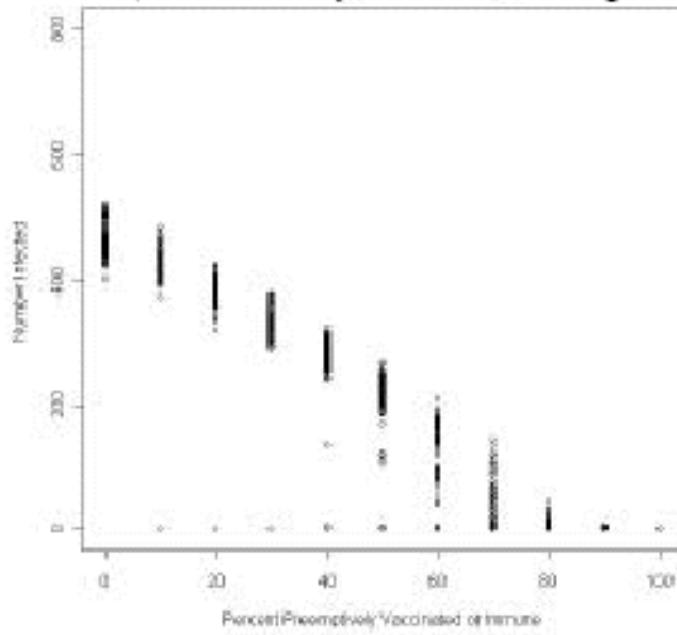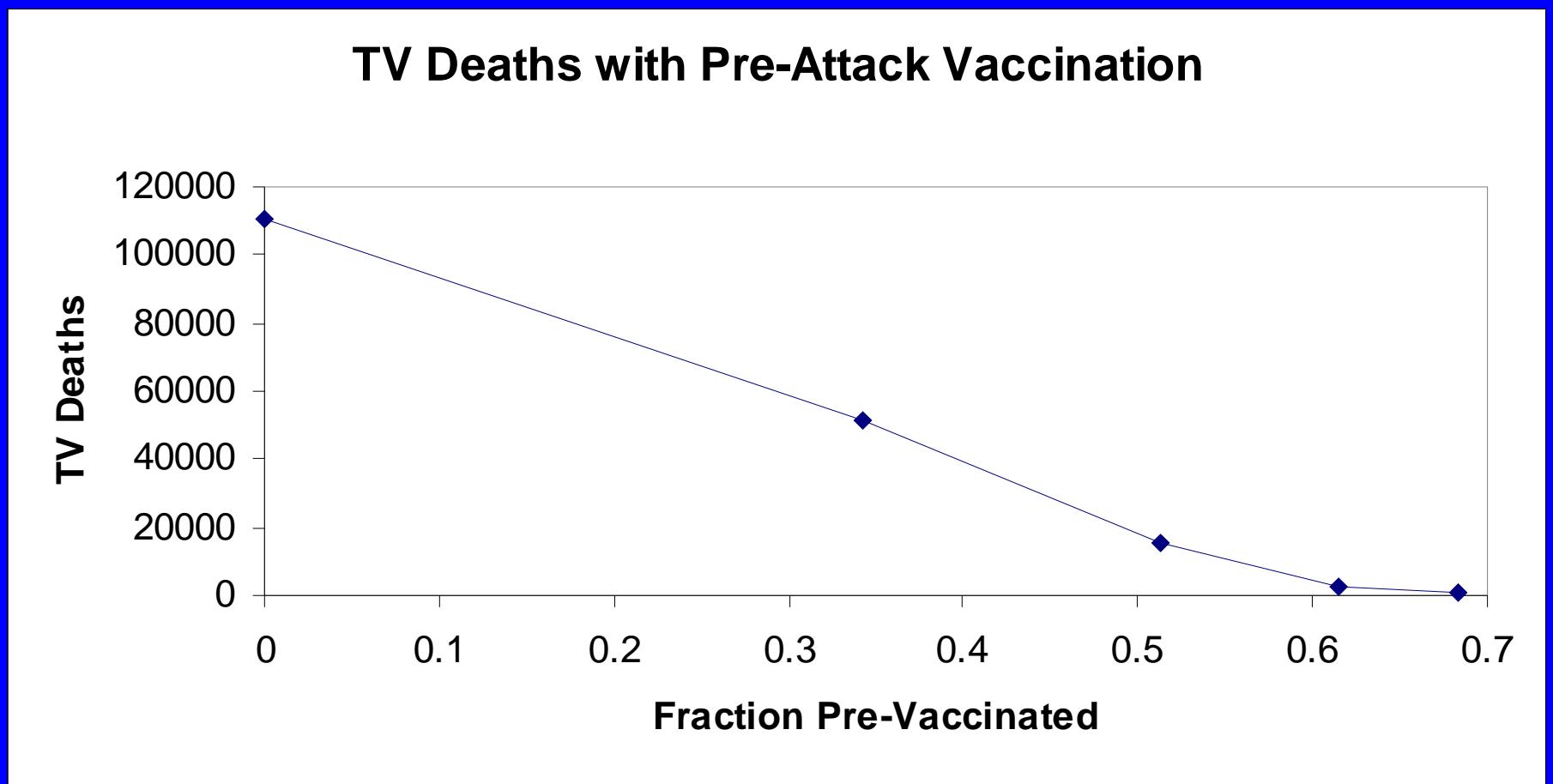
Brookings Model

