Theoretical Epidemiology of Infectious Diseases

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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

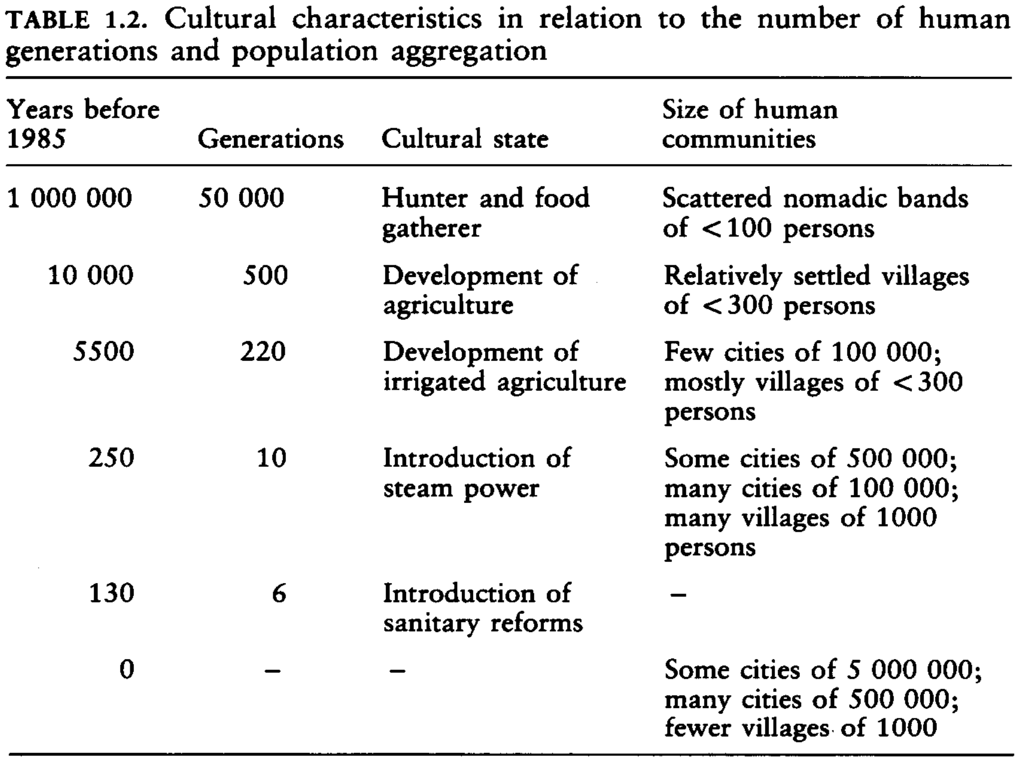


TABLE 1.2. Cultural characteristics in relation to the number of human generations and population aggregation

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

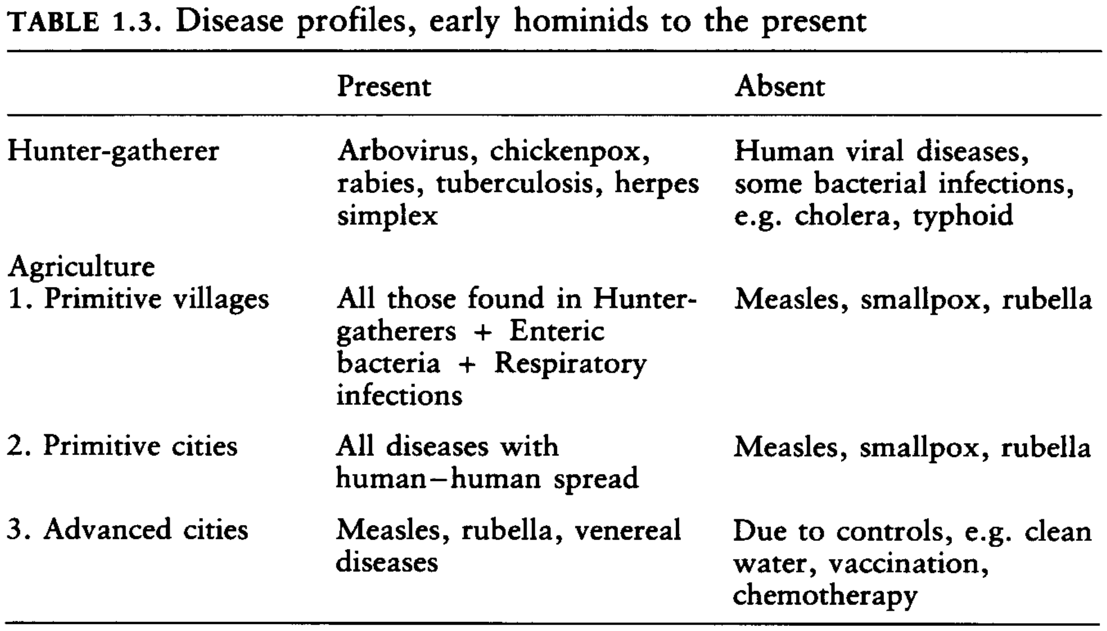


TABLE 1.3. Disease profiles, early hominids to the present

	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)

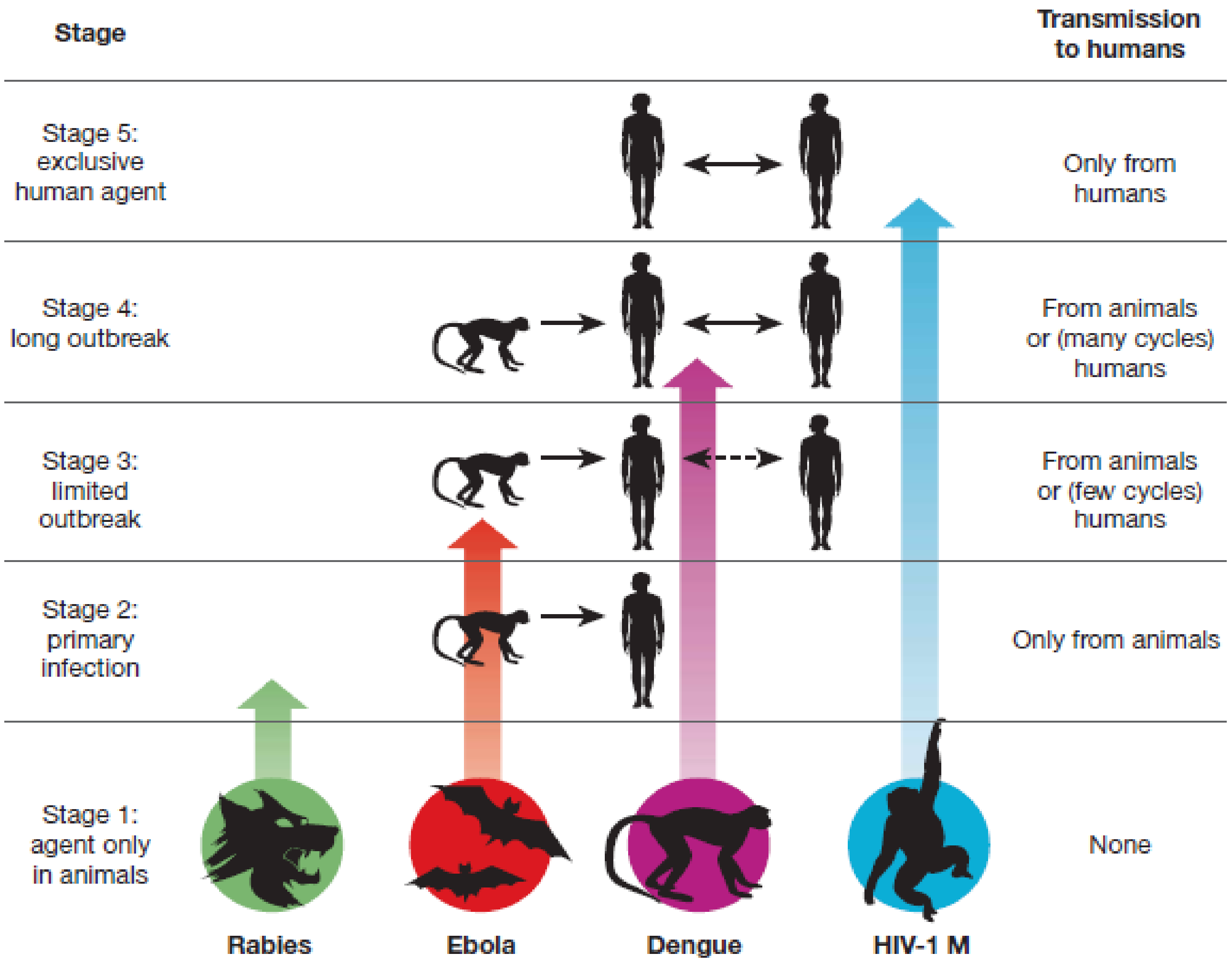
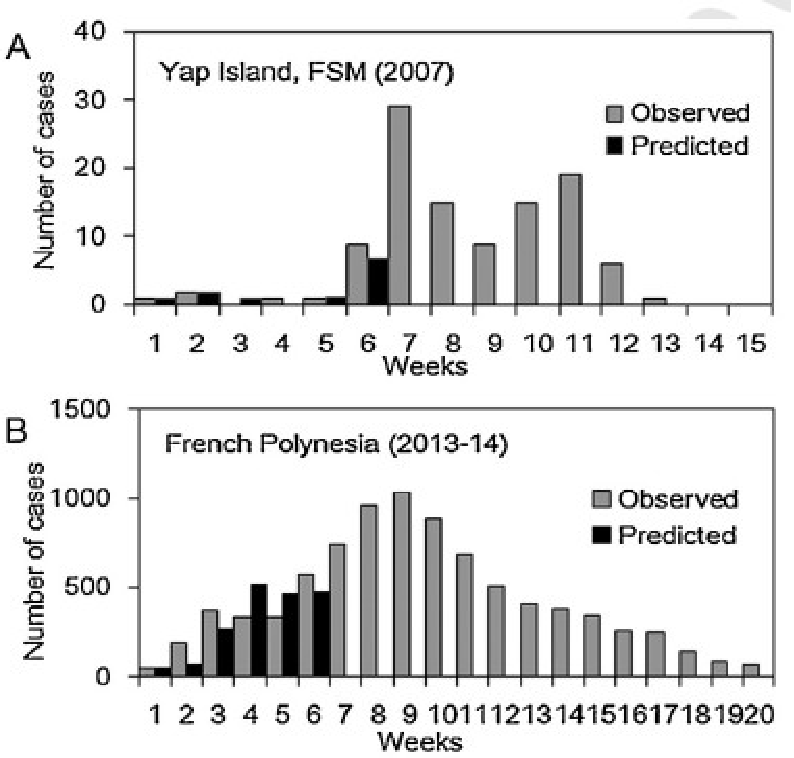


