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.

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)

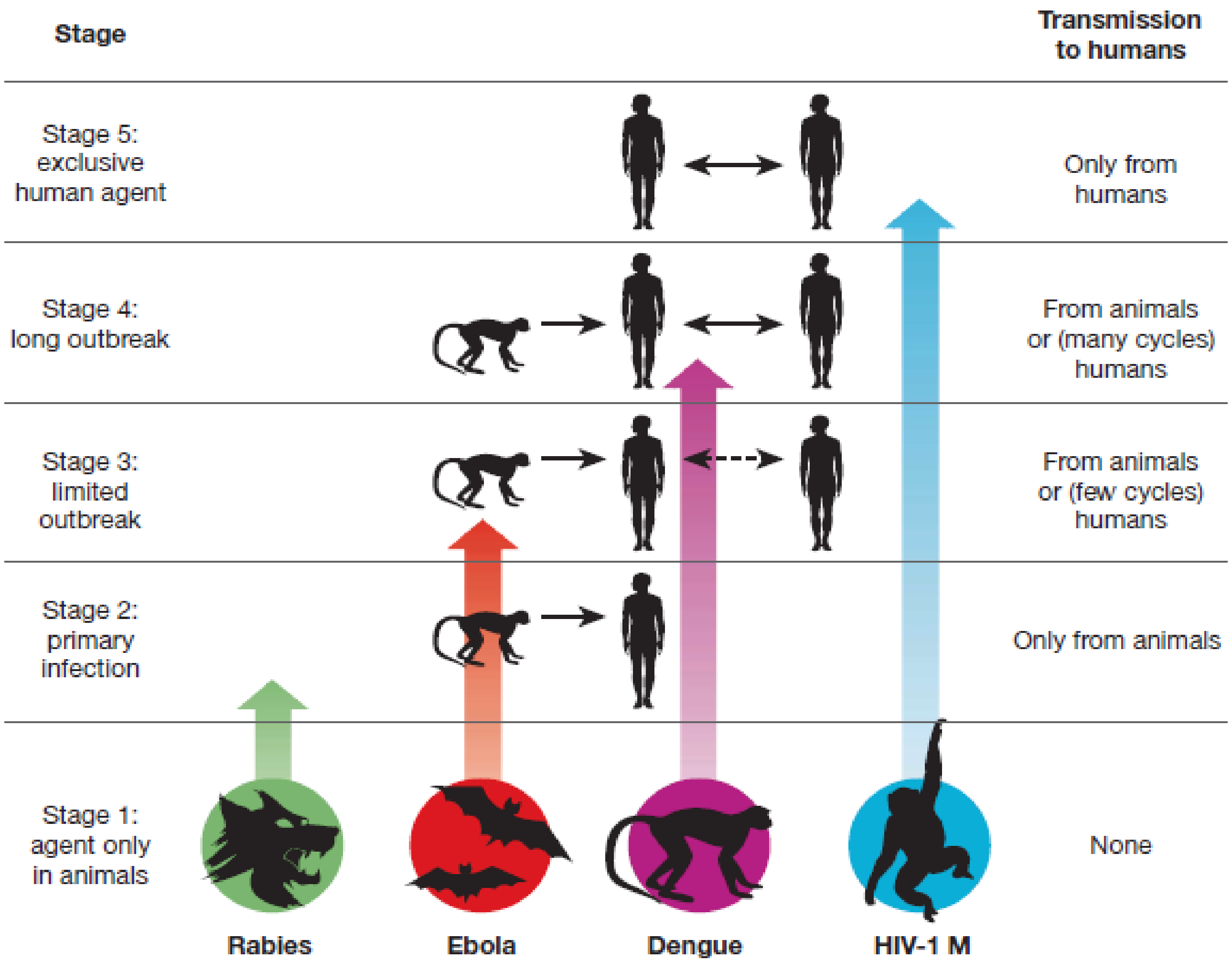

Figure 1 | Illustration of the five stages through which pathogens of animals evolve to cause diseases confined to humans. (See Box 1 for details.) The four agents depicted have reached different stages in the process, ranging from rabies (still acquired only from animals) to HIV-1 (now acquired only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

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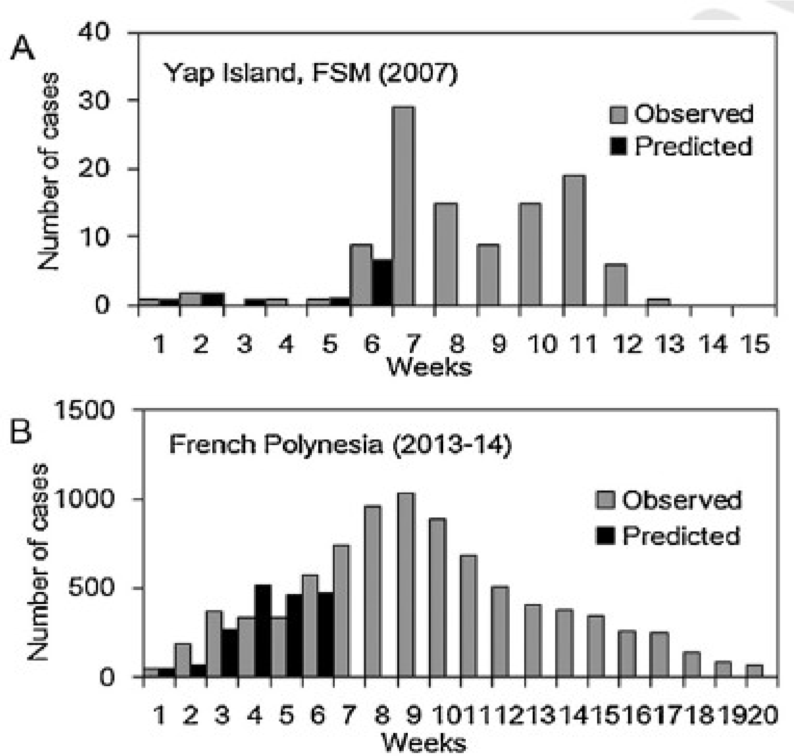
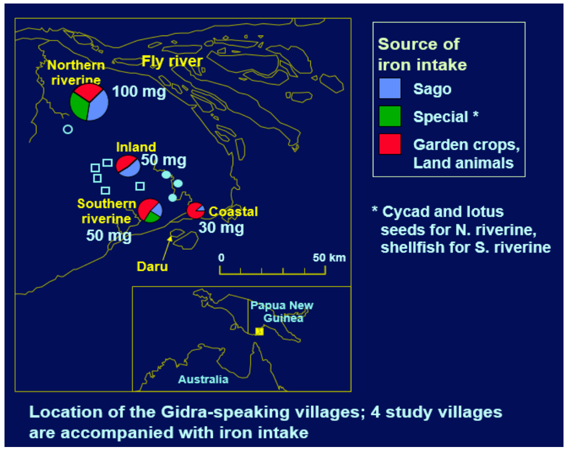
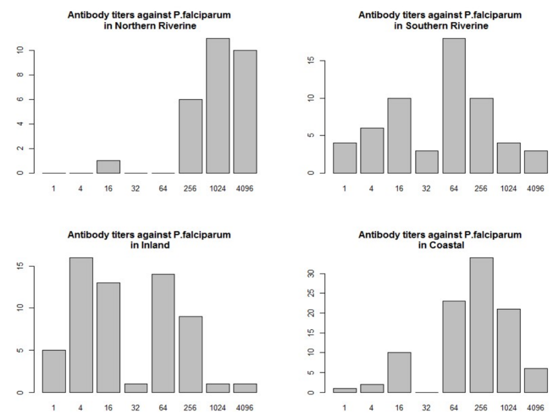
Descriptive epidemiology of infectious diseases

- 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





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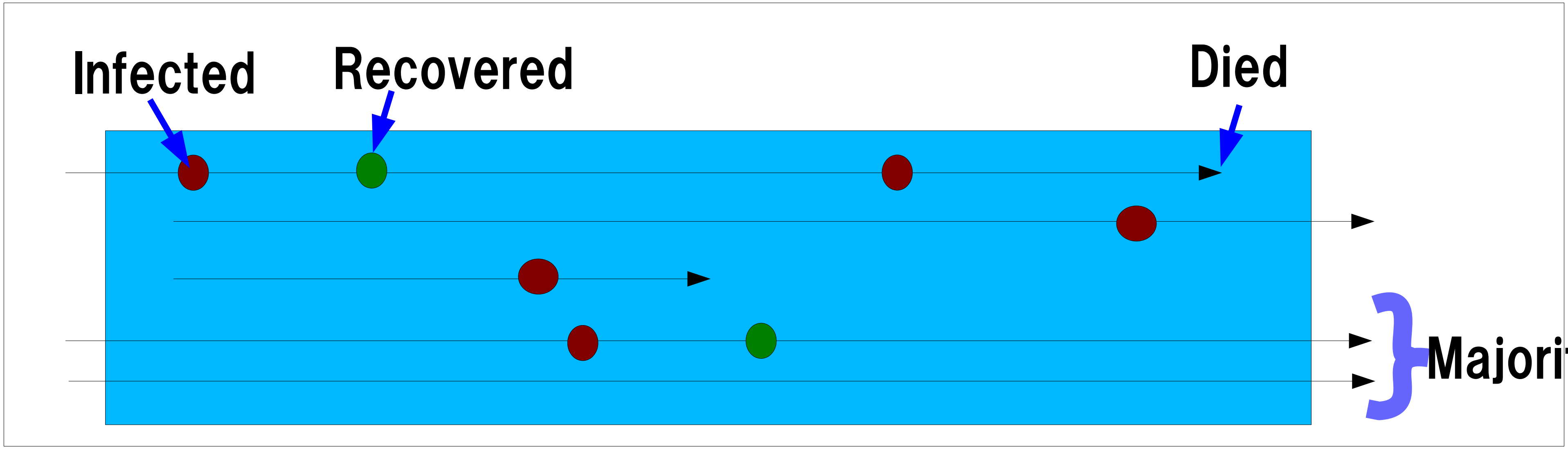
Prevalence and Incidence



