Infectious Disease Epidemiology and Mathematical Models

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  （注）ただしギセックは数理モデルの利用に対して否定的
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What is human infectious disease?

- From the perspectives of ecology, “infectious disease” is a kind of **parasitism** among the 3 types of symbiosys (mutualism, commensalism and parasitism), as one of the inter-species relations.
- Parasites’ survival and reproduction depend on host’s life.
- Dependency on host differs between macro-parasites (which live outside of host cell) and micro-parasites (which live within the host cell)
- Host-parasite co-evolution
  - Gene frequency of malaria-resistant genotype is high in malaria endemic regions
    - High thalassemia prevalence in Mediterranean region
    - High sickle-cell anemia prevalence in Sub-Saharan Africa
    - Interacting with dietary habits: Gene-culture co-evolution
  - Hypoferremic adaptation hypothesis: In malaria endemic region, intra-body distribution of iron shifts from circulating iron in sera to iron storage in liver, which causes hypoferremia, making malaria proliferation difficult. Host having such genetic characteristics more survived so that gene frequency of lower serum iron has become higher.

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)

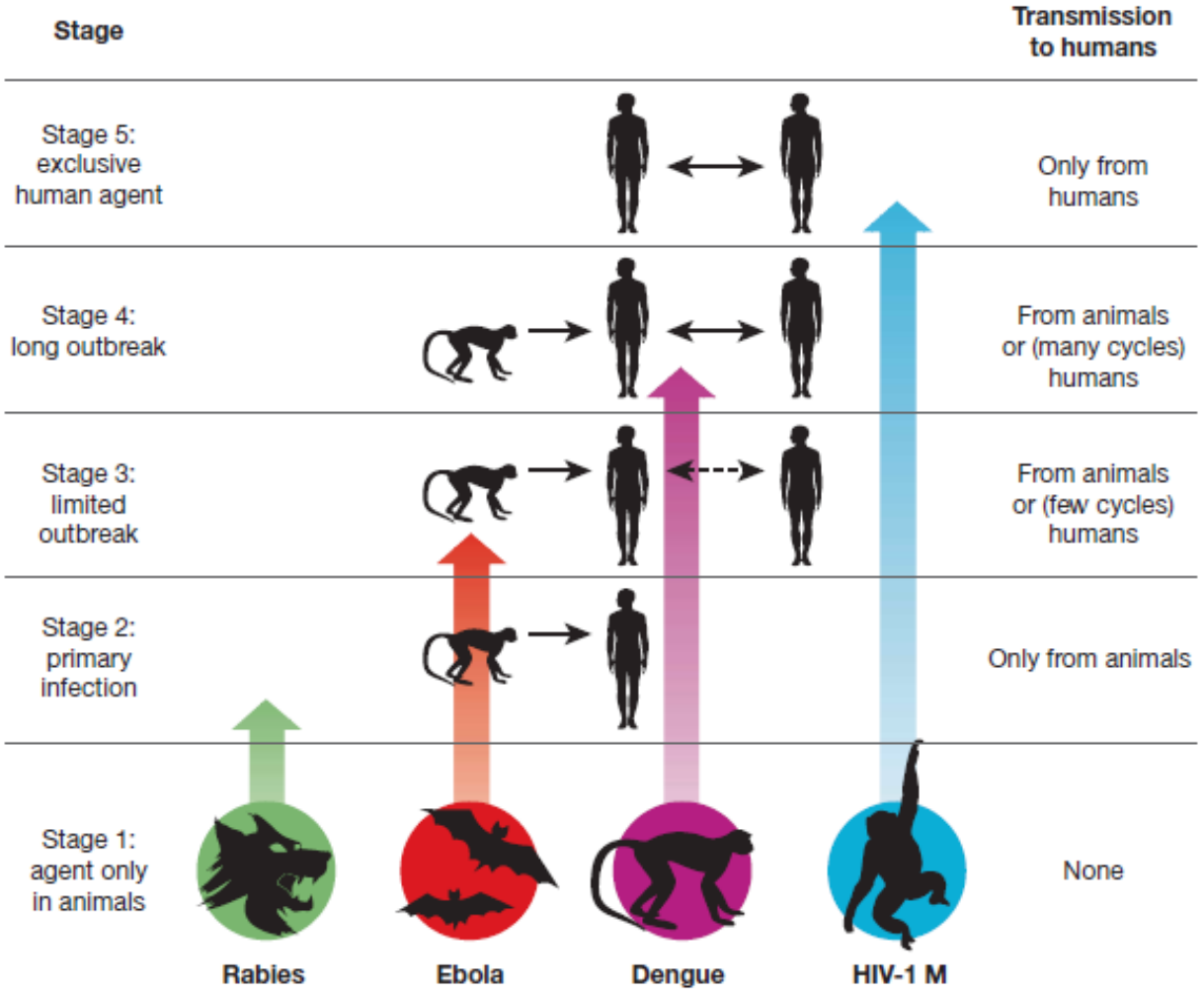


Figure 1 | Illustration of the five stages through which pathogens of animals evolve to cause diseases confined to humans. (See Box 1 for details.) The four agents depicted have reached different stages in the process, ranging from rabies (still acquired only from animals) to HIV-1 (now acquired only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

Approaches in infectious disease epidemiology

- When somewhat new infectious disease occur somewhere,
  - First of all, **case definition**: What conditions are needed to identify that disease?
    - 3 principles of Henle-Koch (But many exceptions)
    - Based on clinical symptoms (Suspicious, Possible, Confirmed)
  - Accumulation of case reports
  - Searching possible causes
    - Finding common exposure for cases
    - Identifying pathogenic microorganism
    - Decision of confirming diagnosis method
  - Description and review of frequency and distribution
    - Drawing **epidemic curve**
    - Drawing **epidemic map**
  - Searching the risk factor of infection
    - Identifying the **route of infection (route of transmission)**
    - Active case detection (if direct transmission, contact tracing)
    - Estimating prevalence in group level by **seroepidemiology**

Chorela study in 19C London (1)

- Many severe diarrhea cases occurred in the Broad St., Soho in London, in 1854. During 24 hours from 2nd to 3rd September, 70 cases died. At that time, major etiology for diseases like cholera was direct contact with patients or miasma (evil air).
- **John Snow**, already known as famous anesthetist, lived close to Soho. He has already read the report of cholera epidemic in 1848. The report showed the physician did not get sick though spending several hours besides the patients (who had severe diarrhea, shared the same air with the physician). Snow concluded that direct contact nor miasma did not cause cholera infection. Considering that the 12 cholera cases died in late July in 1849, who lived in the Surrey Buildings and shared the same well, and that nobody died in the next building where the well was different, Snow hypothesized that cholera transmits by drinking water contaminated with patient's excretes.
- **William Farr**, Public Health Authority of London city, suggested alternative explanation for Snow's observation. The place where more cholera patients are reported locates lower than general, suffering from bad air. Negative correlation between mean altitude of living of parishes and number of cholera death per parish suggested the correctness of miasma theory.
- Then, Snow conducted the following 2 studies, which **epidemiologically** proved that **something** (finding of cholera bacteria by Koch was 1883) contained in drinking water caused cholera.

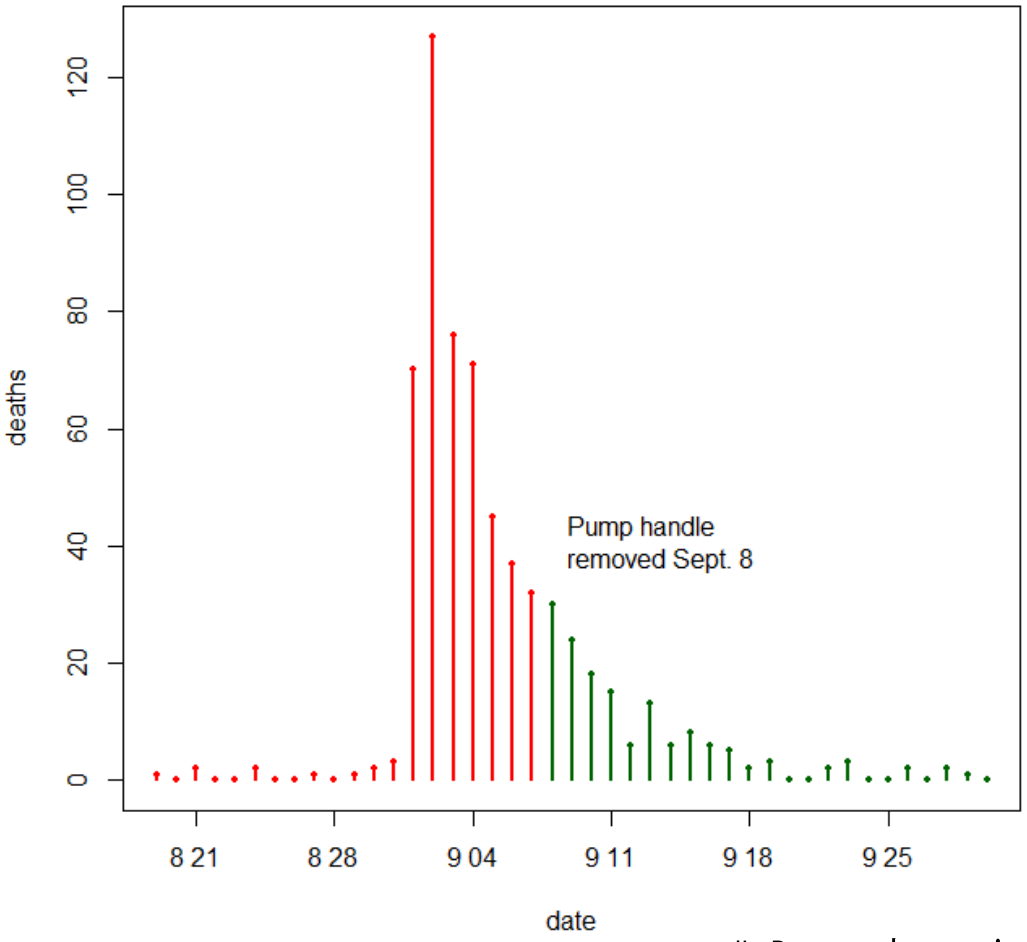
Cholera study in 19C London (2)

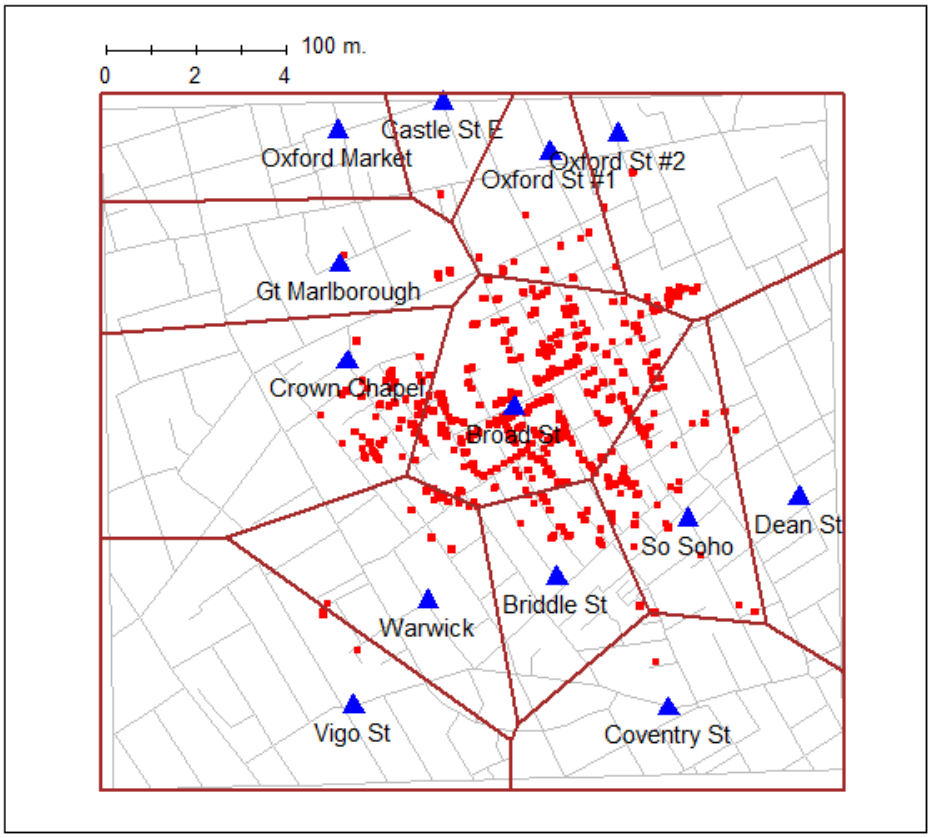
- Natural experiment
  - In the south bank of Thames river, most residents purchased piped water to drink. In 12 parish, all houses purchased drinking water from S&V company, in 3 parish, all houses from Lambeth company, but in remaining 16 parishes, water pipes were connected in complex manner, and thus a house purchased water from S&V and the next house from Lambeth, where those neighborhood houses are almost same only except for water supply company.
  - Among several water supply companies, S&V company fetched source water from Battersea, downstream of Thames river, but Lambeth company fetched source water from Thames Ditton, upstream.
  - Snow visited every houses to get the drinking water and found that the water from S&V included 4 times higher concentration of salt than Lambeth, and thus could identify the water supply company for each household.
  - The numbers of death by cholera were 4,093 among 266,516 residents who purchased water from S&V and 461 among 173,748 residents purchasing water from Lambeth. The risk of cholera death was 5.8 times higher in the people drinking S&V water than in the people drinking Lambeth water.
    - It suggested something causing cholera was added to the Thames river water in London city.

