Theoretical Epidemiology of Infectious Diseases

- Anderson RM, May RM (1991) *Infectious Diseases of Humans: Dynamics and Control.* Oxford Univ. Press
- Diekmann O, Heesterbeek JAP (2000) *Mathematical Epidemiology of Infectious Diseases: Model Building, Analysis, and Interpretation.* Wiley.
- Ebert D, Herre EA (1996) The evolution of parasitic diseases. *Parasitology Today*, 12: 96-101.
- Ewald PW (1994) *Evolution of Infectious Disease.* Oxford Univ. Press
- Giesecke J (2002) *Modern Infectious Disease Epidemiology*. Arnold.
- Mascie-Taylor CGN (1993) *The Anthropology of Disease*. Oxford Univ. Press
- Rothman KJ (2012) *Epidemiology: An Introduction 2nd Ed.* Oxford Univ. Press.
- Vynnycky E, White RG (2010) *An Introduction to Infectious Disease Modelling*. Oxford Univ. Press
- Wolfe ND, Dunavan CP, Diamond J (2007) Origins of major human infectious diseases. *Nature*, 447: 279-283.
- For COVID-19, please see, https://minato.sip21c.org/COVID-19-publichealthmeasure.pdf

What is human infectious diseases?

- "Infectious diseases" from ecological perspective
  - Among the symbiosis (mutualism, commensalism, parasitism), a kind of parasitism
  - The life and reproduction of parasites depend on host's life (differently by macro-/micro-)
  - Host-parasite co-evolution
    - Antimalarial genes in malaria endemic area
      - Thalassemia in Eastern Mediterranean
      - Sickle cell anemia in Sub-Saharan Africa
    - Hypoferremic adaptation hypothesis: relatively lower iron concentration in serum than in liver found in malaria-endemic area

History of human infectious diseases

TABLE 1.2. Cultural characteristics in relation to the number of human generations and population aggregation

Years before 1985	Generations	Cultural state	Size of human communities
1 000 000	50 000	Hunter and food gatherer	Scattered nomadic bands of <100 persons
10 000	500	Development of agriculture	Relatively settled villages of <300 persons
5500	220	Development of irrigated agriculture	Few cities of 100 000; mostly villages of <300 persons
250	10	Introduction of steam power	Some cities of 500 000; many cities of 100 000; many villages of 1000 persons
130	6	Introduction of sanitary reforms	–
0	–	–	Some cities of 5 000 000; many cities of 500 000; fewer villages of 1000

TABLE 1.3. Disease profiles, early hominids to the present

	Present	Absent
Hunter-gatherer	Arbovirus, chickenpox, rabies, tuberculosis, herpes simplex	Human viral diseases, some bacterial infections, e.g. cholera, typhoid
Agriculture 1. Primitive villages	All those found in Hunter-gatherers + Enteric bacteria + Respiratory infections	Measles, smallpox, rubella
2. Primitive cities	All diseases with human–human spread	Measles, smallpox, rubella
3. Advanced cities	Measles, rubella, venereal diseases	Due to controls, e.g. clean water, vaccination, chemotherapy

Source: Mascie-Taylor CGN (1993)

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The origin of human infectious diseases

- 5 Stages from animal pathogen to specialized pathogen of humans (Wolfe et al. 2007) (http://www.nature.com/nature/journal/v447/n7142/full/nature05775.html)

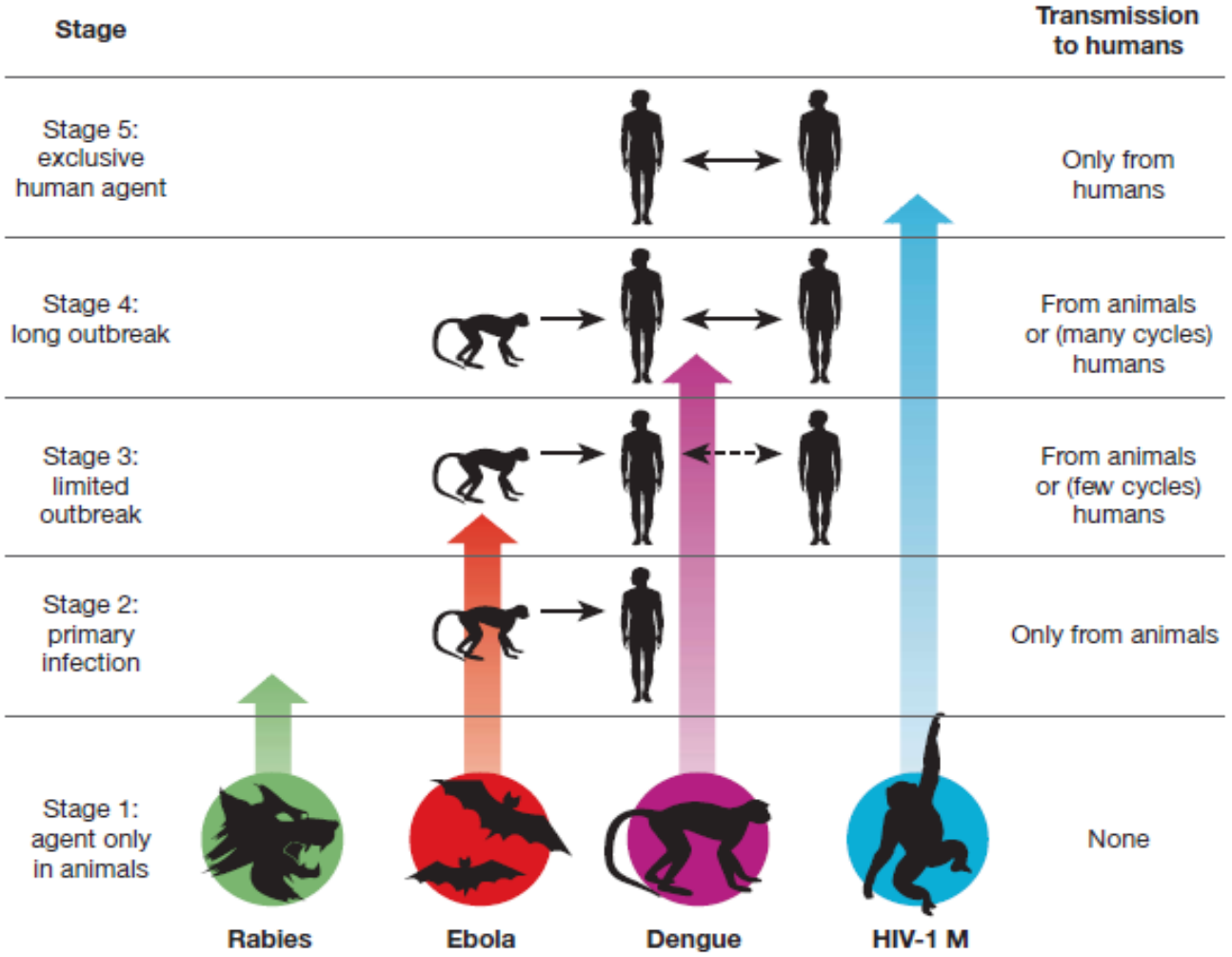
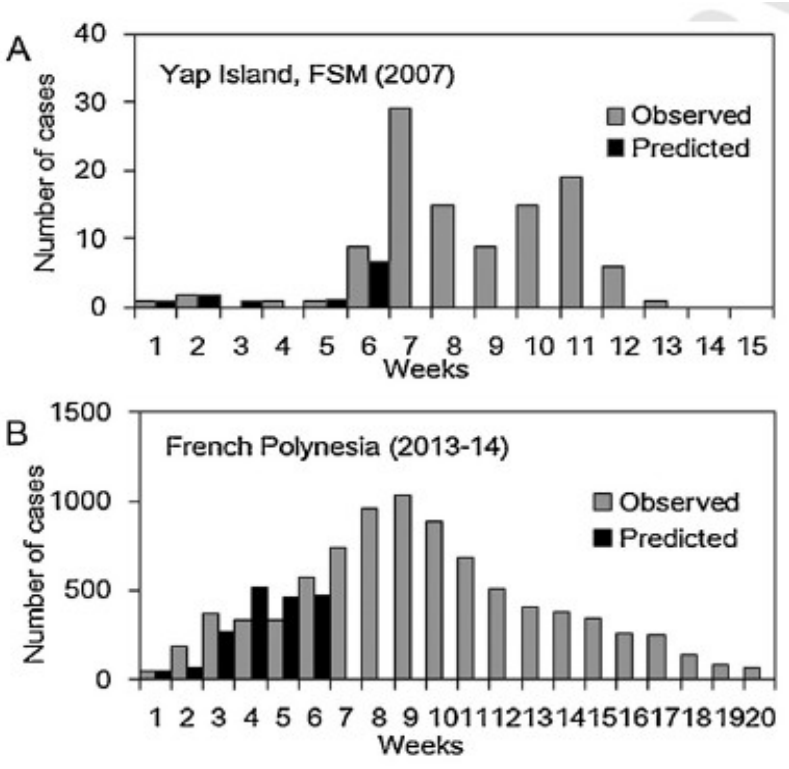


