Statistical Methods for Infectious Diseases
Lecture 1

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Framework

Transmission and Dependent Happenings

Direct and Indirect Effects

Vaccine efficacy and effectiveness

Concepts

Transmission probability

Time Lines of Infection

Basic Reproductive Number, R_0

Contact Structures; Mixing Patterns

Simple SIR Models

Endemic versus Epidemic Models

Framework

- Transmission and Dependent Happenings
- Direct and Indirect Effects
- Vaccine efficacy and effectiveness

Concepts

- Transmission probability
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Simple SIR Models

- Endemic versus Epidemic Models

Transmission

- Transmission from one host to another is fundamental to the survival strategy of most infectious agents.
- Each infectious agent has its own life cycle, modes of transmission, population dynamics, evolutionary pressures, and molecular and immunological interaction with the host.
- Transmission may involve an insect or other vector, and its ecology.
- Our focus is on underlying principles of dynamics and study design common to many infectious diseases.

Dependent versus Independent Happenings

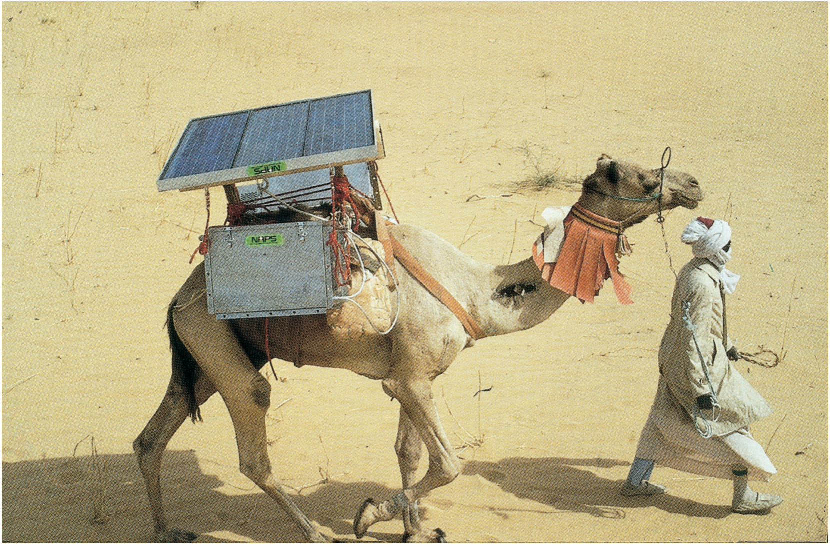
- Sir Ronald Ross 1916
- 2nd Nobel Prize in Medicine : elucidation of mosquitos as malaria transmitters
- Transmission models of malaria
- Theory of happenings
- In dependent happenings, the number of individuals becoming affected depends on the number of individuals already affected.

Dependent Happenings and Vaccine Effects

- Due to the dependent happenings in infectious diseases (Ross 1916), vaccination can produce several different kinds of effects
- At the individual level
- And at the population level.

Direct and Indirect Effects of Interventions

- Direct effects of interventions on those receiving the intervention, such as a protective vaccine
- Indirect effects of interventions, say in reducing infectiousness of breakthrough infections or reducing the number of infectious people exposing others.
- Develop an appropriate terminology to describe different effects
- Interaction in assumptions about transmission dynamics and choice of study design to evaluate the effect of interest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Vaccine efficacy and effectiveness

- generally estimated as one minus some measure of relative risk, RR, in the vaccinated group compared to the unvaccinated group:

$$VE = 1 - RR \ .$$

- The groups being compared could be composed of individuals or of populations or communities.

Historical Example: Typhoid inoculation efficacy

- Karl Pearson versus immunologist A.E. Wright BMJ (1904)
- compared correlation coefficient for typhoid inoculation (about 0.1) with that of smallpox vaccination (0.578 to 0.769)
- claimed antityphoid inoculation should be stopped.