- Put Brookings and *PNAS* on same scale (800 persons) – look what happens – with 100% tracing, no prior immunity, same inputs:

    – Brookings: 6% of population dies

    – *PNAS*: 0.6% of population dies

- Brookings does not consider post-attack MV, but results are implied by pre-attack vaccination coverage charts (since post-attack MV rapidly boosts vaccination coverage)

Bozzette *et al.* (*NEJM* 1/30/03; early web posting 12/02)

- Set transmission based on "chart reviews" of historical studies

- Presumed reproductive numbers R_U pre-attack and R_C post-attack

- Monte-carlo simulation of many different scenarios; determined attack probability thresholds to see when pre-attack vaccination is justified

- *Assumed* $R_C = 0.1$ for ring-vaccination independently of initial numbers infected and available vaccination resources – no modeling of response operations

Bozzette *et al.*

- Kaplan claims that an approximate formula for smallpox deaths in this model given by:

  I(0) x

  (1 - Pre-Attack Vaccination) x

  $[(1+R_U)/(1-R_C)]$ x

  Pr{Death | Infection}

Bozzette *et al.*

Smallpox Deaths in Bozzette *et al.* (*NEJM*)
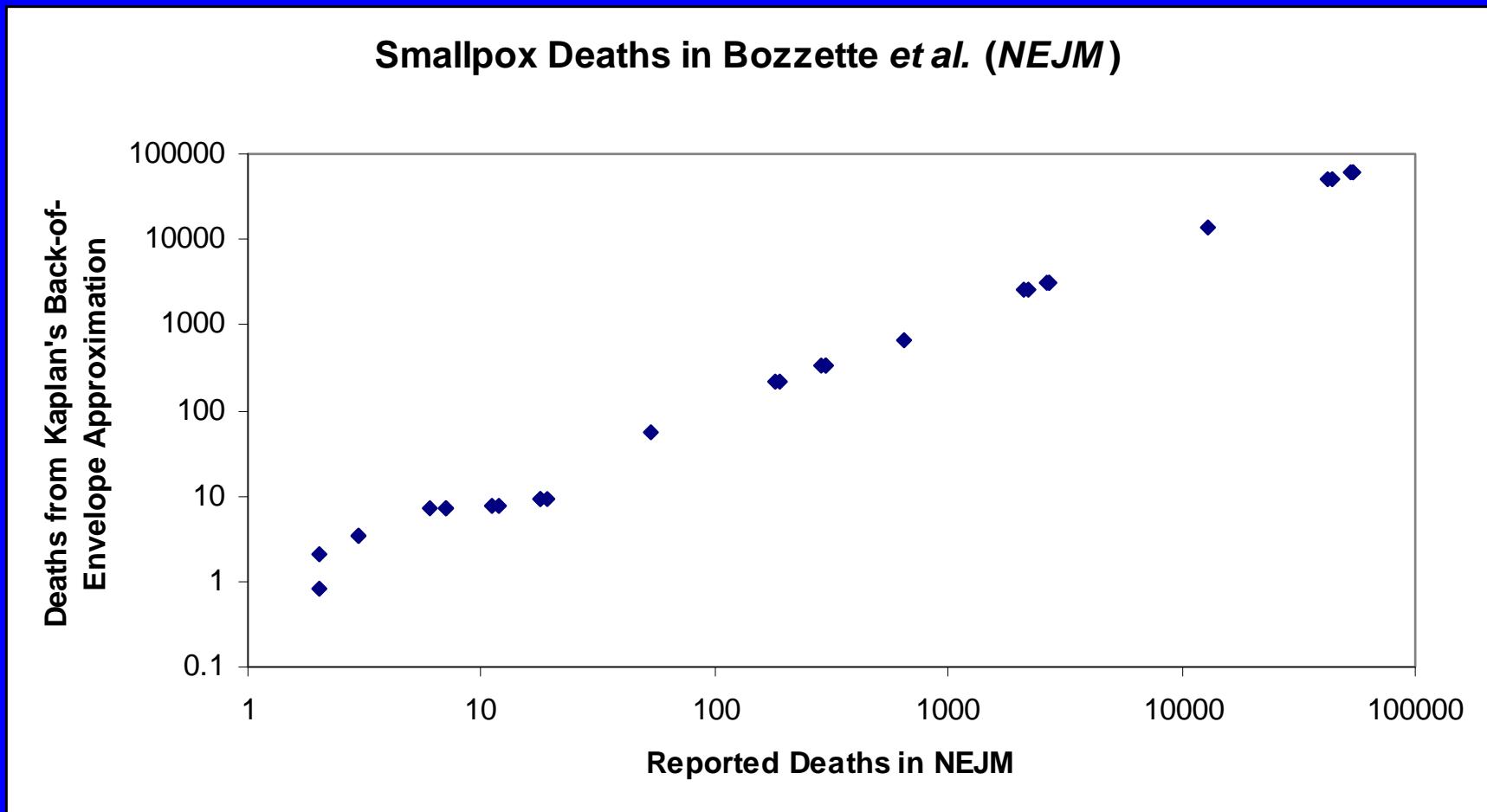
Bozzette *et al.*

- Can show that an approximate formula for smallpox deaths in this model given by:

    I(0) x (1 - Pre-Attack Vaccination) x [(1+R_U)/(1-R_C)] x Pr{Death}

- Proportional to 1 / (1-R_C)

- But R_C = 0.1!!

- *So a perfect policy with no post-attack transmission (R_C = 0) could at most improve matters by 10%!!*

- It is dangerous to evaluate a policy by assuming it works...