- 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

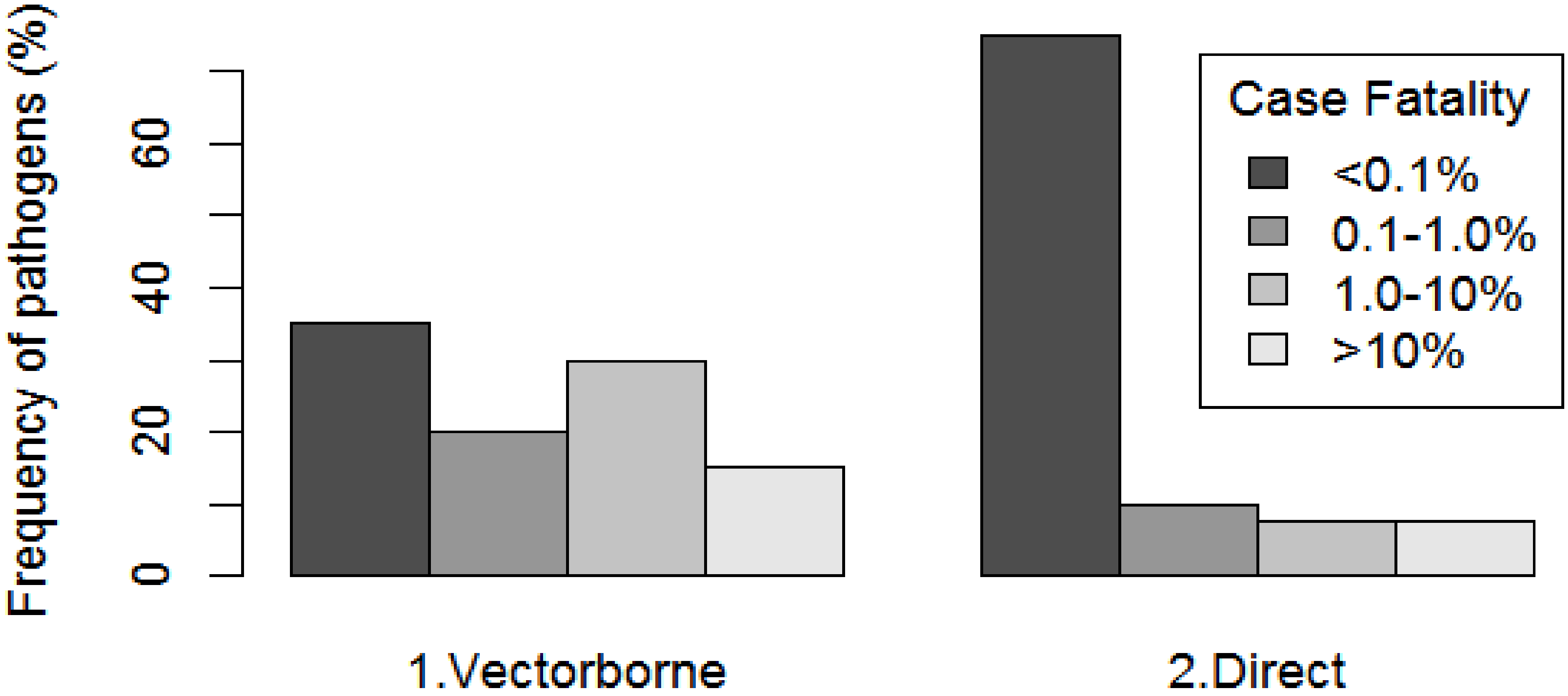
Route of transmission	Characteristics
Contact	Requires direct/indirect contact * Indirect = infected fomite, blood or body fluid * Direct = skin or sexual contact
Food- or water-borne	Ingestion of contaminated food (outbreaks may be large and dispersed, depending on distribution of food)
Airborne (droplet, 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 **<u>reservoir</u>** 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** (<u>Number of death due to that disease divided by the number of diagnosed patients</u>) 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)

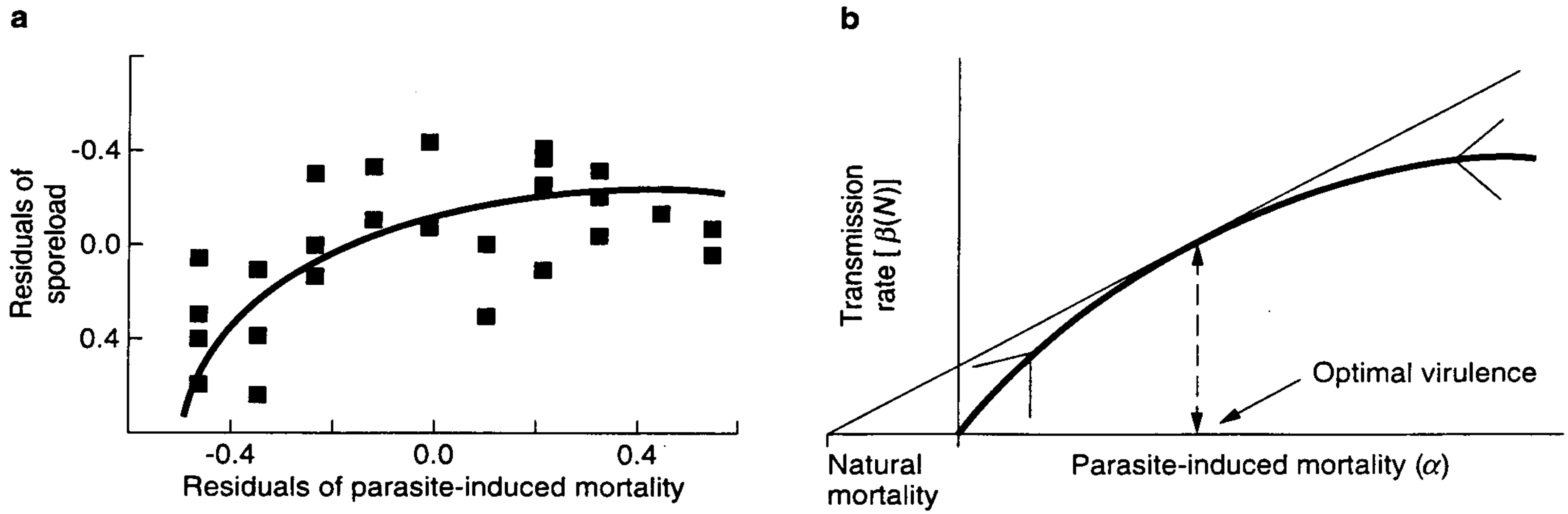


Source: Ewald (1994) [pp.38, Figure 3.1]

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.



17 April 2023
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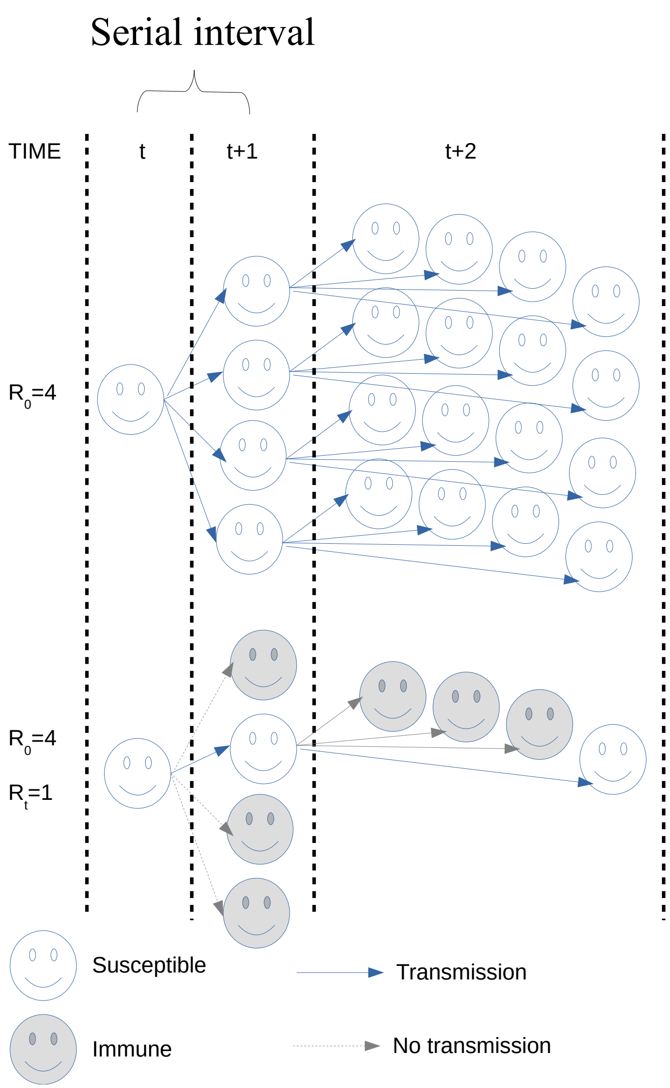
Source: Ebert & Herre (1996)

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

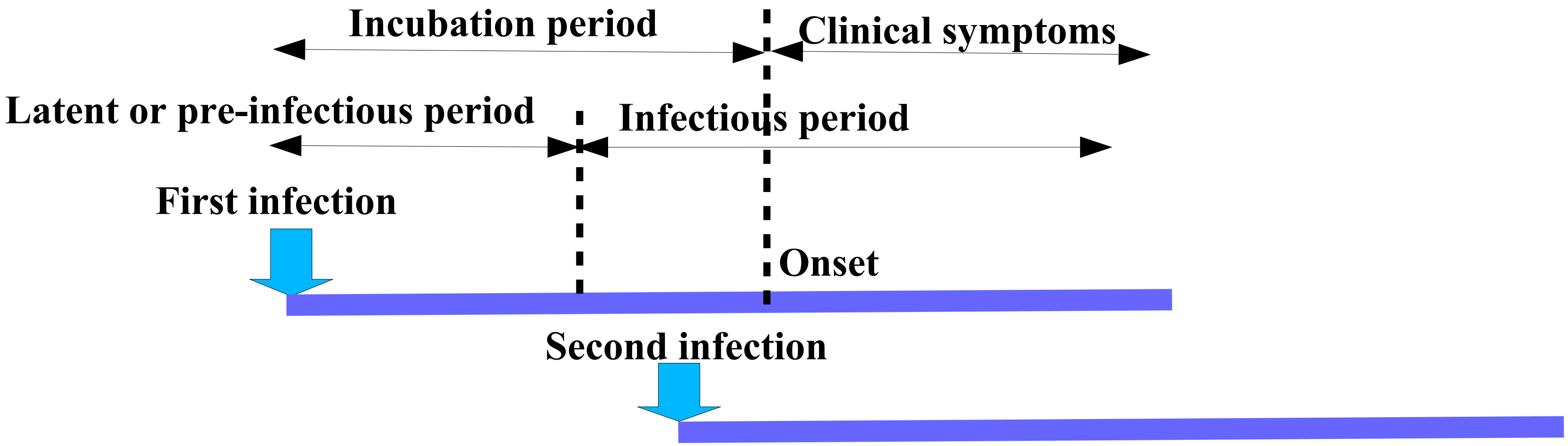
- The reproduction number reflects the biologic potential of the infectious agent and the social intercourse that leads to situations in which transmission might occur
  - If directly transmitted disease patient is too sick to move, there will be few contact with susceptible host, results in low reproductive 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**)