Vaccine efficacy: typhoid and cholera

- Greenwood and Yule (1915) (Proc Roy Soc Med)
- Thoughts on the statistics of evaluating vaccines in the field
- Pre-dates person-time analysis
- Discussion of “confounding”
- Problem of people being inoculated during epidemic

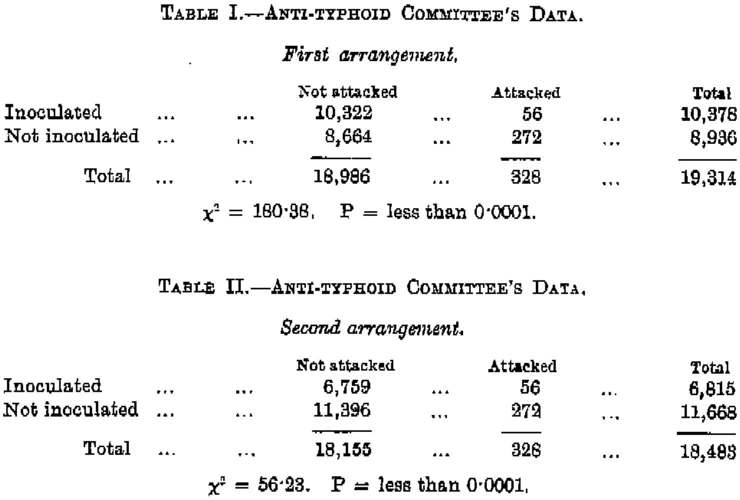


Table I.—Anti-typhoid Committee's Data.

First arrangement.

		Not attacked		Attacked		Total
Inoculated	... ...	10,322	...	56	...	10,378
Not inoculated	... ...	8,664	...	272	...	8,936
Total	... ...	18,986	...	328	...	19,314

$\chi^2 = 180{\cdot}98$. P = less than 0·0001.

Table II.—Anti-typhoid Committee's Data.

Second arrangement.

		Not attacked		Attacked		Total
Inoculated	... ...	6,759	...	56	...	6,815
Not inoculated	... ...	11,396	...	272	...	11,668
Total	... ...	18,155	...	328	...	18,483

$\chi^2 = 56{\cdot}23$. P = less than 0·0001.

Pertussis vaccine efficacy

- Kendrick and Eldering (1939)
- Person-time analysis versus conditional on exposure to infection

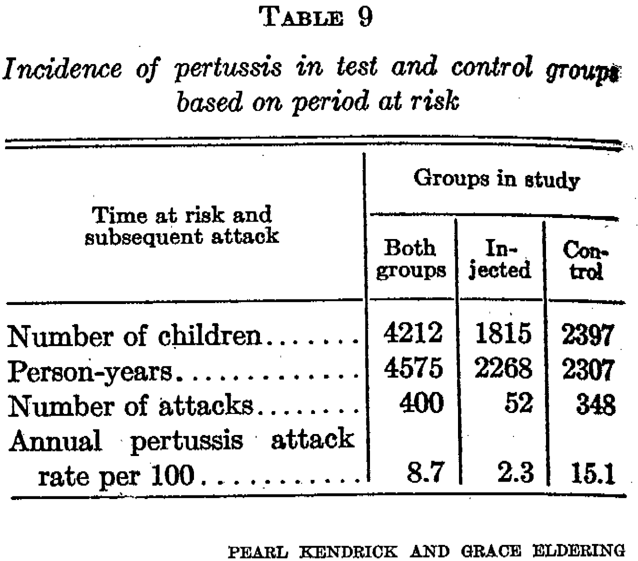


TABLE 9

Incidence of pertussis in test and control groups based on period at risk

Time at risk and subsequent attack	Groups in study		
	Both groups	Injected	Control
Number of children	4212	1815	2397
Person-years	4575	2268	2307
Number of attacks	400	52	348
Annual pertussis attack rate per 100	8.7	2.3	15.1

PEARL KENDRICK AND GRACE ELDERING

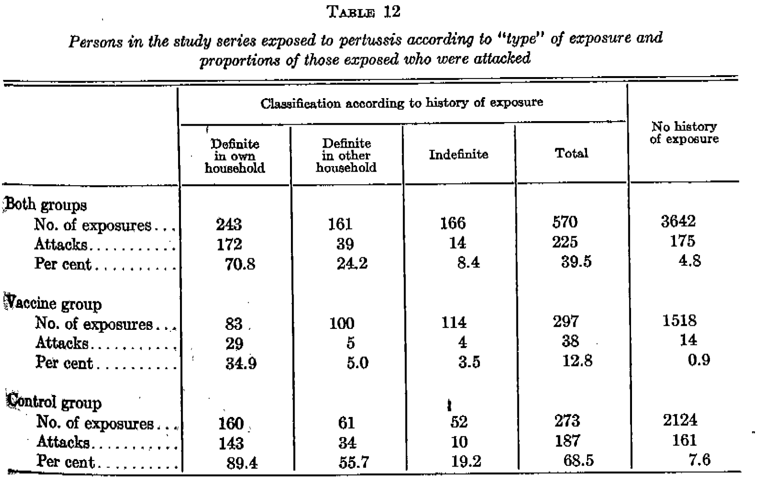


TABLE 12

Persons in the study series exposed to pertussis according to "type" of exposure and proportions of those exposed who were attacked

