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Measuring Disease Dynamics in Populations: Characterizing the Likelihood of Control

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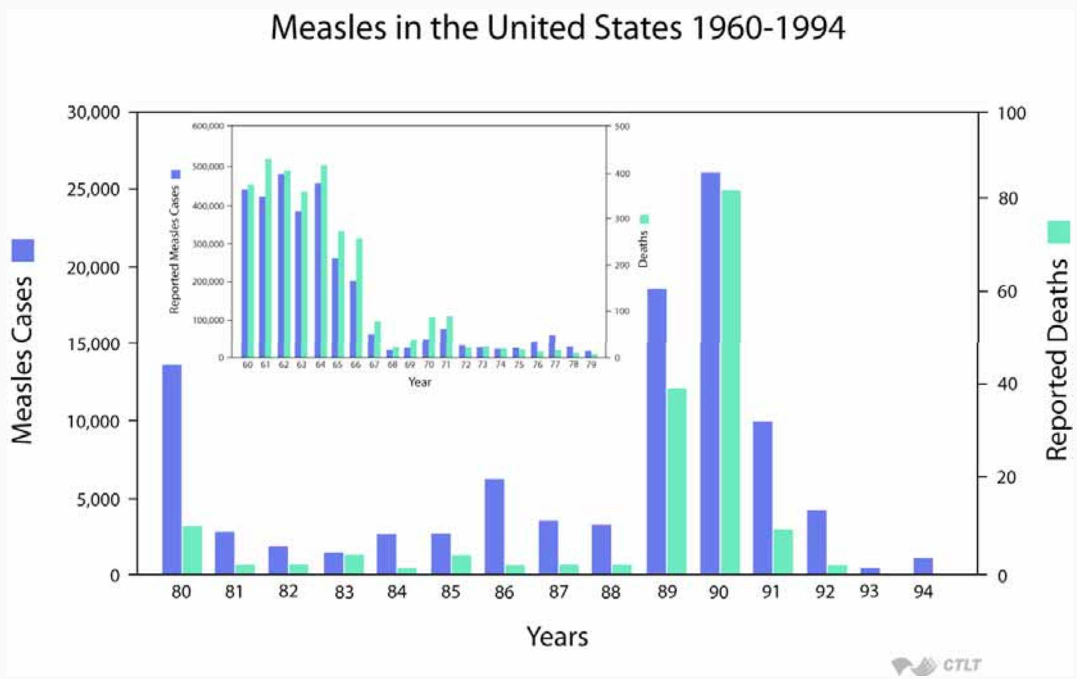
Section A

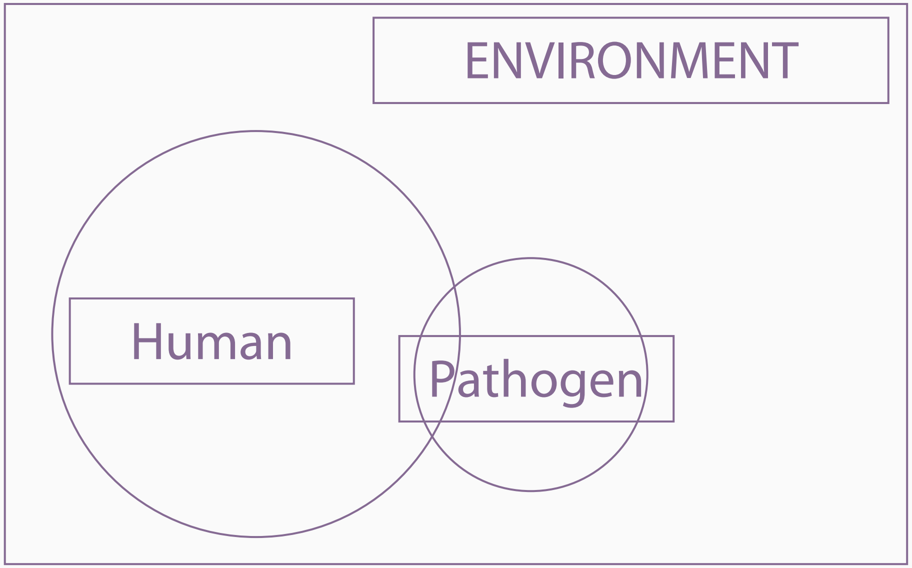
Overview and Net Reproductive Ratio

- In this lecture, we will:
  - Provide an example of emergent properties in disease ecology associated with public health
  - Introduce the concepts of net reproductive ratio and effective reproductive ratio
  - Demonstrate how vaccine programs are related to net reproductive ratio
  - Show the relationship between net reproductive ratio and herd immunity
  - Examine implications for patterns of future diseases

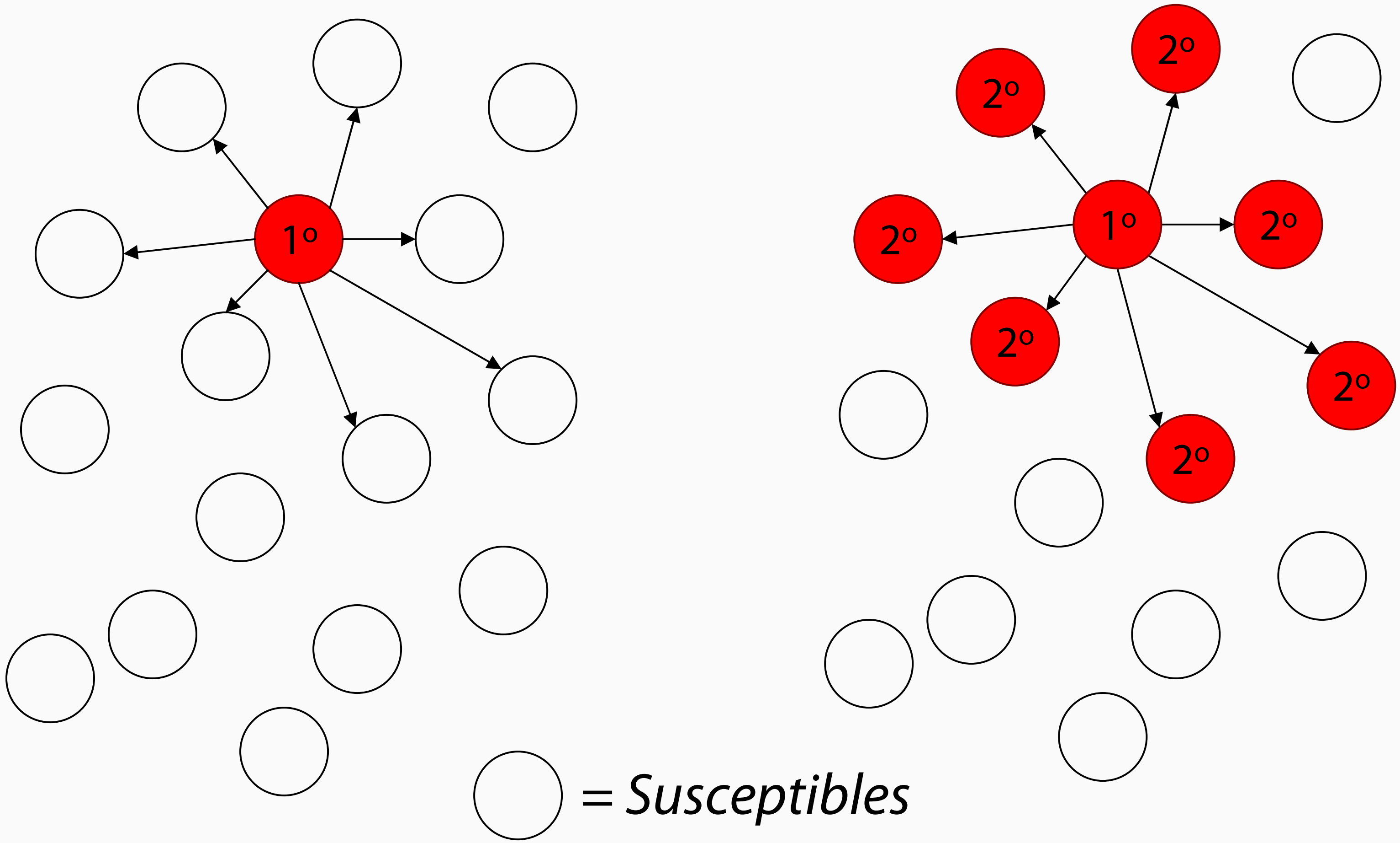
- Prior to 1964 in the U.S., measles was recognized as an acute, childhood illness with occasional complications
- Epidemics occurred on a predictable basis
- First vaccine resulted in major decrease in numbers of cases
- Substantial outbreak in 1989–1990 with large number of deaths