Smallpox Eradication Campaign Claims

- "Surveillance and containment" (isolate patients, vaccinate their contacts)
- Vaccination within three days post-exposure thought to abort/greatly alleviate disease
  - Aside: do available data *really* support this???
- "This method of containment, which led to the ultimate eradication of smallpox, *requires relatively few vaccinations for the contacts of each actual case*." (J. Michael Lane, *Ann Int Med*, March 2003, emphasis added)
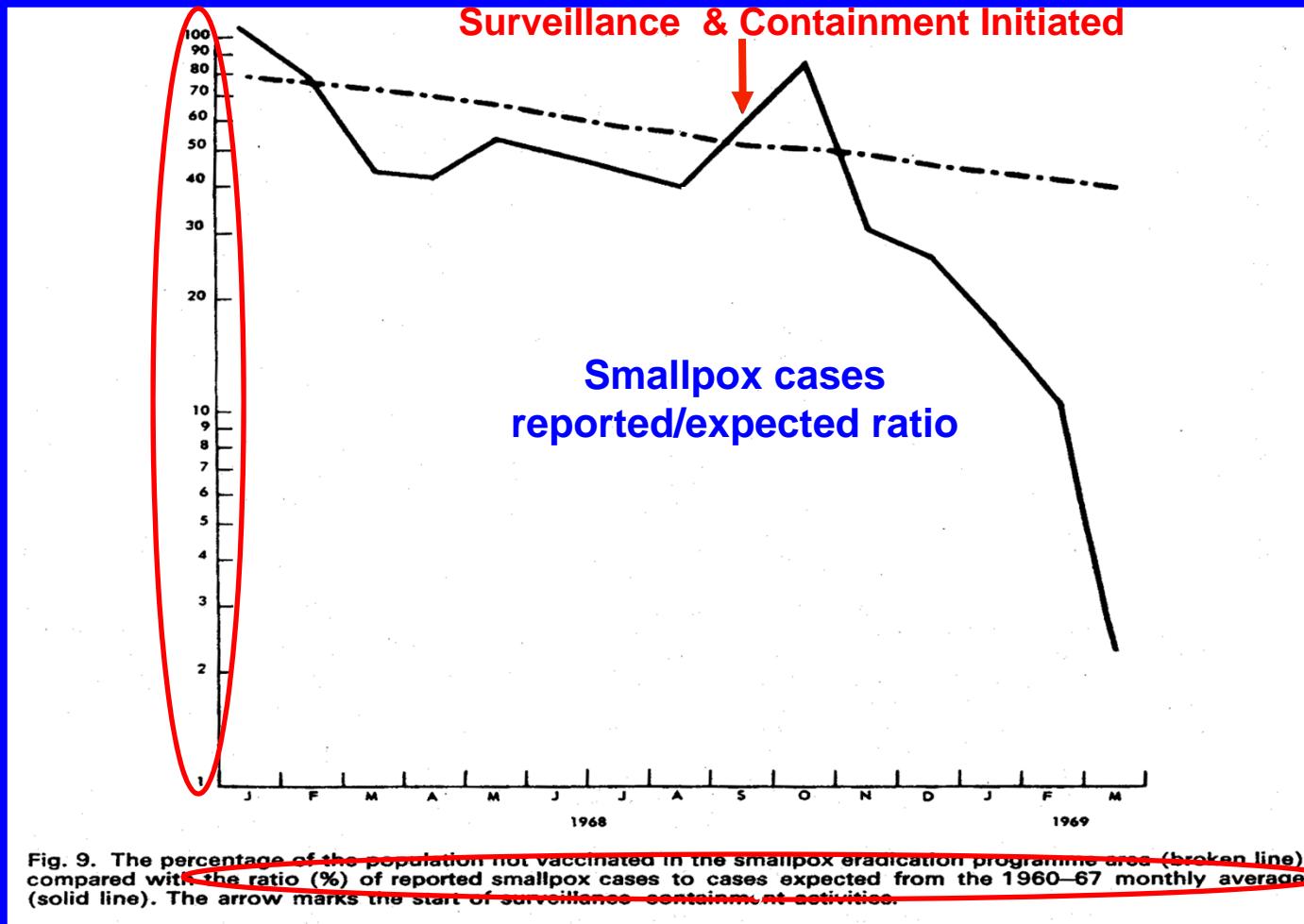
Is This What Really Happened?

- How many persons were actually vaccinated per case of smallpox?
  - Somalia: 512 ('77 – '79)[1]
  - India: 656 (during 1974); 1,462 ('74-'76)[2]
  - Brazil: 5,700 ('67 – '70)[3]
- 500 to 5,700 represents relatively few vaccinations for the contacts of each actual case?????

[1]Jezek *et al*, *Smallpox Eradication in Somalia*, WHO, 1979
[2]Basu *et al*, *The Eradication of Smallpox from India*, WHO, 1979
[3]Fenner *et al*, *Smallpox and its Eradication*, WHO, 1988

Effect of Search and Containment on Reported Smallpox Cases, West and Central Africa 1968-1969 (Figure 9 from Foege *et al*)


Fig. 9. The percentage of the population not vaccinated in the smallpox eradication programme area (broken line) compared with the ratio (%) of reported smallpox cases to cases expected from the 1960—67 monthly average (solid line). The arrow marks the start of surveillance-containment activities.