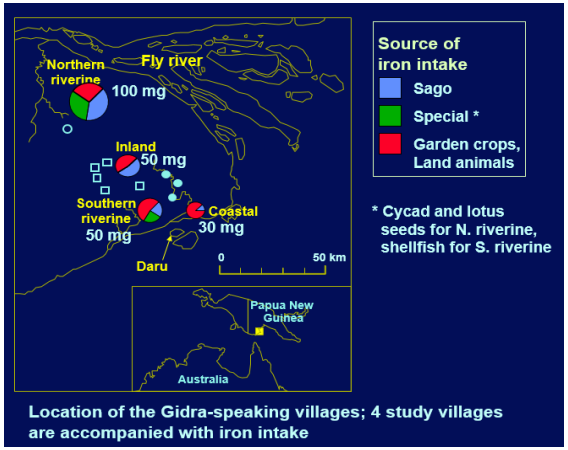
Figure 1 | Illustration of the five stages through which pathogens of animals evolve to cause diseases confined to humans. (See Box 1 for details.) The four agents depicted have reached different stages in the process, ranging from rabies (still acquired only from animals) to HIV-1 (now acquired only from humans).

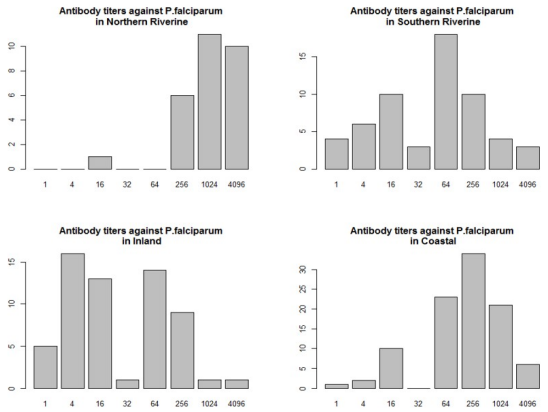
Descriptive epidemiology of infectious diseases

- Epidemic curves (TIME)
  - Bar chart of (or lines connecting) the numbers of newly infected (or died) patients by time after the onset of outbreak
  - Fitted by mathematical models to estimate parameters
- Epidemiologic maps (PLACE)
  - Cholera outbreak map of London by John Snow
  - Recently using GIS
- Sex/Age distribution (PERSON)
- Seroepidemiology
  - Antibody titers' distribution shows endemicity (experience of infection)