- Directly transmissible infectious disease
  - Two-population system
  - Measure how pathogen population is growing in human population



Net Reproductive Ratio



- Net reproductive ratio (R_o)
  - The basic reproductive rate for a finite period of time of the pathogen in the host population when resources (hosts) are not limiting
  - Number of secondary case caused by a primary case (in a population of susceptibles)

Continued

Net Reproductive Ratio (R_o)

- If $R_o > 1$: then each primary case produces more than 1 secondary case ⇒ epidemic
- If $R_o < 1$: then each primary case doesn't produce enough cases to replace itself ⇒ disease should die out
- If $R_o = 1$: then each primary case replaces itself ⇒ disease will continue to persist endemically

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Section B

Net Reproductive Ratio (Continued)

Net Reproductive Ratio (R_o)

- $R_o = B * N * d$
  - R_o = Number of secondary cases
  - B = Transmission parameter
  - N = Population size of susceptibles
  - D = Duration of infectiousness
- Number of “successful” contacts with susceptibles/ unit time x length of time an individual is infectious

Continued

Net Reproductive Ratio (R_o)

- $R_o = B * N * d$
  - $R_o =$ Number of secondary cases
  - B = Transmission parameter
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Some Estimated Values of (R_o)

Disease	Geographical Location	Time Period	R_o
Diphtheria	New York, USA	1918–19	4–5
	Maryland, USA	1908–17	4–5
Scarlet Fever	Maryland, USA	1908–17	7–8
	New York, USA	1918–19	5–6
	Pennsylvania, USA	1910–16	6–7
Mumps	Baltimore, USA	1943	7–8
	England and Wales	1960–80	11–14
	Netherlands	1970–80	11–14
Rubella	England and Wales	1960–70	6–7
	West Germany	1970–7	6–7
	Czechoslovakia	1970–7	8–9
	Poland	1970–7	11–12
	Gambia	1976	15–16
HIV (Type I)	England and Wales (male homosexuals)	1981–5	2–5
	Nairobi, Kenya (female prostitutes)	1981–5	11–12
	Kampala,Uganda (heterosexuals)	1985–7	10–11

Effective Reproductive Ratio

- For a pathogen that is established in a human population, previously infected individuals either die or are immune
  - Fewer susceptibles are available
  - Rate of transmission should be lower than R_o
- Effective reproductive ratio (R_e) = average number of secondary cases per primary case after pathogen is established

Effective Reproductive Ratio (R_e)

- $R_e = B * X * d$
  - R_e = number of secondary cases/primary case
  - B = transmission parameter
  - X = size of susceptible population
  - D = duration of infectiousness

- Some diseases show temporal stability in incidence—endemic
  - Persistent infections
  - Poor natural immunity
  - Low rates of mortality
- Some diseases are characterized by repeated outbreaks on fairly regular basis—epidemics
  - Acute infection
  - Long-lasting immunity and/or
  - High rates of mortality

Continued

- Temporal pattern determined by rate of introduction of susceptibles into population (X)
  - If susceptibles come into the population "rapidly":
    - Then disease tends to be endemic
  - If susceptibles come in "slowly":
    - Then disease tends to be epidemic
  - If susceptibles come in too slowly
    - Then disease dies out

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Section C

Net Reproductive Ratio and Disease Control

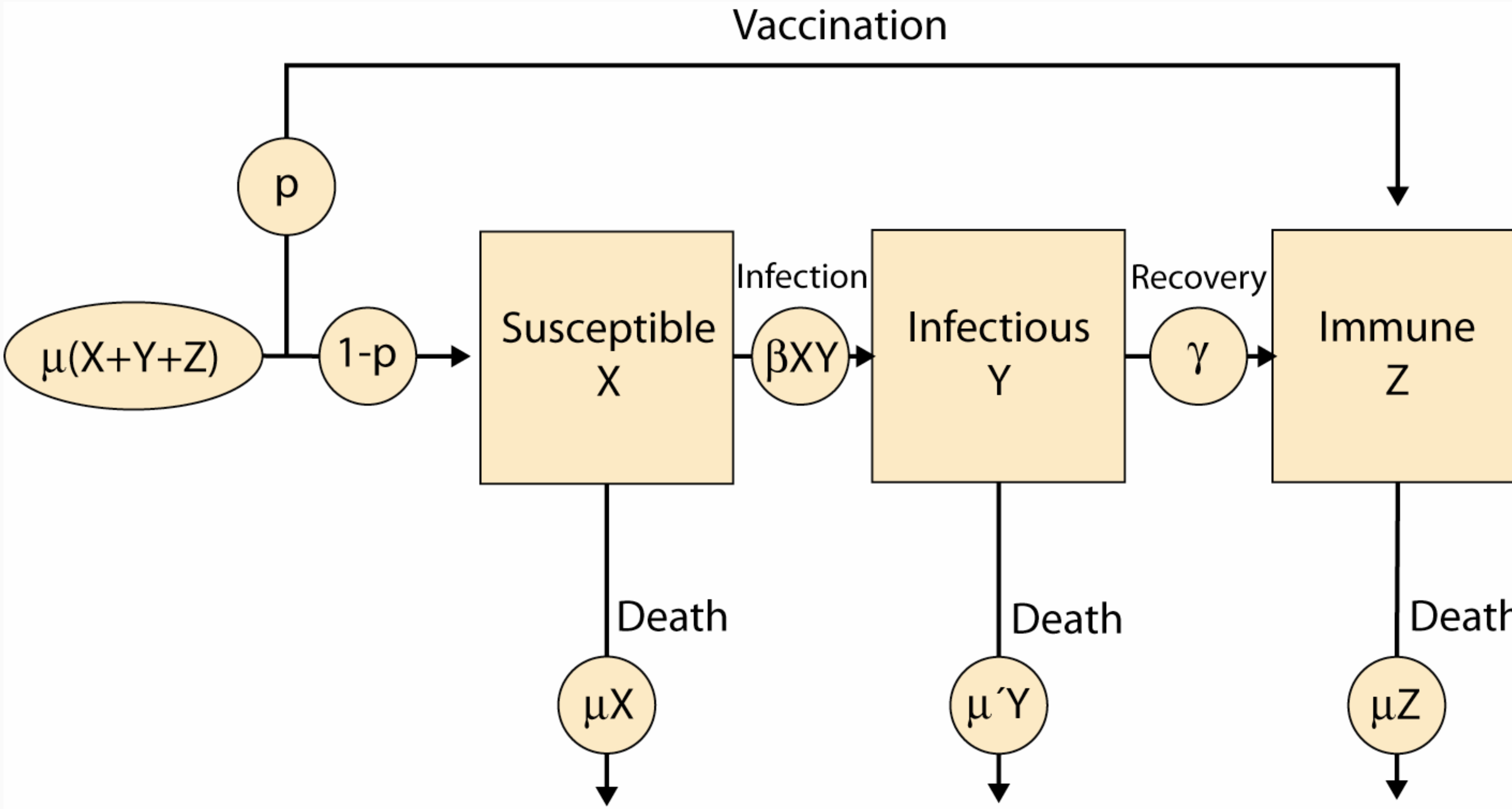
Disease Control and (R_o)