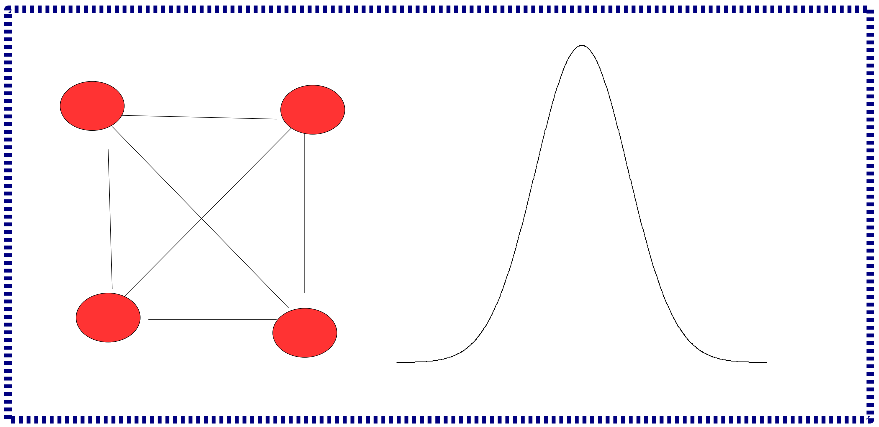
Terms for individual infection history

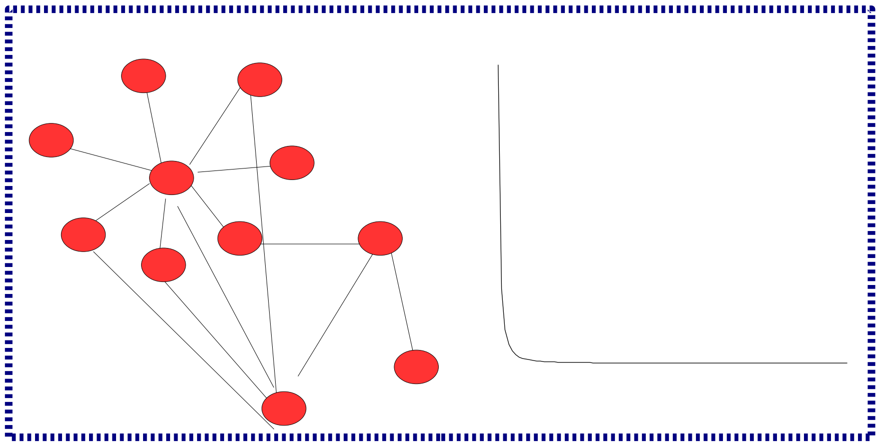


Two general types of infection network topology

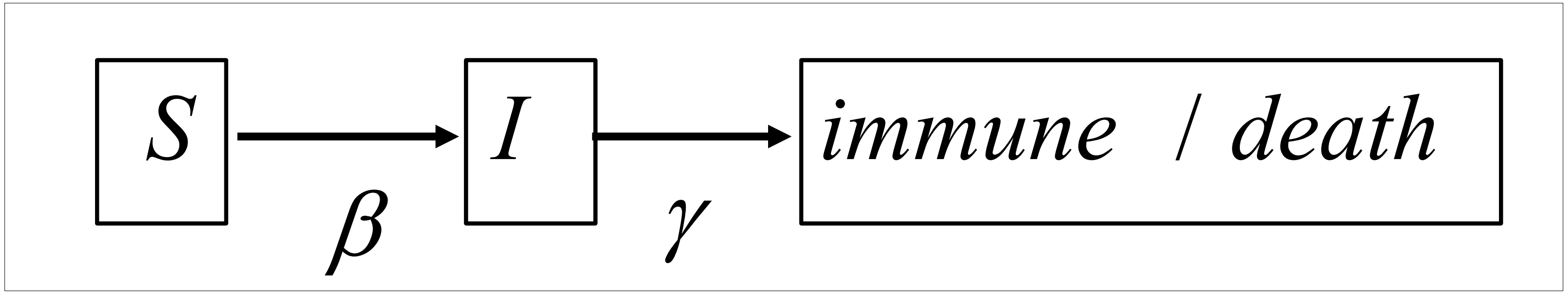
(1) Random link network
* equal infection probability for each
* distribution of infection frequency is unimodal

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

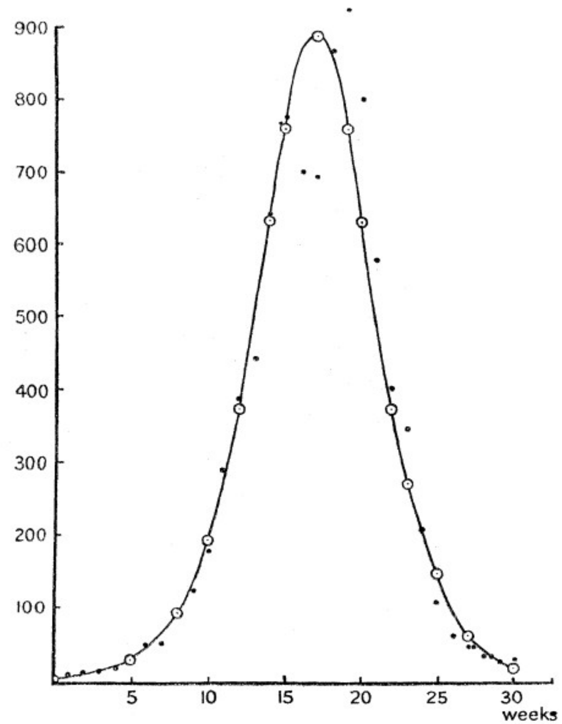




Simplest mathematical model (SI)



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



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

$$\frac{dz}{dt} = 890\,\mathrm{sech}^2\,(0\cdot2t - 3\cdot4).$$

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

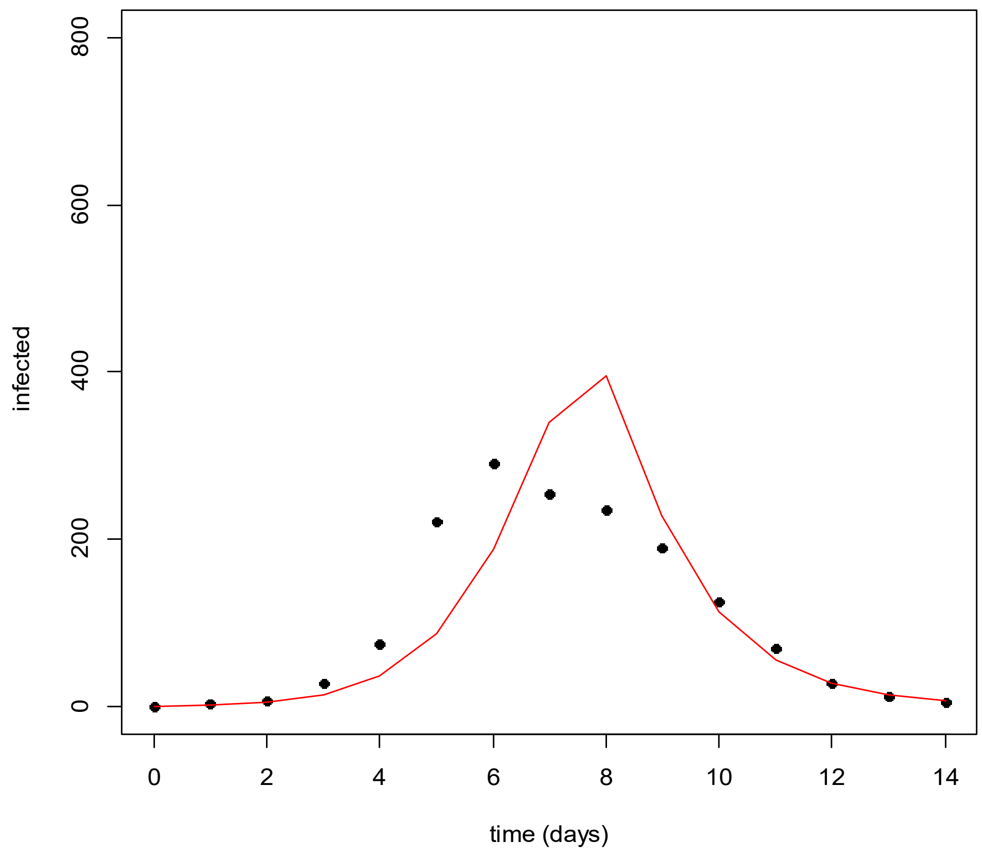
$$\frac{dI}{dt} = \beta SI - \gamma I$$

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

SIR model for flu epidemic

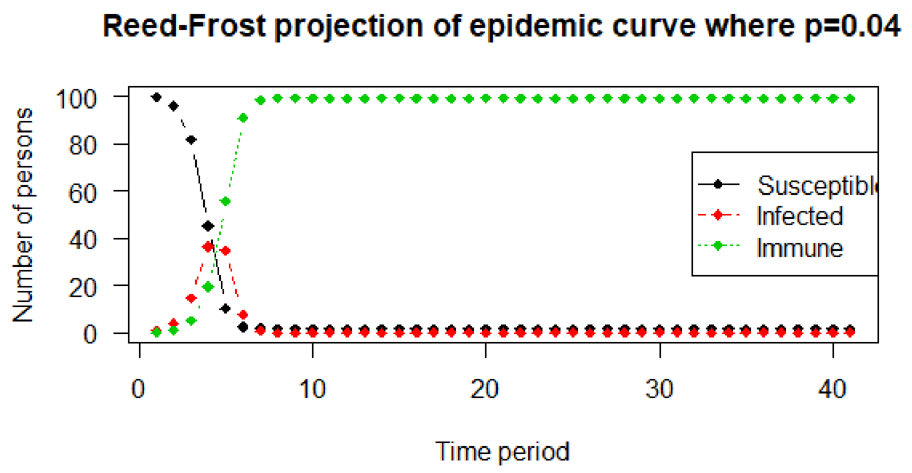
- $dS/dt = -\beta SI + \delta R$
- $dI/dt = \beta SI - \gamma I$
- $dR/dt = \gamma I - \delta R$
- Note: None of S, I, and R can be less than 0. It should be considered in numerical simulation.
- Estimating params
  - β: $\{I(1)-I(0)\}/S(0)$
  - γ: $1/\{\text{mean days of recovery}\}$
  - δ: negligible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

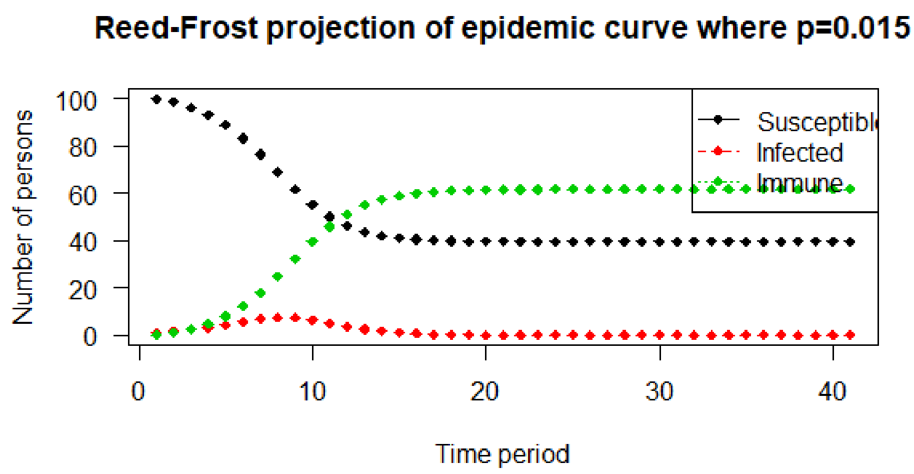
Example: The data in English boys boarding school in 1978



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

COVID-19

- Then, in the end of 2019, novel corona virus, emerged in China, caused epidemic of severe atypical pneumonia there.
- It has quickly spread over the world, pandemic has continued for more than 3 years.

The pathogen of COVID-19

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

- The pathogen of COVID-19 is the 7th corona virus of which host is human, SARS-CoV-2
  - 4 of 7 corona viruses of which hosts are human cause common cold
  - The other 3 are SARS-CoV, MERS-CoV, and currently prevailing SARS-CoV-2 (in early 2020, it has been called as 2019-nCoV). The virus genomes of SARS-CoV and SARS-CoV-2 are the same for 80% of all loci. Among the CoVs of which hosts are bat, the one of which genome is almost 100% similar to SARS-CoV-2 exists.
    - SARS-CoV did host-switch from bat → other animal → human → human
    - MERS-CoV did host-switch from camel → human (→ human)
    - SARS-CoV-2 did host-switch from bat (→ Malayan pangolin) → human → human
      https://doi.org/10.1038/s41586-020-2169-0

The feature of COVID-19

(except for omicron variant)

- Long latent period (median 5 days; Linton et al. 2020 [https://www.mdpi.com/2077-0383/9/2/538]), (for omicron, median 2-3 days)
- Median serial interval was 4 days (for omicron, 2-3 days)
  → Shorter than latent period → About half of infection occurs during latent period (Nishiura et al., 2020 [https://dx.doi.org/10.1016%2Fj.ijid.2020.02.060])
  → Suggests difficulty of contact tracing (asymptomatic patients is difficult to follow)
- 80 % of patients has no or mild symptoms, 20% become severe.
- The risk of severe symptoms / deaths is different by age. Elderly and the people with underlying disease show higher fatality, but young people without underlying disease also suffer from severe symptom and death at non-negligible probability (the paper in Lancet on 24th Jan 2020)
- After hospitalization, it takes about 20 days until recovery or death. (Later, hospitalization period has been shorten.)
- Until mid-2020, vaccine and medicine didn't exist → Respirator or ECMO was needed to rescue severe cases → Fatality largely depends on the medical standard and medical system.
- Early development and implementation of vaccines and medical treatments (especially antibody drugs) contributed to the decrease of fatality, but not enough.