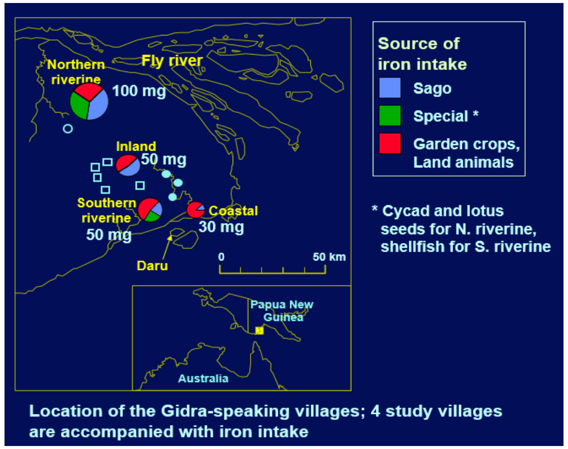
Figure 1 | Illustration of the five stages through which pathogens of animals evolve to cause diseases confined to humans. (See Box 1 for details.) The four agents depicted have reached different stages in the process, ranging from rabies (still acquired only from animals) to HIV-1 (now acquired only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

Descriptive epidemiology of infectious diseases

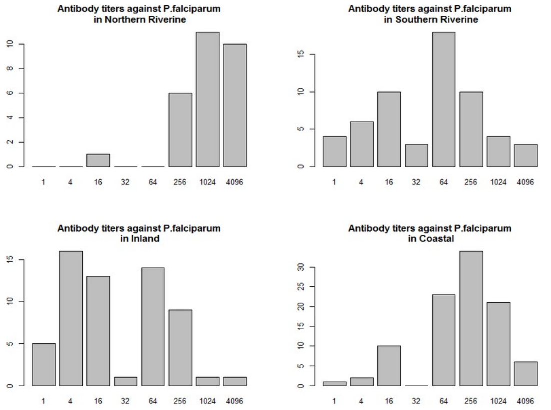
- Epidemic curves (TIME)
  - Bar chart of (or lines connecting) the numbers of newly infected (or died) patients by time after the onset of outbreak
  - Fitted by mathematical models to estimate parameters
- Epidemiologic maps (PLACE)
  - Cholera outbreak map of London by John Snow
  - Recently using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



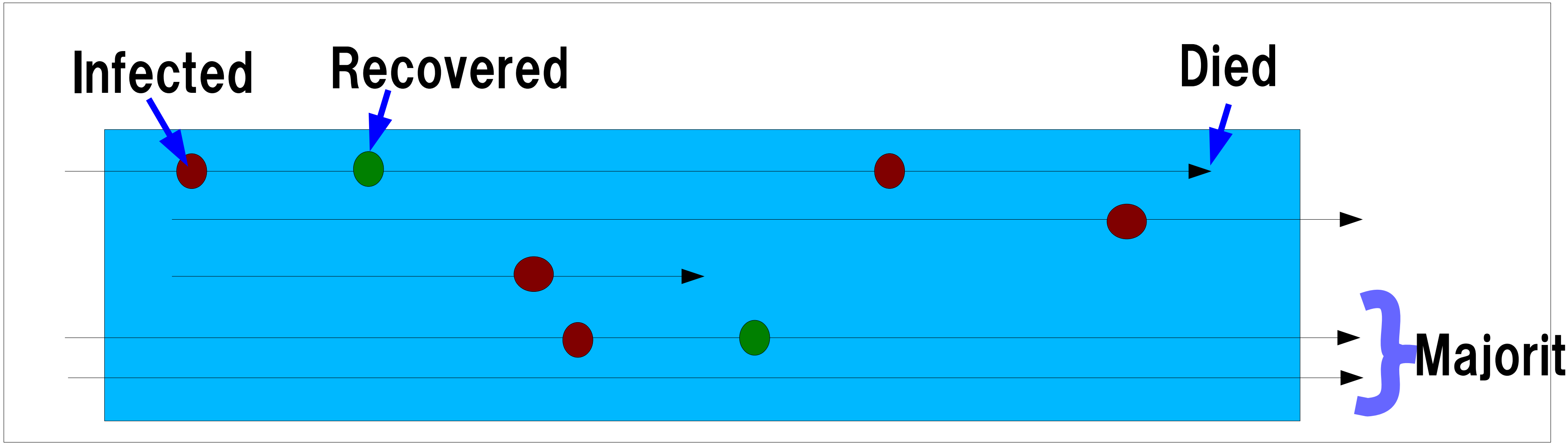
Please cite this article in press as: Nishiura H, et al. Transmission potential of Zika virus infection in the South Pacific. Int J Infect Dis (2016), http://dx.doi.org/10.1016/j.ijid.2016.02.017



Location of the Gidra-speaking villages; 4 study villages are accompanied with iron intake