- Control of epidemics and eradication of disease through use of vaccines does not require that all members of the community be vaccinated
- Vaccinated individuals provide indirect protection to unvaccinated individuals by not serving as a "bridge" between the infectious and unprotected individuals
- Relationship of R_o to disease control is through herd immunity

Relationship of (R_o) to Herd Immunity

- If some fraction of population is protected (**p**), then the remainder (**1–p**) is not directly protected
- Pathogen will not be able to persist in the unprotected portion of the population if **R_o** is now less than 1
- Conversely, the infectious disease will only persist if the number of secondary cases in the susceptible population is at least equal to 1

Vaccination Programs: Compartmental Model



Source: Adapted by CTLT from Angela McLean, Ch. 11, Parasitic and Infectious Diseases, Academic Press, 1994

CTLT

Relationship of (R_0) to Herd Immunity

- **If $(1-p)R_0 < 1$, then $p > 1-1/R_0$**
  - There is a threshold to the fraction of the population that must be protected
  - The proportion that must be vaccinated is a function of the infectiousness of the agent
  - **p** is directly related to R_0
    - The more infectious the agent, the greater the proportion that must be vaccinated
  - However, the relationship between **p** and R_0 is not linear
  - Very small increases in infectiousness can lead to large increases in the proportion that must be vaccinated

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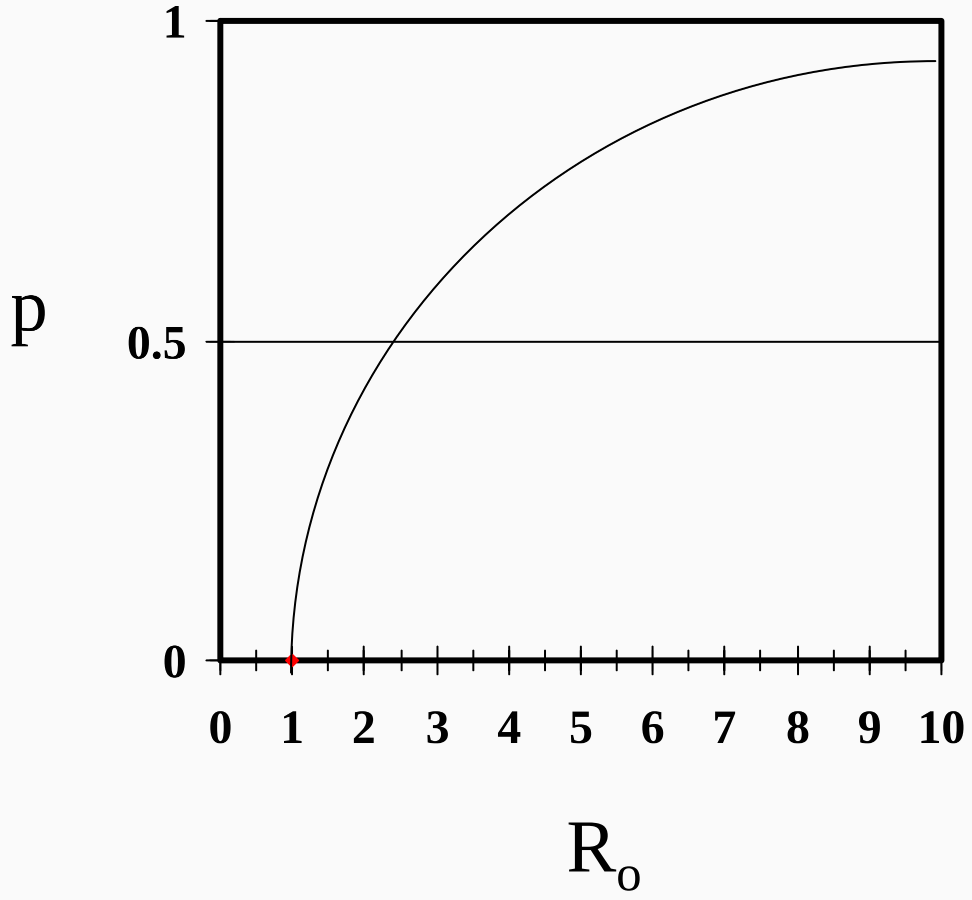
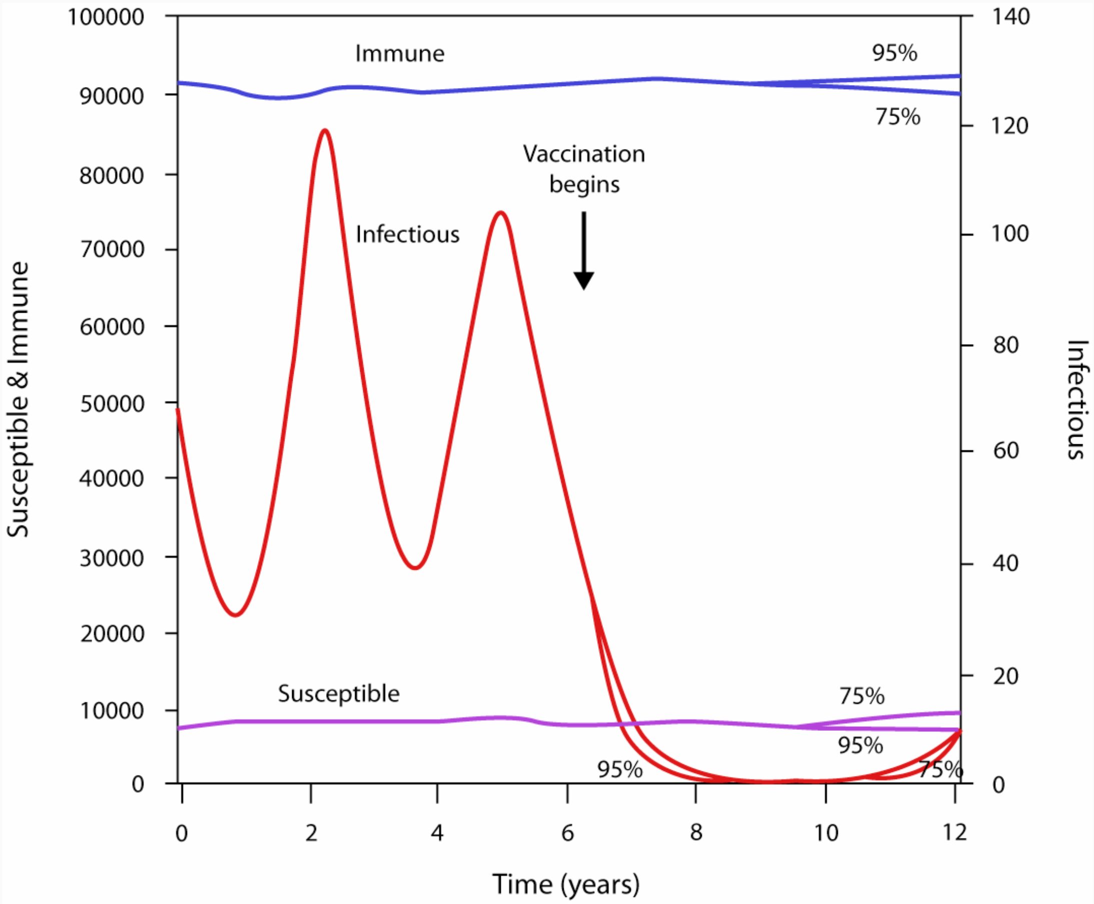
Relationship of (R_o) to Herd Immunity



Disease	R_0	Percent Protected
Small pox	3–5	67–80
Poliomyelitis	6	83
Chicken pox	9–10	89–90
Measles	13	92
Whooping cough	17	94
Malaria (*P. malariae*)	16	94
Malaria (*P. falciparum*)	80	99

- Vaccine programs with divergent levels of protection may appear equally successful in reducing disease over the short term