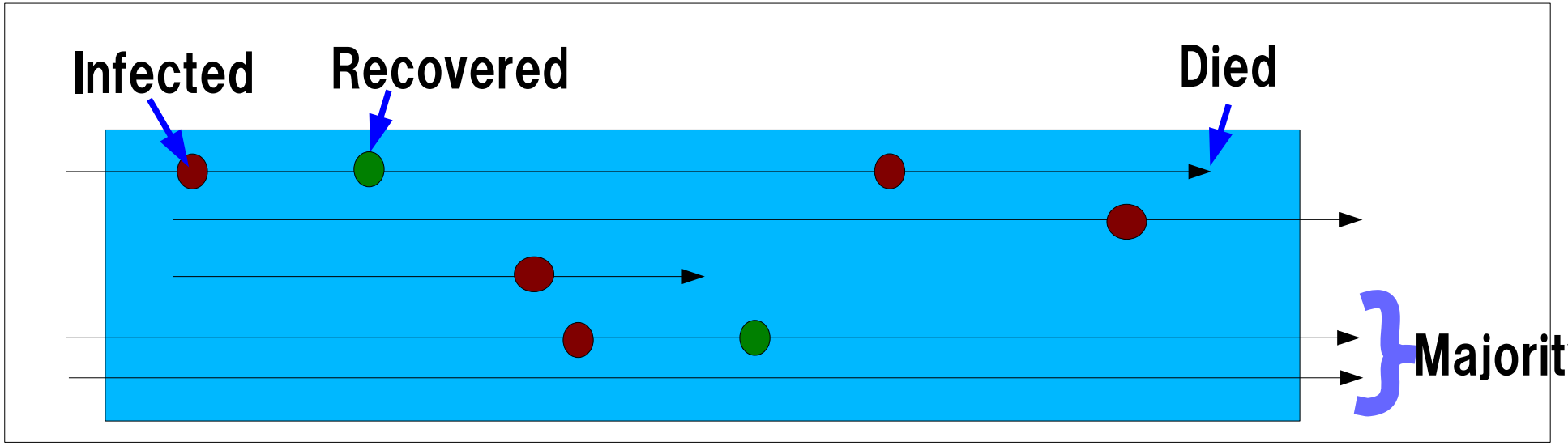


Please cite this article in press as: Nishiura H, et al. Transmission potential of Zika virus infection in the South Pacific. Int J Infect Dis (2016), http://dx.doi.org/10.1016/j.ijid.2016.02.017





Prevalence and Incidence



- Available data is usually limited to prevalence (cross-sectionally, how much proportion among the population is infected) or incidence (newly infected number among the observed population)
  - number of asymptomatic patients needs active detection screening
- Diseases with high virulence are underestimated by cross-sectional study
- Detection of asymptomatic cases is important for diseases with long latent period
- Distribution of infection frequency can be obtained from retrospective study, but longitudinal cohort study is preferable.

Basic elements which affect the transmission of infectious diseases

- Host condition: population (size, density, age-structure), gene (resistant, susceptible), nutritional status, socio-cultural factors (network, behavior)
- Environmental condition: temperature, humidity and vector animals (in the case of vector-borne infection)
- Parasite condition: host-specificity, lifespan, transmission type, etc.
- Interaction: **route of infection**, evolution to optimal virulence based on the interaction between infectiousness and virulence (Ebert and Herre, 1996), virulence decrease in direct transmission (like JC virus) vs no change in vector-borne transmission (Ewald, 1994)

Route of infection

Route of transmission	Characteristics
Contact	Requires direct/indirect contact * Indirect = infected fomite, blood or body fluid * Direct = skin or sexual contact
Food- or water-borne	Ingestion of contaminated food (outbreaks may be large and dispersed, depending on distribution of food)
Airborne (droplet, droplet nuclei, micro-droplet)	Inhalation of contaminated air * Droplet = large droplets by cough * Droplet nuclei = Dried particle from droplets * Micro-droplets = small suspended droplets
Vector-borne	Dependent on biology of the vector (mosquito, tick, snail, etc), as well as the infectivity of the organism
Perinatal	Similar to contact infection; however, the contact may occur in utero during pregnancy or at the time of delivery

TYPES OF TRANSMISSION

- Host population constitutes **reservoir** for the pathogen
  - Primary habitat for pathogen
  - Pathogen can survive and spread via other hosts than human
- Highly virulent pathogen cannot survive and spread because of early death of host
  - Variety of transmission pathway evolution
    - Direct, person-to-person (communicable, contagious): measles (host is only human) viable only for 2-3 hours in droplets
    - Via transmitting animal (vector): malaria (from infected human with 5 types *Plasmodium* gametocytes to *Anopheles* mosquitoes, then sporozoites in salivary gland moves to another human by the next biting). Most vectors are arthropods
    - **Zoonoses** can spread animal reservoirs to humans
      - Vector-borne: Equine encephalitis, plague
      - Directly from animal to human: Toxoplasmosis (from cat), ebola virus (from bat), flu (hosts are human, birds, and pigs), rabies (hosts are all warm-blooded animals)
- **CFR** (Case Fatality Risk: Number of death due to that disease divided by the number of diagnosed patients) of rabies is 100% if untreated (human is dead-end host), but the virus can survive within other animals than humans

Transmission	Route	Examples
Direct	Airborne	Anthrax（炭疽）, chicken pox, common cold, influenza, measles, mumps, rubella, tuberculosis, whooping cough
	Direct contact	Athlete's foot（水虫）, impetigo（とびひ）, warts（いぼ）
	Fecal-oral	Cholera, hepatitis A, rotavirus, salmonella (=typhoid fever)
	Maternal-fetal	Hepatitis B, syphilis
	Sexual	Chlamydia, gonorrhea, hepatitis B, herpes, syphilis, HPV
Indirect	Intermediate host	Tapeworm (from eating inadequately cooked pork)
	Vector-borne	Bubonic plague (by fleas), malaria (by Anopheles mosquitoes), typhus (by lice), West Nile encephalitis (by Culex mosquitoes), yellow fever (by Culex mosquitoes), dengue fever (by Aedes mosquitoes)