Variants of SARS-CoV-2

- (CDC) https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/variant-surveillance/variant-info.html
- (WHO) https://www.who.int/en/activities/tracking-SARS-CoV-2-variants/
- (Pango Lineage) https://cov-lineages.org/
- (Nextstrain) https://nextstrain.org/sars-cov-2/
- (JAMA) Viewpoint "Genetic Variants of SARS-CoV-2-What Do They Mean?" 9 Feb 2020 https://doi.org/10.1001/jama.2020.27124
- (NEJM) Clinical implications of basic research "Emergence of a Highly Fit SARS-CoV-2 Variant" 31 Dec 2020 https://www.nejm.org/doi/full/10.1056/NEJMcibr2032888
- (Vaccines) "Emerging SARS-CoV-2 Variants and Impact in Global Vaccination Programs against SARS-CoV-2/COVID-19" 11 Mar 2021 https://dx.doi.org/10.3390%2Fvaccines9030243

- RNA virus, easy to suffer from mutation, but mutation is slower than HIV
- **Variant** means the virus with different infectiousness and/or severity due to 1 or more mutation in genotype.
- When mutation causes the change in amino-acid sequence, the epidemiologic nature (infectiousness / severity / immunogenecity) may change.
- (eg.) N501Y is the change of the 501st **amino-acid** from N (asparagine) to Y (tyrosine) in spike protein. Variants may include one or more such changes in amino-acid sequence.
- Variants are named in several different systems
  - Name with country name such as UK variant (though it's not recommended) means the first country reported the variant.
  - Pango Lineage: B.1.1.7, B.1.351, P.1, B.1.617.2, B.1.1.529, ...
  - Nextstrain: 20I (V1), 20H (V2), 20J (V3), 21A/21I/21J, 21K/21L/21M, ...
  - WHO (for VOC): Alpha, Beta, Gamma, Delta, Omicron, ...

Age dependency of CFR (in early 2020)

Age-specific CFRs in Mainland China up to 11 Feb 2020. https://doi.org/10.46234/ccdcw2020.032

	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%

WHO Timeline (until 9 Sep 2020)

https://www.who.int/news-room/detail/29-06-2020-covidtimeline
https://www.who.int/emergencies/diseases/novel-coronavirus-2019/interactive-timeline

31 Dec 2019	First report of unusual cluster of atypical pneumonia to WHO from Wuhan, China
1 Jan 2020	WHO asked China health officials to collect information, IMST started
5 Jan 2020	WHO publicly announced the details of cluster of new atypical pneumonia in Wuhan
9 Jan 2020	WHO announced that the cause of new atypical pneumonia was new coronavirus
13 Jan 2020	In Thailand, imported case from China was first confirmed. WHO opened the protocol of RT-PCR to detect the new coronavirus
16 Jan 2020	Japan's MHLW announced the bus driver case as 2nd confirmed outside China
22-23 Jan 2020	WHO's committee discussed whether PHEIC (Public Health Emergency with International Concern) should be issued or not, but didn't approved
24 Jan 2020	The first case in Europe was confirmed in France
30 Jan 2020	WHO announced PHEIC
13 Mar 2020	WHO secretary general Dr. Adanom stated the change of epicenter from China to Europe
Mar-Apr 2020	Lockdowns were done in many European countries
8 Jun 2020	NZ announced the complete elimination of COVID-19 from the nation
13 Jul 2020	UN predicted potential chronic starvation attacking 130 million in the world until the end of 2020 (in the report of "Food Security and Nutritional Status in the World")
31 Jul 2020	WHO and IHR committee judged the continuance of PHEIC
2 Sep 2020	WHO announced the clinical therapy guidance including evidence-based corticosteriods
8-9 Sep 2020	WHO began to review the efficacy of IHR as a response to COVID-19

Asymptomatic vs severe cases

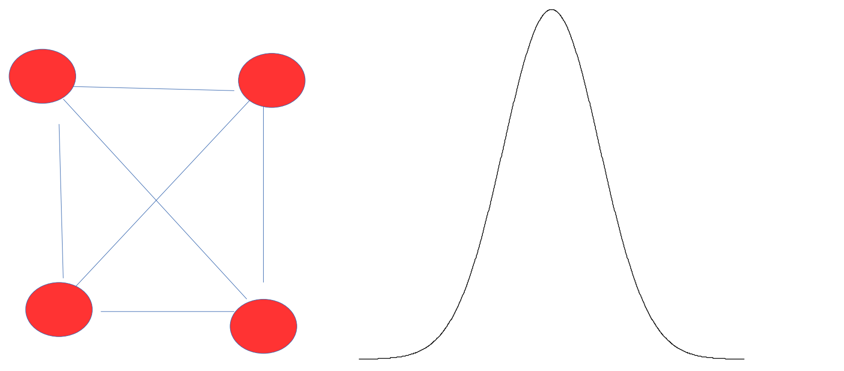
- About 80% of infections cause asymptomatic or mild, 20% become severe.
  - Risks to get severe or to die differ by age. Patients with higher age or underlying disease show higher risk of death. However, young patients without any underlying disease also show considerable risk of death (Lancet paper [https://doi.org/10.1016/S0140-6736(20)30183-5] on 24th Jan 2020 suggested). However, there were many wrong messages.
  - The time from admission to hospital to discharge or death was about 20 days in early 2020. Recently shorter due to the change of discharge criteria.
  - More than 80% of patients show some kinds of symptoms 2 months after onset. (https://jamanetwork.com/journals/jama/fullarticle/2768351, research letter on 9th July 2020, JAMA)
- Large difference in CFR by country
  - Whole body management with respirator and/or ECMO is needed to keep the severe patients alive.
  - CFR is higher in countries or regions with lower medical standard.
  - Public health strategy also differs by country.
- Variants show different infectiousness and/or severity and thus tackling strategy should differ for new variants from previous virus strains.
  - B.1.1.7 (alpha) shows higher risk to get severe in youth than original SARS-CoV-2.
  - B.1.1.529 (omicron) easily infects children and adolescents in schools, very different from previous SARS-CoV-2.

Reproduction Number (R) of COVID-19

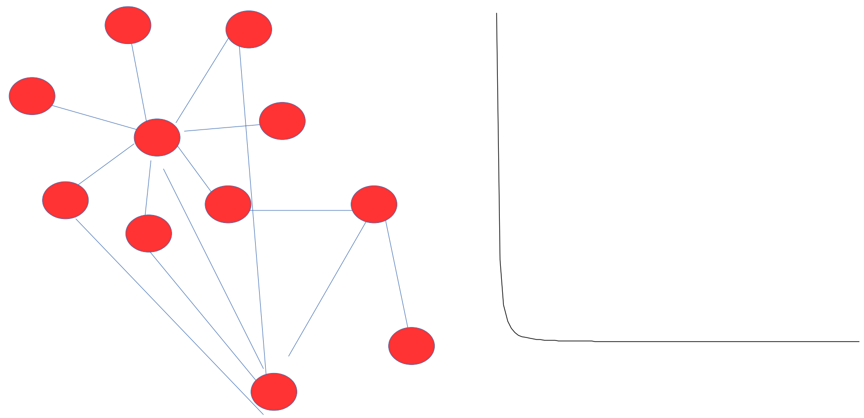
- R <1 means suppression of epidemic.
- R_0 of other infectious diseases
  - Measles (transmission occurs airborne) has 12-18
    (Guerra et al. 2017; https://doi.org/10.1016/S1473-3099(17)30307-9)
  - SARS has about 3 with superspreading events within hospital or airplane.
  - MARS has less than 1 except for nosocomial infection.
    https://www.who.int/csr/disease/coronavirus_infections/risk-assessment-august-2018.pdf
  - Spanish flu has about 2
  - Seasonal / 2009 pandemic flu has 1.1-1.5 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6670001/
- COVID-19 (original) has 1.4-2.5, estimated by WHO based on Wuhan data on 23rd Jan 2020.
  - Much higher estimates: 6.47 (Tang B et al. 2020, https://doi.org/10.3390/jcm9020462)
  - Overdispersion (very large variance of R0 by patients)
    - Grantz et al. [https://hopkinsidd.github.io/nCoV-Sandbox/DispersionExploration.html]
    - Nishiura et al. [https://doi.org/10.1101/2020.02.28.20029272]
    - Bi et al. [https://doi.org/10.1016/S1473-3099(20)30287-5]
    - Hellewell et al. [https://doi.org/10.1016/S2214-109X(20)30074-7]
    - Zhang et al. [https://doi.org/10.3390/ijerph17103705]
    - Althouse et al. [https://arxiv.org/abs/2005.13689]
    - Sneppen et al. [https://doi.org/10.1101/2020.05.17.20104745]
    - Endo et al. [https://wellcomeopenresearch.org/articles/5-67]
- Some variants showed higher transmissibility. Omicron variant has about 2-3, but serial interval is much shorter than original virus and previous variants, and thus doubling time is very short.

Routes of infection (probably both routes below exist)

- Random link route – can be prevented by hand-wash, hygiene, keeping social distance
  - Droplet (airborne): Large droplets from patients reach somebody else by conversation within 2 m
  - Contact: Fomite with droplets from patients has infectiousness for several hours
  - Oral-Fecal: Virus is excreted from patients into feces. Touching something after defecation without hand-wash makes fomite
- Scale-free route
  - Suspended micro-droplets in **3Cs** environment cause cluster infection (super-spreading event)
    - Closed space (poor ventilation)
    - Crowded (high population density)
    - Close contact with conversation
  - Specialists in Japan have focused on this route since February 2020, which led anti-3C campaign by MHLW.
  - Shared appeal by 239 researchers in July 2020 make the possibility of airborne infection popular https://doi.org/10.1093/cid/ciaa939



Random link = equal probability for all



Scale free = super-spreading events

The purposes and performances of various testing

- Presumption in 2020:
  - No perfect testing
  - Even if the infection is detected earlier, effective initial treatment to prevent getting severe or death is not established
- Situation slightly changed since 2021: Effective initial treatment has gradually been established
- The performance of testing is usually assessed by the combination of sensitivity and specificity.
  - To calculate the sensitivity and specificity, the test results must be obtained from the patients and non-patients who are already diagnosed by the gold standard method
  - In COVID-19 testing, RT-PCR is the gold-standard and thus it's impossible to assess its performance
- RT-PCR: Detecting the amplified the 2 RNA sequences which are specific for SARS-CoV-2. As already mentioned, gold standard method. But getting naso-pharyngeal swab or saliva can fail to pick the viral RNA from patients, and thus one-time testing's sensitivity is 80% [https://doi.org/10.7326/M20-1495], specificity is almost 100% (at least 99.99%), but there are false-positive cases due to the errors in labeling samples or contamination
  - Nasal swab and pharyngeal swab: Used from Jan 2020. Healthcare professionals face the risk of infection at the time of sampling
  - Saliva: Self-sampling is possible. It can be kept for several hours at room temperature
- Antigen test of naso-pharyngeal swab or saliva using immunochromatography: Purpose is same as RT-PCR. On-site rapid testing is possible, but the performance such as sensitivity and specificity (largely varies by the kit) is poorer than RT-PCR.
- Antibody test of serum using immunochromatography or ELISA: Purpose is to know the past experience of infection. Antibodies remain for several months after recovery, but it gradually increases after infection and does not exist just after the infection. Not suitable to detect the current infection. Among 2 types of antibodies, IgM can develop soon, IgG later.