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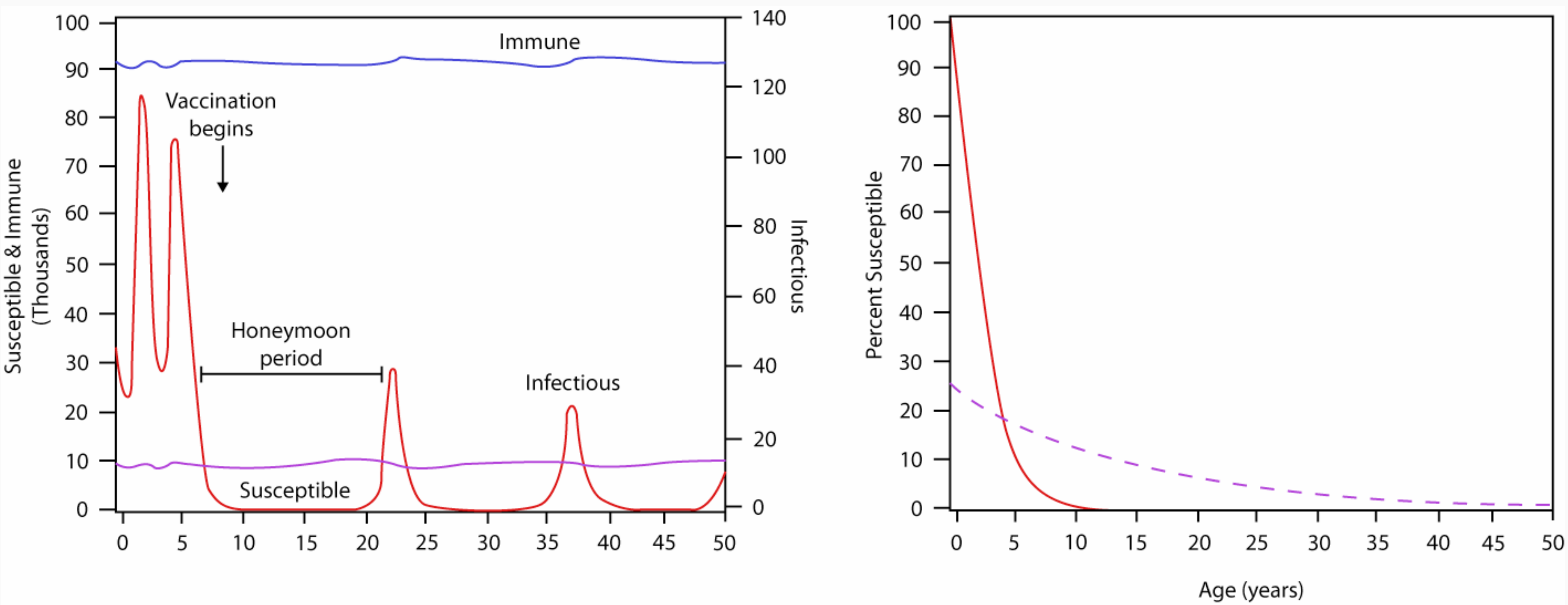
- If you do not eradicate a pathogen, effect is to alter the periodicity and amplitude—not eliminate epidemics
- Reducing contacts (by vaccination) shifts the average age of infection to later age classes



Challenges for Disease Eradication by Vaccination

- If pathology is age related, then vaccination programs may lead to the emergence of sequelae
- More severe morbidity in the population
- True level of p is rarely known
  - Difficult to evaluate (and rarely done) how many individuals are truly protected

Measles Cases, 1987

- Non-preventable cases: 2,642 (72%)
  - <16 months: 20%
  - Born before 1957: 5%
  - Vaccinated: 65%
  - Other: 10%
  - Preventable cases: 1010 (28%)

Summary

- R_o and R_e are key measures of how a pathogen acts in a host population
- The dynamics of infection in host populations depend on the rate that new susceptibles appear relative to the rate of transmission
- R_o is a measure identifying the fraction of the population that needs to be protected to eradicate a disease
- Failure to eradicate disease changes the timing and amplitude of epidemics and the age of infection

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Section D

Challenges

What are the challenges we face in the future?

Understanding Changes in Disease Patterns over Time

- Conceptual framework
  - Germ theory
    - For example, malaria ("bad air") from misunderstanding of transmission of malaria through swamp gases
  - Koch's postulates
    - Key to basis for early attempts to impute causality of disease
  - Epidemiological reasoning

Continued

Understanding Changes in Disease Patterns over Time

- Technological developments
  - Microscope
  - Tissue/cell culture
  - PCR
  - Microarrays

Continued

Understanding Changes in Disease Patterns over Time

- Large-scale public health interventions
  - Safe food preparation
  - Clean water
  - Sanitation
- Scientific discoveries
  - Antibiotics
  - Vaccines
  - Genetics

- Early 1970s
  - Perception by public and health professionals was that infectious diseases were no longer a threat
- Consequence
  - Major policy shifts in types of research funded, health problems studied (environmental health, chronic disease, injuries, etc.)

- 1992: Institute of Medicine published "Emerging Infections: Threats to Health in the United States"
- Web sites
  - http://www.cdc.gov/ncidod/EID
  - http://www.promedmail.org/pls/askus/f?p=2400:1000

- Since the mid 1970s, 1–2 diseases per year are linked to infectious agents

Year	Agent	Disease
1970	Lassa virus	Lassa fever
1973	Rotavirus	Infantile diarrhea
1975	Parvovirus B19	Fifth disease, Aplastic crisis in CHA
1976	*Cryptosporidium parvum*	Acute enterocolitis
1976	Ebola virus	Ebola hemmorrhagic fever
1976	Hantaan virus	HFRS
1977	*Campylobacter* sp.	Enteric disease
1977	*Legionella pneumophila*	Legionnaire's disease
1980	HTLV-1	T-cell lymphoma
1981	Staphylococcus toxin	Toxic shock syndrome
1982	*E. coli* O157:H7	Hemorrhagic colitus, HUS
1982	*Borrelia burgdorferi*	Lyme disease
1983	HIV	AIDS

Continued

- Most “new” infectious diseases establish linkages of agent to known disease

Year	Agent	Disease
1983	*Helicobacter pylori*	Gastric ulcers
1984	Human herpesvirus-6	Roseola subitum
1989	*Ehrlichia chaffeensis*	Human ehrlichiosis
1989	Barmah Forest virus	Polyarthritis, encephalitis
1989	Hepatitis C	Parenteral non-A, non-B hepatitus
1990	HPV	Cervical cancer
1991	Guanarito virus	Venezuelan hemorrhagic fever
1992	*Vibrio cholerae* O139	Epidemic cholera
1993	Sin Nombre virus	Hantaviral pulmonary syndrome
1994	Black Creek Canal virus	Hantaviral pulmonary syndrome
1994	HGE agent	Human Grandulocytic Ehrlilchiosis
1994	Sabia virus	Brazilian hemorrhagic fever
1995	Morbillvirus—unnamed	Pneumonia

Emerging Infectious Disease (EID)

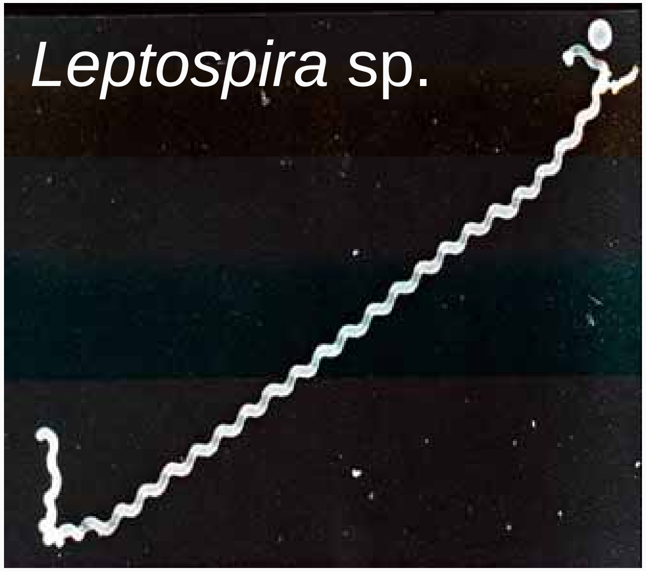
- EID: disease of an infectious origin whose incidence in humans has increased within the past two decades or threatens to increase in the near future
- Often appears as outbreaks of (relatively) large numbers of cases restricted in space and time
- Produces stress on health care and economic infrastructure
  - Example: “plague outbreak” in India, 1990s