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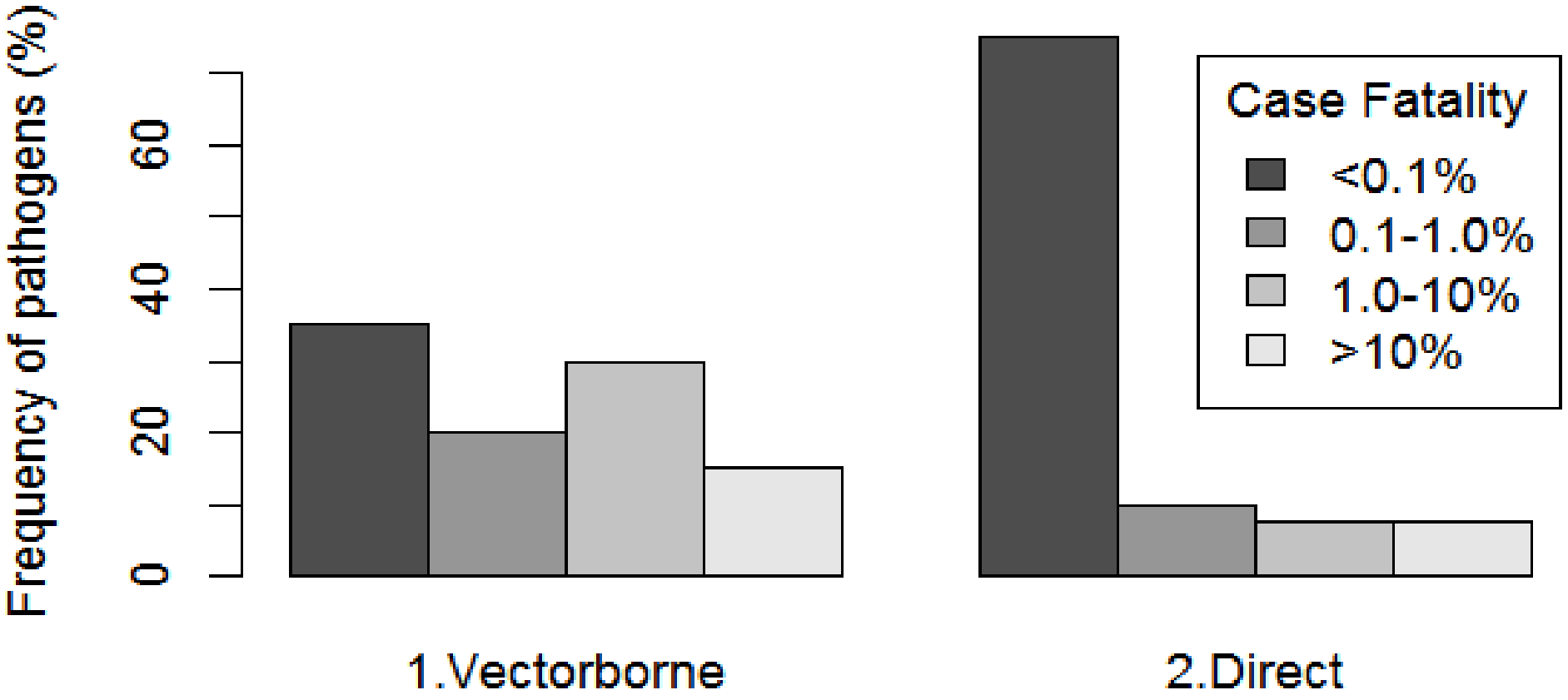
Different frequency distributions between the diseases with vector-borne and direct transmission by virulence (case fatality rates)

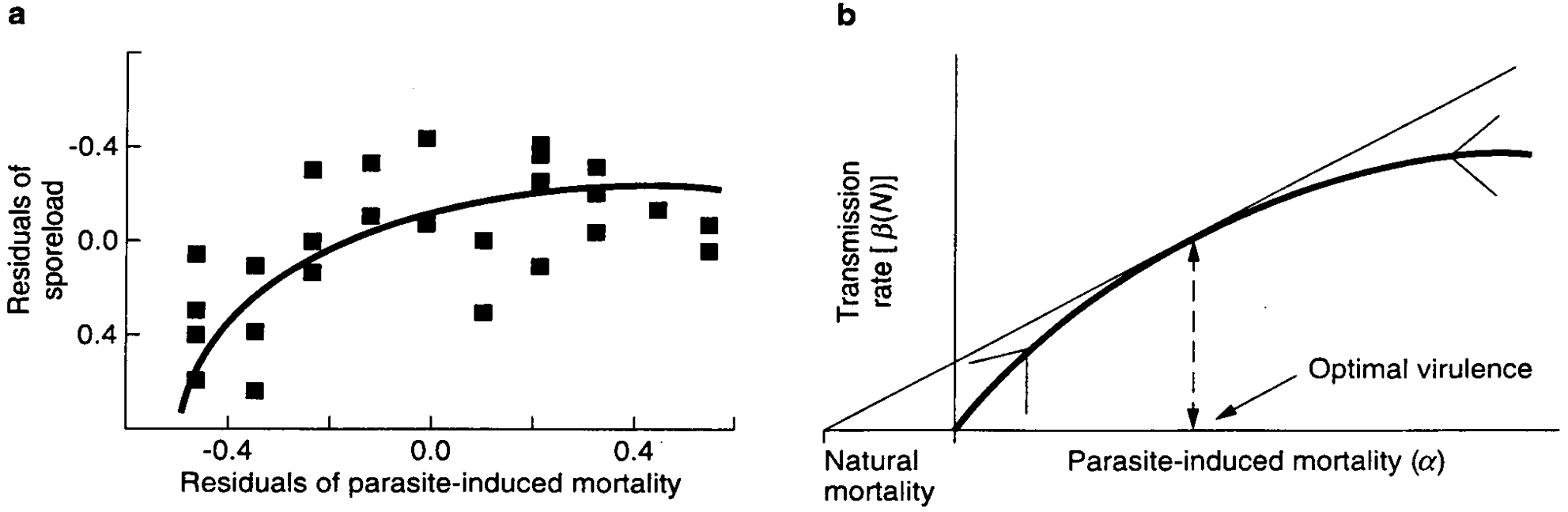


Source: Ewald (1994) [pp.38, Figure 3.1]

The evolution of optimal virulence

Box 1. Genetic Correlations can Maintain Virulence

Consider a case in which parasites that kill their host quite quickly by reproducing rapidly within the host have an increased capacity to transmit to new hosts, relative to parasite strains that reproduce (and kill) more slowly. In the Fig., (a) gives an example from a microsporidian parasite in the planktonic crustacean *Daphnia magna*. The sporeload, which correlates well with transmission rate, of different strains of *Pleistophora intestinalis* is positively correlated with host mortality. The plot shows residuals after correcting for host clone effects. (Line fitted by eye; data from Ref. 9.) Part (b) shows a rate maximizing approach to find the level of virulence which would maximize R_0 of the parasite. The approach refers to the mathematical model discussed in the text (Eqn 1). The thick line shows the relationship between transmission rate, β and virulence, α. Using the marginal value theorem, the level of parasite-induced host mortality which maximizes parasite fitness is the point the tangent touches the functional constraint[21]. Box 2 discusses some limitations to this approach. Note that (a) does not give parameter estimates as rates, as they are used for the marginal value approach. Nevertheless, the estimates in part (a) correlate with transmission rate and parasite-induced host mortality rate.