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

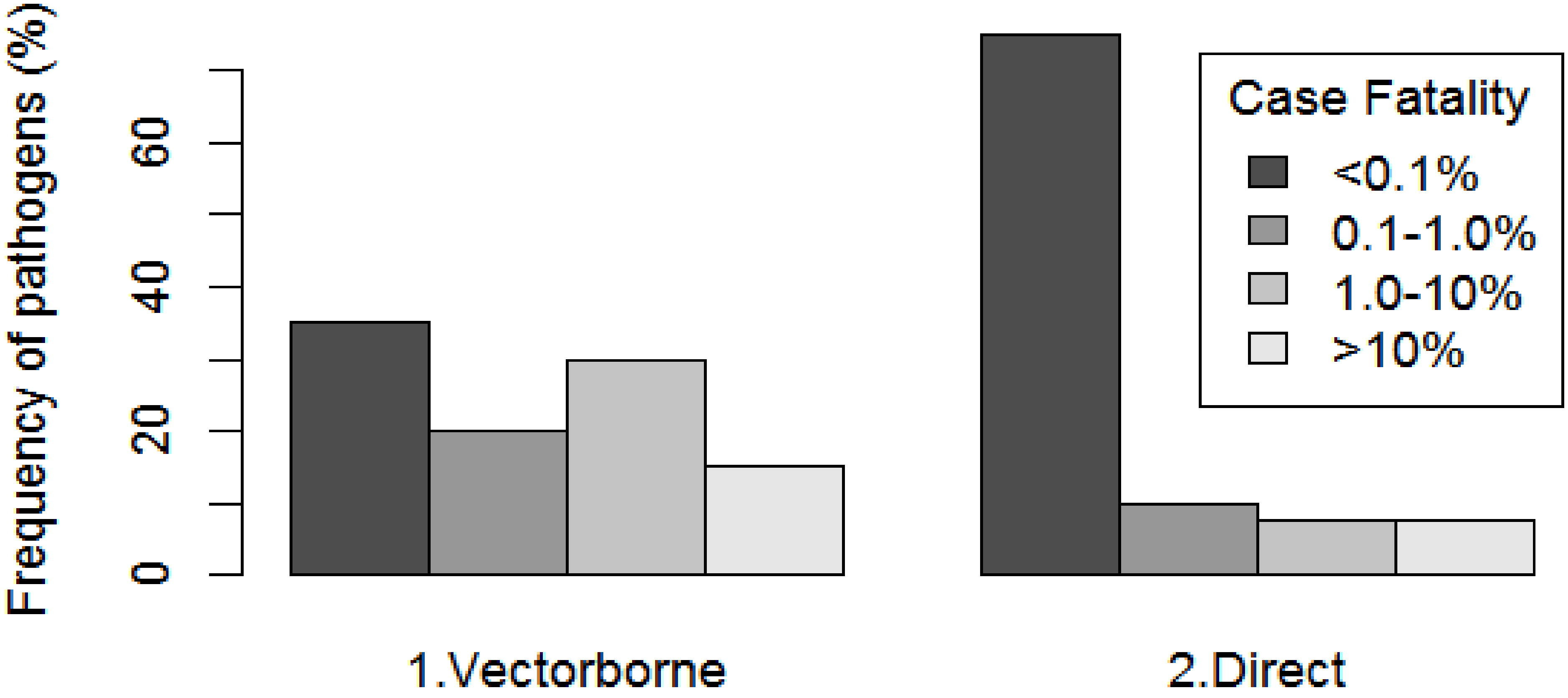
Route of transmission	Characteristics
Contact	Requires direct/indirect contact * Indirect = infected fomite, blood or body fluid * Direct = skin or sexual contact
Food- or water-borne	Ingestion of contaminated food (outbreaks may be large and dispersed, depending on distribution of food)
Airborne (droplet, 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** (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

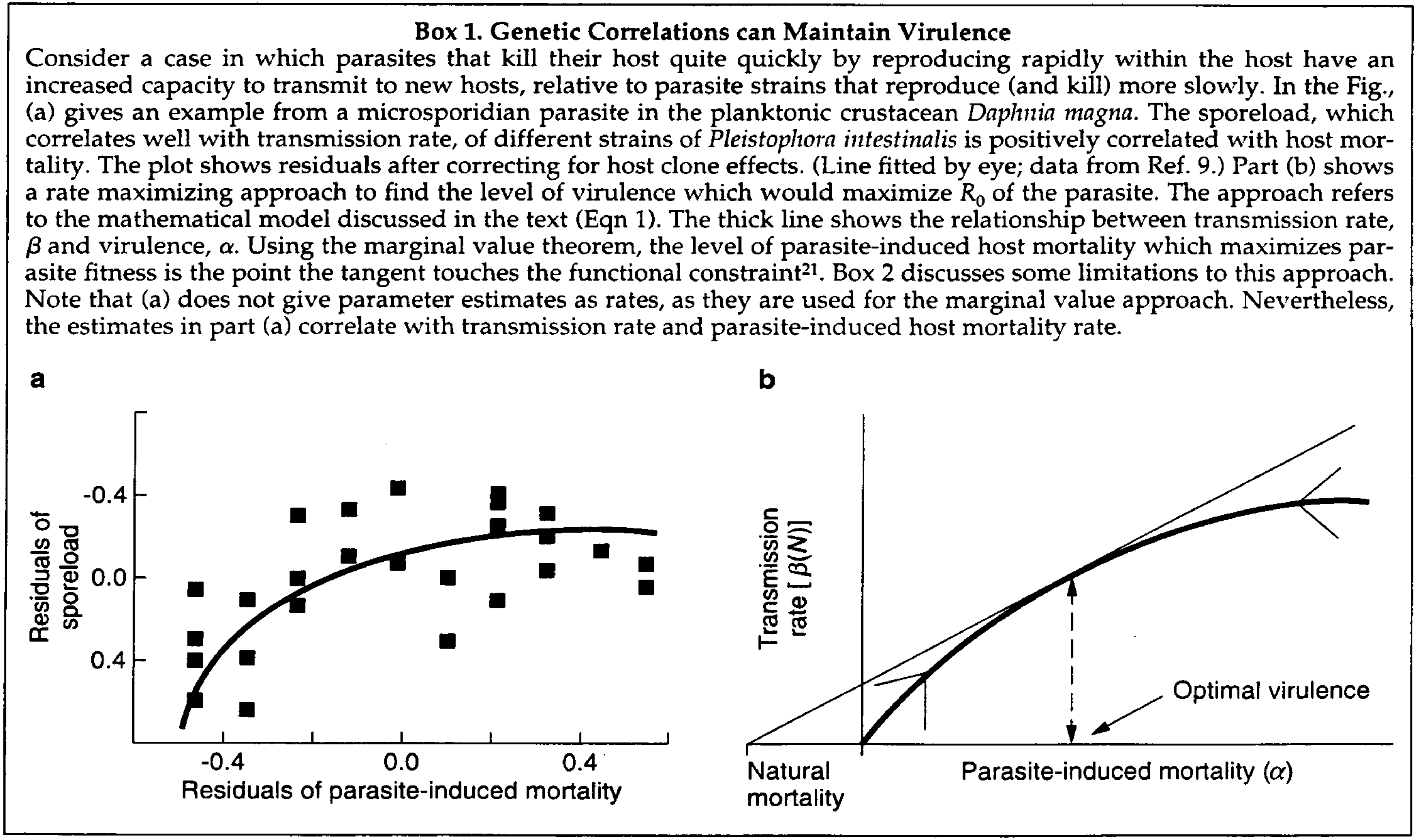
Transmission	Route	Examples
Direct	Airborne	Anthrax（炭疽）, chicken pox, common cold, influenza, measles, mumps, rubella, tuberculosis, whooping cough
	Direct contact	Athlete's foot（水虫）, impetigo（とびひ）, warts（いぼ）
	Fecal-oral	Cholera, hepatitis A, rotavirus, salmonella (=typhoid fever)
	Maternal-fetal	Hepatitis 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)

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)

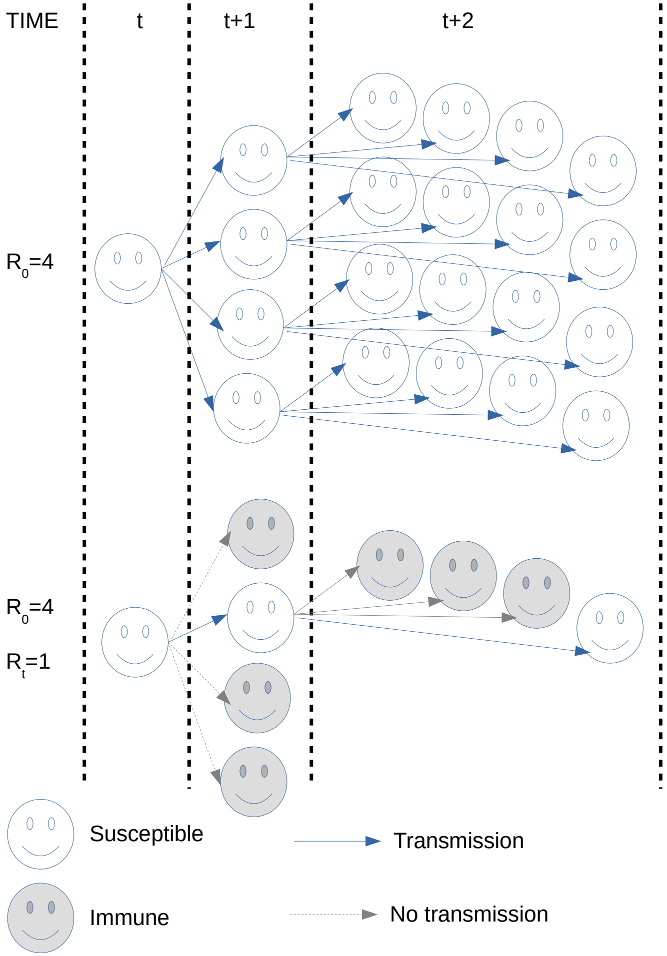
13 April 2020
Minato Nakazawa

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 <u>with enormous numbers of deaths and illness</u> (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.