Types of Emerging Infectious Diseases

- Apparent EIDs
  - Those EIDs for whose basis for increase in incidence is due to changes in our ability to assess the etiologic agents' importance in disease
- Real EIDs
  - Those EIDs whose incidence is increasing because of changes in the interactions of populations with the environment

- Changes in technology to implicate etiologic agent in disease
  - Example: PCR and subtypes of HPV associated with cervical cancer
  - Prior to this, had to rely on epidemiologic associations to implicate an STI as a cause of cancer

- How common is the disease?
  - Inner-city residents prevalence: 17%
  - No cases reported in 10 years—why??
- Micro agglutination test (MAT)
  - Need live spirochetes for agglutination test, and all types
  - Used to take several weeks for diagnosis
  - Impractical public health or diagnostic applications



Courtesy of Joseph Vinetz

Changes in Technology

- Technology can change pattern of disease by making detection easier
  - Example: PCR test and Western blotting, to replace MAT in leptospirosis diagnosis

- Development of a PCR test for leptospirosis
  - Can perform test on any body fluids
  - Can detect spirochetes in fluid at time of clinical symptoms
  - Takes 6–8 hours to complete
  - Can impact treatment of patient
- Five cases in three months in ER

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Section E

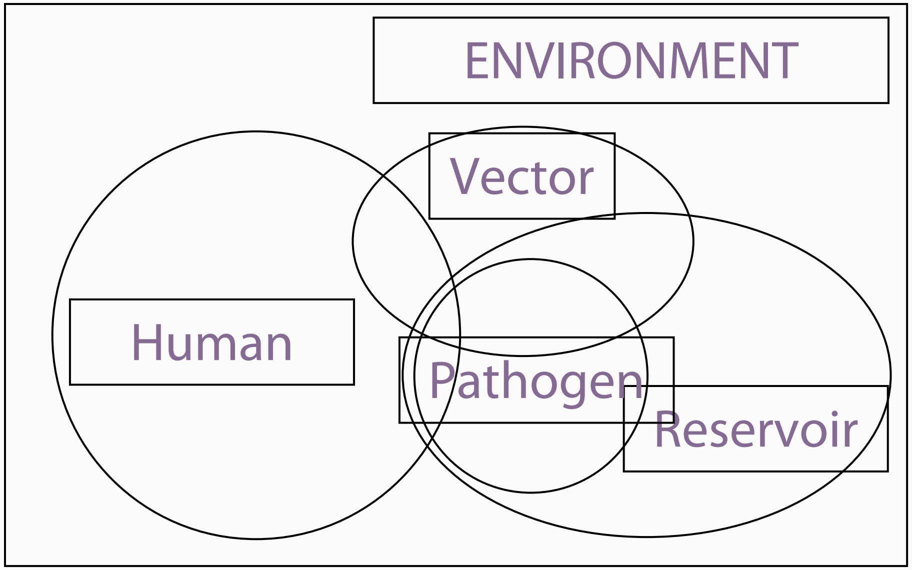
Ecological Drivers that Change Patterns of Disease

What Will be the New Disease?

- It’s hard to identify the specific disease
- It’s easier to know what types of diseases will appear

What Are the Components of the Disease Systems?

- Identify the factors that can alter the timing and extent of the overlap among the components
- Identify which of these factors is most likely to occur
- Identify potential interactions



Disease Patterns May Change

- Changes may be due to:
  - Changes in the pathogen population
  - Changes in the environment
  - Changes in the human population
  - Changes in the reservoir/vector population

Pathogen Adaptation

- Pathogen adaptation to a "new" host is the necessary first step
- Adaptation takes place at the molecular/cellular level

Changes in the Pathogen Population

- Genetic variability makes it possible for initially rare variants to increase in frequency if they are relatively more successful
- Selection may be influenced either by population dynamics of parasite or artificial selection by humans
- Example: emergence of drug-resistant forms of pathogens in response to antibiotic/drug treatment regimes
  - Such as MDR-TB, chloroquine resistance in malaria parasites, VRE
  - Development of escape mutants of HIV due to antiviral treatment

Continued

Changes in the Pathogen Population

- Example: emergence of influenza pandemic of 1918
  - Killed 20 million people worldwide
  - Due to changes in viral proteins that rendered most of world's population susceptible
- SARS

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Section F

Changes in the Environment

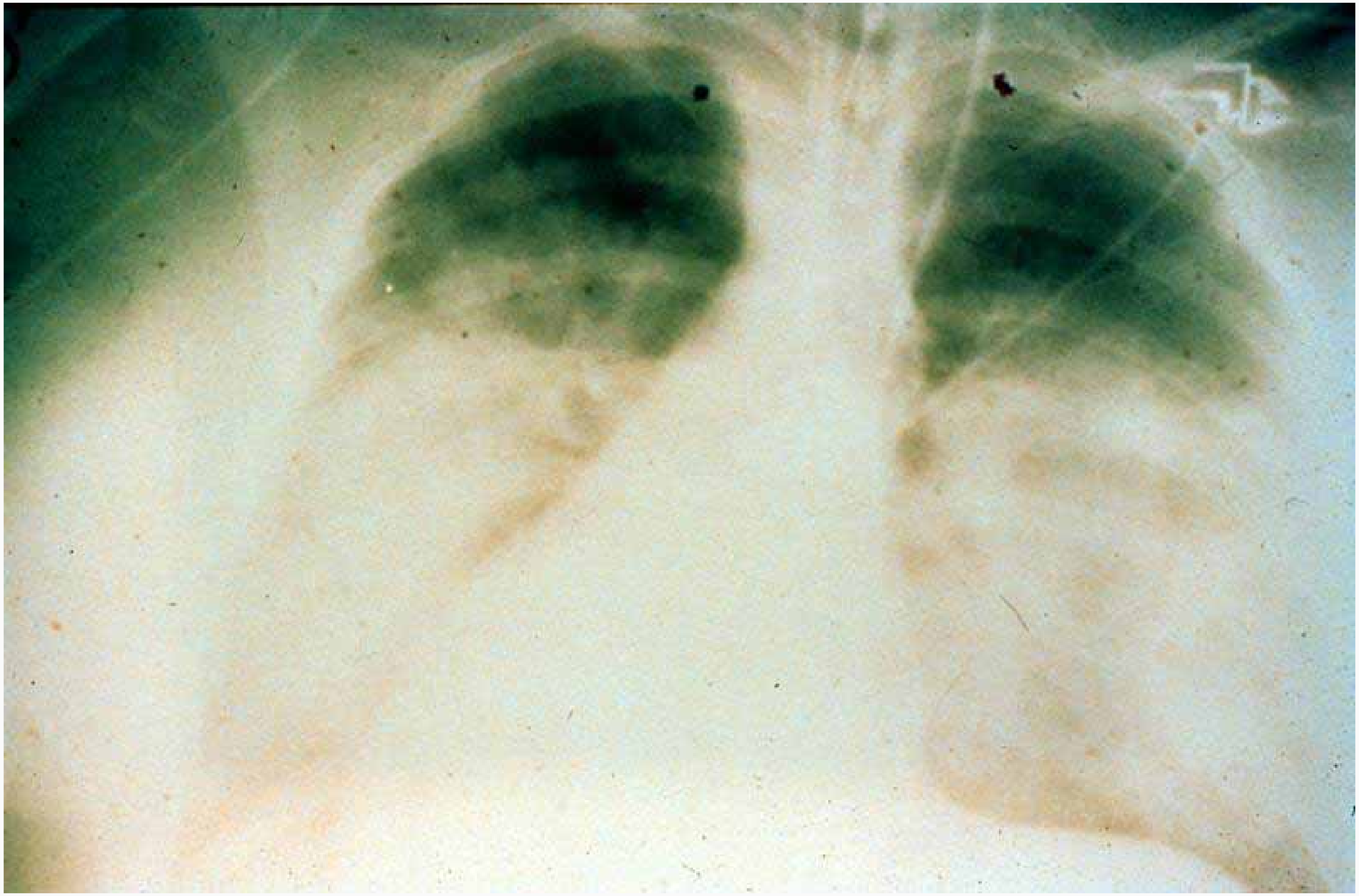
Disease Patterns May Change

- Changes may be due to:
  - Changes in the pathogen population
  - Changes in the environment
    - Environmental changes can alter disease patterns by changing niche overlap that has experienced changes in the human population
  - Changes in the reservoir/vector population