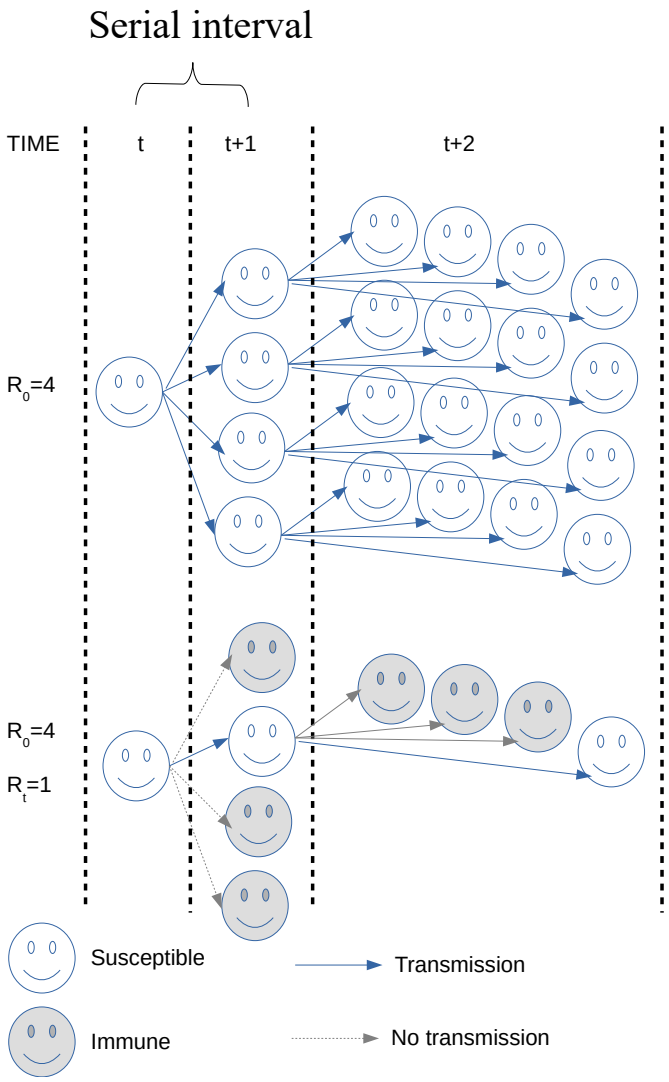
Source: Ebert & Herre (1996)

What makes pandemic?

- Definition of pandemic
  - An epidemic of unusually high occurrence of disease.
  - An epidemic occurring worldwide or over a very wide area, crossing boundaries of several countries and usually affecting a large number of people (Dictionary of epidemiology)
  - An influenza pandemic occurs when a new influenza virus appears **against which the human population has no immunity**, resulting in several, simultaneous epidemics worldwide with enormous numbers of deaths and illness (WHO, before pandemic H1N1 flu in 2009)
  - An influenza pandemic occurs when a new influenza virus appears against which the human population has no immunity, resulting in several, simultaneous epidemics worldwide (WHO, after pandemic H1N1 flu in 2009)
- Change of definition of pandemic flu by WHO was to answer to the critics that the pandemic declaration for H1N1 flu in 2009 was motivated by the ties between WHO and pharmaceutical industry (though WHO denied such ties)

HERD IMMUNITY AND BASIC REPRODUCTION NUMBER (R_0), effective reproduction number (R_t)

- The relative proportions of immune and susceptible persons in a population can determine whether the infection will take hold in the community or die out quickly
- When substantial proportion is immune (**herd immunity** situation), an infected person will be less likely to spread the pathogen
- R_0 (basic reproduction number) is the average number of secondary cases that occur from a single index case in a susceptible population
  - If $R_0 < 1$, the outbreak will die out unless fueled by external re-infections
- R_t (effective reproduction number) is the value of reproduction number that takes into account the mix of immunity and social interaction at any point in time as an outbreak progresses



Disease	Primary mode of transmission	R_0
Measles	Airborne	15
Pertussis (whooping cough)	Airborne droplet	15
Diphtheria	Saliva	6
Smallpox	Social contact	6
Polio	Fecal-oral	6
Rubella	Airborne droplet	6
Mumps	Airborne droplet	5
HIV/AIDS	Sexual contact	3
SARS	Airborne droplet	3
Ebola	Bodily fluids	2
1918 flu	Airborne droplet	2
2009 flu	Airborne droplet	1.5
COVID-19	Airborne droplet	1.4-3?

Note: If average R_0 is same, control efficacy may largely differ by variance.