Cholera study in 19C London (3)

- Epidemic map
  - People in Soho mainly used tube well water, and thus Snow fetched tube well water around Soho.
    - The water from Broad St. pump was clean. No microorganism was found. (Probably fetching water was too late.)
    - Half of cholera victims in Soho in 1854 summer lived the houses where Broad St. pump was visible. Most of remaining victims lived one or two blocks apart from such location, 4 victims lived in Cross St. drank the water from Broad St. pump on the way back from school.
    - On the other hand, none of hundreds people in St. James bedehouse in Broad St. and none of workers of Lion brewery died by cholera. People there drank safe piped water or their own well's water.
  - Plotting each cholera victim as stacked thick bar at one's house on the map with the plot of pumps, concentration of cholera victims around Broad St. pump was clearly shown.
  - In addition, the nearest (reachable within the shortest time) pump from each house was identified. From 13 pumps as bases, the houses share the nearest pump were surrounded by the curves: Voronoi map. The area including Broad St. pump had the highest number of cholera victims.

Cholera study in 19C London (4)






```
# Draw these in R
# if not installed yet,
# install.packages("HistData", dep=TRUE)
library(HistData)
example(Snow)
```

O-157 outbreak in USA

- Cieslak PR et al. "Hamburger-associated *Escherichia coli* O157:H7 infection in Las Vegas: A hidden epidemic." American Journal of Public Health, 87(2): 176-180, 1997. https://ajph.aphapublications.org/doi/abs/10.2105/AJPH.87.2.176
- Jan 1993, a lab in Washington State confirmed O157:H7 in a patient, suspected hamburger in a fast-food chain as a source. Health authority issued press release on 18 Jan 1993, leading to the interest of national mass-media. Finally 501 cases, 45 HUS (hemolytic uremic syndrome), 3 died.
- In this initial outbreak, no case was reported in Nevada State. But on 21 Jan 1993, a pediatrician visited Las Vegas and found a girl aged 4 years suffering from HUS. Press release has issued on 22 Jan and all hemorrhagic diarrhea cases were asked to report.
  - Case definition: From 1 Dec 1992 to 7 Feb 1993, visited Las Vegas, suffering from HUS or hemorrhagic diarrhea (within 24 hours, 3 or more visible bloody watery stools), no identification of other pathogens than O157:H7.
  - Asked all hospitals in Las Vegas to report, interviews were conducted using standardized questionnaire.
  - Epidemic curve by the date of onset (Figure 1)
  - Odds ratio of eating regular size hamburger was 9.0 (95%CI: 1.02 – 433.4)
  - Epidemic curve by the size of hamburger (Figure 2)
  - On site inspection of the fast-food chain shop → low temperature in cooking regular size hamburger was suspected.
  - Improving the cooking method to sterilize (Figure 3) → Solved.

History of infectious disease control

- Even before finding pathogens, intervening route of infection could control epidemic (eg. Cholera study by John Snow)
- Two epoch-making discoveries
  - Antibiotics → Ultimate protection from bacterial infection?
  - Vaccines → All viral disease can be eradicated as in the case of smallpox?
- However, those were not perfect
  - Antibiotic spectrum: each antibiotic can only kill a limited number of specific bacteria
  - Pathogens rapidly reproduce and have high mutation rate to overcome the artificial protection
  - Drug-resistant bacteria were caused by unnecessary abuse of antibiotics
  - Urbanization and increased intercontinental movement elevated the risk of infectious disease expansion
  - New social activity and medical treatment made new route of infection such as nosocomial infection
- Obvious triumphs by infectious disease epidemiology were only two in global scale (locally many).
  - Eradication of smallpox by vaccination
  - Close to eradication of polio by vaccination
- Potential candidate of eradication? Malaria? → difficult
  - Many kinds of effective medicine such as quinine, chloroquine and artemisinine were developed but drug-tolerant parasite happen to appear
  - Insecticide such as DDT was effective to reduce anopheles mosquitoes density, but had eco-toxicity and the mosquitoes got resistance
  - Effective vaccine is very difficult to develop because of several reasons such as complexity of plasmodium life cycle, escaping from host immunity by spraying junk antigens in *P. falciparum*, simultaneous circulation of multistrains.
  - Malaria parasites sometimes switch their host from monkey to human: Recently *P. knowlesi* switched their host from cynomolgus monkey to human in southeast Asia.

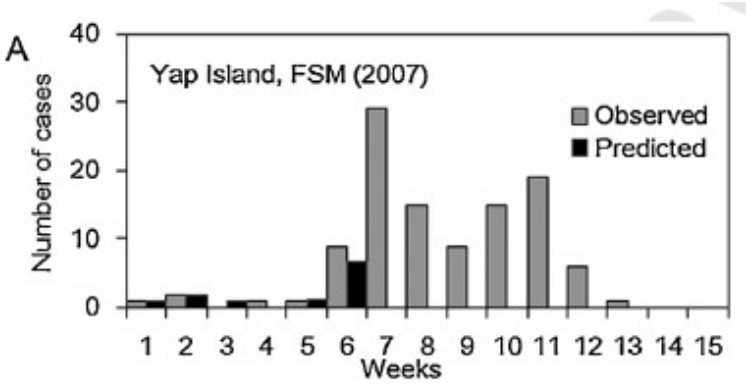
Uniqueness of infectious disease epidemiology

see, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7176237/
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7178878/

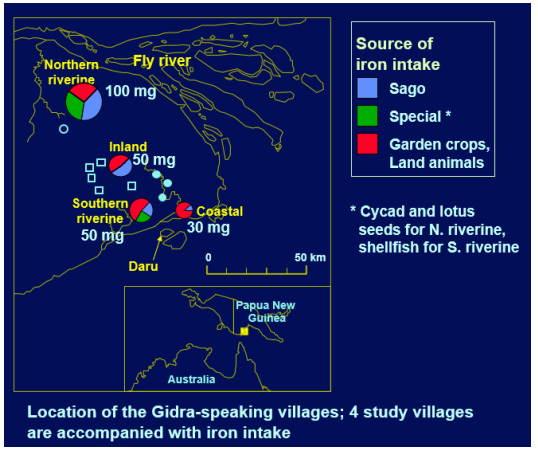
- **Contact tracing**: During very early stage of epidemic, finding potentially infected person before onset to isolate may prevent further spread, which reduce R to less than 1.
- **Outbreak research**: When a local epidemic occurs, describe the outbreak and investigate the spread from initial case. A detective job to identify the cause such as potato salad caused diarrhea outbreak among the participants on a supper in a church.
- **Seroepidemiology**: Antibody titer in recently infected people is higher than the people already recovered long time ago. Antibody titer distribution using ELISA and/or IFAT for a series of diluted serum samples can evaluate the extent of prevalence within the population.
  See, http://minato.sip21c.org/2019-nCoV-im3r.html#ANTIBODYTEST (in Japanese)
- **Trials for vaccine efficacy**: Randomized trials for protective measures are much more difficult than curative measures. It's a kind of field trials. It's very difficult to detect the status of "protected" because no-onset can be a result of non-exposure or other reasons than protected from exposed pathogens. Exposure is not controllable.

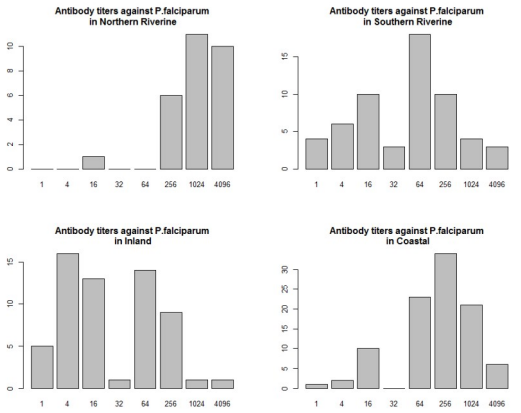
Descriptive epidemiology of infectious diseases

- 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)

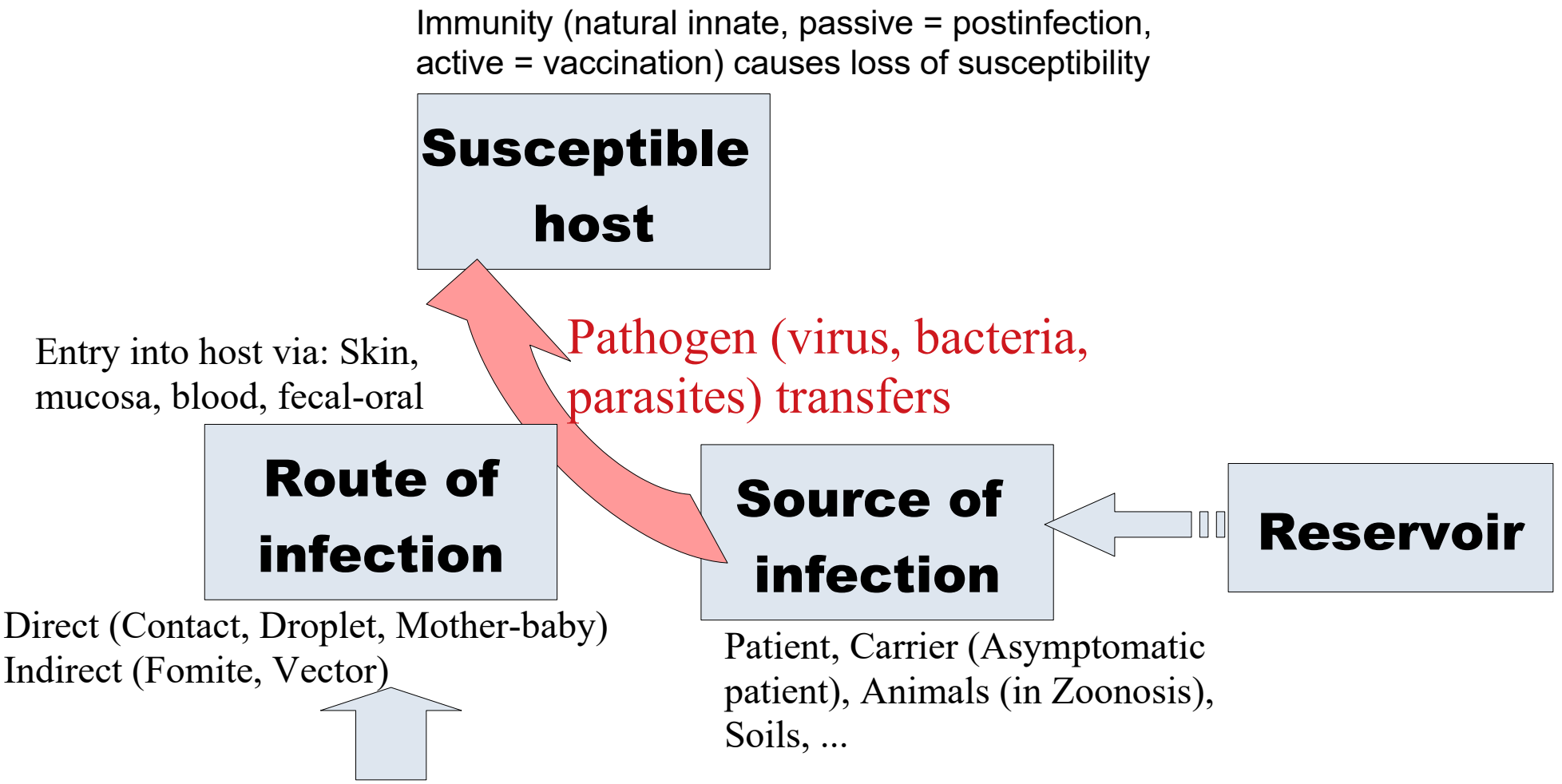


Please cite this article in press as: Nishiura H, et al. Transmission potential of Zika virus infection in the South Pacific. Int J Infect Dis (2016), http://dx.doi.org/10.1016/j.ijid.2016.02.017





