Theoretical Epidemiology of Infectious Diseases

- Anderson RM, May RM (1991) *Infectious Diseases of Humans: Dynamics and Control.* Oxford Univ. Press
- 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.

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)

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)

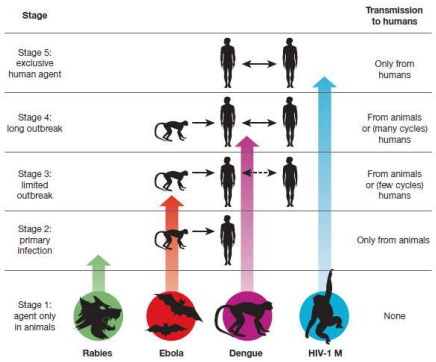
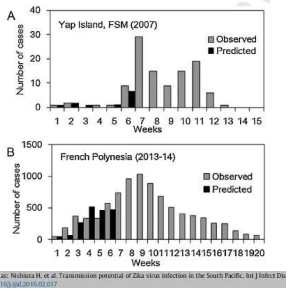
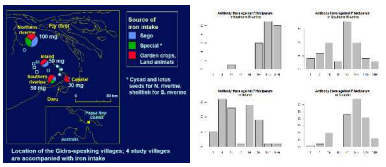


Figure 1 | Illustration of the five stages through which pathogens of animals evolve to cause diseases confined to humans. (See Box 1 for details.) The four agents depicted have reached different stages in the process, ranging from rabies (still acquired only from animals) to HIV-1 (now acquired only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

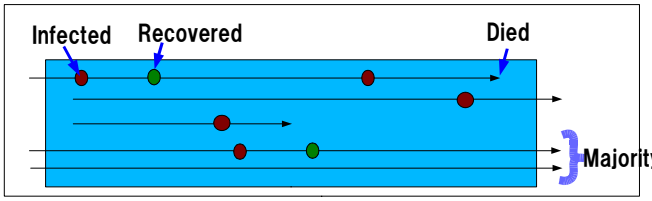
Descriptive epidemiology of infectious diseases

- 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





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

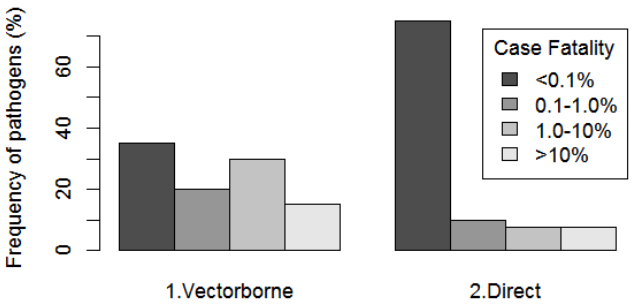
- Host condition: population (size, density, age-structure), gene (resistant, susceptible), nutritional status, socio-cultural factors (network, behavior)
- Environmental condition: temperature, humidity and vector animals (in the case of vector-borne infection)
- Parasite condition: host-specificity, 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

TABLE 2-3 Means of Transmission of Infectious Diseases and Their Characteristic Features

Transmission	Characteristics
Contact	Requires direct or 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	Inhalation of contaminated air
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

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

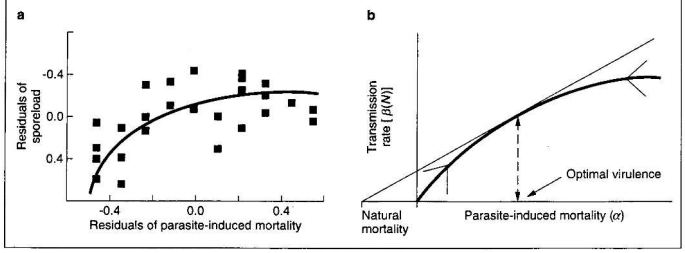


Source: Ewald (1994) [pp.38, Figure 3.1]

The evolution of optimal virulence

Box 1. Genetic Correlations can Maintain Virulence

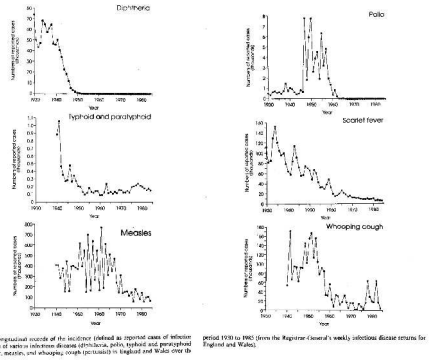
Consider a case in which parasites that kill their host quite quickly by reproducing rapidly within the host have an increased capacity to transmit to new hosts, relative to parasite strains that reproduce (and kill) more slowly. In the Fig., (a) gives an example from a microsporidian parasite in the 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)

Infectious Disease Modeling

- The longitudinal changes of incidence rates for each infectious disease seem to show some regularity – Does it follow mathematical function? (Source of the right graphs: Anderson and May, 1991)
- If we can find any mathematical formula which fit the actual changes of incidence rates, we can predict the future number of patients – It enables preparation and mitigation for the disease outbreak.



Basic Reproduction Number (R_0) and Net (Effective) Reproduction Number (R_n or R_t)

- R_0: How many newly infections occur from the first patient when all others were susceptible.
- R_n (R_t): How many newly infections occur from the first patient when some people were already immune.