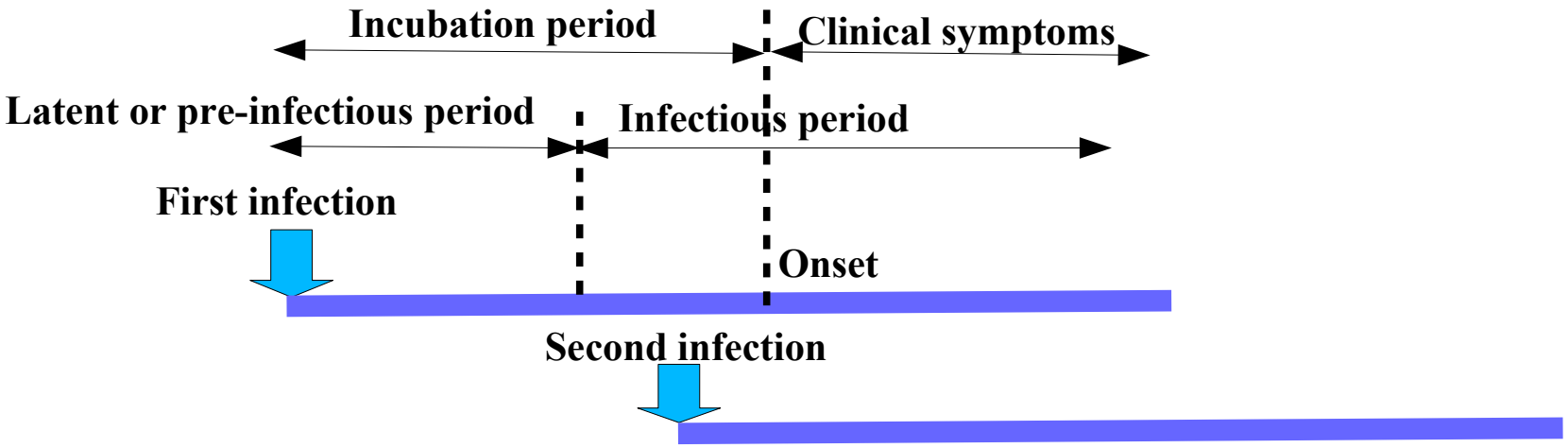
The nature of R_0 and R_t

- The reproduction number reflects the biologic potential of the infectious agent and the social intercourse that leads to situations in which transmission might occur
  - If directly transmitted disease patient is too sick to move, there will be few contact with susceptible host, results in low reproductive number
- R_0 varies by population (due to behavioral difference by age and so on)
- Even if R_0 is low, some social networks within a population may form a subset with rapid spread of infection. (eg. a few "**superspreaders"** such as needle-sharers transmitting a blood-borne infection can suffice to spark an outbreak)
- Superspreading is not always an attribute of person, sometimes a condition of the field setting (in the case of COVID-19).
- While $R_t>1$, epidemic continues
- Eventually R_t becomes 1 or below, because the proportion of susceptible people decreases or control measures are implemented
- If $R_t=1$ (**endemic equilibrium**), the prevalence of infection remains level over time as new susceptibles are added to the population to balance those who acquire immunity
  - $R_t = 1 = R_0 \times p_s$, where p_s is the proportion of the population susceptible to infection at equilibrium, thus $R_0 = 1/p_s$
- Basic strategy to reduce transmission is isolation of infected persons.
- Related strategy is quarantine to restrict contacts among people who are not yet ill but already contacted with infected persons
- (For bioterrorism by smallpox, ring-vaccination is to be conducted to reduce R_t)
- In Japan, restriction of behavior to fill the conditions for superspreading events was taken to reduce R_t as a countermeasure against COVID-19 outbreak.

Example of SARS, and if vaccine would be available?

- The strategy of isolation and quarantine worked well against SARS
  - SARS nearly became pandemic in 2003, rapidly spread from China to 37 countries (infected more than 8000 people, CFR was almost 10%).
  - Canadian officials quarantined more than 23000 people who had been in contact with SARS cases, about 100 persons for every identified case of SARS. Movement of those under quarantine was restricted until 10 days after the last contact
  - SARS was emerging disease in 2003 and thus no vaccine existed
- If vaccine would be available, R_t depends on vaccine efficacy (V_e) and coverage (V_c)
  - $R_t = R_0 (1 – V_e \times V_c) \leftrightarrow R_t/R_0 = 1 - V_e \times V_c \leftrightarrow V_c = (1 - R_t/R_0)/V_e$
  - $R_t < 1 \leftrightarrow V_c > (1 – 1/R_0)/V_e$
  - When R_0 is large, to succeed in curtailing the epidemic, high efficacy and coverage are needed (If R_0 is 10 and V_e is 95%, V_c has to be larger than 95% needed to reduce R_t below 1; $(1 – 1/10)/0.95 = 0.947\ldots \approx 0.95$)
  - In the case of measles, R_0 is 15. Even if V_e is 100%, V_c has to be larger than 93% to reduce R_t below 1; $(1 – 1/15)/1 = 0.933\ldots \approx 0.93$
  - If R_0 is 2 and V_e is 95%, V_c needs to be larger than 53% to reduce R_t below 1; $(1 –1/2) /0.95 = 0.526\ldots \approx 0.53$.
- The same relationship may stand for not only vaccination but also naturally acquired immunity after infection. Vaccine efficacy corresponds to the proportion of immunized by single infection and coverage corresponds to the proportion of people ever infected and recovered (**herd immunity threshold**)

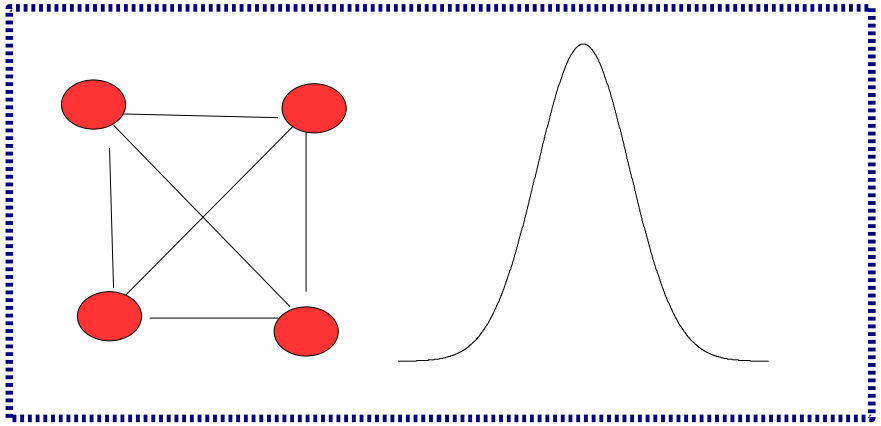
Terms for individual infection history

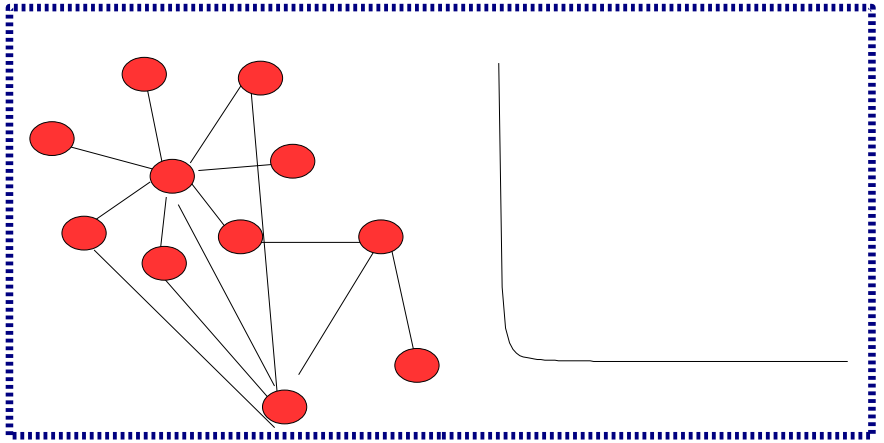


Two general types of infection network topology

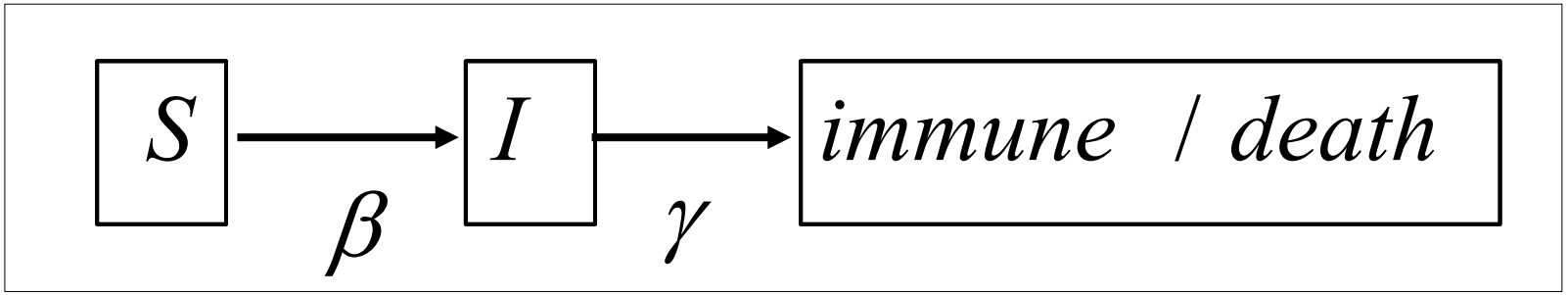
(1) Random link network
* equal infection probability for each
* distribution of infection frequency is unimodal