Three elements of infectious diseases



Basic elements which affect the transmission of infectious diseases

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

Route of infection

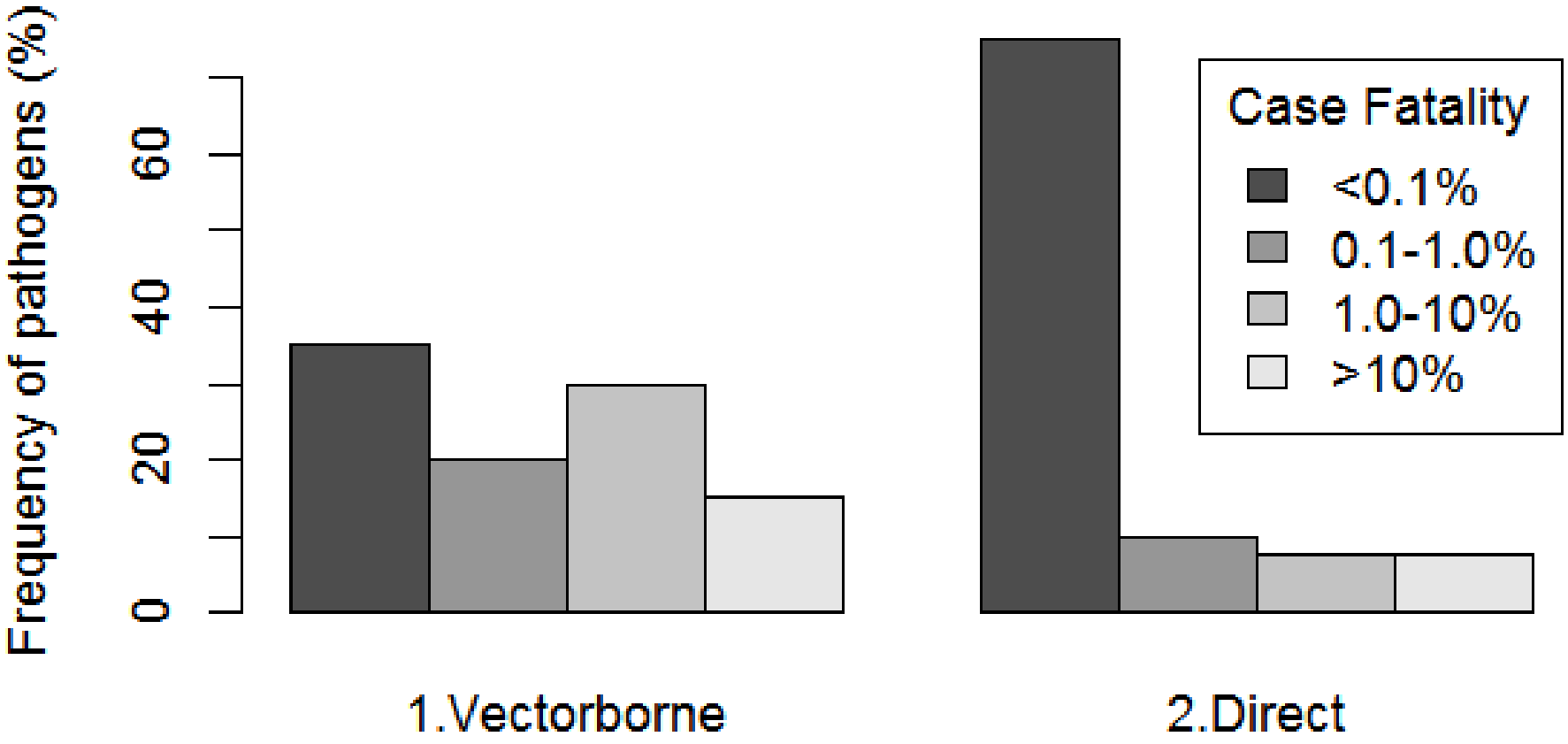
Route of transmission	Characteristics
Contact	Requires direct/indirect contact * Indirect = infected fomite, blood or body fluid * Direct = skin or sexual contact
Food- or water-borne	Ingestion of contaminated food (outbreaks may be large and dispersed, depending on distribution of food)
Airborne (droplet,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

TYPES OF TRANSMISSION

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

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

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

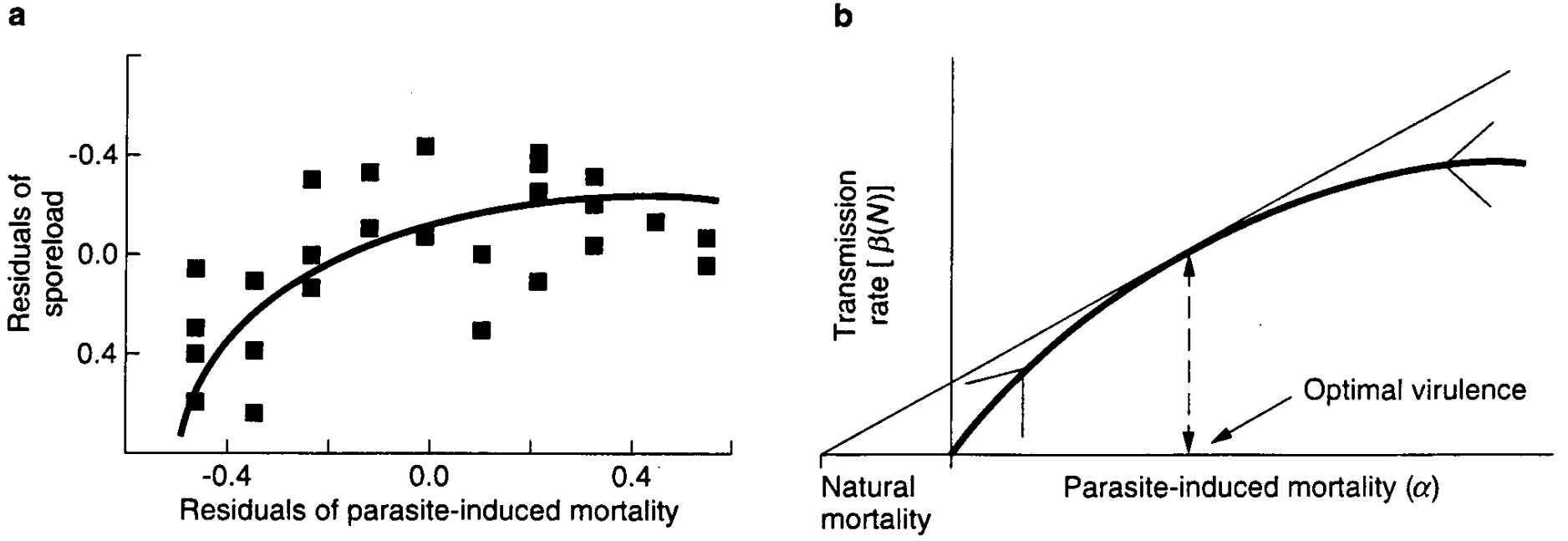


Source: Ewald (1994) [pp.38, Figure 3.1]

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)

Virulence evolution

- When there are wide variety of infectiousness and virulence among parasites, variants with faster proliferation and stronger infectiousness become more dominant, but faster proliferation causes stronger virulence in general, then hosts will die before secondary infection occurs. As the results of such trade-offs, **optimal virulence** will evolve (Ebert and Herre, 1996)
- If the route of infection is exclusively direct transmission, infected host's mobility is necessary for transmission, and thus the variants with weaker virulence tend to be dominant (such as JC virus). If the route of infection includes vector-borne (such as malaria) or water-borne (such as cholera), host's mobility has no relation with the chance of transmission, and thus virulence has no relation with prevalence (Ewald, 1994).
- However, the route of infection of COVID-19 is mostly airborne (contact with fomite, inhalation of droplets or suspended micro-droplets), later variants showed higher infectiousness and stronger virulence at the same time.
  - Delta and omicron variants had lower Rt than alpha variant but shorter generation time. The speed of spread is (Rt)/(generation time). Rt is related with virulence but generation time is not necessarily related with virulence.
  - More than half of infection occurs before the onset of symptoms, which is very specific feature of COVID-19, virulence has less relation with virulence. https://www.who.int/news-room/commentaries/detail/transmission-of-sars-cov-2-implications-for-infection-prevention-precautions

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)
- The latest pandemic of COVID-19 still continues as an endemic disease with several times higher CFR than seasonal flu. The phase shifted from emergency to long-term management.
  https://minato.sip21c.org/COVID-19-publichealthmeasure.pdf

Infectious Disease Modeling

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

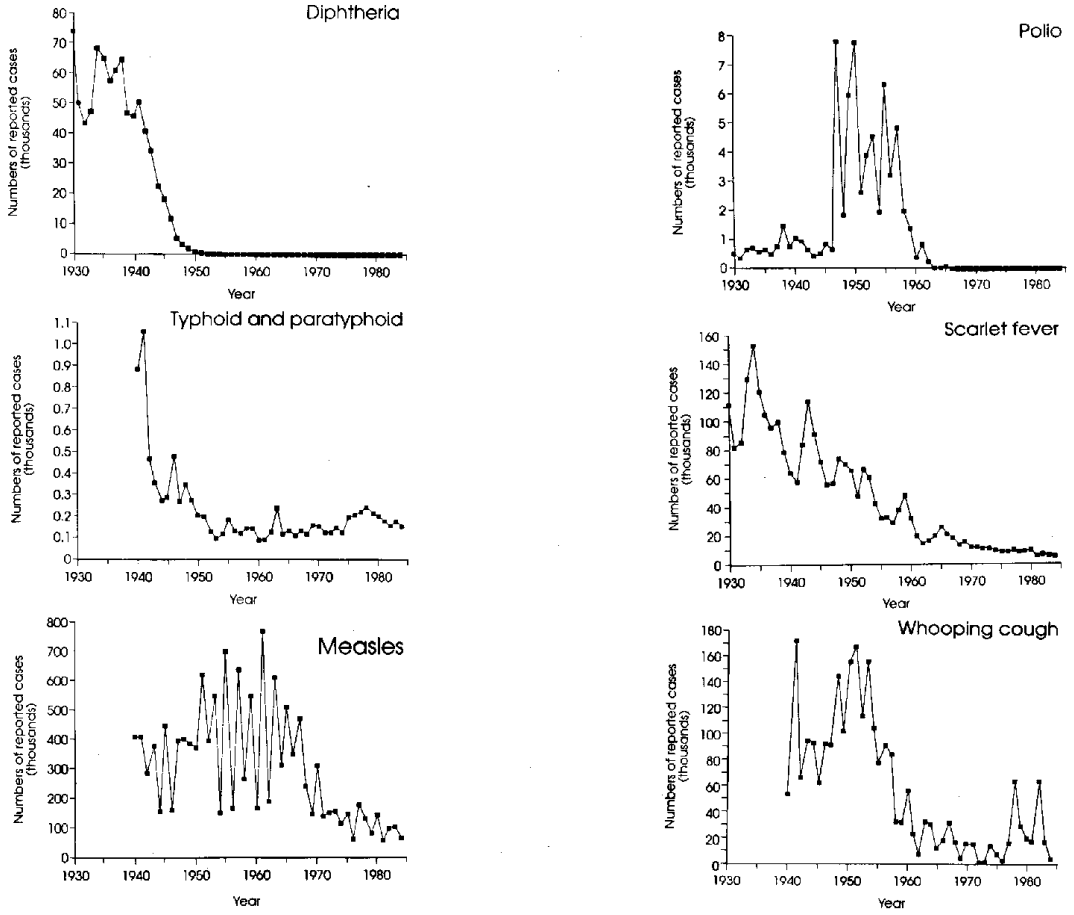


Fig. 3.5. Longitudinal records of the incidence (defined as reported cases of infectior per annum) of various infectious diseases (diphtheria, polio, typhoid and paratyphoid scarlet fever, measles, and whooping cough (pertussis)) in England and Wales over th period 1930 to 1985 (from the Registrar-General's weekly infectious disease returns for England and Wales).