Environmental Changes

- Natural fluctuations in environmental conditions
  - Precipitation, temperature, humidity
- Time variations
  - Seasonal, yearly, multi-annual, decadal cycles
- Example: emergence of Hantaviral Pulmonary Syndrome in U.S. southwest
  - Associated with ENSO events
- Example: emergence of coccidioidmycosis in California
  - Linked to occasional heavy rains following prolonged droughts

- Abnormal chest X ray



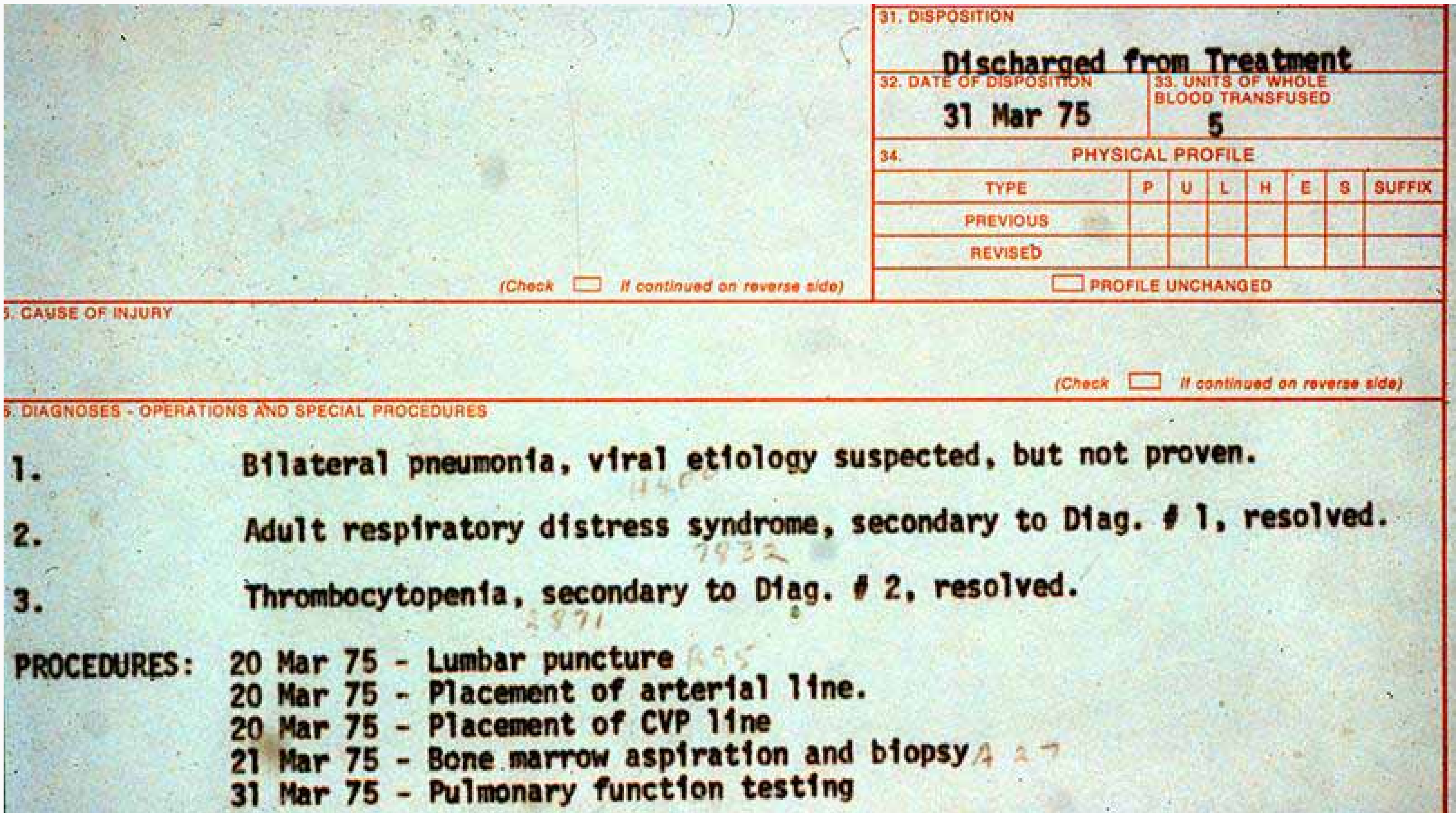
- Host habitat: most cases were associated with rural residences, very few urban cases

Photo: Greg Glass

Hantavirus: Trophic Cascade Hypothesis

- El Niño events boost the size of the rodent populations periodically, every 4–5 years
  - Rodents move to human residences for cover
  - The increase in overlap between the rodent populations and human populations resulted in the emergence of HTNV as a human disease

- Cases had occurred but not been recognized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31. DISPOSITION
Discharged from Treatment

32. DATE OF DISPOSITION
31 Mar 75

33. UNITS OF WHOLE BLOOD TRANSFUSED
5

34. PHYSICAL PROFILE

TYPE	P	U	L	H	E	S	SUFFIX
PREVIOUS							
REVISED							

☐ PROFILE UNCHANGED

5. CAUSE OF INJURY

(Check ☐ if continued on reverse side)

6. DIAGNOSES - OPERATIONS AND SPECIAL PROCEDURES

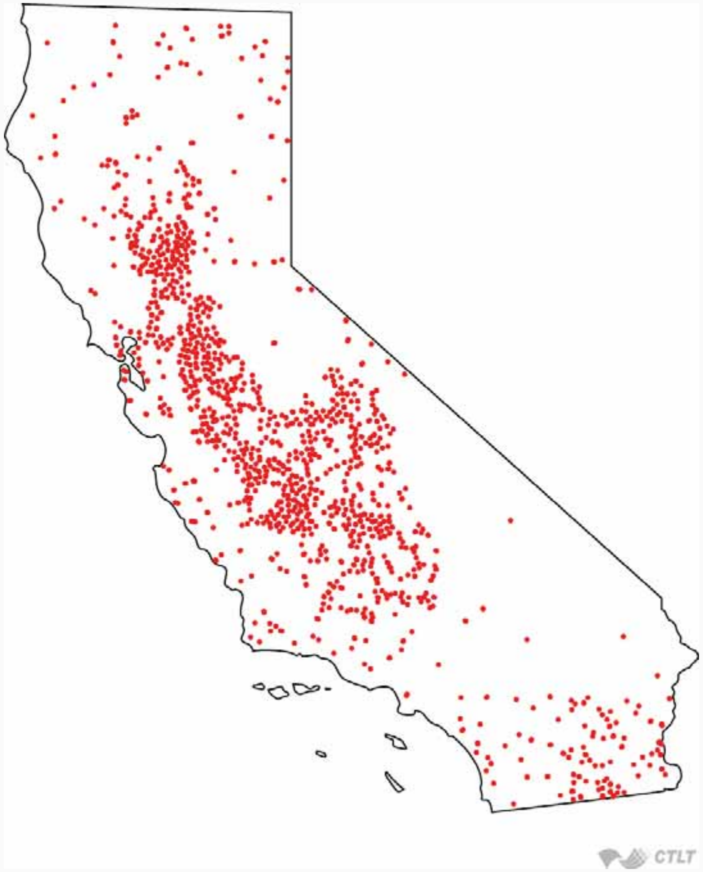
1. Bilateral pneumonia, viral etiology suspected, but not proven.
2. Adult respiratory distress syndrome, secondary to Diag. # 1, resolved.
3. Thrombocytopenia, secondary to Diag. # 2, resolved.