	Classification according to history of exposure				No history of exposure
	Definite in own household	Definite in other household	Indefinite	Total	
Both groups					
No. of exposures	243	161	166	570	3642
Attacks	172	39	14	225	175
Per cent	70.8	24.2	8.4	39.5	4.8
Vaccine group					
No. of exposures	83	100	114	297	1518
Attacks	29	5	4	38	14
Per cent	34.9	5.0	3.5	12.8	0.9
Control group					
No. of exposures	160	61	52	273	2124
Attacks	143	34	10	187	161
Per cent	89.4	55.7	19.2	68.5	7.6

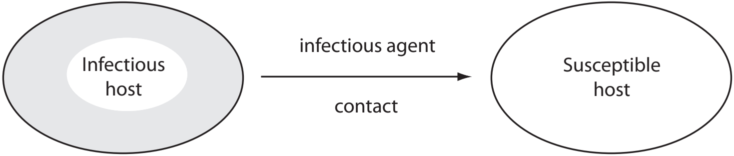
PEARL KENDRICK AND GRACE ELDERING

Polio vaccine trials

- Francis et al (1955)
- Observed Control Study, "to administer vaccine to children in the second grade of school; the corresponding first and third graders would not be inoculated, but would be kept under observation for the occurrence of poliomyelitis in comparison with the inoculated second graders."
- Placebo Control Study, "children of the first, second, and third grades would be combined. One half would receive vaccine; the other matching half, serving as strict controls, would receive a solution of similar appearance...."

Transmission probability, p

- $p =$ probability that, given a contact between an infective source (host) and susceptible host, successful transfer of the infectious agent will occur so that the susceptible host becomes infected (or a carrier).



Infectious host

infectious agent

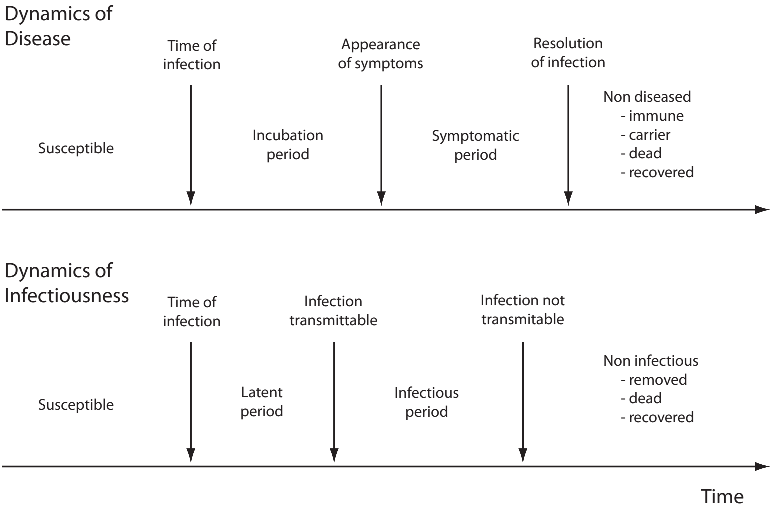
contact

Susceptible host

Transmission probability depends on:

- Type and definition of contact
- Infectious agent
- Infectious host
- Susceptible host