When RT-PCR should be applied

- (A) When doctor judged the needs of confirmatory diagnosis based on clinical examination showing high possibility of infection such as pneumonia.
  - Definitely needed. If confirmed, the patients have to be hospitalized and carefully monitored to apply respirator or ECMO when the symptoms become severe.
    - Recommended by WHO since early 2020. In Japan, about 300 patients could not get this testing during 3 weeks in March 2020. In January 2022, many symptomatic people could not get any diagnosis/treatment by physician due to rapid increase of new cases of the 6th wave of epidemic.
- (B) Testing the people who contacted with patients proved by contact tracing
  - To prevent the spreading from presymptomatic patients by isolating them.
    - Recommended by WHO since early 2020.
    - Some countries did, but others could not do so.
    - When the new cases increase too rapidly, this testing become impossible due to capacity limit of contact tracing.
  - Some papers recommended isolation of symptomatic people with close contact before testing. It's effectively preventing the spread, shown by the result of mathematical models.
- (B') Many papers recommended frequent testing of the healthcare workers who have high risk of infection. (eg. https://www.imperial.ac.uk/mrc-global-infectious-disease-analysis/covid-19/report-16-testing/)
- (C) Area-wide screening or widely available free testing
  - If prevalence is very low, positive detection proportion is very low. If the situation becomes more or less endemic (prevalence becomes high), widely available free testing is desireble.
  - Because of imperfect sampling efficacy, there remains the possible false-negatives and thus it's not recommended as screening measure.
  - For early isolation for presymptomatic patients to prevent the spread from them, conducted in many countries, since early 2020, such as Iceland, China, South Korea, Germany, some states in USA, etc. (Japan has never done until late 2021)
  - China conducted this in some cities (eg. 10 million in Wuhan) to confirm the elimination (though temporarily)

Effectiveness of Digital Contact Tracing

- 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
  - 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.
  - Apple and Google cooperated to develop API to keep proximity information using Bluetooth without location/privacy as well as Trace Together, equipped in iOS and Android. They allowed each country to develop only one application using this API.
    - Very early application releases were done by Australia and Switzerland.
    - UK once developed their unique application and provided it for the public at GitHub, but due to the less performance, gave up it and moved to Apple/Google API.
    - Germany developed an application to use Apple/Google API at GitHub platform.
    - **Japan released COCOA in June 2020**, which was linked with the national patient database called "HER-SYS", specially developed for COVID-19. **However, the registration of the COVID-19 patients to HER-SYS was delayed and incomplete, and additional man-power in health center was required for manual contact tracing from patients and high-risk people with close contact**. In addition, there were **many bugs** in COCOA, so that it wasn't effectively working.
- According to the paper by Fraser et al. (Ferretti et al., 2020 [https://science.sciencemag.org/content/368/6491/eabb6936]), "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, too.

Needed epidemiological studies, suggested in early 2020

- 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

How to tackle COVID-19

- Human's **technology** against infectious diseases
  = Preventive medicine (vaccine and Non-Pharmaceutical Interventions [=NPIs])
  + Medical care (effective drug to cure and life-saving treatment)
- Against emerging infectious disease, at least during early days, there is no vaccine nor effective drug to cure
  → Human can do nothing but the NPIs and the life-saving treatment
  → Life-saving treatment such as respirator and ECMO is hardly available in LMICs.
- For COVID-19, development of effective vaccines and drugs succeeded very early.
  - Efficacy of mRNA vaccines was very high. Especially hospitalization and death could be prevented more than 90% by 2 doses. However, significant loss of immunity occurred after half year and thus 3rd (booster) dose is promoted. Immunity against omicron variant was relatively poor.
  - There are some drugs to prevent symptoms, getting severe and death and/or to shorten hospitalization, but efficacy is not so high. Injection of antibody-based drugs shows relatively higher efficacy, but expensive and not perfect.
- NPIs include **behavioral changes** by **language** and **social organization**
  - Decreasing the chance of face-to-face contact
  - Lockdown
  - Remote working
  - "New normal"s such as always wearing face-mask, frequent hand-washing, ...

Behavioral changes as NPIs

- Since 2007, US-CDC stated the necessity of NPIs as community mitigation measure under pandemic situation. NPIs can reduce reproduction number and the peak height of epi-cuve and postpone the peak timing. By doing so, CDC aimed to prevent the number of patients exceeding the medical capacity.
- **The report No.9 from Imperial College of London** examined the effect of various NPIs on COVID-19 using micro-simulation model. [https://www.imperial.ac.uk/media/imperial-college/medicine/sph/ide/gida-fellowships/Imperial-College-COVID19-NPI-modelling-16-03-2020.pdf]
  - Predicted epi-curves were compared among several NPIs such as the mitigation strategy by weak restriction of behavior such as school closure and the suppression strategy by stay-at-home and lockdown (of city functions such as public transportation)
    - School closure itself was not effective. However, it may be effective against omicron variant.
  - Any mitigation strategy led to the rapid increase of patients exceeding the capacity of medical care. In the second wave of epidemic, many patients will die by the lack of medical care.
  - To prevent the large number of death due to the lack of medical care, repeated application of suppression strategy was inevitable.
  - The most difficulty was the decision of when suppression can be lifted.
- The timings of lifting suppression varied by country.
  - Only after no newly reported cases continued for several days, lift the suppression: China, NZ, Taiwan
  - Soon after daily new cases decreased to the level within medical treatment capacity: USA, Europe, Japan, ...
- Behavioral restriction partly violates basic human rights and gives damage to economic activities.
  → Compensation for economy is needed
  → Comprehensive prediction based on several scenarios is required
- Public health specialists should address such comprehensive intervention policy. Specialists in Taiwan and NZ did so. Advisory committee (as the representative of specialists) in Japan didn't.

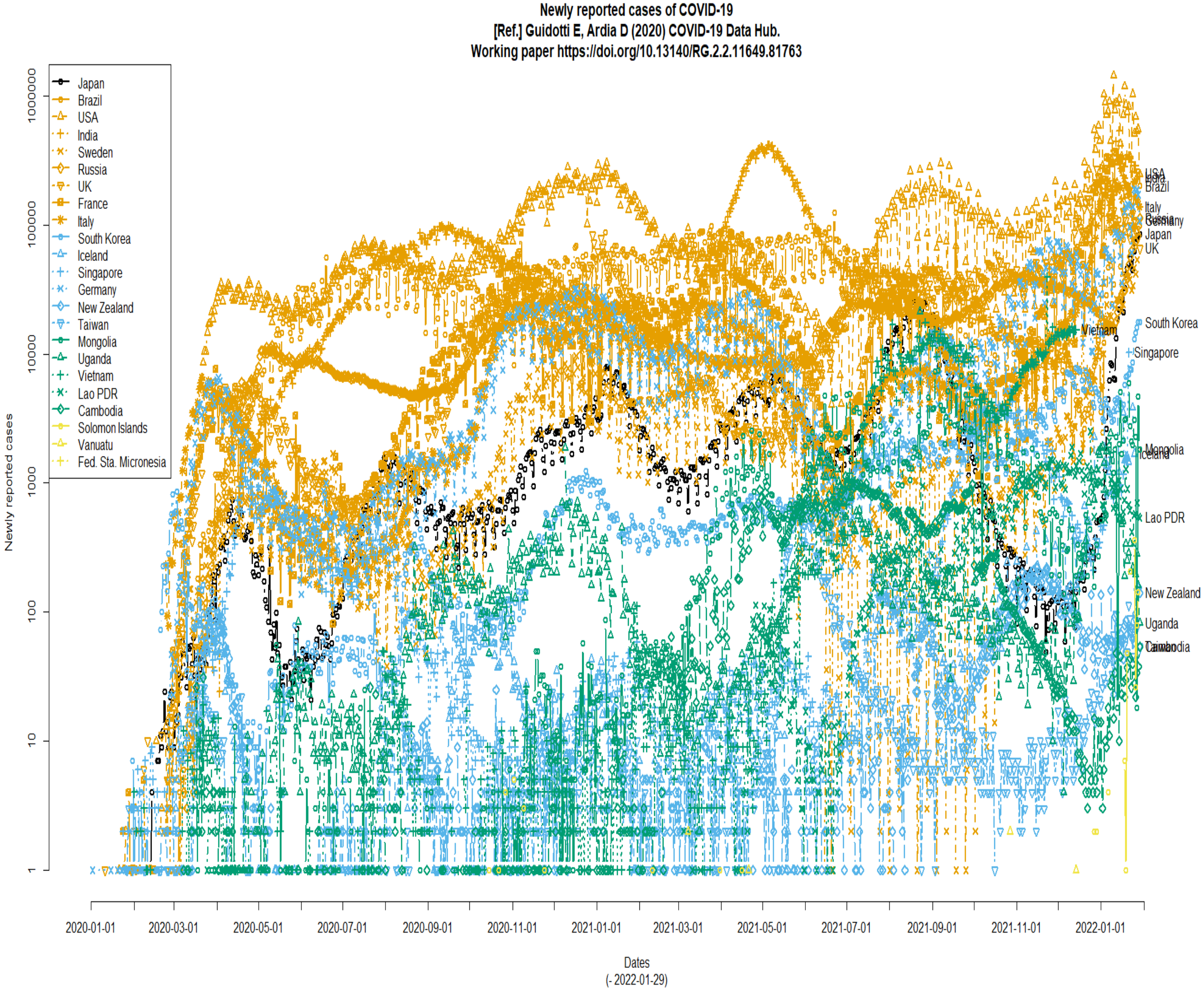
What kind of factors may determine governmental responses?

- **Age structure**
  - LMIC shows lower IFR than HIC, because the proportion of youth population is high.
  - HIC is aged, so that IFR tends to be high even though the medical standard is high.
- **The extent of avoidance of economic restriction by the government**
  - Under the government which does not want to restrict economic activities, testing, isolation, treatment, contact tracing, behavioral restriction and quarantine are suppressed.
  - Taking responses such as testing **requires materials and equipment, which costs much**.
  - Taking responses affects the mental and socio-economic aspects, to inactivate socio-economic activities.
- **The extent of social gap**
  - Poor people living in slum and ethnic minority are vulnerable (less immune against invading pathogen and inaccessibility to medical care)
  - If the government focuses less on social justice, response against pandemic becomes inactive.