Foege WH, Millar JD, Henderson DA. Bull WHO 1975; 52: 209-222

Decline in Reported Smallpox Cases Matches Decline in Susceptibility Over Time!
(*Epidemiology*, 14:90-92, 2003)

Reported Cases and % Unvaccinated from Foege *et al*
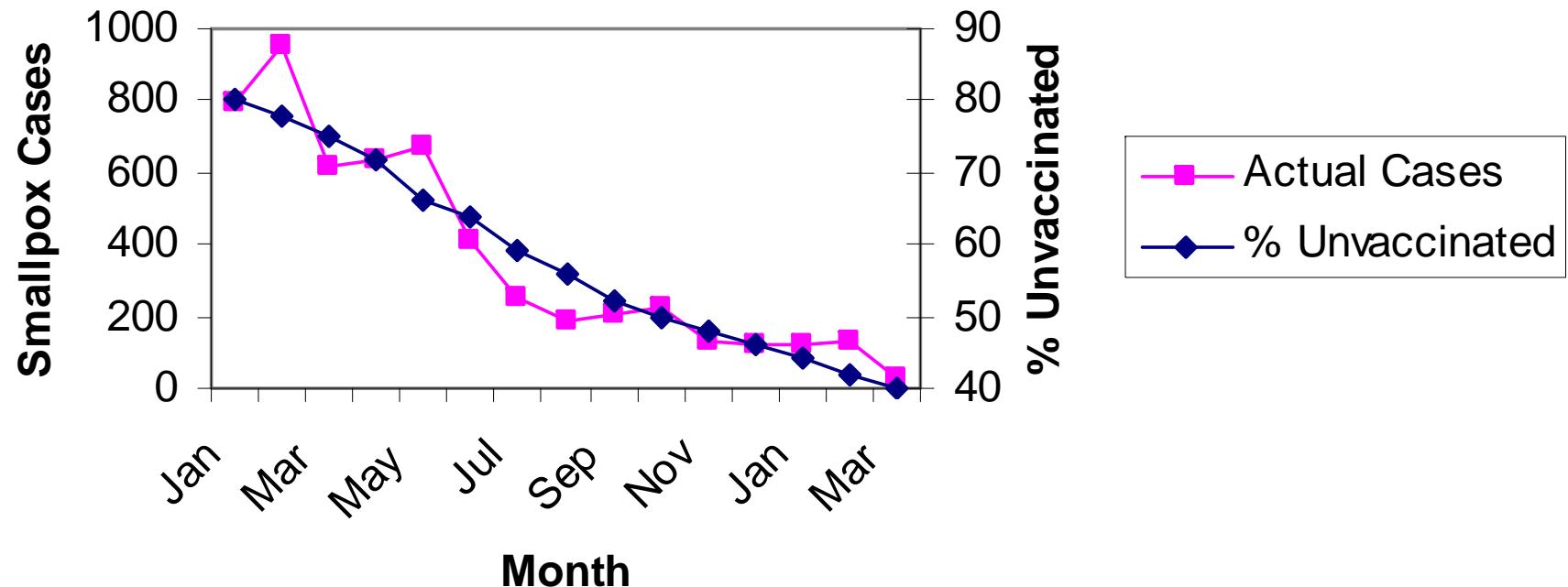
Relationship Between Reported Cases and Vaccination Coverage Corresponds to Standard Theory
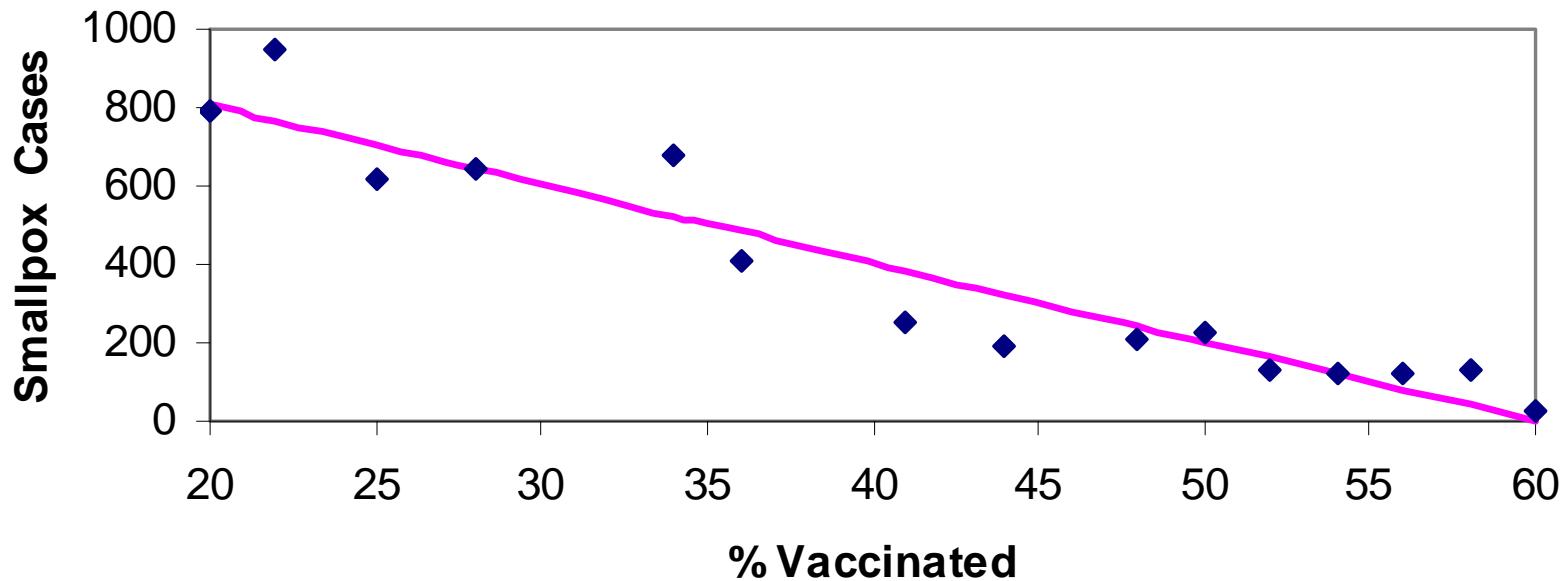
Clear Conclusion