Time Lines of Infection



Dynamics of Disease

Susceptible

Time of infection

Incubation period

Appearance of symptoms

Symptomatic period

Resolution of infection

Non diseased
- immune
- carrier
- dead
- recovered

Dynamics of Infectiousness

Susceptible

Time of infection

Latent period

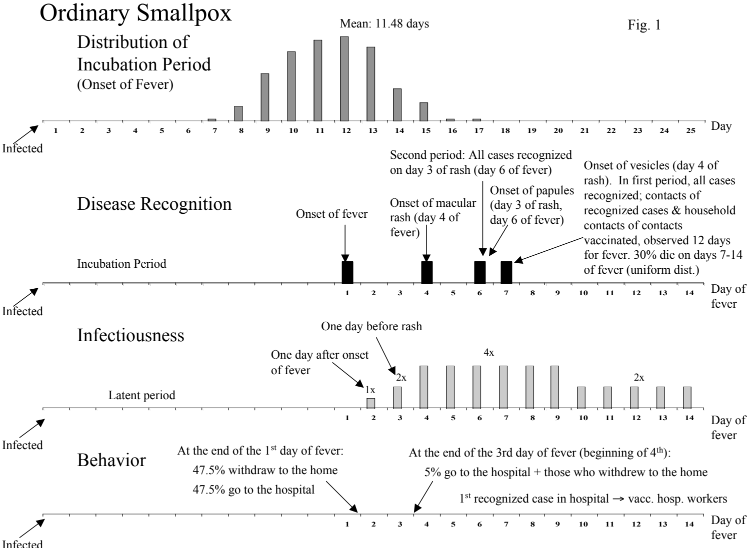
Infection transmittable

Infectious period

Infection not transmittable

Non infectious
- removed
- dead
- recovered

Time



Ordinary Smallpox

Fig. 1

Distribution of Incubation Period (Onset of Fever)

Mean: 11.48 days

Disease Recognition

Onset of fever

Onset of macular rash (day 4 of fever)

Second period: All cases recognized on day 3 of rash (day 6 of fever)

Onset of papules (day 3 of rash, day 6 of fever)

Onset of vesicles (day 4 of rash). In first period, all cases recognized; contacts of recognized cases & household contacts of contacts vaccinated, observed 12 days for fever. 30% die on days 7-14 of fever (uniform dist.)

Infectiousness

One day after onset of fever

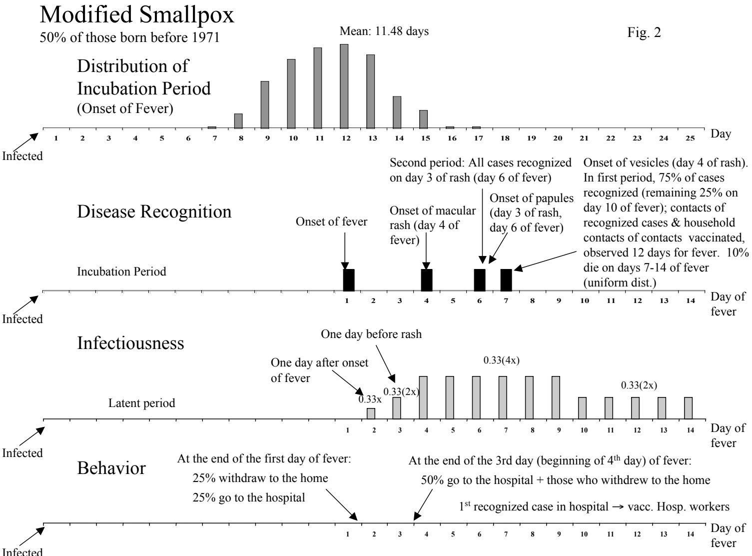
One day before rash

Behavior

At the end of the 1st day of fever:
47.5% withdraw to the home
47.5% go to the hospital

At the end of the 3rd day of fever (beginning of 4th):
5% go to the hospital + those who withdrew to the home

1st recognized case in hospital → vacc. hosp. workers



Modified Smallpox

50% of those born before 1971

Fig. 2

Distribution of Incubation Period (Onset of Fever)

Mean: 11.48 days

Disease Recognition

Second period: All cases recognized on day 3 of rash (day 6 of fever)

Onset of vesicles (day 4 of rash). In first period, 75% of cases recognized (remaining 25% on day 10 of fever); contacts of recognized cases & household contacts of contacts vaccinated, observed 12 days for fever. 10% die on days 7-14 of fever (uniform dist.)

Onset of fever

Onset of macular rash (day 4 of fever)

Onset of papules (day 3 of rash, day 6 of fever)

Infectiousness

One day before rash

One day after onset of fever

Behavior

At the end of the first day of fever:

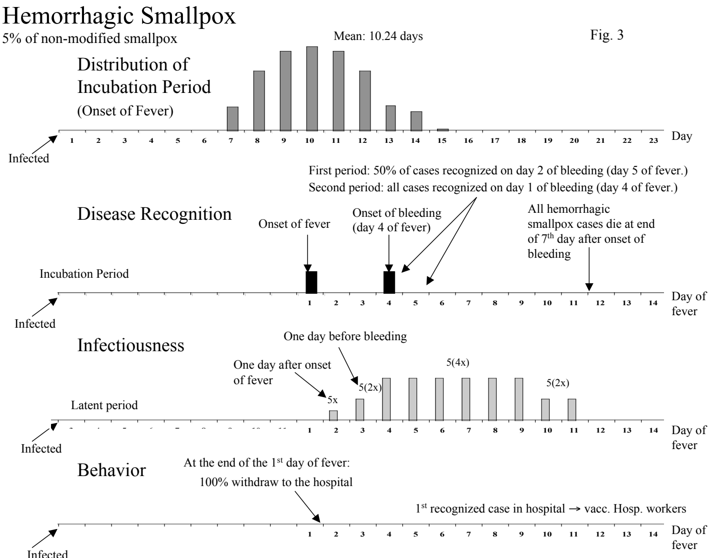
25% withdraw to the home

25% go to the hospital

At the end of the 3rd day (beginning of 4th day) of fever:

50% go to the hospital + those who withdrew to the home

1st recognized case in hospital → vacc. Hosp. workers



Hemorrhagic Smallpox

5% of non-modified smallpox

Fig. 3

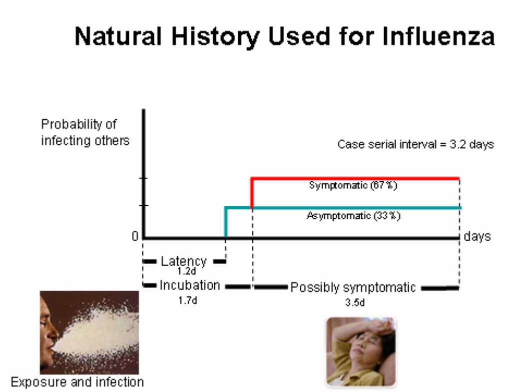
First period: 50% of cases recognized on day 2 of bleeding (day 5 of fever.)

Second period: all cases recognized on day 1 of bleeding (day 4 of fever.)

All hemorrhagic smallpox cases die at end of 7th day after onset of bleeding

At the end of the 1st day of fever: 100% withdraw to the hospital

1st recognized case in hospital → vacc. Hosp. workers



Natural History Used for Influenza

Basic Reproductive Number, R_0

- the average number of new infectious hosts that a *typical* infectious host will produce during his or her infectious period
- in a large population (absence of density-dependent effects)
- if the population were completely susceptible

Basic Reproductive Number, R_0

- heuristically, thought of as product of
    - contact rate, c
    - transmission probability, p
    - duration of infectious period, d

- $R_0 = cpd$

- tricky to measure, but important public health concept

- interventions act on components of R_0

Basic Reproductive Number, R_0

- average, or expectation
- particular population
- all susceptible (or absence of intervention)
- microparasitic diseases (in contrast to macro-parasitic diseases)
- dimensionless

(Net or effective) Reproductive Number, R

- if not all susceptible, or after intervention
- need $R > 1$ for an epidemic to take off or sustained transmission
- at equilibrium, $R = 1$
- goal is to reduce R, and if possible < 1
- monitoring R in real-time can aid in evaluating success of intervention

R_0 in Macroparasitic Infections

- macroparasites are larger, such as helminths
- related to R_0 in general population theory
- average number of reproducing female offspring that one adult female will produce in the absence of crowding
- generally require distributional theory and different approaches for study of macroparasites

Generation time, T_g

- The expected time between the infection of a person and the infection of the persons infected by the initial person.
- Case serial interval: expected time between onset of a case and the onset of cases produced by an initial case.
- subtle differences in definitions
- different variability

Contact Structures; Mixing Patterns

- homogeneous mixing
- heterogeneous mixing

Population Heterogeneities

- m mutually exclusive groups that form a partition, e.g., age groups, gender
  - number of people in group i, where $\sum_i n_i = n$
- Overlapping subgroups, e.g., households, schools, workplaces, neighborhoods, where a person can belong to more than one group.

Hazard Function for Infection: Force of Infection

- Let $I(t)$ be number of infectious people.
- Homogeneous mixing:

$$\lambda(t) = \frac{1}{n} c p I(t)$$

- Heterogeneous mixing, m group partition

$$\lambda_i(t) = \frac{1}{n_i} \sum_j c_{ij} p_{ij} I_j(t)$$

- contrast $\lambda(t)$ and $R(t)$

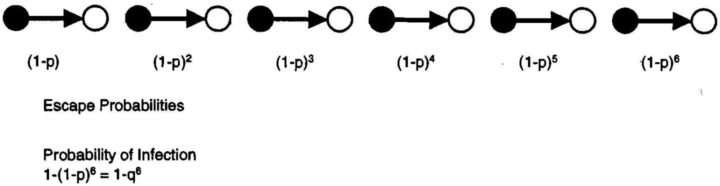


Figure 4 – 3A. The probability of infection with six consecutive contacts.