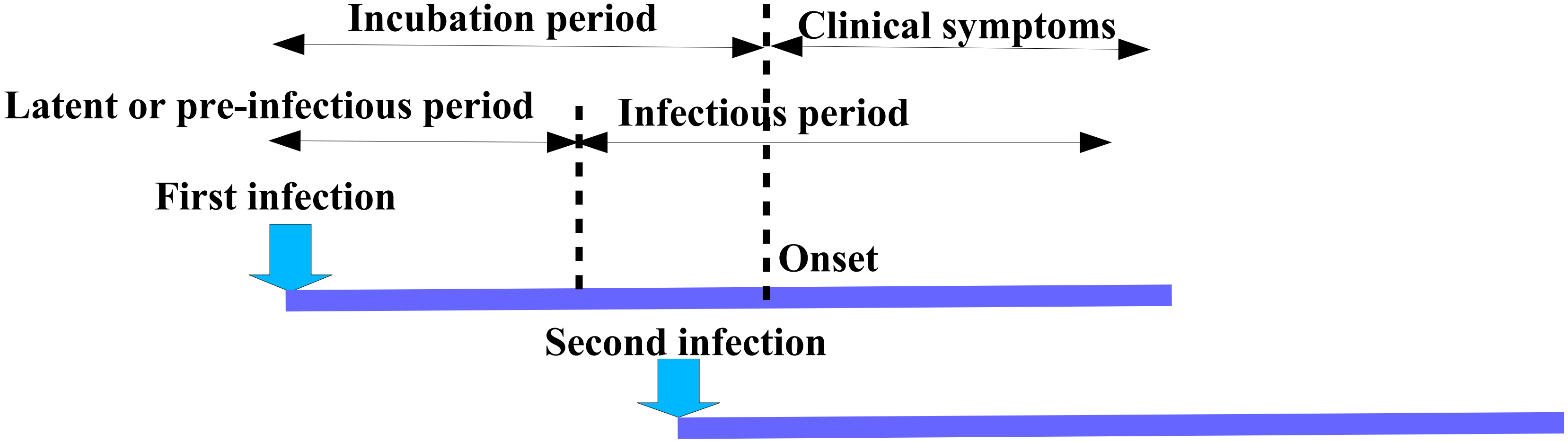
The nature of R_0 and R_t

- 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; $(1 – 1/10)/0.95 = 0.947… \approx 0.95$)
  - 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; $(1 – 1/15)/1 = 0.933… \approx 0.93$
  - If R_0 is 2 and V_e is 95%, V_c needs to be larger than 53% to reduce R_t below 1; $(1 –1/2) /0.95 = 0.526… \approx 0.53$.
- 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



Incubation period

Clinical symptoms

Latent or pre-infectious period

Infectious period

First infection

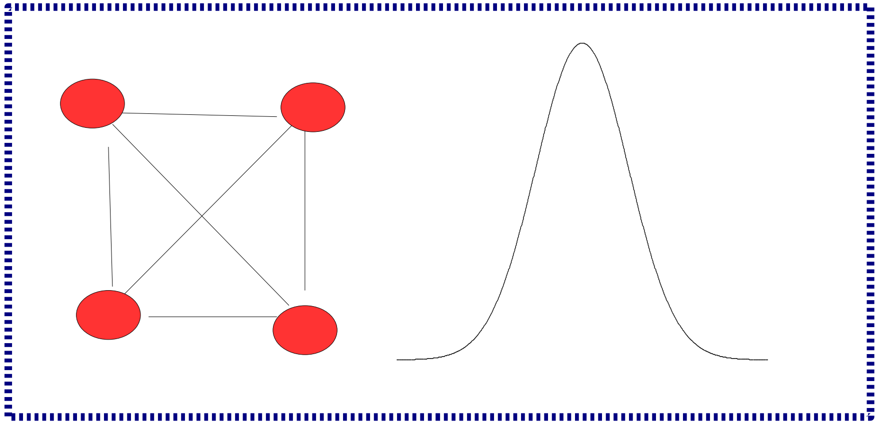
Onset

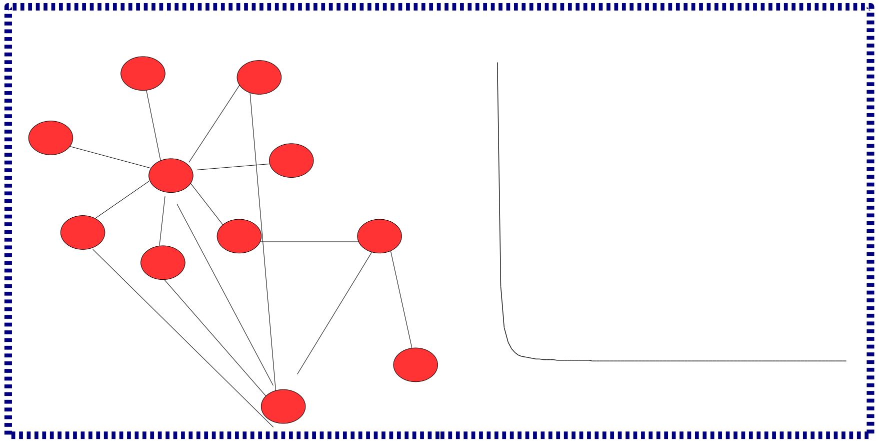
Second infection

Two general types of infection network topology

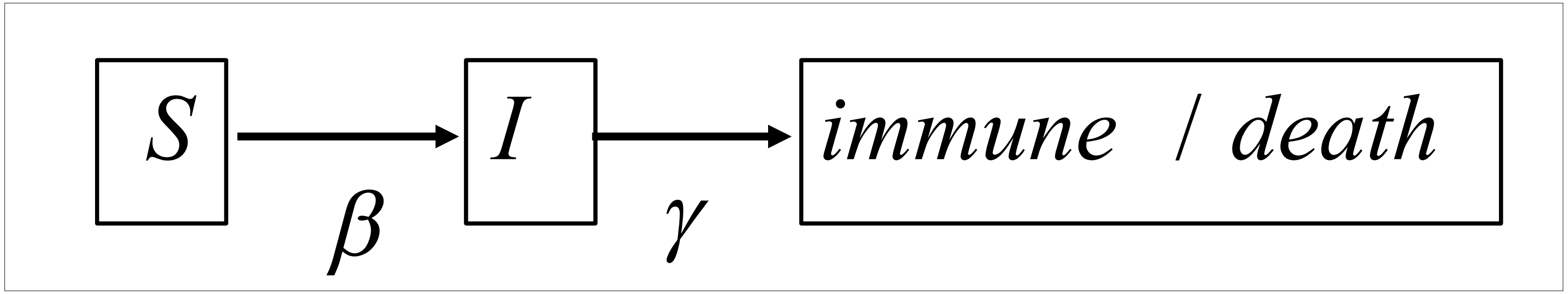
(1) Random link network
* equal infection probability for each
* distribution of infection frequency
  is unimodal

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



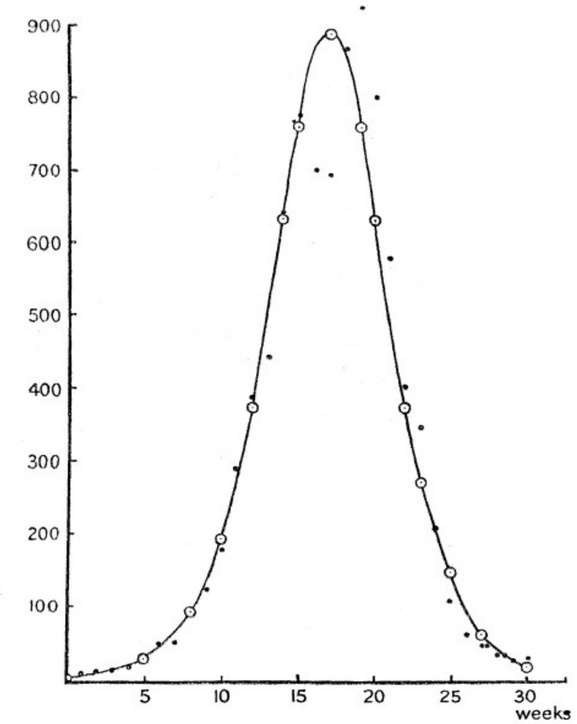


Simplest mathematical model (SI)