- Increasing vaccination coverage reduces incidence of infection
    - Consistent with the *simplest* models of vaccine-controllable infectious disease
    - Consistent with complex smallpox models
   - Consistent with data from the field

Common Claim for India

- Transmission continued even when 90%+ of the population was vaccinated!!

- When ring vaccination started in India, new cases were higher than they had been in decades!!

Fig. 15.3. India: number of reported cases of small-pox, by year, 1950-1975.
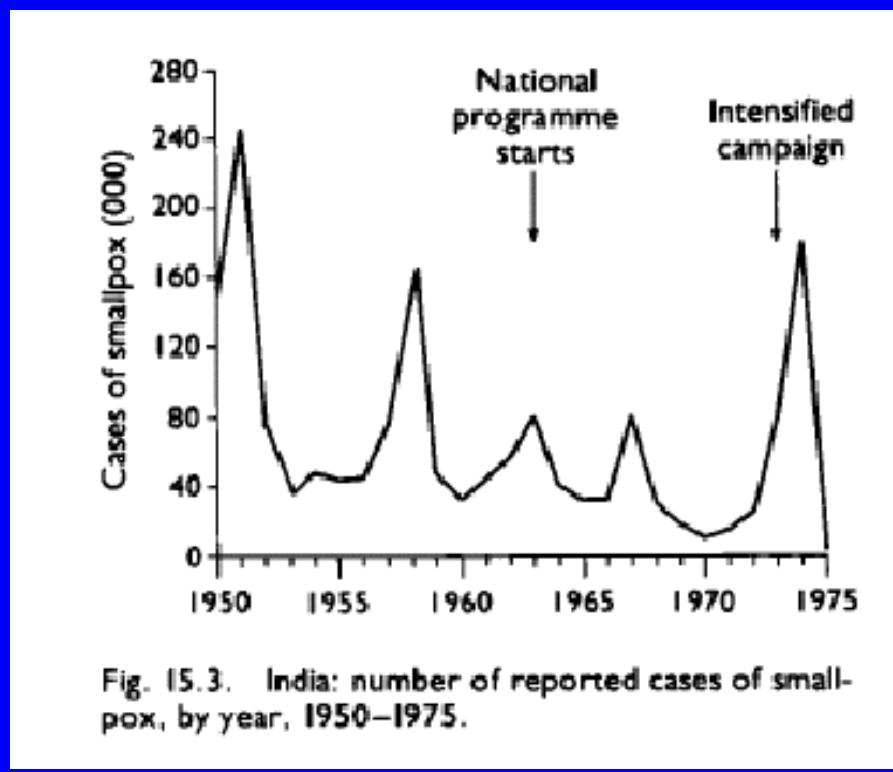
from Fenner *et al.*, *Smallpox and its Eradication*