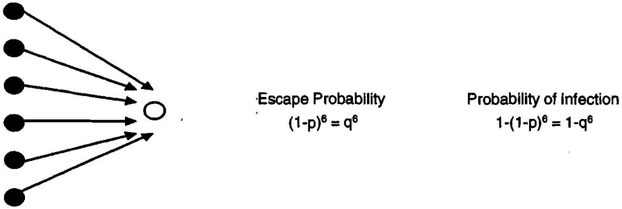


Figure 4 – 3B. The probability of infection with six simultaneous contacts.

Simple S-I-R Model

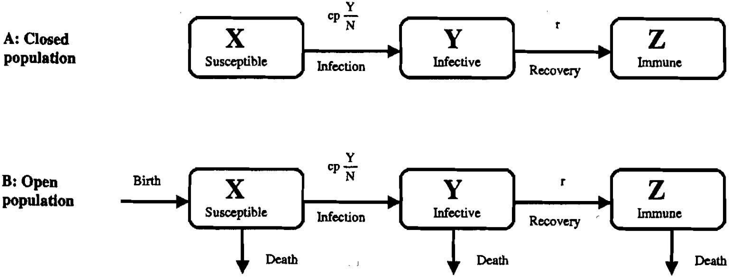
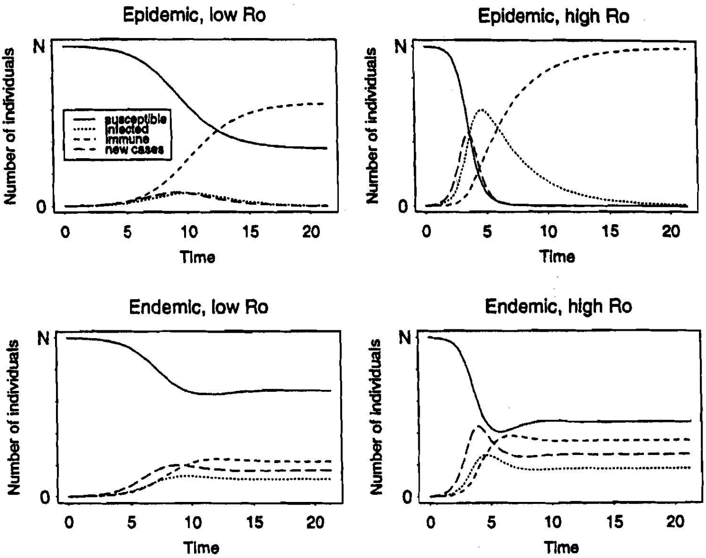


Figure 4–8A,B. Transmission model for an infectious disease in a host population. The three compartments represent susceptible (X), infective (Y), and immune (Z) hosts at time *t*. The total host population is of size $N = X + Y + Z$. Susceptible hosts become infected at an incidence rate (force of infection) of cpY/N, where *c* is the contact rate, *p* is the transmission probability, and Y/N is the prevalence of infective hosts at time *t*. The rate of recovery is *r*. Arrows represent transitions in and out of compartments.


Epidemic, low Ro
Epidemic, high Ro
Endemic, low Ro
Endemic, high Ro
Number of individuals
N
0
0
5
10
15
20
Time
susceptible
infected
immune
new cases

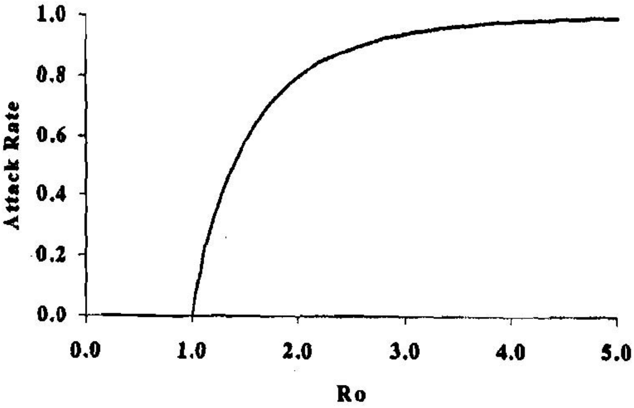


Figure 4–10. The attack rate as a function of the basic reproductive number, R_0.

Differences in diseases

- Smallpox versus polio

Thank you!