$S \xrightarrow{\beta} I \xrightarrow{\gamma}$ immune / death

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



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

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

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

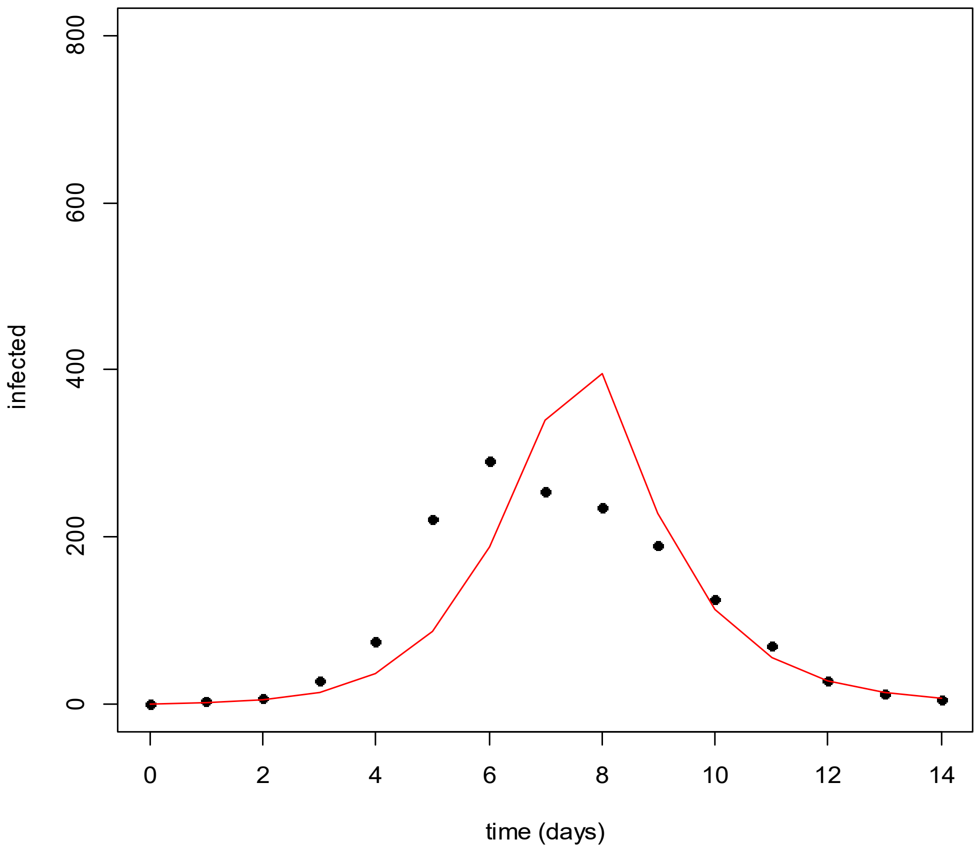
$$\frac{dI}{dt} = \beta SI - \gamma I$$

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

SIR model for flu epidemic

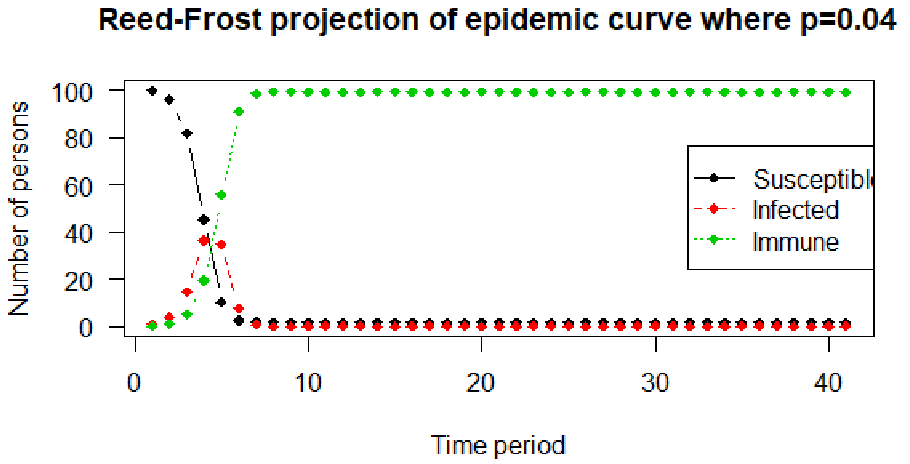
- $dS/dt = - \beta SI + \delta R$
- $dI/dt = \beta SI - \gamma I$
- $dR/dt = \gamma I - \delta R$
- Note: None of S, I, and R can be less than 0. It should be considered in numerical simulation.
- Estimating params
  - β: {I(1)-I(0)}/S(0)
  - γ: 1/{mean days of recovery}
  - δ: negligible (loss of immunity)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

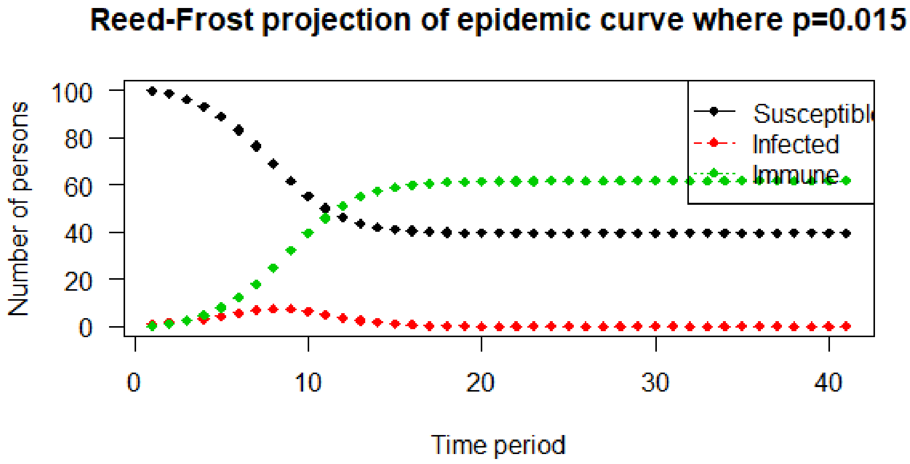
Example: The data in English boys boarding school in 1978



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.





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

INFECTIOUS DISEASE EPIDEMIOLOGY INVESTIGATIONS

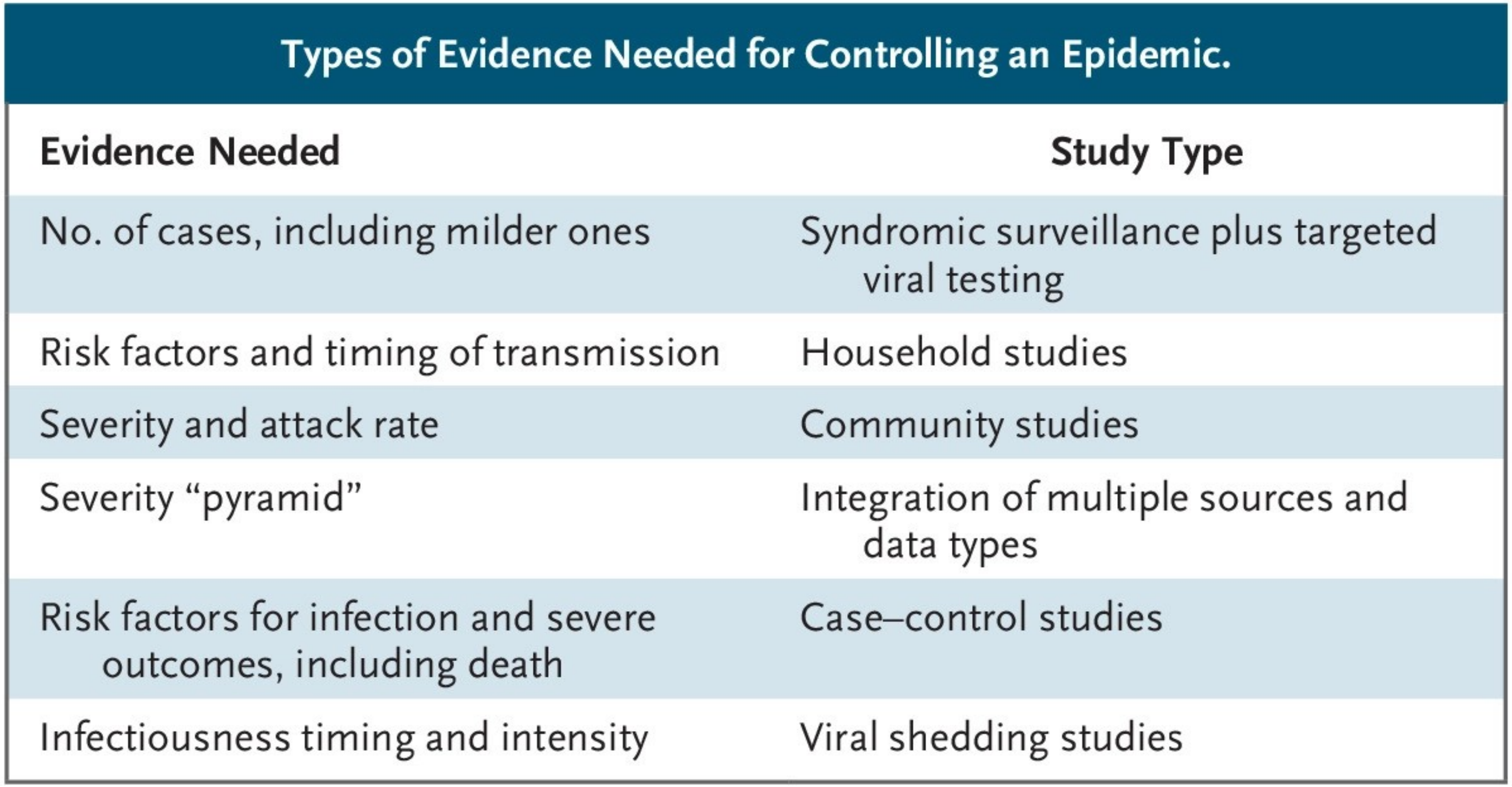
- Several types of epidemiologic studies are unique to the investigation of infectious disease
- Four types are worthy to mention
  - Contact-tracing studies: In the early stage of an epidemic, it may be possible to interrupt person-to-person transmission enough to bring R_0 below 1 by isolation, treatment 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