Basic reproduction numbers of macroparasitic infection (Source: Anderson & May, 1990)

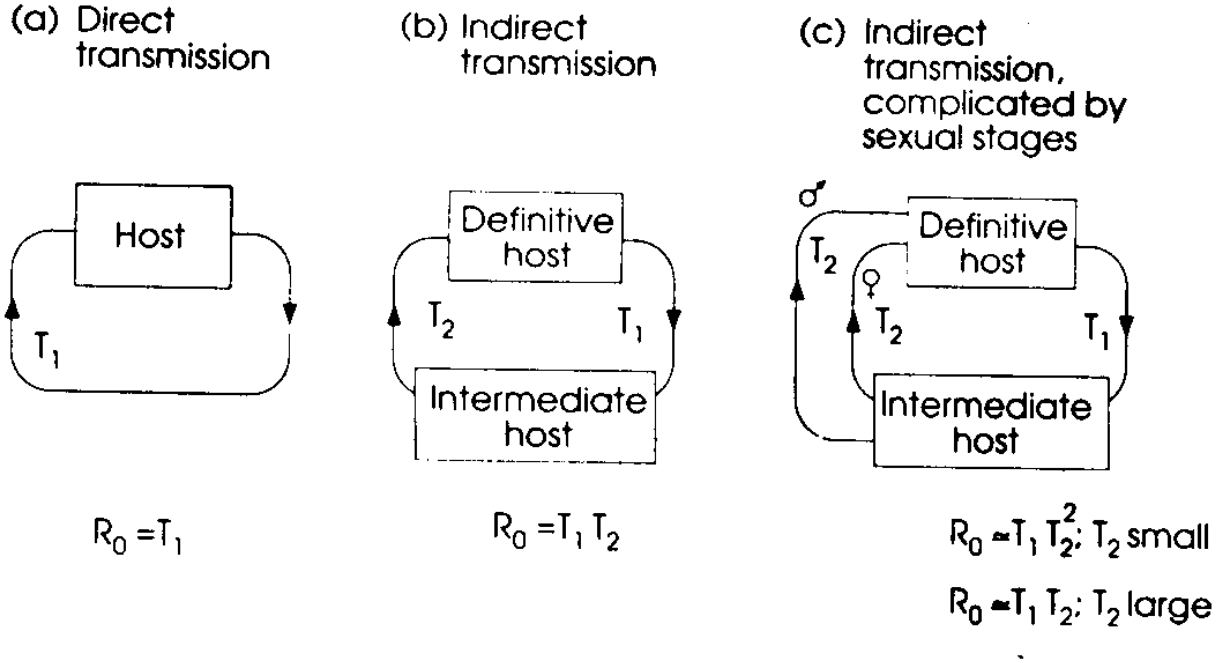
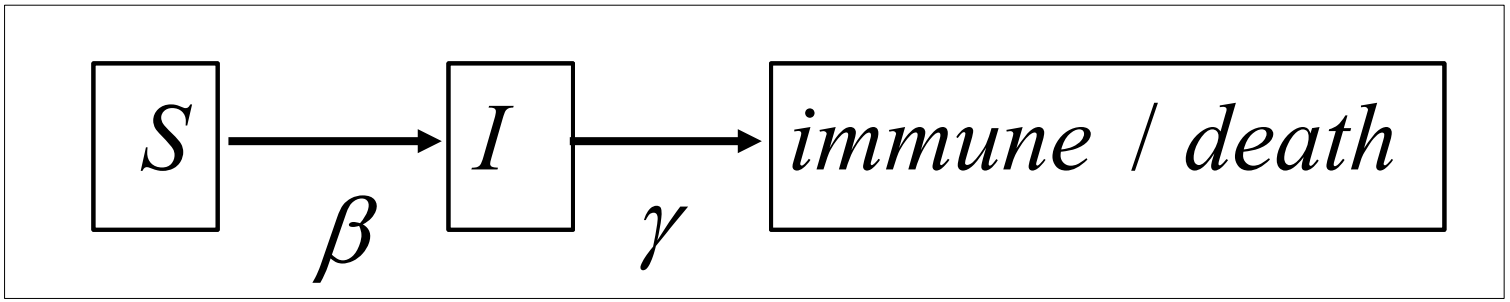
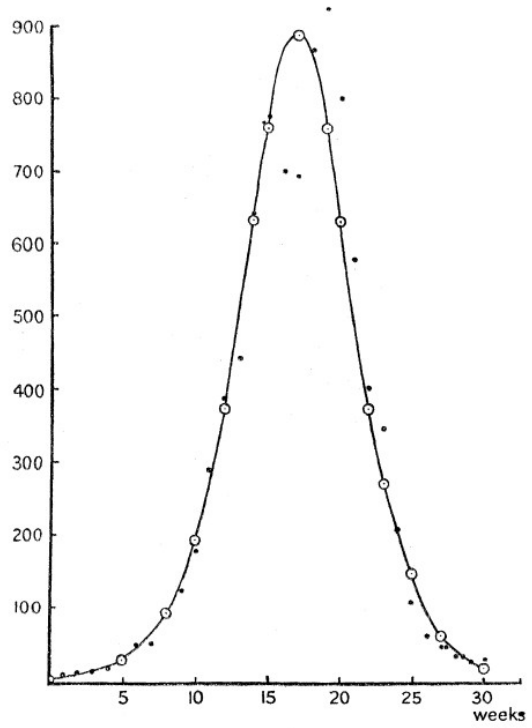


Fig. 2.4. Diagrammatic representation of direct and indirect transmission and the complications introduced by the sexual stages of macroparasitic organisms. The quantities T_1 and T_2 denote summary transmission parameters for the flow of parasites from definitive host to intermediate host (T_1) and intermediate host to definitive host (T_2). (See text for details.).

Simplest mathematical model (SI)



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



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

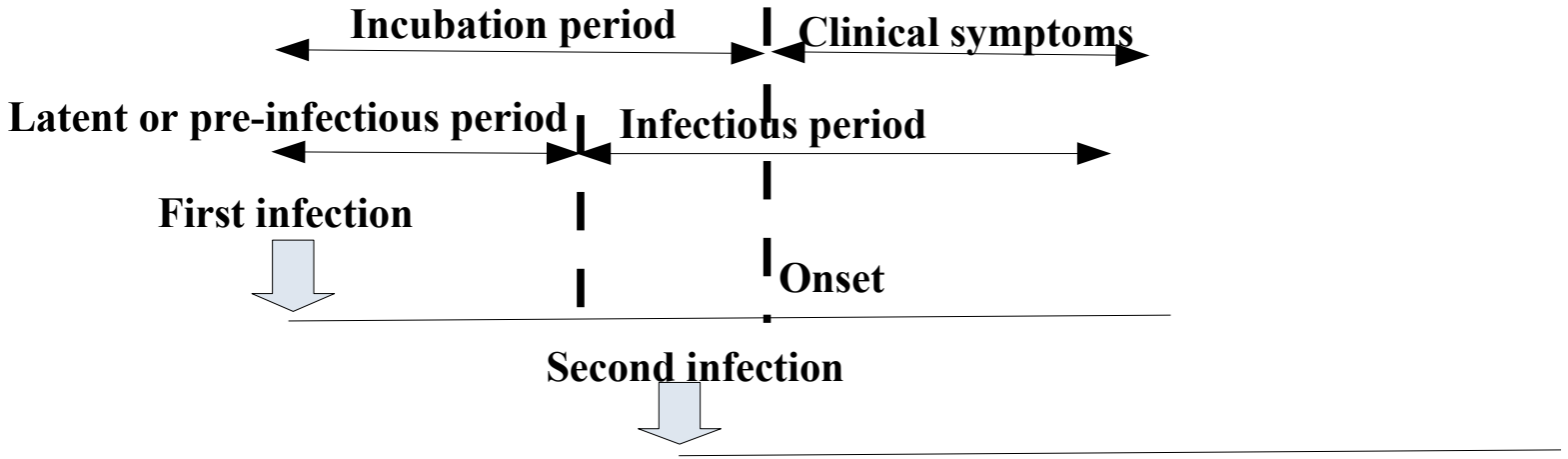
$$\frac{dz}{dt} = 890\,\operatorname{sech}^2(0{\cdot}2t - 3{\cdot}4).$$