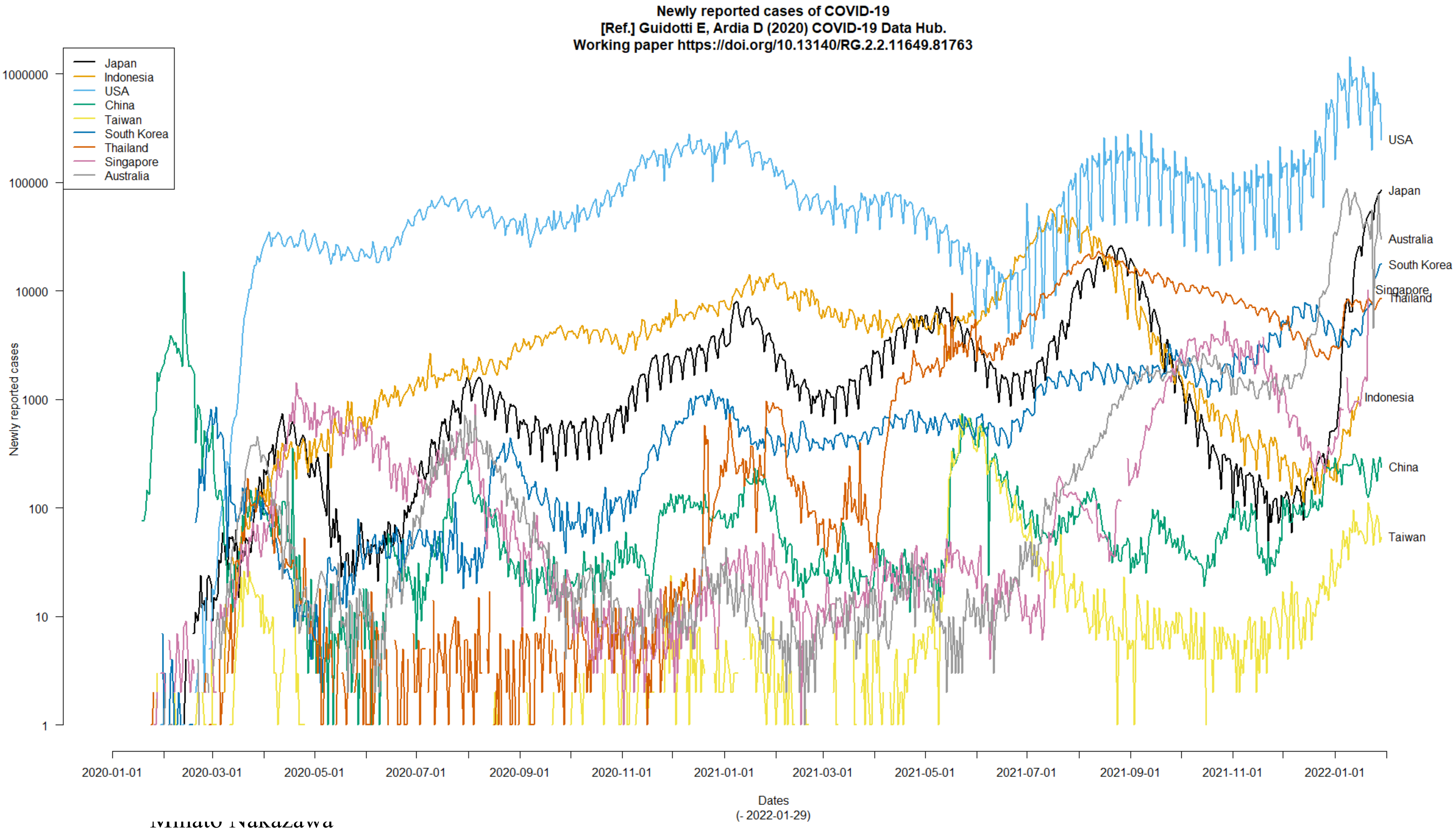
- The responses by LMICs tend to be polarized to either of the following 2 strategies
  - (L-strategy) Less restriction on economic activity, let the infection expand to establish early herd immunity. If the age structure is young and there are many competing causes of death, the IFR by COVID-19 may be socially acceptable.
  - (P-strategy) Due to lack of the life-saving medical facilities such as respirator and ECMO, the government strictly conducted quarantine and border control to prevent the invasion of pathogen totally since very early stage of pandemic. → Succeeded in Polynesian and Micronesian countries. Especially FSM's cumulative number of patients is still zero.

Changes of newly reported cases for selected countries by 5 strategies

- **Japan (black)**: NPIs with special emphasis to prevent 3Cs. Suffering 6th wave now.
- **Less controls (orange) = L strategy**: Only if the newly reported cases exceeds the capacity of medical facility, conduct strong NPIs including lockdown. Vaccination started earlier but coverage was not so high → Brazil, USA, India, Sweden, Russia, UK, France, Italy, ...
- **Middle level controls (light blue)**: Based on extensive testing and contact tracing, early isolation introduced, followed by lockdown if necessary → Germany (insufficient isolation and quarantine), South Korea, Iceland, Singapore, New Zealand and Taiwan (early lockdown until suppression)
- **Strong controls (green)**: Similar testing-based isolation and lockdown were done earlier → Mongolia, Uganda, Vietnam, Lao PDR, Cambodia
- **Strongest controls (yellow) = P strategy**: Preventing invasion by rigid quarantine and border control → Solomon Islands, Vanuatu, FSM, ...



Changes of newly reported cases in several Asia-Oceania countries and USA



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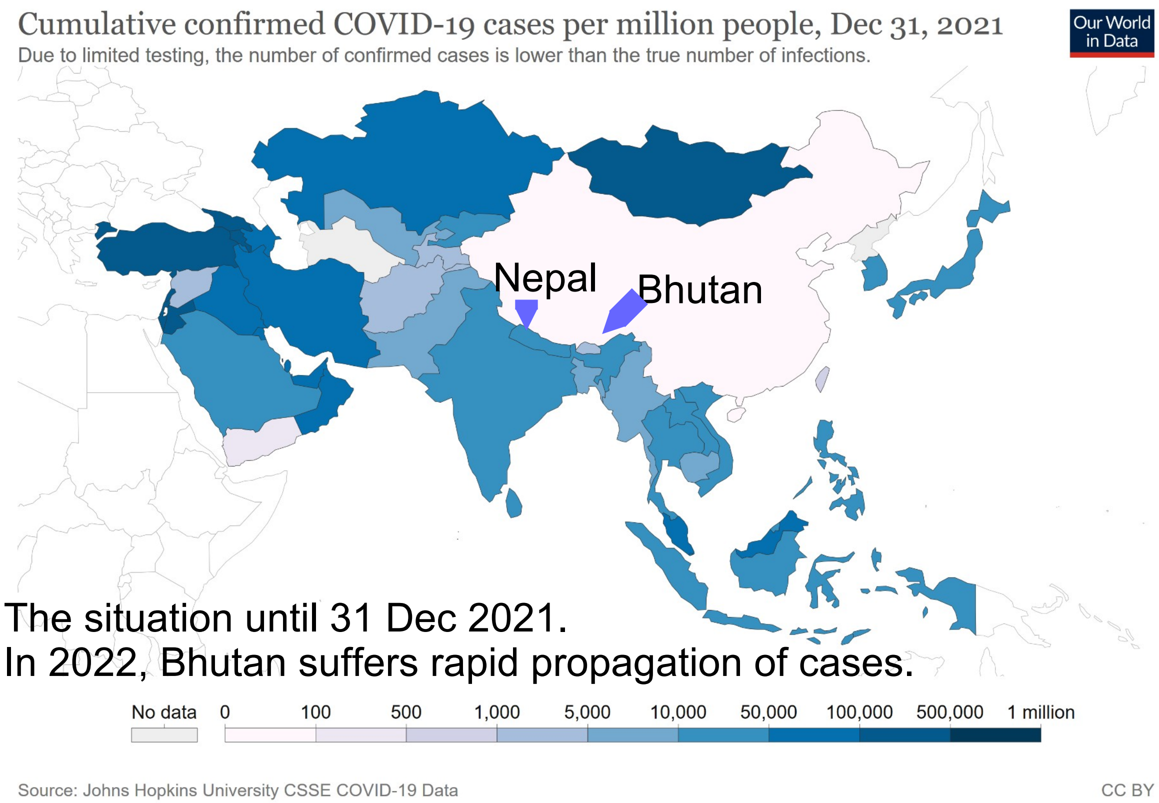
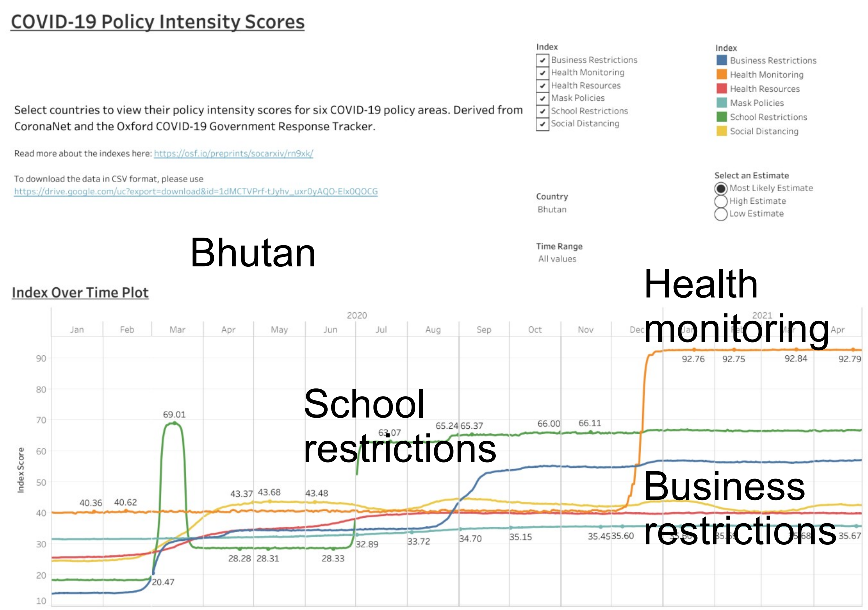
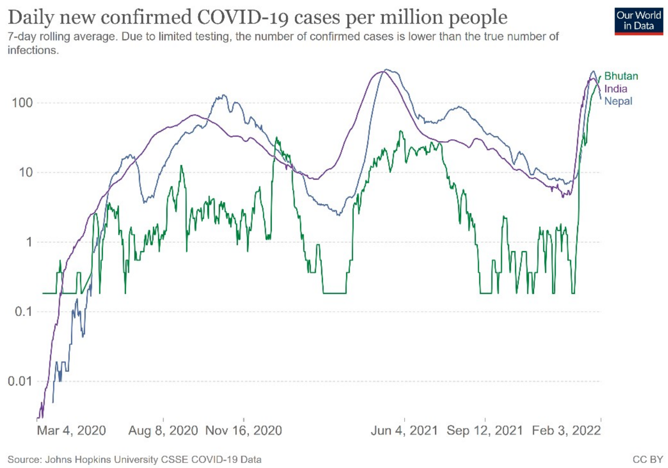
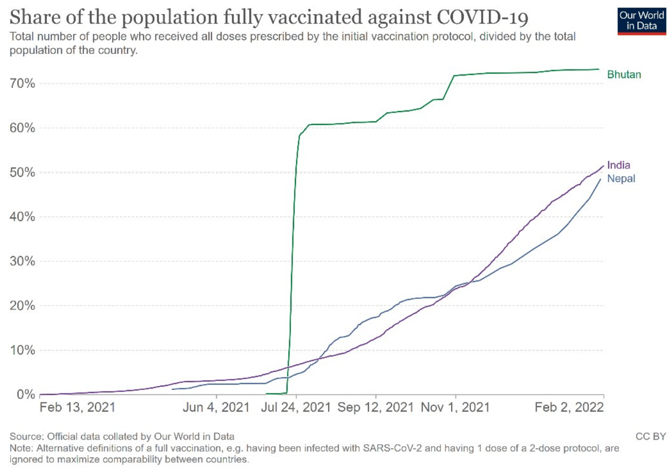
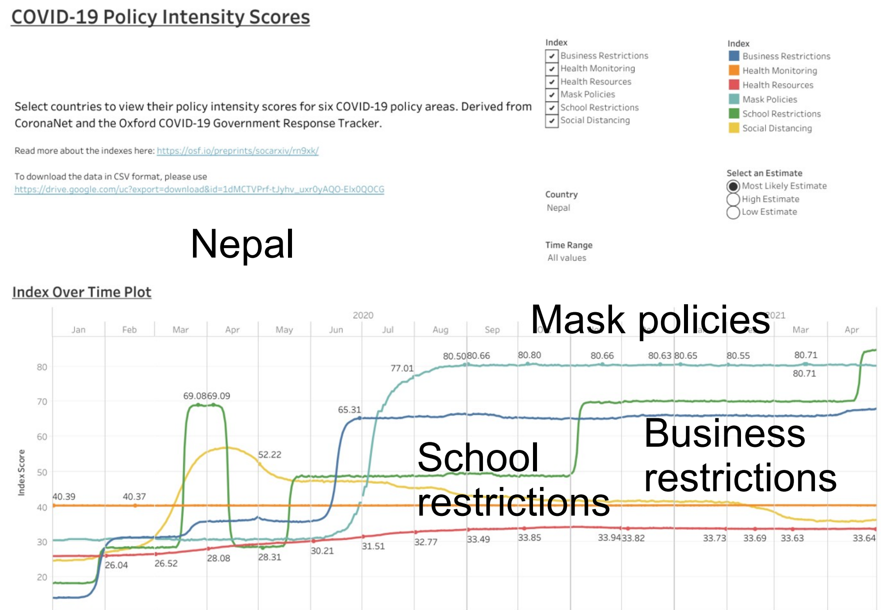
Comparison between Bhutan and Nepal