Epidemiology of COVID-19

- Lipsitch M, Swerdlow DL, Finelli L (2020) Defining the epidemiology of Covid-19 – Studies Needed. *New England Journal of Medicine*, 382: 1194-6, 26 Mar. https://www.nejm.org/doi/full/10.1056/NEJMp2002125



Types of Evidence Needed for Controlling an Epidemic.

Evidence Needed	Study Type
No. of cases, including milder ones	Syndromic surveillance plus targeted viral testing
Risk factors and timing of transmission	Household studies
Severity and attack rate	Community studies
Severity "pyramid"	Integration of multiple sources and data types
Risk factors for infection and severe outcomes, including death	Case–control studies
Infectiousness timing and intensity	Viral shedding studies

What is pathogen of COVID-19?

(Lai C-C et al. https://doi.org/10.1016/j.ijantimicag.2020.105924)

- The pathogen of COVID-19 is SARS-CoV-2, which is the 7th corona virus for human host.
  - Among the corona viruses for human host, 4 types cause common cold.
  - Other 3 types are SARS-CoV, MERS-CoV, and currently prevailing SARS-CoV-2 (it was called as 2019-nCoV at first). The genomes of SARS-CoV and SARS-CoV-2 have similarity of 80%. A kind of bat CoV genome showed almost complete similarity with SARS-CoV-2 genome.
    - SARS-CoV originated from bat, through other animal, then human to human
    - MERS-CoV originated from camel, rarely human to human
    - SARS-CoV-2 originaned from bat, probably through other animal, human to human
- Characteristics of SARS-CoV-2
  - Latent period (from infection to symptom) is 5 days in average (Linton et al. 2020)
  - Serial interval (between the occurrence of symptoms of first case and second case) is 4 days in average, which means infection occurs in presymptomatic period. Contact tracing is difficult (Nishiura et al., 2020)
  - About 80% of the infected persons are asymptomatic or showing mild symptoms (Severity pyramid).
  - The risk of severe symptoms or deaths depends on the patients age. Elderly and the people with underlying diseases show high risk, but some young patients without any underlying diseases may also die at much higher risk than influenza.
  - The periods from admission to the hospital to either getting well or death are about 20 days.
  - Because of no vaccine nor effective medicine, severe cases have to be treated by respirator or ECMO in ICU, otherwise die at high risk. The risk of death depends on medical standard.

Severity

- The common indicator of severity is CFR (Case Fatality Ratio/Risk). It's the number of deaths caused by a disease divided by the number of confirmed cases of that disease.
  - CFRs for SARS, MERS, Spanish flu and Asian flu were 10%, 35%, 3% and 0.5%, respectively.
  - It is widely misunderstood that the CFR of seasonal flu is "less than" 0.1%. Actually, the estimates of confirmed cases of seasonal flu in Japan is about 10 million, and the number of death due to seasonal flu is 2000 to 3000, so that CFR is 0.02-0.03%.
  - The CFR of COVID-19 ranges from 1 to 10%.
    - The wide range of CFR is caused by large difference of examination ability, medical capacity, and the age distribution of the patients.
    - Like in South Korea and Germany, extensive RT-PCR examination for many people leads to large number of confirmed patients, subsequently smaller CFR estimates. In South Korea, younger patients with lower fatality shared majority of positives, which made CFR lower.
    - Like in Italy and France, if the number of patients went beyond the medical capacity with rapid increase (so-called "overshoot" in Japan, analogously with "overshoot" in ecology, which means excess population growth beyond the carrying capacity), CFR goes higher.
- In the case of COVID-19, as above mentioned, CFR depends on examination and medical capacity, so that the meaning of CFR is difficult to interpret. Based on the data from China, where the examination coverage was already assessed, estimated CFR ranged from 3% to 6% and the confirmed cases were considered to share about 10% of all infected patients, Infection Fatality Risk/Ratio (IFR) was suggested as 0.3-0.6%. IFR may be applicable as universal indicator of disease severity (Nishiura 2020).
  - The IFR of seasonal flu seems to range from 0.005 to 0.01%.

Age dependency of CFR

Age-specific CFRs in Mainland China up to 11 Feb 2020. http://weekly.chinacdc.cn/en/article/id/e53946e2-c6c4-41e9-9a9b-fea8db1a8f51

	Confirmed cases	Deaths	CFR(%)
0-9yr	416	0	0
10-19yr	549	1	0.2
20-29yr	3619	7	0.2
30-39yr	7600	18	0.2
40-49yr	8571	38	0.4
50-59yr	10008	130	1.3
60-69yr	8583	309	3.6
70-79yr	3918	312	8.0
80yr+	1408	208	14.8
All	44672	1023	2.3

- Age-specific CFR of Pandemic flu 2009
  - MHLW data in Japan (https://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou04/dl/infu100608-03.pdf)

0-4yr	0.0007%
5-9yr	0.0003%
10-14yr	0.0001%
15-19yr	0.0001%
20-29yr	0.0005%
30-39yr	0.0009%
40-49yr	0.0031%
50-59yr	0.0066%
60-69yr	0.0147%
70yr+	0.0282%

  - NY city H1N1pdm2009 (https://doi.org/10.1371/journal.pone.0011677)

0-17yr	0.0008-0.0012%
18-64yr	0.0081-0.0132%
65yr+	0.0094-0.0147%

Other severity factors than age

(Zhou F et al. 2020, Lancet, 2020Mar11)

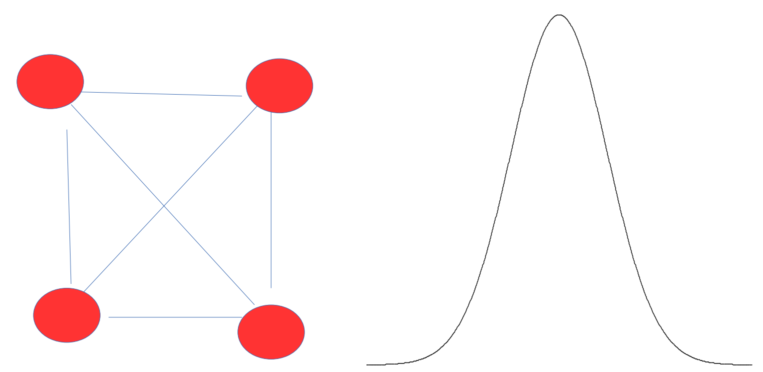
- Patients discharged or died from 2 hospitals in Wuhan until 31 Jan 2020, ages higher than 18 yr: 191 (137 discharged, 54 died; mean days from onset to admission were 11 days for each)
- Result from the multiple logistic regression analysis, higher risk of death was attributable to the following factors
  - Age (1.1 times by 1 age increase)
  - Higher SOFA score at admission (used to diagnose sepsis) (OR 5.65， 95％CI [2.61, 12.23])
  - Higher d-dimer than 1μg/mL (Comparing with less than 0.5μg/mL, OR18.42, 95％CI [2.64, 128.55])
- As another result of this paper, for discharged patients, the median duration of virus shedding from onset was 20 days (IQR 17-24 days), but for died patients, virus shedding was observed until death.