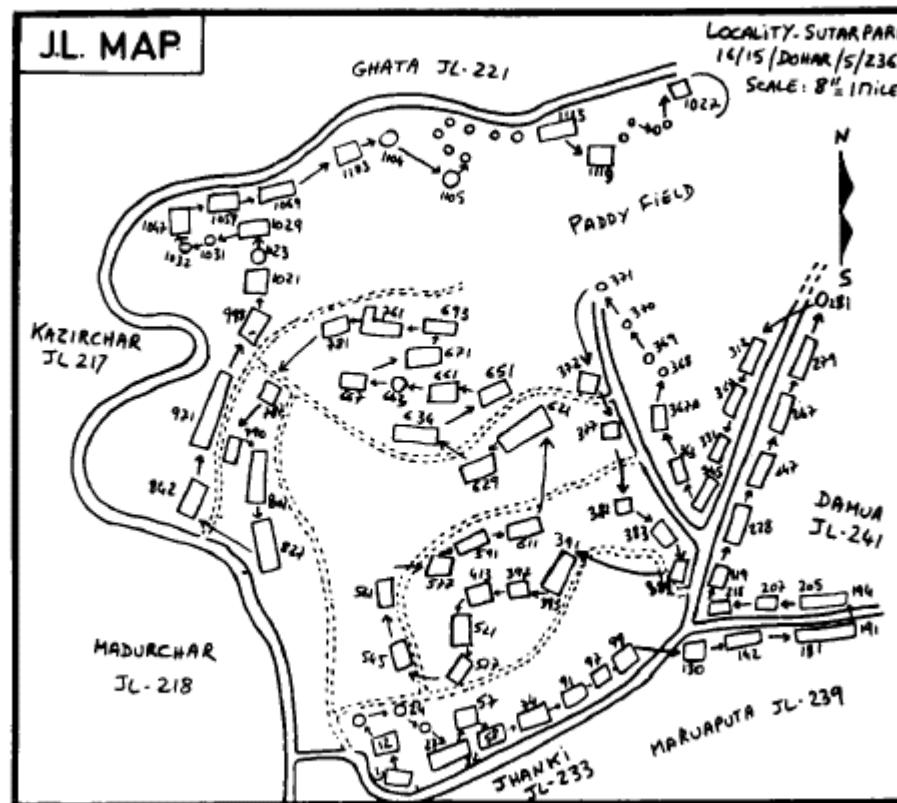*Of course, the population of India was also higher than it had been in decades!!*

Accounting For Population...