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

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

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

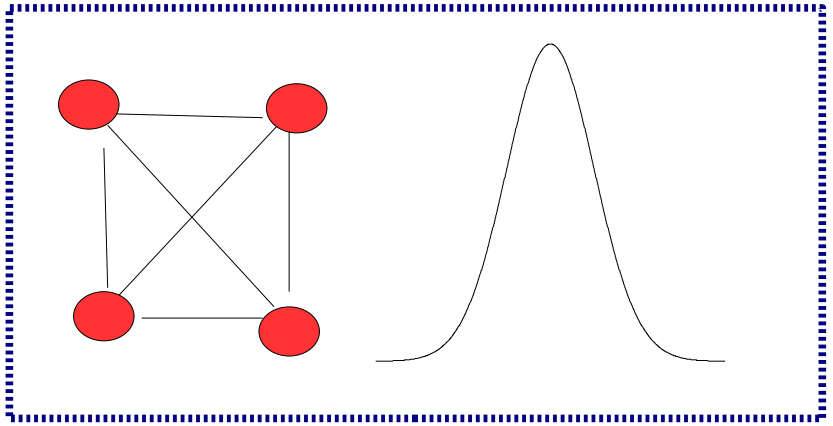
Terms for individual infection history

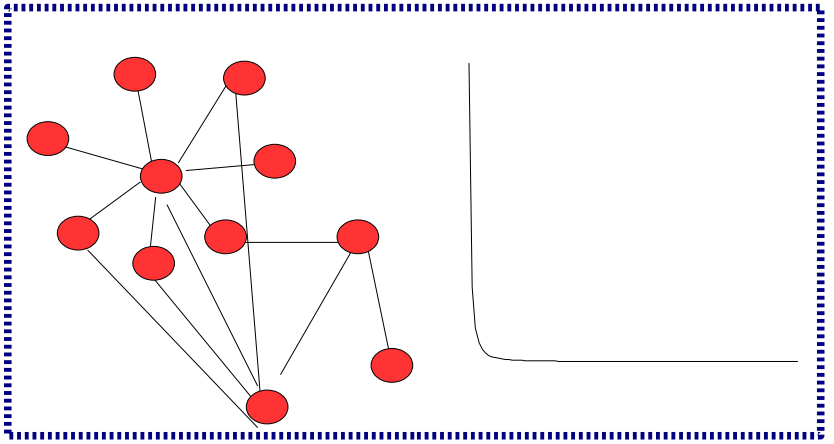


Two general types of infection network topology

(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

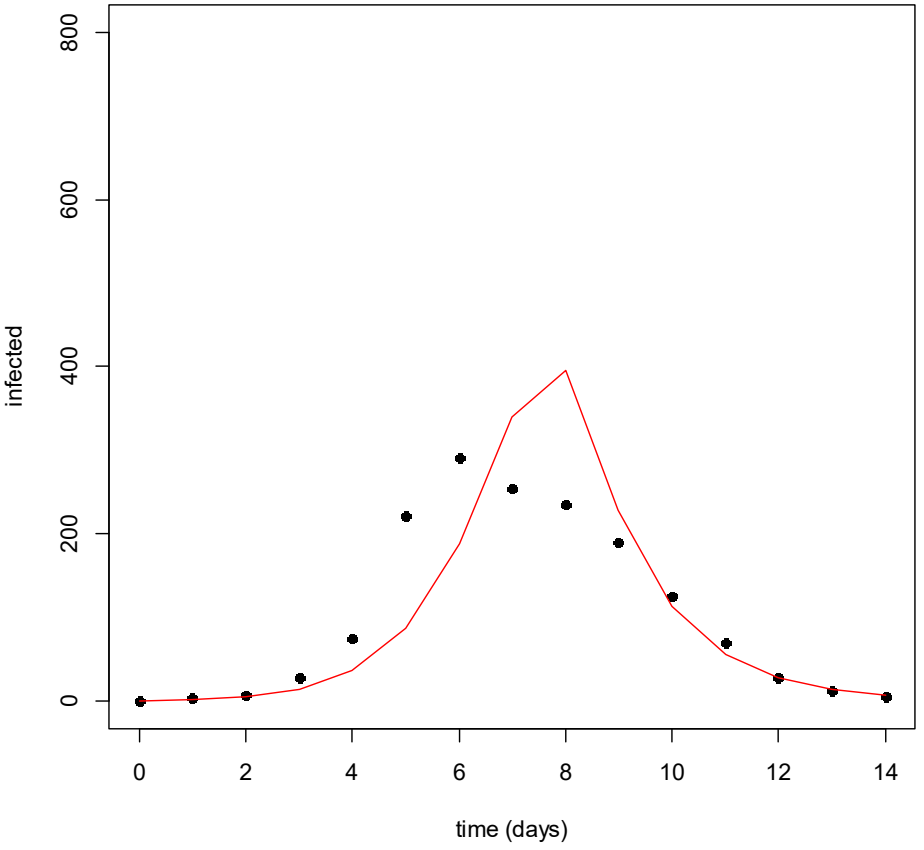




SIR model for flu epidemic

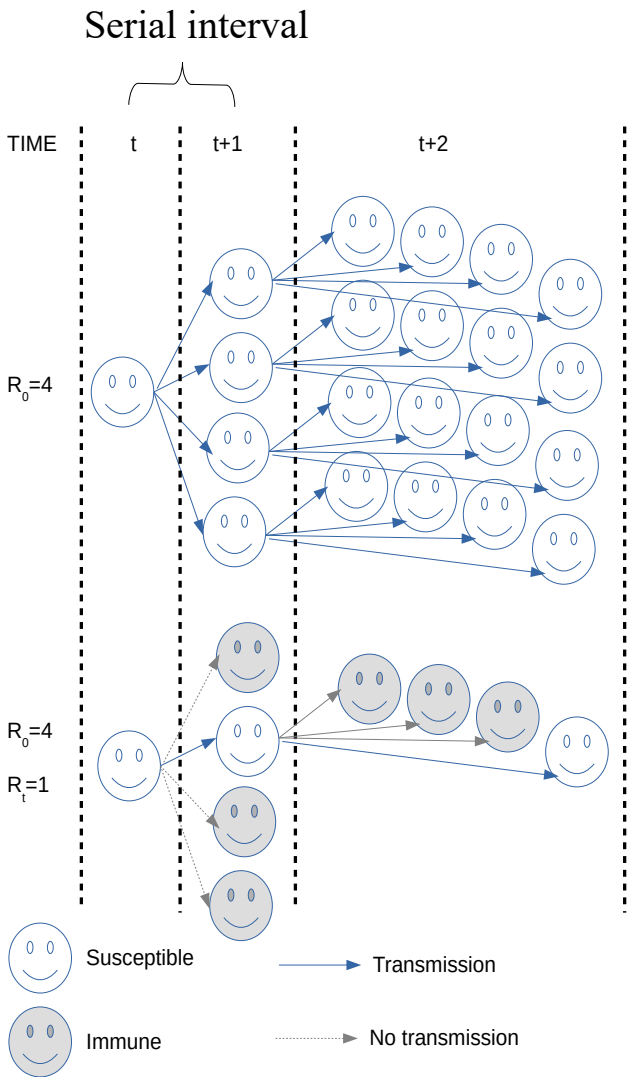
- $dS/dt = -\beta SI + \delta R$
- $dI/dt = \beta SI - \gamma I$
- $dR/dt = \gamma I - \delta R$
- Note: None of S, I, and R can be less than 0. It should be considered in numerical simulation.
- Estimating params
  - β: {I(1)-I(0)}/S(0)
  - γ: 1/{mean days of recovery}
  - δ: negligible (loss of immunity)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

Example: The data in English boys boarding school in 1978



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 (See, right figure, based on Vynnycky and White, 2010)



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. https://doi.org/10.1093/infdis/jis443

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.

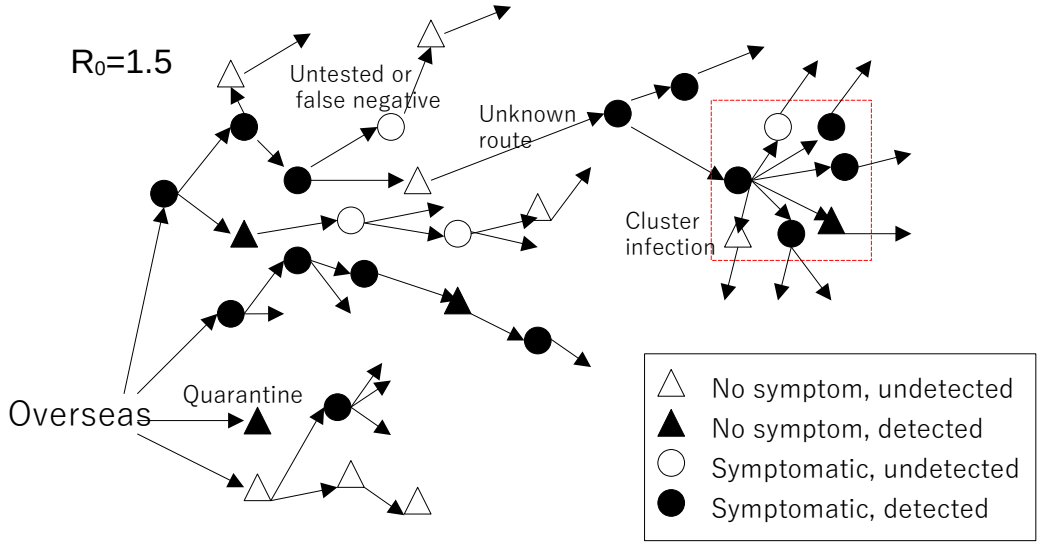
Estimating R_0 from data

- Let the populations at time t for each compartment of susceptible, infected, and recovered S(t), I(t), and R(t), respectively. Let the transmission coefficient (proportionate to infection probability per 1 contact) β, rate of recovery or isolation γ,
  - $dS(t)/dt = -\beta S(t)I(t)$
  - $dI(t)/dt = \beta S(t)I(t) - \gamma I(t)$
  - $dR(t) = \gamma I(t)$
- $N(t)=S(t)+I(t)+R(t) \rightarrow dN(t)/dt=0$ $\rightarrow N(t) =$ constant N
- Initially $S(0)+R(0)=N$
- $dI(t)/dt = (\beta S(0) - \gamma)I(t)$ $\rightarrow I(t)=I(0)\exp\{(\beta S(0)-\gamma)t\}$
- Simply thinking, coefficients of exponential regression can give R0, which is implemented as “EG” of R package “R0” https://doi.org/10.1186/1472-6947-12-147
- Let generation time T (average waiting time from initial case infection to secondary infection), which can be approximated by serial interval (average waiting time from onset of initial case to onset of secondary cases), $R_0=1+(\beta S(0)-\gamma)T$
  - If we know or estimate T, we can estimate R_0 by maximum likelihood method (“ML” in R0 package)

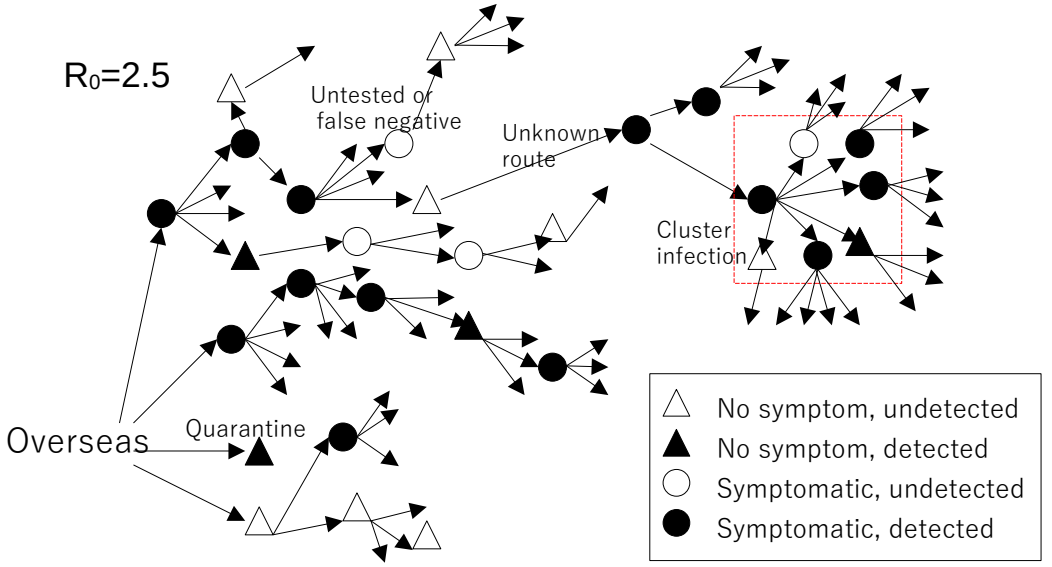
- (eg.) Flu epidemic in UK boarding school http://minato.sip21c.org/tiid/R0.R
- Available methods for estimate are "EG", "ML", “AR", "TD", and "SB". However, “AR” didn’t give the solution for this data.
  - "AR" using Dietz (2013) equation. Let the infected proportion among total population AR, $R_0 = -\ln((1-AR)/S(0))/(AR-(1-S(0)))$
  - "TD" assumes time-dependent reproduction numbers by Cauchemez et al. AJE (2006)
  - "SB", sequential Bayesian estimates, also assumes time-dependent reproduction and uses Bayesian estimation by Bettencourt & Ribeiro (2008)
- EG gives R : 8.91 [7.57, 10.52]
- ML gives R : 6.83 [6.10, 7.62]
- SB gives a series of
  3.96, 4.57, 4.15, 4.22, ...
- TD gives a series of
  11.78, 8.82, 6.22, 3.65, ...

What's ignored in the previous estimation

- Direct estimation from contact tracing data (Very rare)
  - Failure to catch the contact leads underestimate of R_0
  - False negative diagnosis also underestimate R_0
- Based on daily reports of new daily cases (Usual), assuming the spread from initial case causes
  - Invasion of cases from outside leads overestimate (in Japan, 2020 Spring, asymptomatic or presymptomatic cases returned back from Europe caused this)
  - Asymptomatic cases not tested and thus not detected as cases cause underestimate
- Super-spreading causes overdispersion of R, which makes precision of average R worse



Among 30 cases, secondary infections were 0 in 2, 1 in 16, 2 in 10, 3 in 1, 6 in 1 → (0x2+1x16+2x10+3x1+6x1)/30 = 1.5 In fact, among the detected 18 cases, secondary infections were 0 in 3, 1 in 8, 2 in 5, 3 in 1, 4 in 1 → (0x3+1x8+2x5+3x1+4x1)/18=1.39



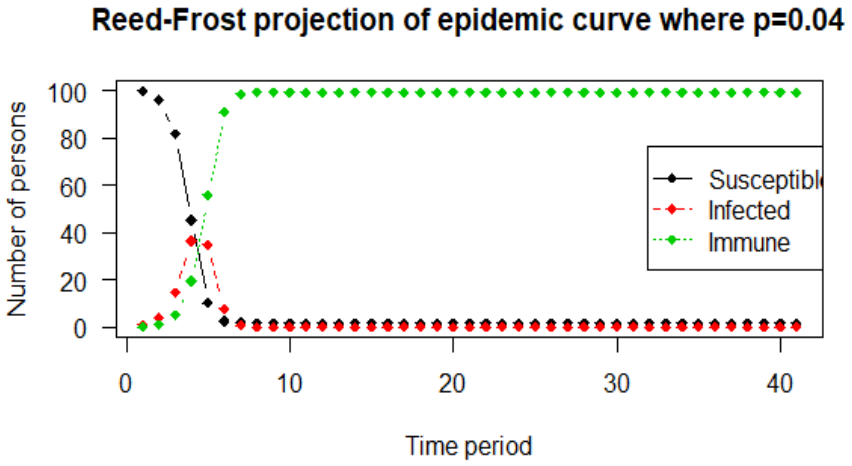
Among 30 cases, secondary infections were 0 in 2, 1 in 6, 2 in 5, 3 in 11, 4 in 5, 6 in 1 → (0x2+1x6+2x5+3x11+4x5+6x1)/30 = 2.5

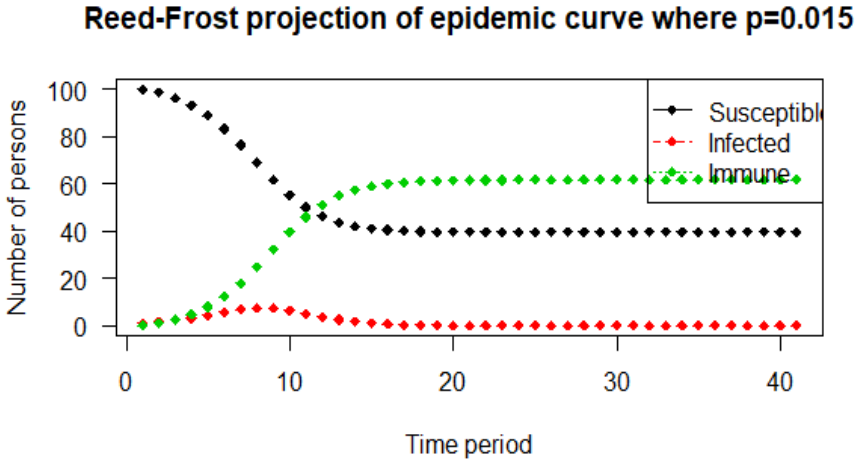
Example of SARS, and if vaccine would be available?