Infectiousness (ability of transmission)

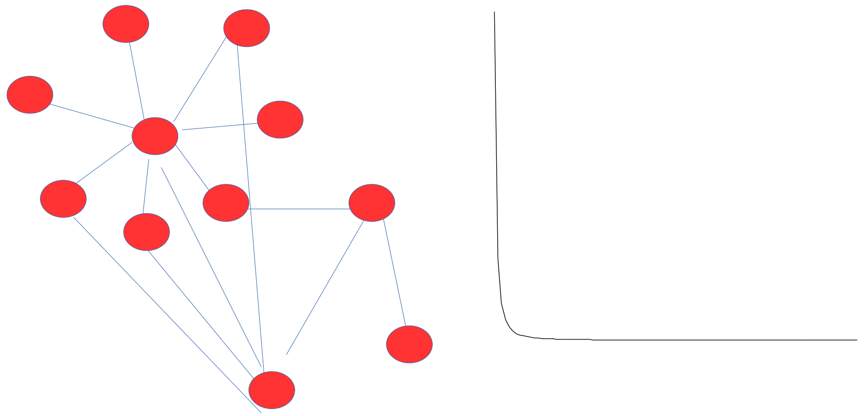
- Commonly used measure of infectiousness is the Reproduction Number (R), which means the average number of secondary infected people from the first case.
  - In the beginning of epidemic, nobody has immunity. Under such situation, where everybody is susceptible, if one index case invades, R is called as Basic Reproduction Number (R0). R0 depends on the nature of pathogen, host behavior, and environment.
  - After the progress of epidemic, recovered (immune) people increase. Some of the population are vaccinated, immune people also increase. In either case, the proportion of susceptible people decreases and thus R decreases, which is called as Effective Reproduction Number (Rt or Re). Rt depends on R0, protective measure, and the size of the population.
- If R<1, the epidemic will be suppressed.
- The R0 of SARS was about 3, but the variance of R0 was very large because of many cluster infection occurred in the airplane or hospital, where superspreading event may occur. The R0 of MERS was generally less than 1 except for nosocomial infection (https://www.who.int/csr/disease/coronavirus_infections/risk-assessment-august-2018.pdf).
- The R0 of Spanish flu was estimated around 2. The R0 of seasonal flu or Influenza (A) H1N1pdm2019 ranges 1.1-1.5 (eg. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6670001/).
- The R0 of COVID-19 was initially estimated as 1.4-2.5 based on the data obtained Wuhan (WHO, 23rd Jan 2020). With accumulation of data, the estimates of R0 largely varied by model or data, at highest, 6.47 (Tang B et al. 2020). However, inter-individual difference was very large, so-called "overdispersion" (Voltz E et al. 2020; Grantz K, Metcalf CJE 2020; Nishiura H et al. 2020).

The routes of infection in SARS-CoV-2 (PV)

- Random link routes of infection, where everybody have the same risk of infection (same as flu)
  - Droplets: face-to-face conversation without mask with distance within 2m.
  - Contact with contaminated material surface: touch the material surface contaminated by droplets, saliva or something else excreted from patients
  - Fecal-oral: The viral shedding occurs to feces, so that without washing hands after defecation, the patients touch something, which become source of contact infection
- Scale free route of infection (The cause of overdispersion of R)
  - Cluster infection due to suspended micro-droplets, which likely occur under 3Cs env. See, the movie provided by NHK: https://www3.nhk.or.jp/news/special/coronavirus/protection/?tab=3
    - Closed space (poor ventilation)
    - Crowded (high population density)
    - Close contact with conversation



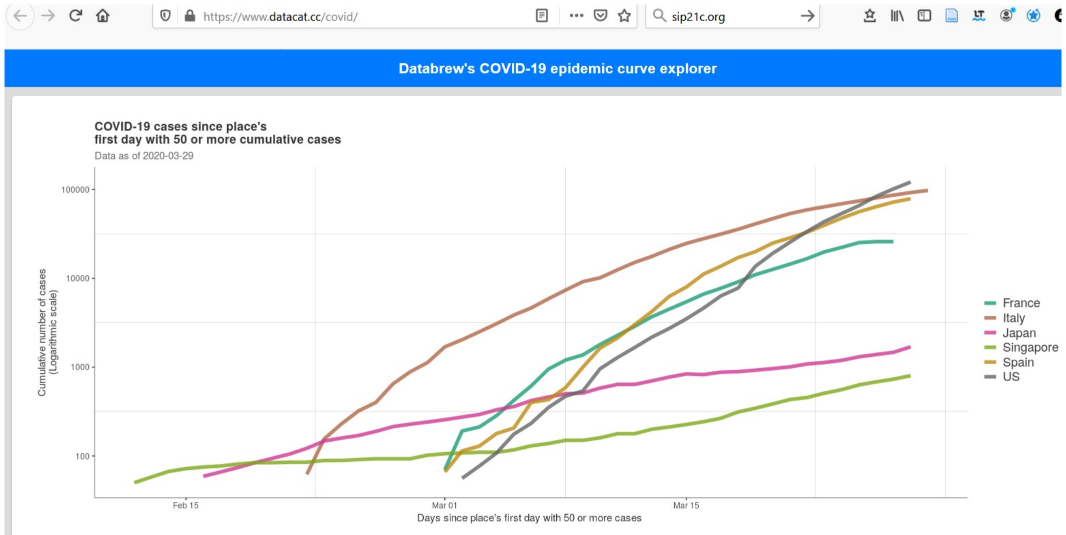
Random link network = everybody have the same probability of infection.



Scale free network causes cluster

The fewer number of testing in Japan than Europe/USA was caused by fewer patients

- Presumption
  - Testing performance is not perfect (RT-PCR cannot detect positive patients if the nasal/throat swab could not sample viral RNA particles)
  - Early detection cannot lead to effective early treatment to prevent severity or death
- The 3 purposes of RT-PCR to confirm infection (A is crucially needed, B is more effective than C when contact tracing is successfully conducted. If the disease becomes prevailing, B is difficult because it may excess the capacity of manpower of health center)
  - (A) When doctor judged the necessity of confirmation from atypical pneumonia or other results of clinical inspection, to prepare ICU beds, respirator, and ECMO (WHO recommends, many countries incl. Japan do)
  - (B) Detect positive patients (incl. asymptomatic, or with only mild symptoms) from all closely contacted people with patients [active case detection] to prevent spread by isolation of detected cases. (Also WHO recommends, impossible after excess number of new patients as in Europe/USA, Singapore and Taiwan succeeded, Japan did until mid-March and try to continue)
  - (C) Widely examine suspected people to detect all cases (under low prevalence situation, efficacy is low) to prevent spread by isolation (South Korea and Germany did)
- Wrong doubt: The number of patients looks few due to limited testing
  - Until mid-March, the change of cases by date plotted by semi-log scale, Japan and Singapore showed sharrower slopes from Europe and USA, but both groups showed linear relation. Linear relation in semi-log scale means exponential growth. https://www.datacat.cc/covid/
  - If untested cases are hidden behind the detected cases at a considerable probability, the slope doesn't change, only the intercept changes. **Shallower slope means smaller R**.



Estimates of detected proportion and prevalence in Japan

- In the paper (2nd April 2020) linked from https://www.uni-goettingen.de/en/606540.html, Prof. Sebastian Vollmer from University of Goettingen estimates the proportion of detected cases among total patients.
- Methods
  - Assume that the number of reported death by COVID-19 is correct (Japan reported 56 on 31st March)
  - Assume that the age-specific IFR in the paper "Estimates of the severity of coronavirus disease 2019: a model-based analysis" in Lancet Infectious Diseases on 30th March 2020 by Verity R et al. (The groups of Imperial College London) is universally applicable.
  - Weighing by age-structure of each county from UN database, age-adjusted IFR is obtained (Japan is 1.60%).
  - Divide the number of death by age-adjusted IFR, then the number of total infected people in 2 weeks before is obtained (Japan on 17th March is 3490, which is 56/0.016).
  - Divide the number of confirmed cases (878 in Japan on 17th March) of each country by estimated total infected people, the proportion of detected cases among total patients is estimated.
- Results
  - It's rough estimate, **the proportion of detected cases in Japan on 17th March was about 25%**, which is third highest level following 49% of South Korea and 38% of Norway. Germany is 16%, Denmark is 13%. Many European counties incl. Italy, France, UK and USA are all less than 5%.
  - Assume that the proportion of detected cases doesn't change, divide the confirmed cases on 31st March (in Japan, it's 1953) by that value (0.25), the estimates of total infected cases can be obtained (in Japan, it's 7762). Divide it by the total population, the prevalence can be obtained (in Japan, it's 0.01%). By this method, the countries with the prevalence higher than 10% on 31st March were Spain and Turkey.
- According to the result of antibody test from 500 sample in a city of Germany, about 14% showed positive (MIT, https://www.technologyreview.com/2020/04/09/999015/blood-tests-show-15-of-people-are-now-immune-to-covid-19-in-one-town-in-germany/). The important information is that remaining 86% is still susceptible.