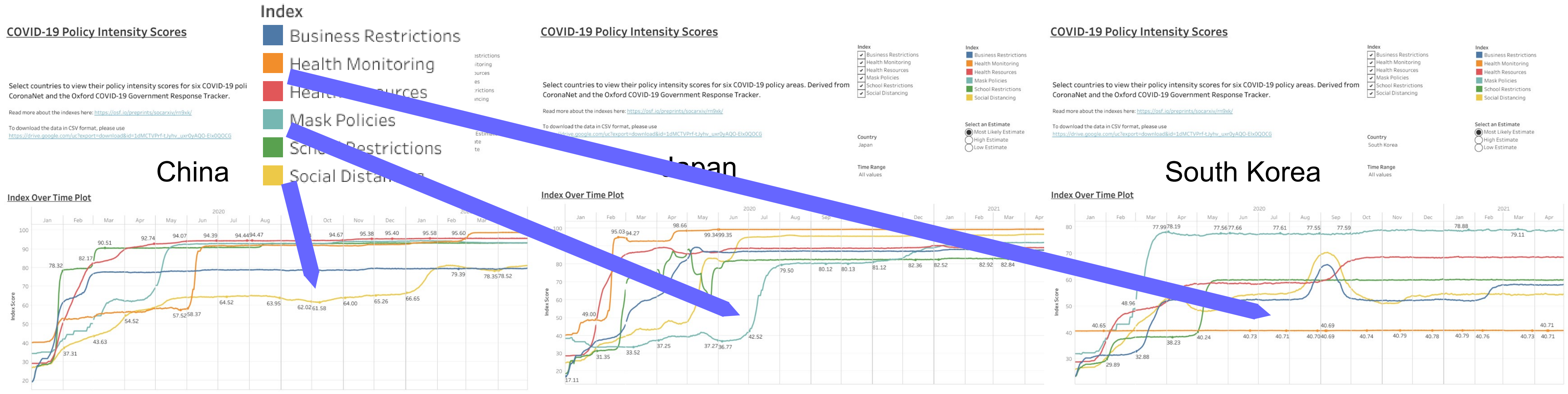


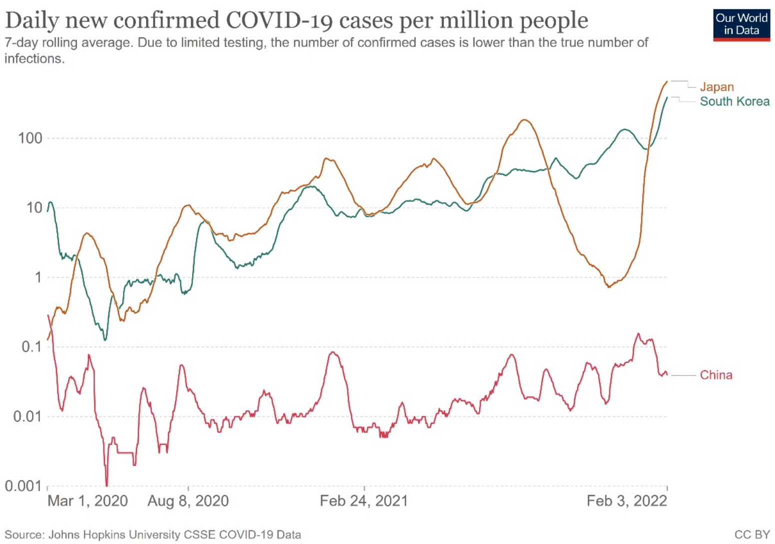


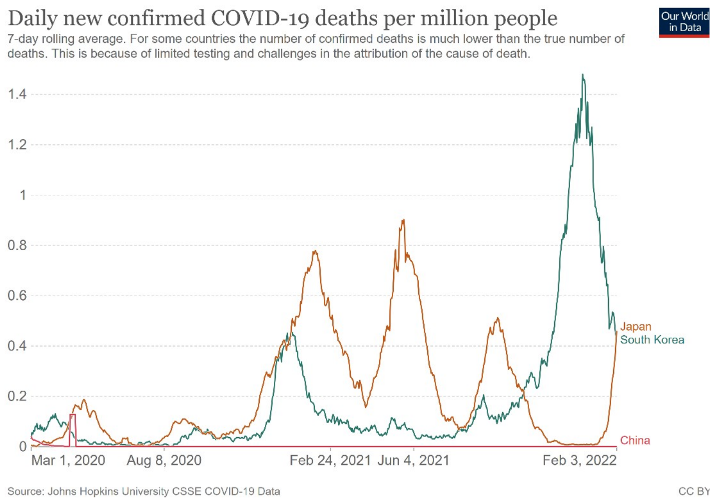


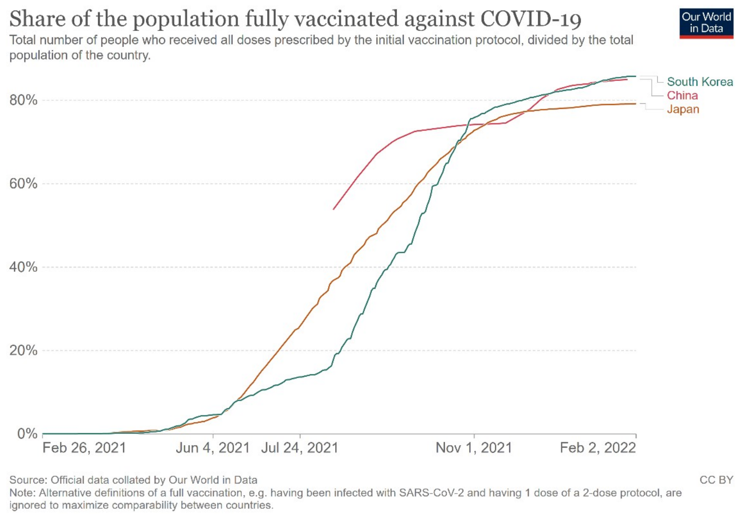


Comparison among China, Japan and South Korea (NPIs until Apr 2021)









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The reason why the spread of COVID-19 was so slow in East Asia (personal view)

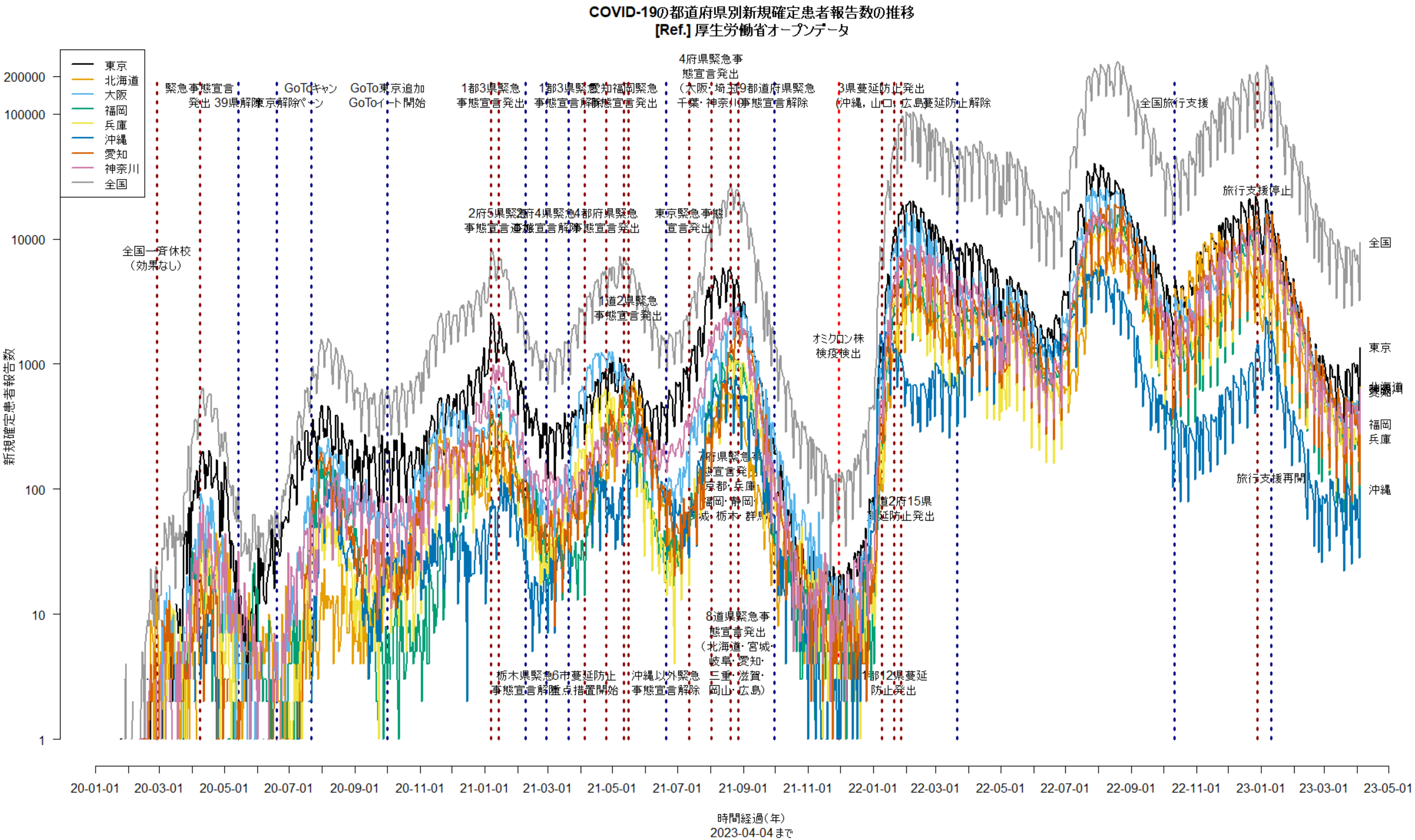
- Infection via random link route may occur from a primary case to 0-2, at most 3.
  - East Asian countries including Japan culturally had longer inter-individual distance (wider personal space). Greetings is not done by handshake, kiss and hug, but by bow and nodding.
  - Relatively rich water resources contributed to establishment of hand-washing habits using soap.
  - In Japan, the importance of handwashing was emphasized since January 2020.
- Due to the 3 reasons shown above, the number of transmission from primary case to secondary cases is mostly 0 or 1 in East Asia, but mostly 1 or 2 in Europe or USA.
- Average of "0 or 1" is less than 1, but average of "1 or 2" is more than 1, which differentiates epidemic. The former shows $R < 1$ and the epidemic will shrink, but the latter shows $R > 1$ and the epidemic will continue to spread.

- Western countries asked people to keep inter-individual distance larger than 2 m since Spring 2020, to reduce R.
- In addition, Japan and Malaysia did campaign to avoid 3Cs situation to prevent the occurrence of cluster infection (super-spreading events).
- There were many countries in East Asia to suppress by strict quarantine and/or by doing contact-tracing and isolation.
- Taiwan succeeded containment and suppression due to testing, isolation and quarantine.