- 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**)

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.





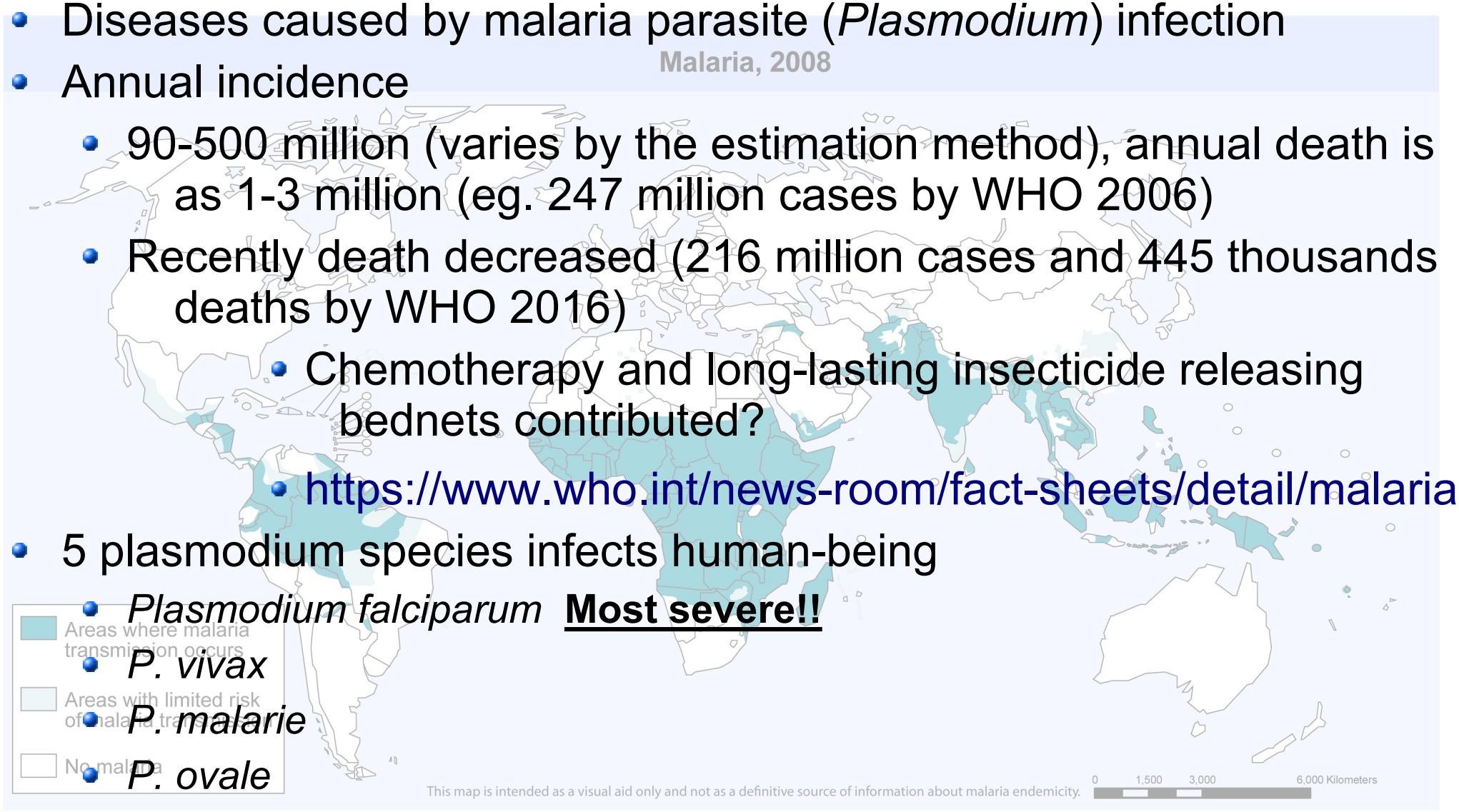
https://minato.sip21c.org/tiid/ReedFrost.R

Mathematical models on **malaria**

- Transmission situations are quite different by place
  - Epidemic
    - Usually no patients, sometimes transmission occurs
  - Mesoendemic
  - Holoendemic
    - Prevalence is always higher than approx. 20%
    - Many children have splenomegaly
- Difficulty to find simple pattern in transmission
- Modeling must consider the infection cycle

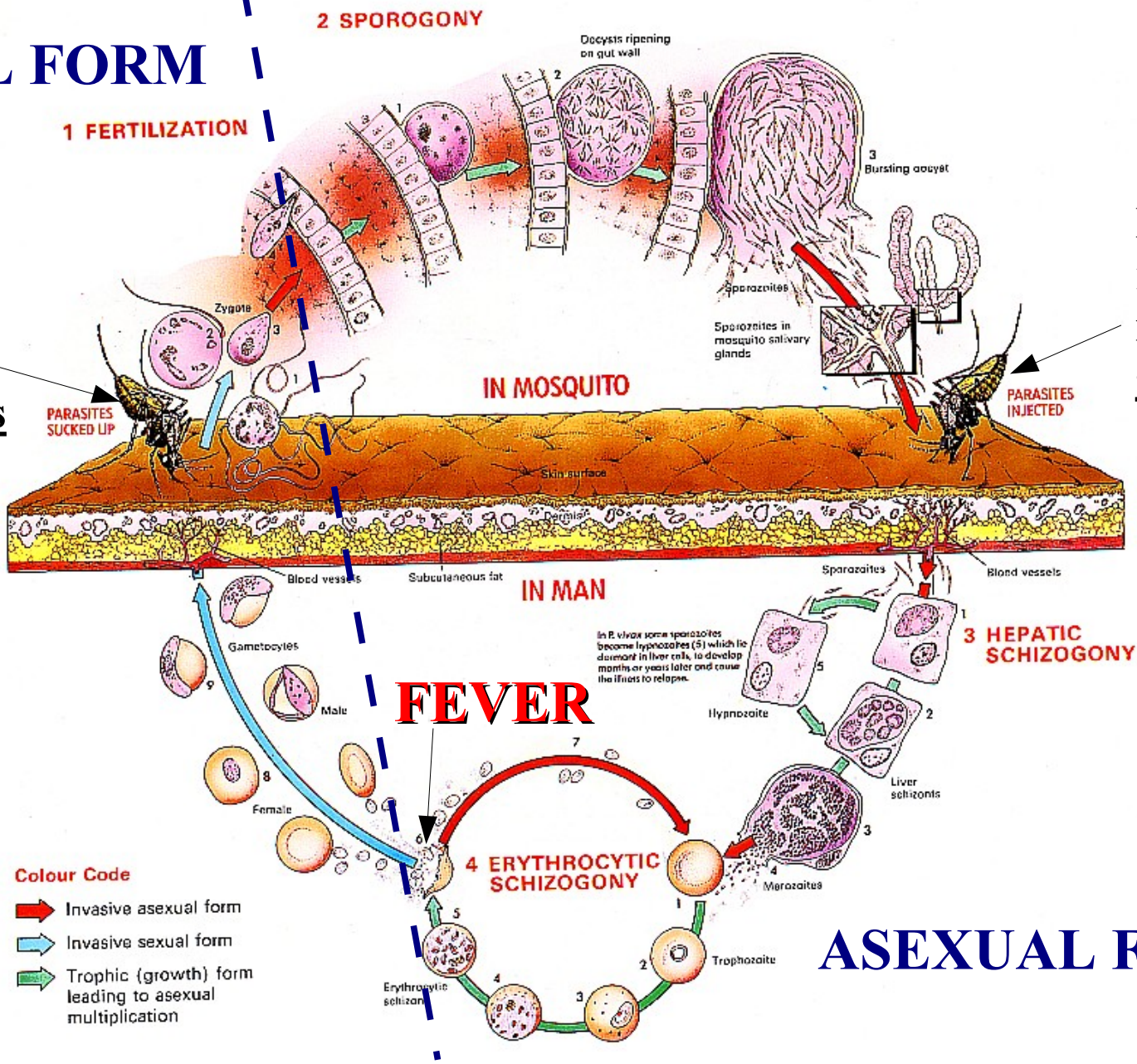
What is malaria?

- Diseases caused by malaria parasite (*Plasmodium*) infection
- Annual incidence
  - 90-500 million (varies by the estimation method), annual death is as 1-3 million (eg. 247 million cases by WHO 2006)
  - Recently death decreased (216 million cases and 445 thousands deaths by WHO 2016)
    - Chemotherapy and long-lasting insecticide releasing bednets contributed?
      - https://www.who.int/news-room/fact-sheets/detail/malaria
- 5 plasmodium species infects human-being
  - *Plasmodium falciparum* **<u>Most severe!!</u>**
  - *P. vivax*
  - *P. malarie*
  - *P. ovale*
  - Recent reports on *P. knowlesi*
- Vector is *Anopheles* mosquitoes



Life cycle of malaria parasite

(Source: Knell AJ, "Malaria" Oxford Univ. Press, 1991)



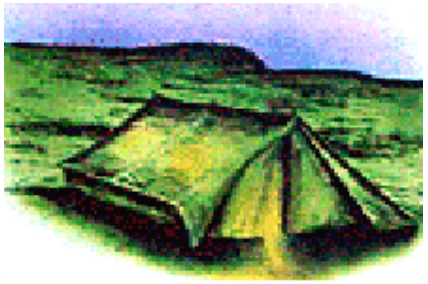
Intact mosquitoes suck <u>gametocytes</u>

Infected mosquitoes inoculate <u>sporozoites</u>

Various ways of individual protection

(cited and modified from Knell AJ: "Malaria", Oxford Univ. Press, 1991)

Avoid visiting malarious areas, especially spending over the night there

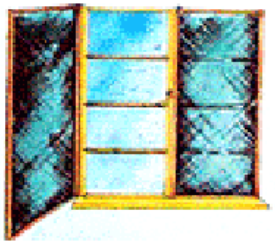


Wear clothes with long sleeves and long trousers from the dusk till dawn

Use insect repellents (ex. DEET) on exposed skins

Take prophylactic tablets as recommended there

Live in screened house, which must keep good conditions

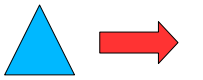
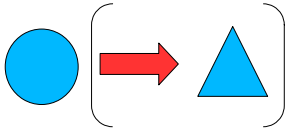