To continue the type (B) testing, "Digital Contact Tracing" may be effective

- Type (B) testing becomes difficult when the newly found cases (especially with unknown link) increased, because manual contact tracing requires huge time and effort of the professionals of health center, which exceed the capacity soon.
- If we can easily find the people who had close contact with the infected case, even after propagation of epidemic, type (B) testing can more effectively detect the infected cases than type (C) testing, and thus type (B) testing may have higher priority than type (C) testing.
- There may be a solution. It's the use of big data automatically collected by smartphone apps (https://www.cnbc.com/2020/03/27/coronavirus-surveillance-used-by-governments-to-fight-pandemic-privacy-concerns.html)
  - China seems to have enhanced the information collection system using GPS tracking and surveillance camera since Beijing Olympic. The report 11 from the group of Imperial College used the population movement data from GPS record by Baidu.
  - South Korea has a strong regulation based on the law of infection control, by which the movement of the infected cases using GPS data is visualized and opened to public.
  - In Singapore, the smartphone app "TraceTogether" is recommended to install for everybody. When the smartphone with the TraceTogether running comes close each other, the other's information without location information is automatically detected using bluetooth and recorded with time in each smartphone. The information is kept for 21 days within each smartphone. When a person is proved to be infected, it's possible to find all close contactees of the person during previous 21 days.
- According to the paper by the groups Prof. Fraser in Science (Ferretti et al., 2020), "digital contact tracing" using smartphone app may enable the suppression of epidemic to avoid "overshoot" without "lockdown". They also discussed ethical issue in that paper.

Why the number of cases increased more slowly in Japan than Europe (PV)

- Infection via droplets or contact randomly occurs from one case to 0, 1, 2, or at most 3 secondary cases, so that the distribution of the number of secondary infection may obey normal distribution.
  - In Japan, the number may be mostly 0 or 1, so that the part of R0 due to this route of infection may be less than 1.
    - As cultural norm, personal space has been wider than Europe/USA (distant bow vs handshake/kiss/hug)
    - Clean piped water is available for everybody at very cheap price.
    - Handwashing with soap before school lunch is strongly forced in elementary school. In addition, handwashing has been strongly recommended since January.
  - In Europe/USA, the number may be mostly 1 or 2, so that the part of R0 due to this route may be more than 1.
    - In most European countries and USA, keeping the more than 2m inter-individual distance away from each other is recommended due to this reason.
- R>1 leads to spread of epidemic.
- Actually, the distribution of the number of secondary infections from the first case may obey the mixture of normal distribution and power distribution representing cluster infection.
  - The cluster control group under the specialists committee of the government on 25th Feb set by Dr. Omi and Dr. Oshitani's leadership, in which Prof. Nishiura is responsible for analysis and modeling, tried to decrease R less than 1 by finding the common condition for cluster infection and preventing it.
    → They found 3 Cs (Closed environment, Crowded population, Close contact with conversation) and promoted campaign to prevent the 3 Cs (Nishiura et al., 3rd March 2020 at preprint server).
  - This "prevention" of 3 Cs was specially featured in Japan's strategy.
  - To prevent cluster infection, banning mass-gathering event is conducted in most countries.
- **Until mid-March, probably due to low mean level of the part of R0 due to contact/droplet infection and the cluster control strategy, Japan could suppress the number of infected cases.**

Why the increase of cases accelerated after late March (PV)

- The global basic strategy to tackle infectious diseases is IHR2005 (International Health Regulations 2005 revision). It includes the minimizing the restriction of trade and traffic. Complete closure of each country is ideal to prevent pandemic, but it's impossible, because the social system largely depends on the international traffic and trades.
- The first wave of COVID-19 patients influx to Japan from China was suppressed by "cluster-control". However, the number of new patients has rapidly increased since the late March.
- The second wave of COVID-19 patients (mostly asymptomatic) influx from Europe/USA was much larger than the first wave. It caused rapid increase of newly confirmed cases without links since late March.
  - According to the opinion by Prof. Oshitani, the second wave caused many hidden clusters, then each one sporadic case was detected from each hidden cluster. Since rapid increase of sporadic cases means increase of hidden clusters, active case detection by contact tracing and isolation becomes impossible. Remaining possibility of suppression is to decrease the human-to-human contact by 80% (According to Prof. Nishiura, 79% based on the detailed model analysis) by emergency declaration.
  - The virus attacked Japan in the second wave has mutated from the original virus and got higher infectiousness (?).
  - (My PV) If the increased cases due to the second wave was not the part of hidden cluster but the result of hidden chain of random link due to droplets or contact route, there is a possibility that the cluster control is still effective. (It's possible to check by making the model including the different distribution for different route of infection and movement.)
- Essential problem in cluster control strategy
  - Though the some workplaces with 3 Cs can be modified to prevent cluster infection (of course, guaranteeing the basic income or other life support is necessary), but other workplaces especially lifelines, hospital, elderly care center and day service cannot avoid 3 Cs as their own nature. Most cluster infection after the end of March was shared by such essentially vulnerable workplace or the places to be hidden with hesitation (in relation to so-called nightlife). 80% reduction strategy consider those as inevitable part of 3 Cs. Break-through for this issue is expected.
  - For most people, long-term "self-regulation" to avoid 3 Cs and human-to-human contacts is impossible. The government should take huge financial support.
- In early April, to prevent "overshoot", the prime minister issued emergency declaration on 7th April (He said it being different from lockdown), 80% reduction of human-to-human contact (based on the calculation by cluster control group) was asked for the citizens strongly.

How long will it continue? At least 1 year.

- Until the vaccine or specific drug with high efficacy become widely available (Ultimate solution)
  - At least 1 year and half or 2 years, or more.
  - There is no guarantee to reach this goal, because there are many infectious diseases without effective vaccines though huge efforts were paid to do so for decades.
- Until the population establish herd immunity (Bad end)
  - According to the projection by Prof. Marc Lipsitch on 15th Feb, COVID-19 will infect 40-70% of the world population in 1 year, herd immunity will be established and Rt becomes less than 1, then pandemic will end.
    - However, at least 7.5 billion x 0.4 x 0.003 = 9 million will die.
    - If "overshoot", which means explosive increase of new cases and exceeds the capacity of medical treatment, will occur in many countries, at worst, 7.5 billion x 0.7 x 0.01 = 52.5 million will die.
- Until the number of newly infected cases decreases under a certain level without herd immunity (It's not ultimate suppression)
  - The No.9 report from the Imperial College of London, written by Prof. Neil Ferguson and colleagues showed the possibility to control the epidemic for 1.5-2 years under the capacity of medical treatment by repeated suppression (combination of several behavioral changes) for 1-3 months. Their model was individual based simulation model using actual contact frequency indicator and population density by region, modified from a kind of flu-model, and thus overestimating the effect of school closure, but solo-intervention by school closure only reduces total infected cases by 2%.
  - Since the community mitigation measures such as social distancing to reduce the number of death postpone the timing of the peak of the epidemic curve, the pandemic will continue longer than 1 year.
  - In addition, this strategy cannot lead to herd immunity in the total population, so that the behavioral change to avoid explosive increase of the infection has to be continued even after suppression.

For the safe campus life

- According to the announcement from Ministry of Education, Culture, Science and Technology (https://www.mext.go.jp/content/20200324-mxt_kouhou01-000004520_4.pdf, in Japanese), lectures in the University can take various methods including remote learning via Internet.
  - Remote learning is strongly recommended.
  - It may last for a year, the student should prepare PC and the conditions for networking at home.
  - In special cases, the students can go to the campus (except for lockdown situation). But the students have to keep properly modified behavior listed below.
- Needed behavior
  - To avoid infection from yourself to others (even if you have no symptom, you may have virus in your body)
    - Don't go out and stay home if you feel, even slightly, ill (If your symptom seems severe, you should consult with health center or physician by phone). Wear mask always when you talk
  - To prevent the infection by droplets or contact
    - Frequent proper handwash, social distancing to keep yourself away from others by at least 2m, avoidance of face-to-face talk
    - Any private conversation in the class is prohibited
  - To avoid cluster infection
    - Prevent 3 Cs (Closed environment with poor ventilation, Crowded population and Close contact with conversation).
    - Keep door and window opened during the class.
    - See, Notice from WHO https://www.who.int/docs/default-source/coronaviruse/getting-workplace-ready-for-covid-19.pdf
- <Important thing> Even if you pay attention to avoid infection, you may have non-zero risk of infection. It's same for anybody else. Therefore, stigmatization or discrimination of infected cases is strongly prohibited.