The 9 waves of epidemic curve in Japan

- IHR 2005 states the importance of minimizing the effect of response on global traffic and trade.
- Originally "wave" refers the sudden increase of patients from imported cases.
- The very first wave is often ignored now. It was originated in the traveler from China to Japan in January to February 2020, and was suppressed by the anti-cluster campaign. It was confirmed by genotyping of virus.
- So-called **1st wave** occurred in late March 2020 by many return migrants from Europe and USA.
  - Prof. Oshitani stated the reason of rapid increase of untraceable patients was hidden cluster. He judged that contact tracing and isolation were impossible. → Specialists committee suggested issuing emergency condition statement.
    - Emergency call has been issued since 7th April 2020. The government requested to reduce face-to-face contact by 80%.
    - The imported cases from Europe and USA were too large to suppress by anti-cluster measure, which led to the first wave.
- The essential problems in anti-cluster measure
  - Prohibiting the most business activities with compensation may be possible, but some essential workplaces such as hospital and care facility have to continue, in which avoiding 3Cs is almost impossible. Such workplaces showed many cluster infections.
  - Long-lasting mild suppression of behavior without compensation is impossible for human-being. Rather short-term strict suppression with compensation seems better.
- The **2nd wave** occurred in July-August 2020. Lifting of emergency statement for the 1st wave was done after successful suppression in most prefectures, but lifting was in much earlier stage in Tokyo, led to relapse with additional imported cases from Europe and USA.
- Due to lifting the restriction of immigration since October 2020, "GoTo" campaign, especially "go to eat", lifting the restriction of mass-gathering events, and other factors, the number of daily new cases suddenly increased since October 2020, which led to the **3rd wave** in winter 2020-2021, the management of medical systems faced the risk of collapse.
- The **4th wave** occurred in spring 2021, the **5th wave** occurred in summer 2021, largely due to the delta variant and Tokyo Olympic. From September to December 2021, suppression continued, but largely due to the invasion of omicron variant, the **6th wave** has come to Japan in January 2022. After that, 7th and 8th waves attacked. Now 9th wave happens to start.
- But actually since 2022, Japan entered into endemic phase.

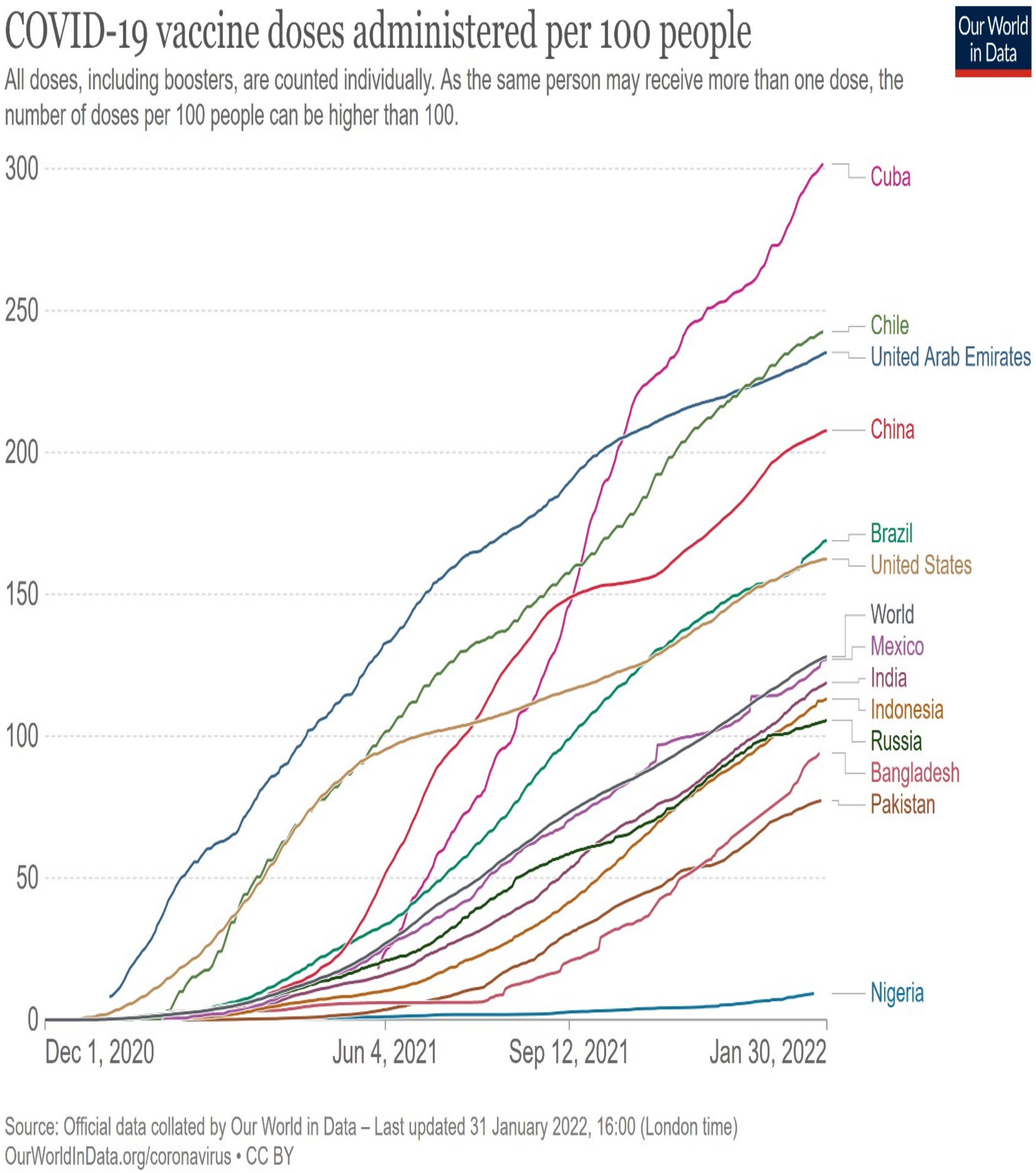
Changes of daily new reported cases by prefectures in Japan (Red: preventive NPIs, Navy: lifting)

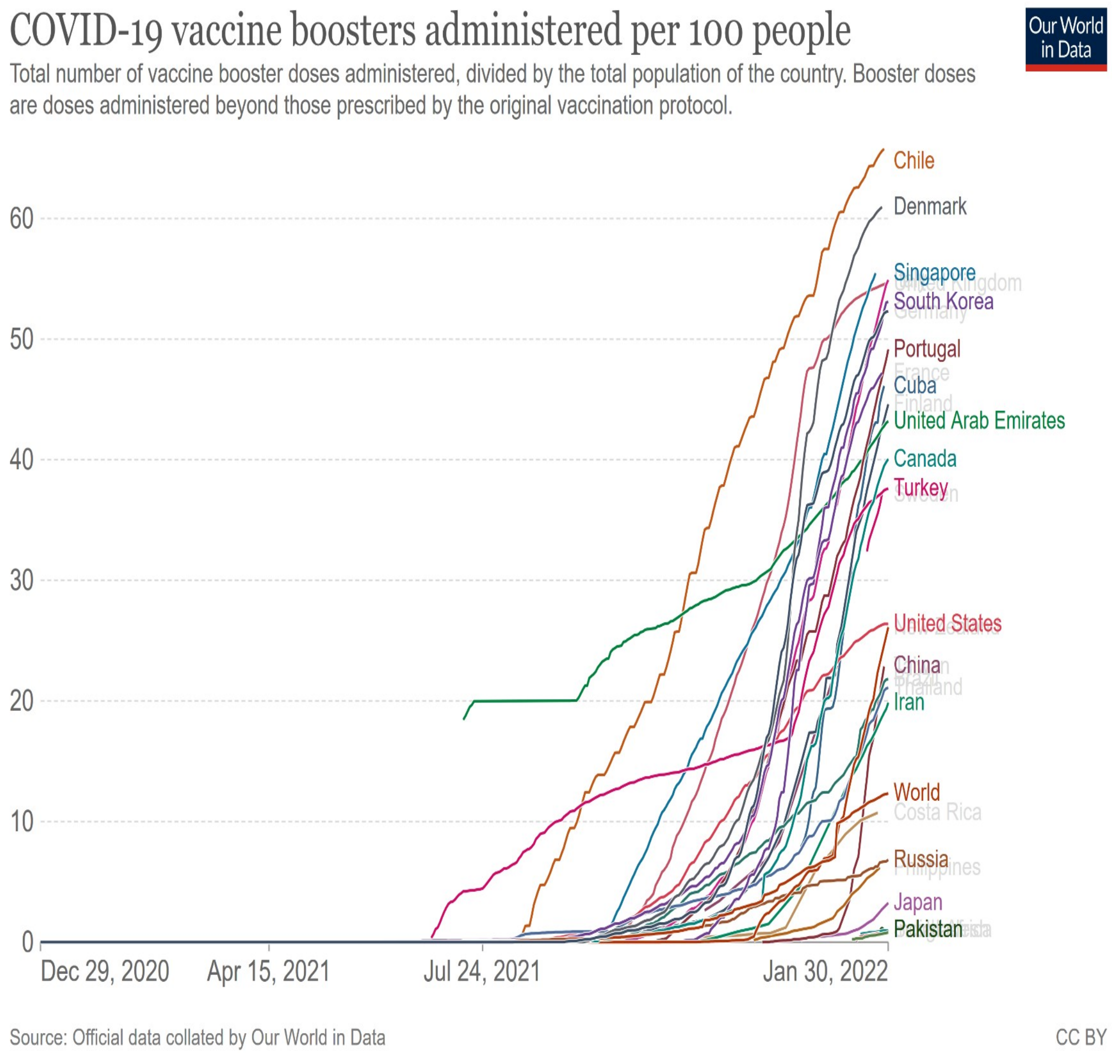


Behavioral restriction should be continued until elimination as "new normal"

- The government has to establish the infrastructure to enable remote working.
- Mass gathering events should be restricted. Especially with close contact or conversation.
- Needed behavioral change
  - To prevent infection from oneself
    - If feel ill, never go out. Test if past close contact with patients and/or suspicious symptoms such as the body temperature being higher than 37.5 degree C or SPO_2 being less than 90%
    - **<u>Conversation should always done with face-mask even asymptomatic.</u>**
      - To the contrary, mask is not necessary in outside, keeping quiet, and no symptom.
  - To prevent random link infection
    - Frequent hand-washing with soap or sterilization of hand by alcohol
    - Keeping inter-individual distance more than 2 meters
    - Avoiding face-to-face conversation without mask
  - To prevent cluster infection events
    - Avoiding 3Cs
    - Ventilation. To check the extent, monitoring CO2 levels is useful https://doi.org/10.1021/acs.estlett.1c00183
    - https://www.who.int/docs/default-source/coronaviruse/getting-workplace-ready-for-covid-19.pdf
- Never stigmatize the infected patients
- Almost all behavioral restriction can be lifted after elimination, except for border control, quarantine and surveillance
- **<u>This is the challenge: Can human adapt to new biological environment by establishing the new normal through social organization, language and technology?</u>**

Vaccination: Once effectively suppressed pandemic, but omicron variant broke the protection





Using language adequately, act against infodemic

- Enormous amount of information filled the world by the globalization of information network with multichannel
  - For lay people, it's very difficult to judge correctly what is the right information
  - Some politician intentionally spread wrong information
- WHO has the website for infodemic management https://www.who.int/teams/risk-communication/infodemic-management/
- The Editorial of *Lancet Infectious Diseases* stated very important thing ("The Covid-19 infodemic" https://doi.org/10.1016/S1473-3099(20)30565-X, 17 July 2020)
  - "… sometimes deliberately misleading reactions, such as those of US President Donald Trump or Brazilian President Jair Bolsonaro. Such miscommunication is not helped by mass media, which are often guilty of favouring quick, sensationalist reporting rather than carefully worded scientific messages with a balanced interpretation. The outcome is erosion of public trust and a sense of helplessness, the perfect conditions for the spread of harmful misinformation that begins a vicious circle"
  - "Although we have long worked with authors and media outlets to create factually correct, unbiased stories fit for public consumption, perhaps now is the time for a more proactive response. Journals (including this one) should consider actively countering misinformation about themselves and the work that they publish."
- The Editorial of *New England Journal of Medicine* stated ("Dying in a Leadership Vacuum" https://www.nejm.org/doi/full/10.1056/NEJMe2029812, 8 Oct 2020)
  - "Our current leaders have undercut trust in science and in government, causing damage that will certainly outlast them. Instead of relying on expertise, the administration has turned to uninformed "opinion leaders" and charlatans who obscure the truth and facilitate the promulgation of outright lies"
- Fact check is very important, but it's difficult for lay people.
- To revive the trustworthiness of scientific information, regular polite explanation from the single responsible authority is effective, as done in NZ and Taiwan.