PROCEDURES:
20 Mar 75 - Lumbar puncture
20 Mar 75 - Placement of arterial line.
20 Mar 75 - Placement of CVP line
21 Mar 75 - Bone marrow aspiration and biopsy
31 Mar 75 - Pulmonary function testing

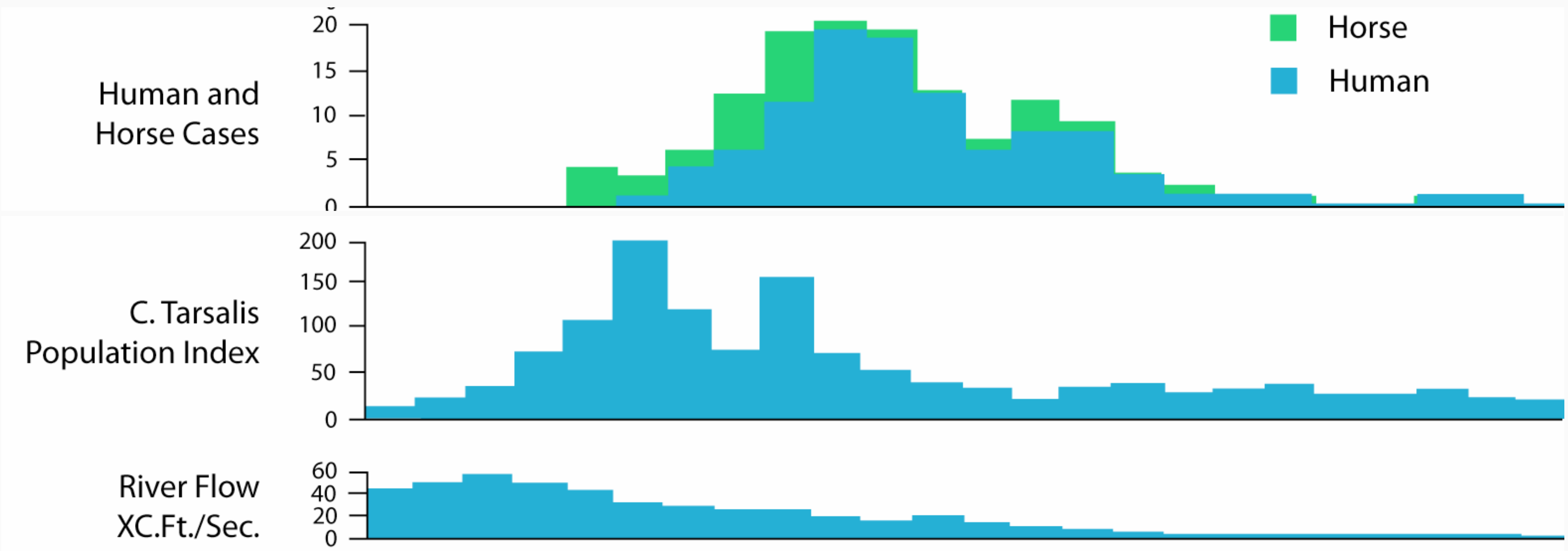
- Anthropogenic changes in environmental conditions
  - Often a result of large-scale environmental manipulations
- Large-scale water irrigation projects in the United States

Mosquito-Borne Encephalitis

- Central Valley of California was previously arid during most of the year
- Increase in mosquito breeding sites and vector populations



Mosquito-Borne Encephalitis



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Section G

Changes in the Human Population

Disease Patterns May Change

- Changes may be due to:
  - Changes in the pathogen population
  - Changes in the environment
  - Changes in the human population
    - Disease patterns change with changes in host population
  - Changes in the reservoir/vector population

- Disease patterns and processes reflect interactions of individuals within populations

Net Reproductive Ratio (R_o)

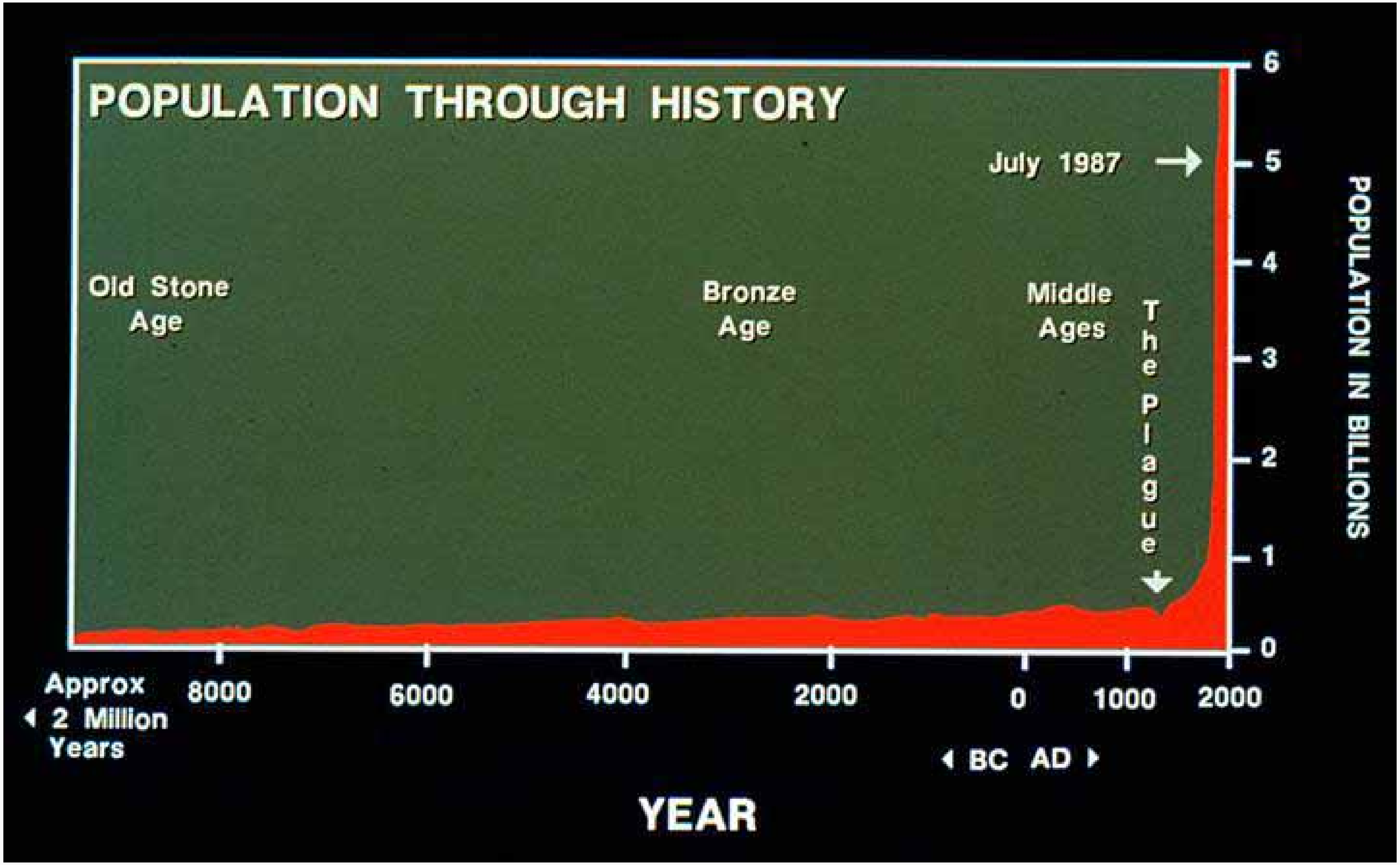
- $R_o = B * N * d$
  - R_o = number of secondary cases
  - B = transmission parameter
  - N = population size of susceptibles
  - D = duration of infectiousness
- Number of "successful" contacts with susceptibles/ unit time x length of time an individual is infectious

- R_o depends on the size of the susceptible population
  - Increased population size directly influences whether epidemics occur
  - Additional indirect influences of population size on societal infrastructure
    - For example: delivery of health care, clean water

How Is the Size of the Susceptible Population Increased?