Let young children be in a bed under the net before 7 pm

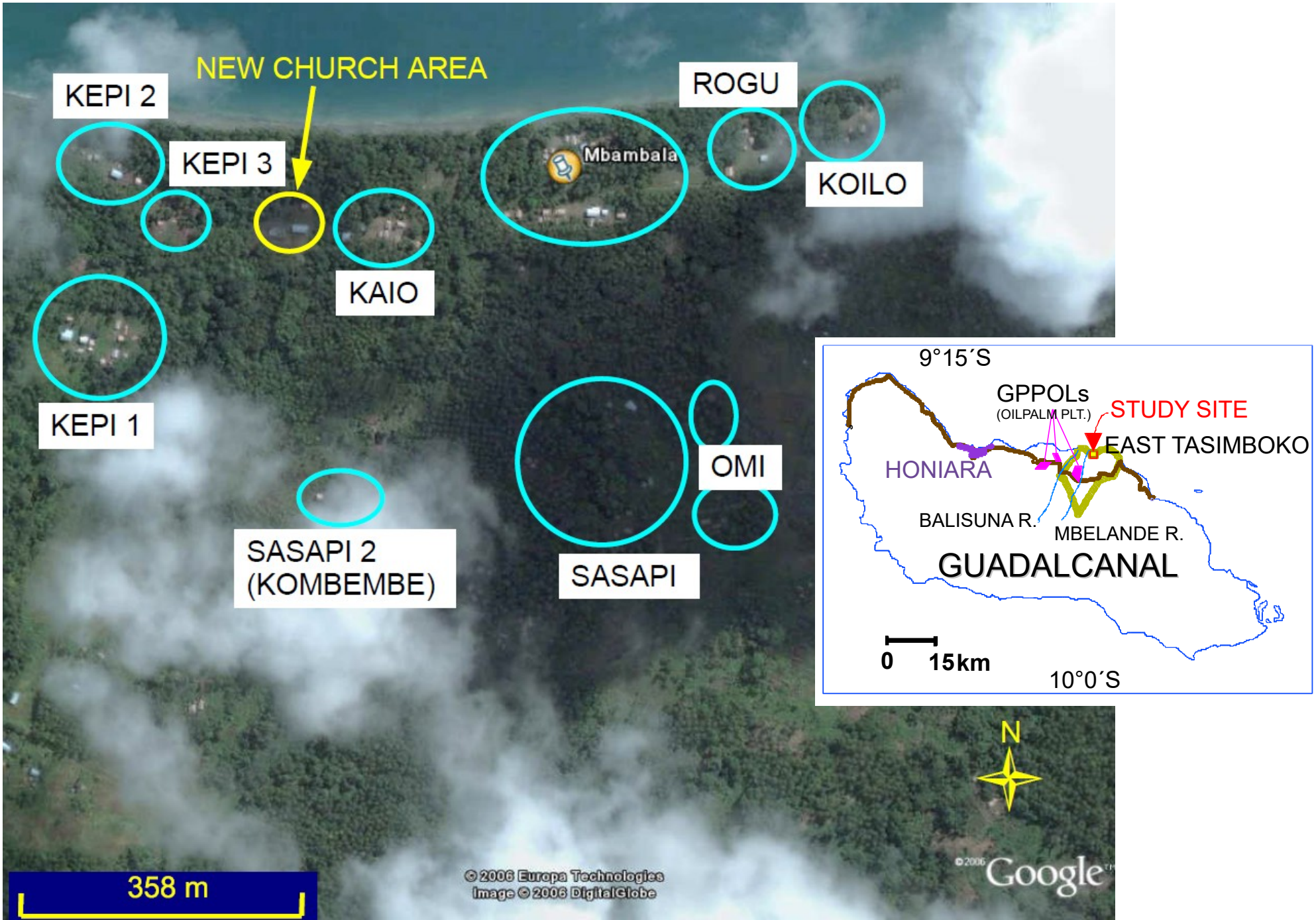
Use bednets properly, preferably insecticide treated nets (ITNs)

Burn mosquito coils or use vaporization mats or use sprays

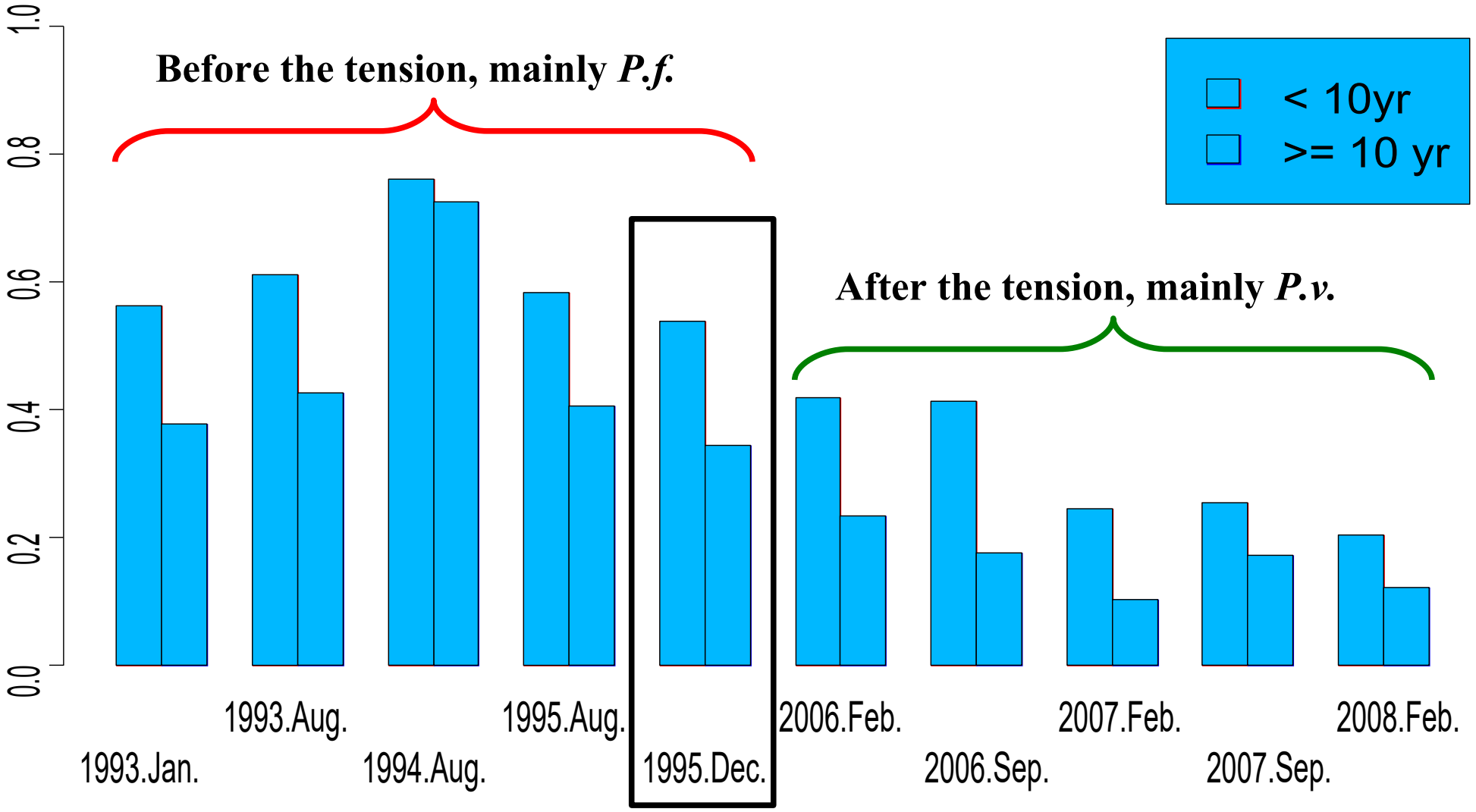
Malaria control measures

- Prevention
  - Medical prevention
    - Vaccines 
    - Chemoprophylaxis 
  - Environmental prevention
    - Reduce mosquitoes (ITN, IRS, Larvicides) 
  - Behavioral prevention
    - Reduce human-mosquito contact ?
- Screening and Treatment
  - Active case detection and ACT 

Mbambala, East Tasimboko



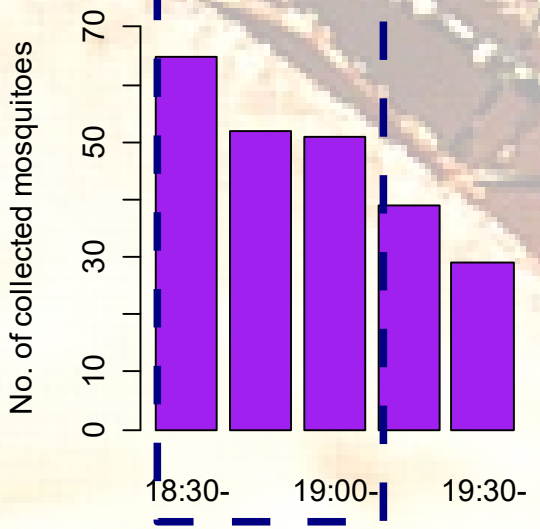
Change of malaria parasite rates in active case detections

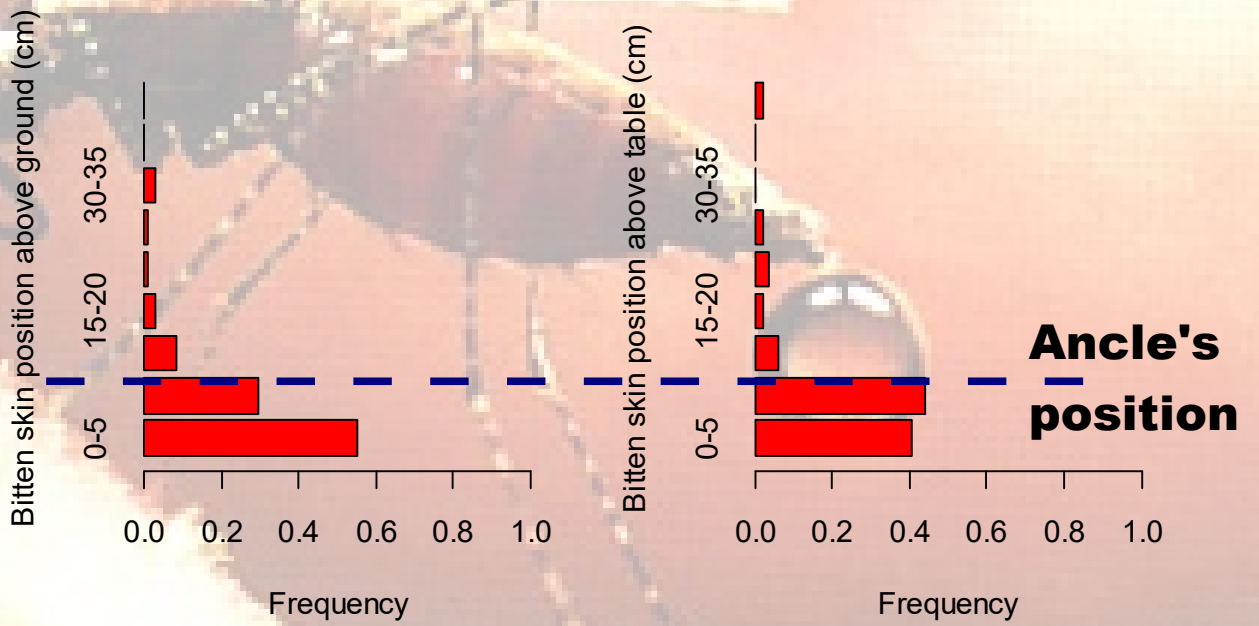


Nature of *An. farauti No.1*

(source: Susuki H: "Malaria vector mosquitoes in the Solomon Islands." In: Ishii A et al. [Eds.] "*Malaria research in Solomon Islands*", 1998, Inter Group Coop., pp.104-113.)

Most mosquito bites occurs before 19:30





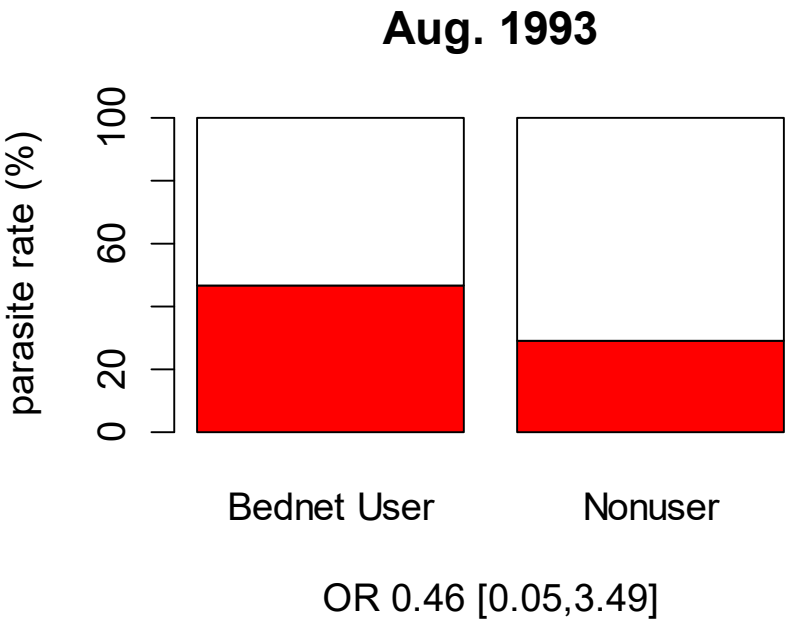
Applicability of bednet/IRS was very limited, because of the nature of prevalent mosquito, *An. farauti No.1* such as

(1) It sucks human blood mostly just after the sunset.