Smallpox Incidence in India (Cases per Million)
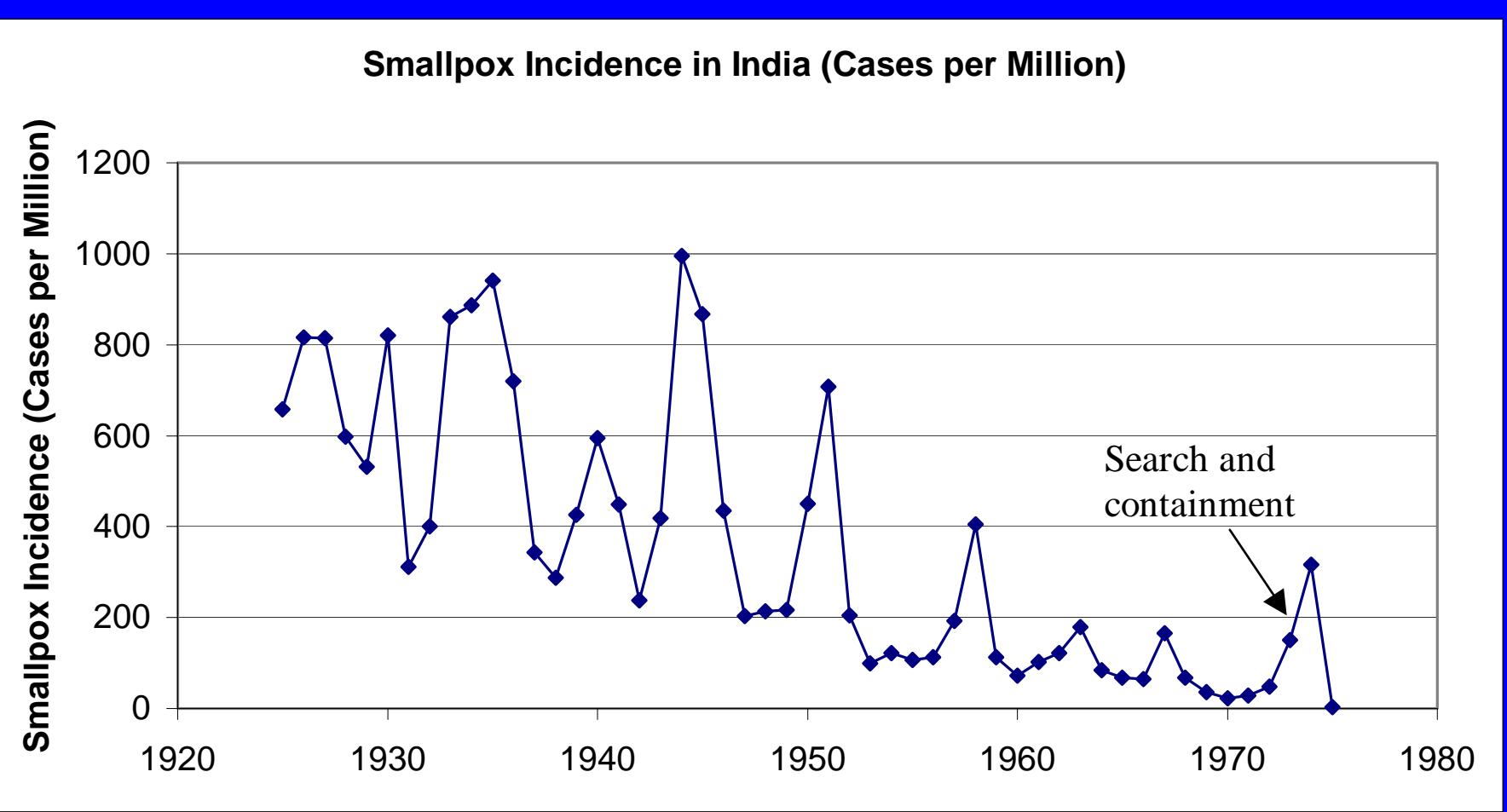
TV = MV ???

Plate 10.38. A sketch map of an infected village, prepared for containment activities in Bangladesh. All the houses were numbered; arrows indicated the order in which the houses were to be searched.

Source: Fenner *et al*, Smallpox and its Eradication

More on TV=MV

- "During the second half of 1974 ... The entire population of each infected village and mohalla was carefully enumerated and vaccinated ... Close contacts and members of the affected household were first priority followed by members of the 50 surrounding households." (Basu *et al*, *The Eradication of Smallpox from India*, WHO 1979)

And, Obvious Differences Between Then and Now

- Bioterror attack: *deliberate*, *strategic* spread of infection by *people trying to kill us* (versus natural outbreaks)

- Population susceptibility today: very high (versus immunity due to prior vaccination campaigns and epidemics)

- Population mobility today: much greater

Reprise

- Models
- Principles of decision-making
- Costs of delay
- Low risks of vaccination relative to smallpox
- Increased risk of further attack
- Data from the eradication program
- *all* support mass vaccination in response to a smallpox bioterror attack