- Increase in absolute numbers
- Increase in density/contact
- Increase in susceptibility

Changes in the Human Population



Courtesy of James E. Childs

Changes in the Human Population

- Increased urbanization results in higher population densities, making disease control difficult
- Example: eradication of smallpox
  - Easier to eradicate in West Africa than in India due to lower population densities in Africa

- Increased ease of travel makes it possible for infectious individuals to spread disease to places where it would have been previously impossible
- Changes in medical technology make it possible for highly susceptible individuals to survive for longer periods of time
- Aging population may differ in susceptibility
- Increased malnutrition may decrease immune functioning, making people more susceptible and increase duration of infectiousness

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Section H

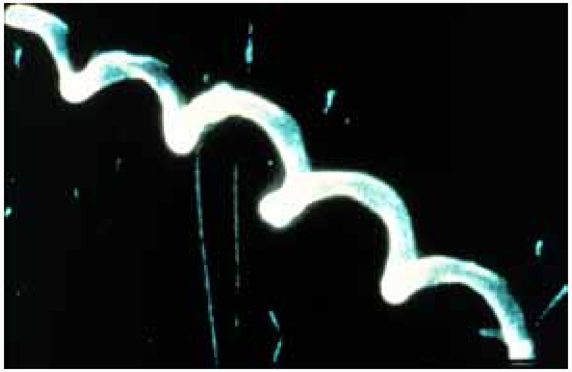
Changes in the Reservoir/Vector Population

Disease Patterns May Change

- Changes may be due to
  - Changes in the human population
  - Changes in the environment
  - Changes in the pathogen population
  - Changes in the reservoir/vector population
    - Real emerging diseases

Changes in the Reservoir/Vector Population

- Due to natural variability in these populations or in response to long-term changes in environment—making it possible for changes in the rates of contacts with humans
- May also be in conjunction with anthropogenic changes
- Example: change in risk of raccoon rabies in eastern United States
  - Introduction of raccoons infected with rabies virus into the eastern United States
  - Linked to adaptation of raccoons to peri-urban habitats and increased contact with humans



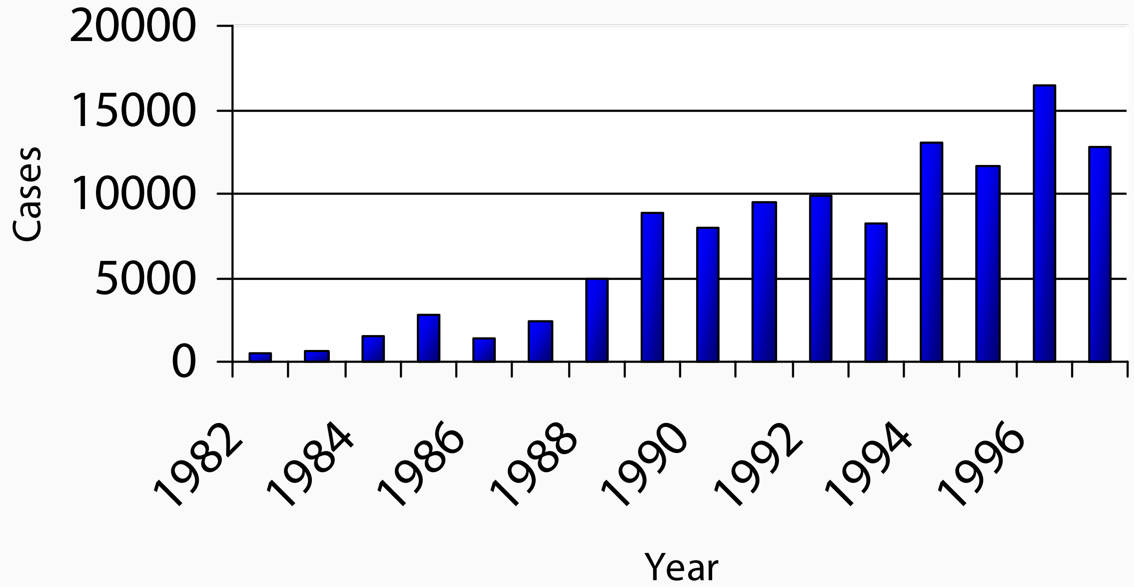
Etiologic agent
Borrelia burgdorferi

Vector
Ixodes scapularis
(Black-legged tick)

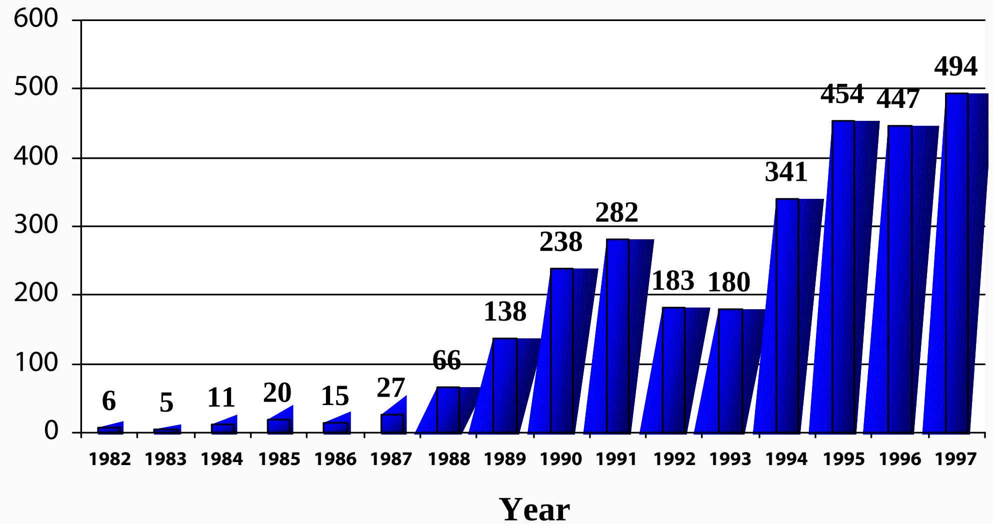
Reservoir
Peromyscus leucopus
(White-footed mouse)

Reported Cases of Lyme Disease

United States, 1982–1997



Maryland, 1982–1997



Graphs courtesy of Alvina Chu.

- Example: emergence of Lyme disease in eastern United States
  - Increases due to technological developments
  - Increases due to recognition of the disease
  - Increases due to policy decisions
- Also due to long-term environmental changes
- Linked to changes in tick/white-footed mouse and deer populations

Continued

- European settlement in the 17–18th centuries cleared forest for agricultural development
- Reduced abundance and geographic extent of forest-dwelling species
- In mid 1900s, conservation movement and economic/social changes led to the abandonment of marginal lands and return of forest
- Subsequent increase in forest species which previously were regionally extinct

Continued

- Reappearance of these habitats and reintroduction of indigenous forest species which can maintain the vector cycle

- Social changes led humans to move into suburban areas, overlapping the niches in which disease cycles are maintained

Greg Glass

Example: host habitat

- Patterns of diseases in human populations can change for many reasons
- Reasons in (approximate) rank order
  - Attention (e.g., LCMV)
  - Methods to identify etiology (HTNV)
  - Changes in interactions of disease system components
    - Size of susceptible human population
    - Changes in environment—”natural” and human
    - Pathogen changes
    - Reservoir/vector changes

Continued

- Next 25 years
  - Highly infectious
  - Highly lethal
  - Because these agents can persist for longer periods of time associated with high-density human populations with person-to-person transmission