(Right figure cited from Vynnycky and White, 2010)

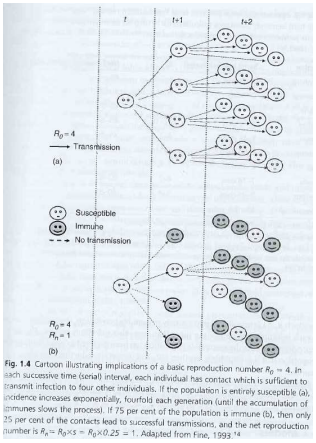


Fig. 1.4 Cartoon illustrating implications of a basic reproduction number $R_0 = 4$, in each successive time (serial) interval, each individual has contact which is sufficient to transmit infection to four other individuals. If the population is entirely susceptible (a), incidence increases exponentially, fourfold each generation (until the accumulation of immunes slows the process). If 75 per cent of the population is immune (b), then only 25 per cent of the contacts lead to successful transmissions, and the net reproduction number is $R_n = R_0 \times s = R_0 \times 0.25 = 1$. Adapted from Fine, 1993.[14]

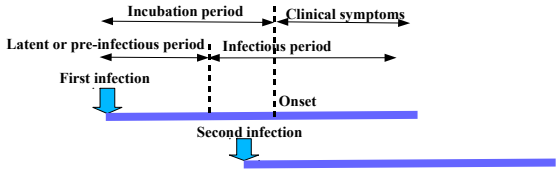
Basic reproduction number for several infectious diseases

Table 1.2 Approximate serial intervals, basic reproduction numbers and implied crude herd immunity thresholds (calculated as $1-1/R_0$) for common potentially vaccine-preventable diseases. Estimates drawn from [16, 12, 17, 18, 19, 20]. Adapted from Fine, 1993.[14]

Infection	Serial interval (range)	R_0	Herd immunity threshold (%)
Diphtheria	2–30 days	6–7	85
Influenza	2–4 days	2–4	50–75
Malaria	20 days	5–100	80–99
Measles	7–16 days	12–18	83–94
Mumps	8–32 days	4–7	75–86
Pertussis	5–35 days	12–17	92–94
Polio	2–45 days	2–4,* 8–14†	‡
Rubella	7–28 days	6–7	83–85
Smallpox	9–45 days	5–7	80–85
Tuberculosis§	Months–years	–	–

* populations with good hygiene; † populations with poor hygiene.[20]
‡ The herd immunity threshold for polio is controversial because immunity to infection is not solid.
§ R_0 and herd immunity threshold for tuberculosis are not well defined because of changes in contact over time and the long serial interval, as well as controversial issues over immunity and the extent of reinfection.

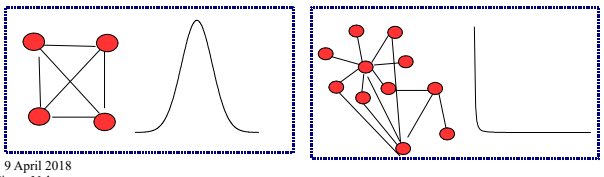
Terms for individual infection history



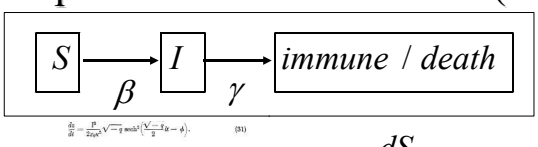
Two general types of infection network topology

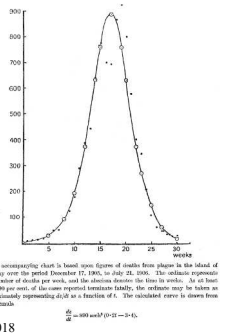
(1) Random link network
* equal infection probability for each
* distribution of infection frequency is unimodal

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



Simplest mathematical model (SI)





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 $\frac{dx}{dt}$ as a function of t. The calculated curve is drawn from the formula

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

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

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

SIR model for flu epidemic

- $dS/dt = -\beta SI + \delta R$
- $dI/dt = \beta SI - \gamma I$
- $dR/dt = \gamma I - \delta R$

Example: The data in English boys boarding school in 1978

```
NI <- c(3, 8, 28, 75, 221, 291, 255, 235, 190, 125, 70,
28, 12, 5)

sir.I <- function(S0=762, I0=1, R0=0, days=1:14,
 beta=0.0026, gamma=0.5, delta=0.0001) {
  S <- I <- R <- double(length(days)+1)
  S[1] <- S0
  I[1] <- I0
  R[1] <- R0
  for (i in days) {
    S[i+1] <- S[i] - beta*S[i]*I[i] + delta*R[i]
    I[i+1] <- I[i] + beta*S[i]*I[i] - gamma*I[i]
    R[i+1] <- R[i] + gamma*I[i] - delta*R[i]
  }
  return(I)
}

plot(0:14, c(1, NI), pch=16, type="p",
 ylim=c(0, 800), xlab="time (days)",  ylab="infected")
lines(0:14, sir.I(762, 1, 0, 1:14, 0.0026, 0.5, 0.0001),
col="red", lty=1)
```