(2) Scale free network
* host preferences
* distribution obeying power law
* superspreader exists

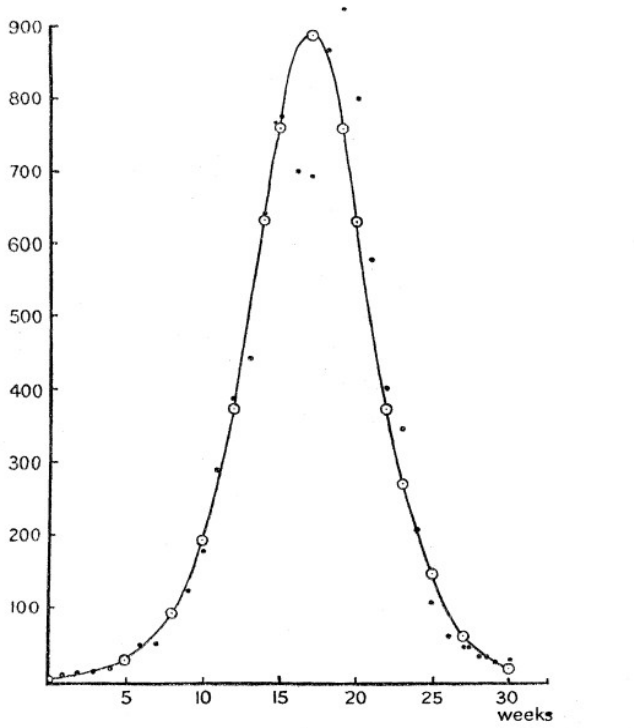




Simplest mathematical model (SI)



$$\frac{dz}{dt} = \frac{l^3}{2x_0\kappa^2}\sqrt{-q}\,\mathrm{sech}^2\left(\frac{\sqrt{-q}}{2}lt - \phi\right). \qquad (31)$$



The accompanying chart is based upon figures of deaths from plague in the island of Bombay over the period December 17, 1905, to July 21, 1906. The ordinate represents the number of deaths per week, and the abscissa denotes the time in weeks. As at least 80 to 90 per cent. of the cases reported terminate fatally, the ordinate may be taken as approximately representing dz/dt as a function of t. The calculated curve is drawn from the formula

$$\frac{dz}{dt} = 890\,\mathrm{sech}^2\,(0{\cdot}2t - 3{\cdot}4).$$

$$\frac{dS}{dt} = -\beta SI$$

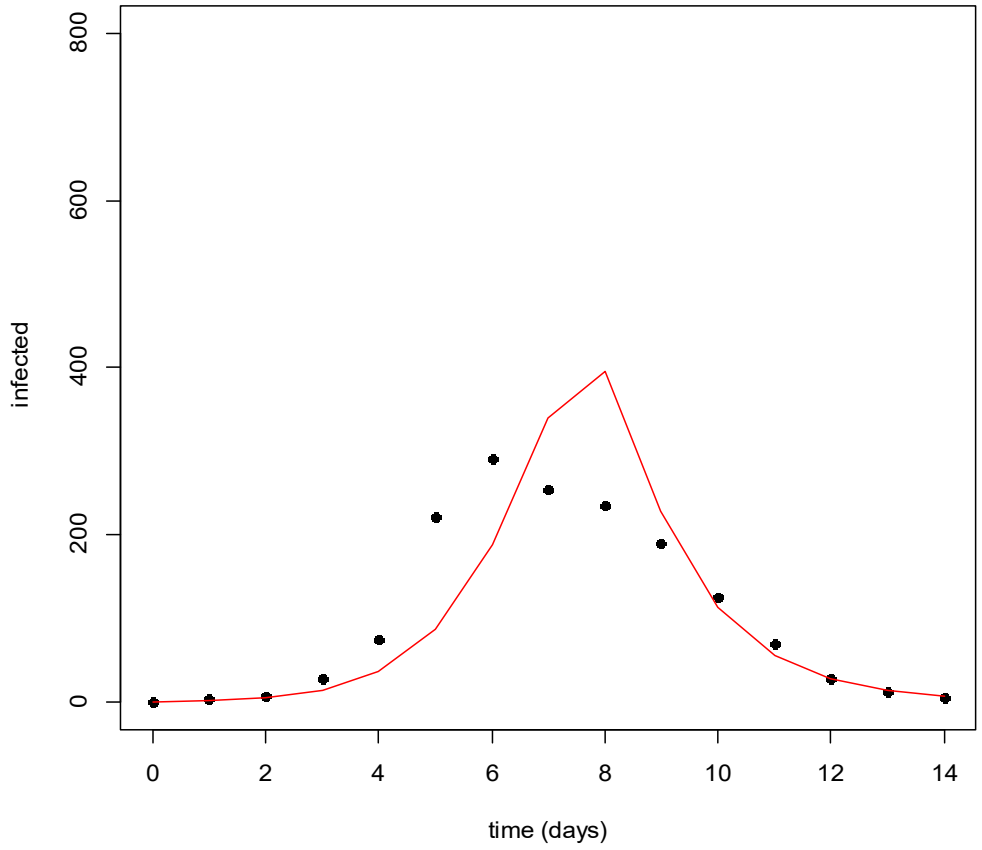
$$\frac{dI}{dt} = \beta SI - \gamma I$$

Kermack-McKendrick model (1927) for plague outbreak in Bombay from December 17, 1905 to July 21, 1906.

SIR model for flu epidemic

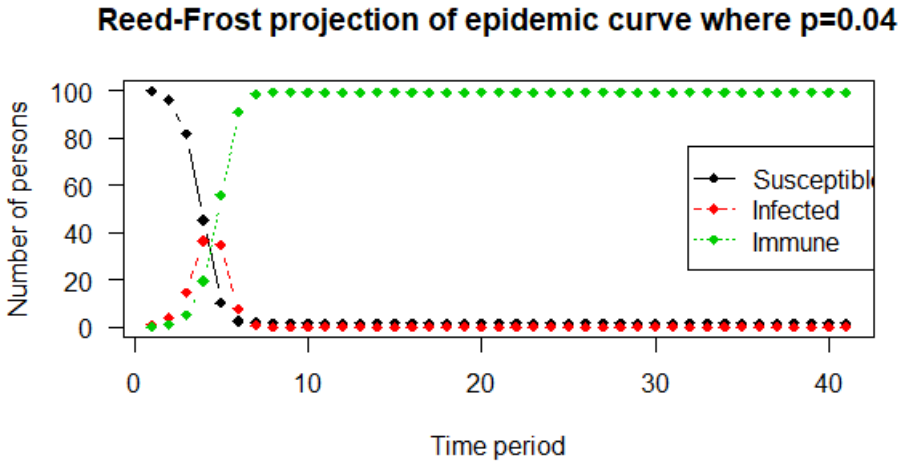
- $dS/dt = -\beta SI + \delta R$
- $dI/dt = \beta SI - \gamma I$
- $dR/dt = \gamma I - \delta R$
- Note: None of S, I, and R can be less than 0. It should be considered in numerical simulation.
- Estimating params
  - β: {I(1)-I(0)}/S(0)
  - γ: 1/{mean days of recovery}
  - δ: negligible (loss of immunity)
- https://minato.sip21c.org/tiid/flu-sir-2020.R

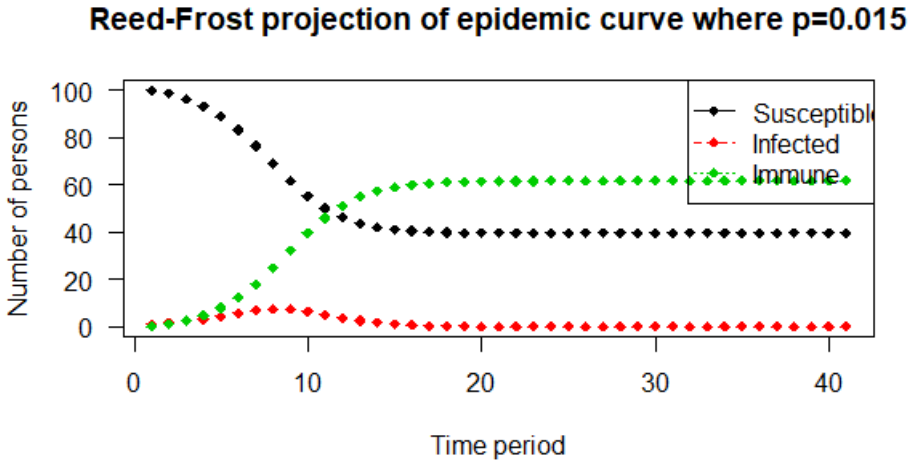
Example: The data in English boys boarding school in 1978



THE REED-FROST EPIDEMIC MODEL

- Assumptions
  - There is random mixing, with contact between infected people and susceptible people within the population during each time period
  - There is a uniform, fixed probability that a contact between an infected person and a susceptible person would result in transmission
  - An infection is always followed by immunity
  - The population is isolated from other populations
  - These conditions remain constant with time
- $C(t+1) = S(t)\ \{1 - (1 - p)^{C(t)}\}$
  - C(t): the number of newly infected people at time t
  - S(t): the number of susceptible people at time t
  - p: the probability that within one time period an infected person will transmit the infection to a susceptible person with whom there is contact
- Reed-Frost projection of epidemic curve for infected, susceptible, and immune sub-populations among 100 people with one initial infected person and an effective contact probability of 4% (high R_0 in upper panel) and 1.5% (low R_0 in lower panel). The time scale is measured in generation times
- If R_0 is small, susceptible people remain after the epidemic.





https://minato.sip21c.org/tiid/ReedFrost.R

INFECTIOUS DISEASE EPIDEMIOLOGY INVESTIGATIONS

- Several types of epidemiologic studies are unique to the investigation of infectious disease
- Four types are worthy to mention
  - Contact-tracing studies: In the early stage of an epidemic, it may be possible to interrupt person-to-person transmission enough to bring R_0 below 1 by isolation, treatment and quarantine of patients (shoe-leather approach).
  - Outbreak investigation: When a local epidemic occurs, documenting outbreak and investigating its origin and propagation. Often detective work such as identification of the cause of diarrhea outbreak as the church supper on the potato salad.
    - (Note: AIDS is an acronym of Acquired Immuno-Deficiency Syndrome, not Acute)
  - Seroprevalence surveys (sero-epidemiology): Distribution of prevalence of a specific disease is reflected in the distribution of the antibody titers against that disease agent in the blood, since the antibody titers remain for several months after infection. It can assess the vulnerability of a population to existing infectious agents, for finding susceptible subgroups
  - Vaccine trials: A randomized trial of preventive measure is called a field trial (Chapter 5). It's much more difficult than clinical trials. One of the reasons is the outcome (prevented) is rare. (eg.) Salk vaccine trial. Infection of polio virus was popular but paralysis symptoms were rare.

OUTLOOK FOR INFECTIOUS DISEASE EPIDEMIOLOGY

- In the very beginning period after the invention of antibiotics, human misunderstood that the ultimate defense against infection from bacteria was found
- For vaccines, human also misunderstood that viral illness might be tamed and possible to eradicate as smallpox
- However,
  - High reproductive rate of microorganisms and their ability to mutate have enabled them to evade many of our technologically driven defenses
  - Widespread and unnecessary use of antibiotics produced antibiotic-resistant bacteria
  - Increasing urbanization and intercontinental travel added risk of communicating infectious diseases
  - Social and medical practices opened new routes of transmission
- Infectious disease epidemiology is a frontier that has observed 2 remarkable triumphs
  - Eradication of smallpox
  - Near-elimination of poliomyelitis
- The hope of eradication of other diseases: malaria is candidate but challenging
  - Quinine, chloroquine, artemisinine, and other chemotherapy were effective to cure patients but resistance developed
  - DDT and other insecticides were effective to reduce anopheles mosquitoes but those were toxic for environment and mosquitoes got resistance
  - Development of highly effective vaccine is very difficult because life-cycle of malaria parasite is very complex and multi-stage and *P. falciparum* can escape from antibody by distributing junk antigens
  - Previously nonhuman (simian) malaria, *P. knowlesi* switched the host from monkeys to human