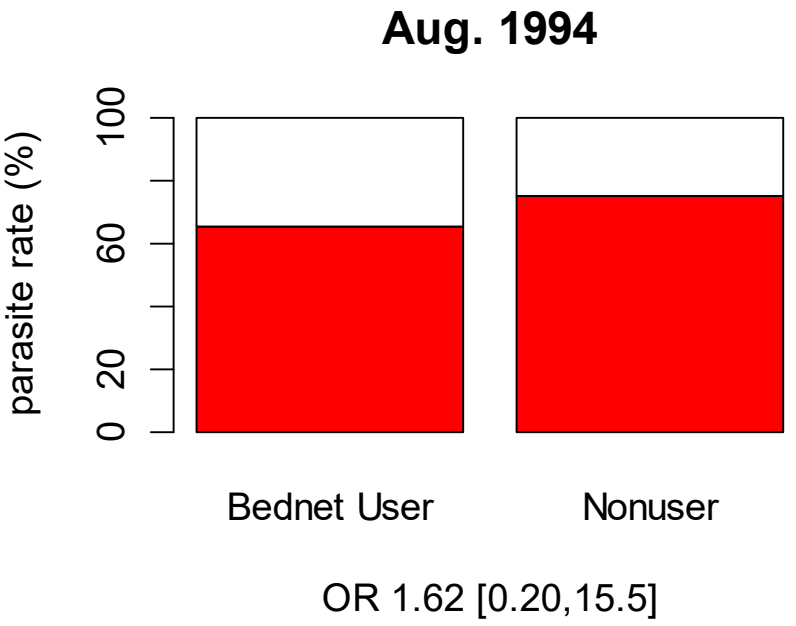
(2) It doesn't rest within a house in the morning after biting.

(3) But it almost exclusively sucks blood under the ankle.

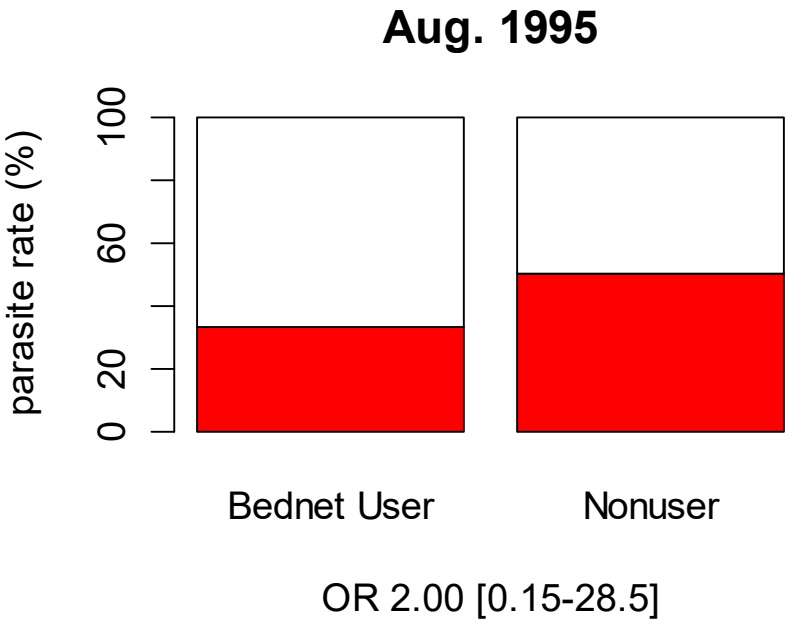
Not significant effect of bednet use



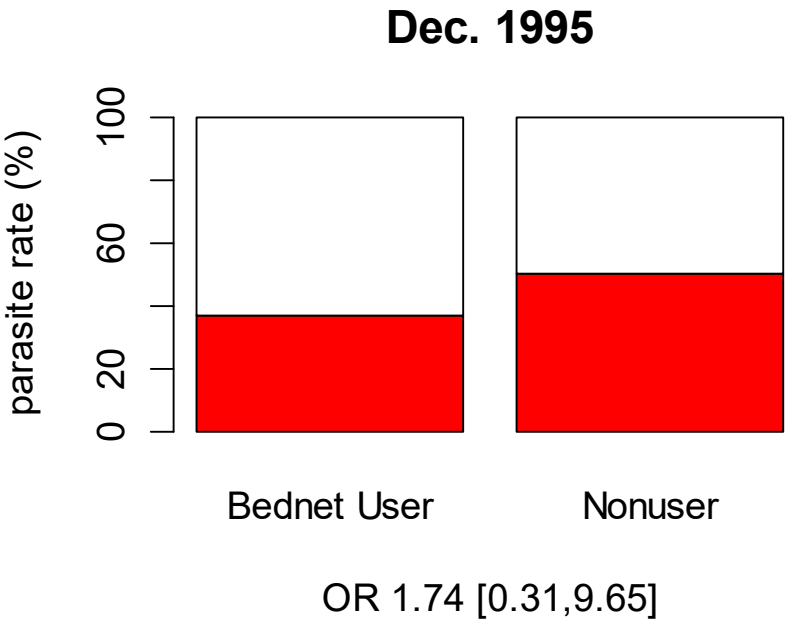
OR 0.46 [0.05,3.49]



OR 1.62 [0.20,15.5]



OR 2.00 [0.15-28.5]

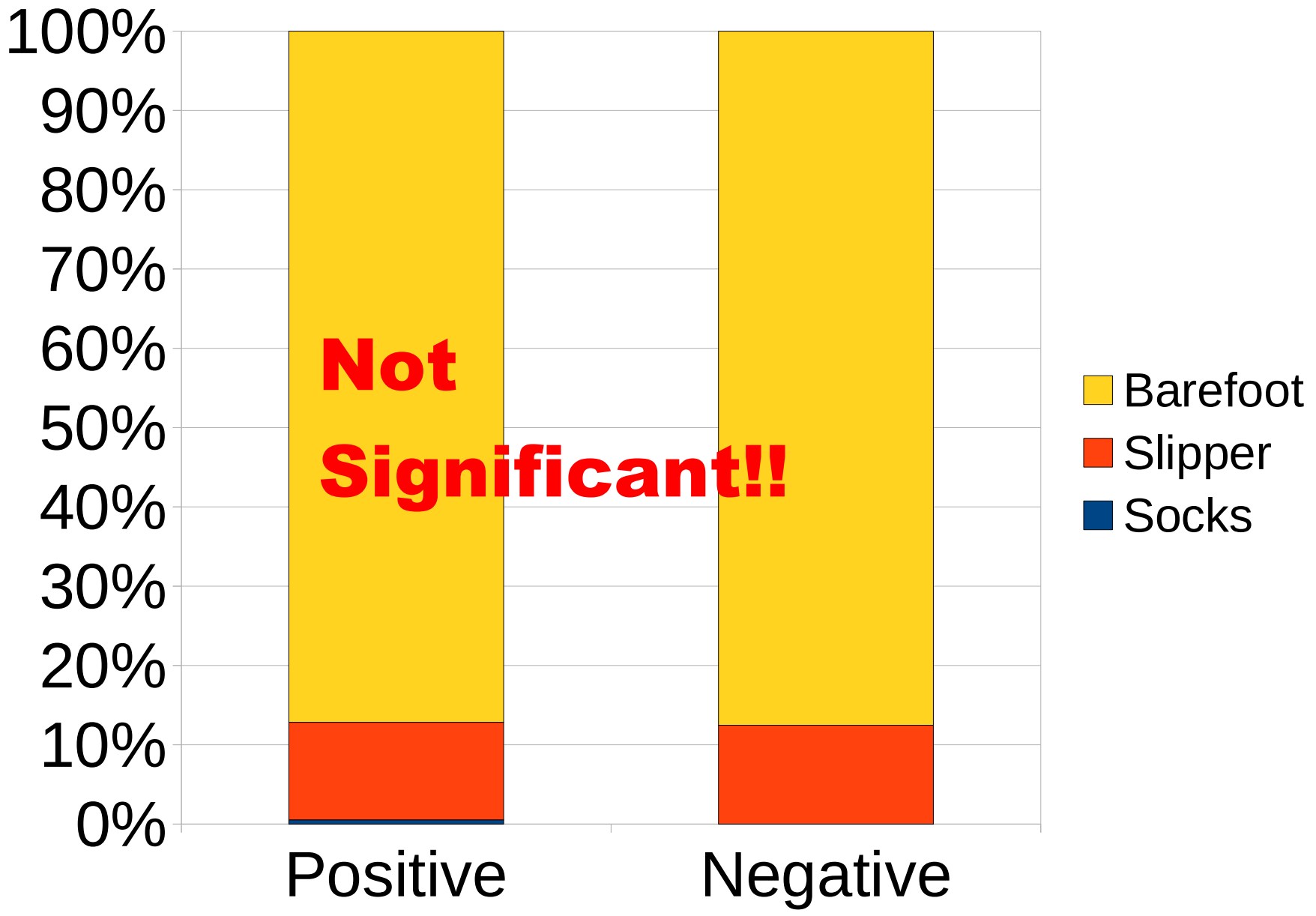


OR 1.74 [0.31,9.65]

Human behavioral effects on malaria infection

- December 1995 data
- From the sunset (18:00), the time-saving spot-check observation for 2 hours (until 20:00) was conducted every day for 3 weeks, to check (1) foot status, (2) place to stay, (3) clothes.
- After 3 weeks, all the village people were checked by blood-slide.

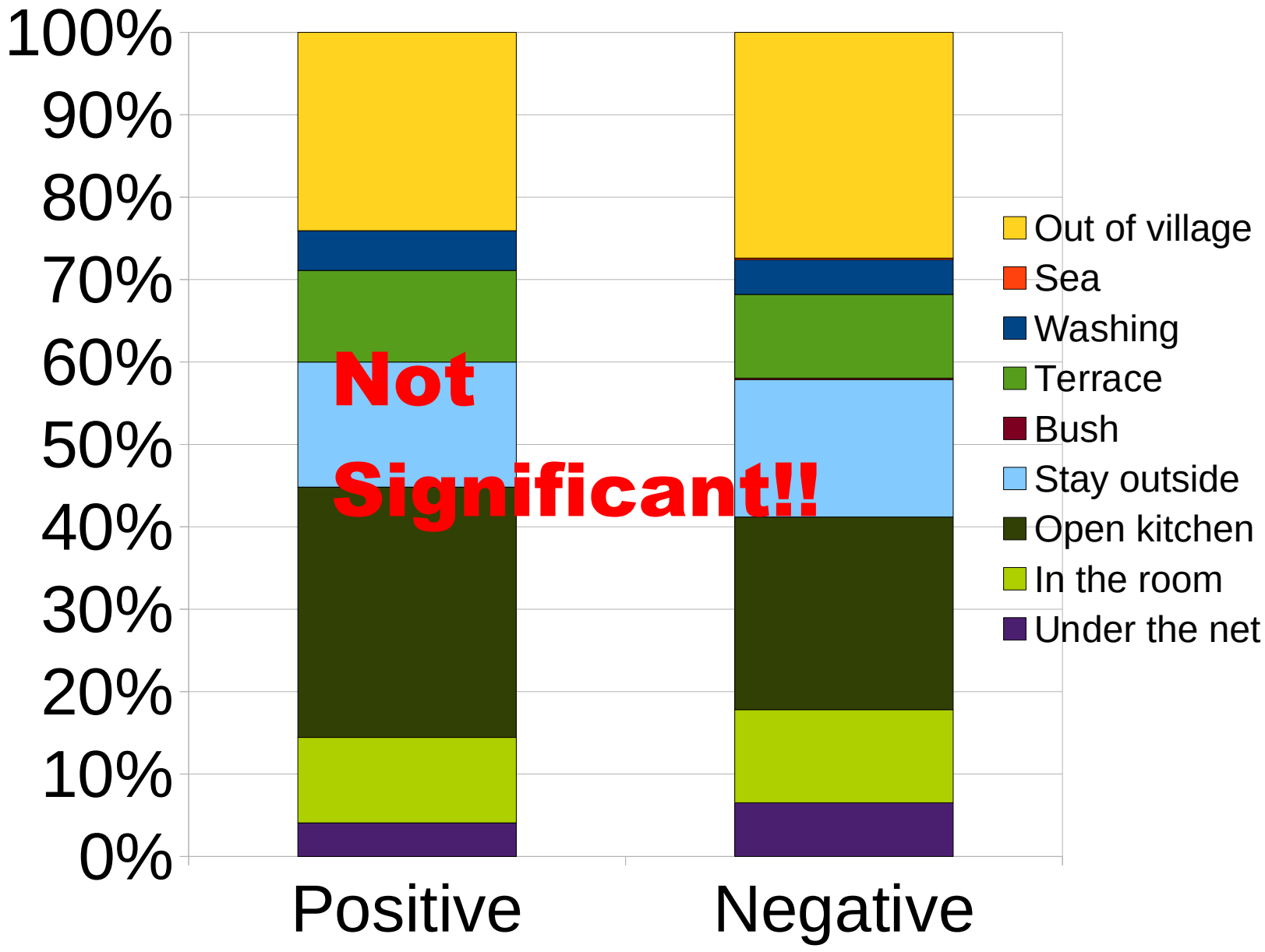
Foot status and malaria infection



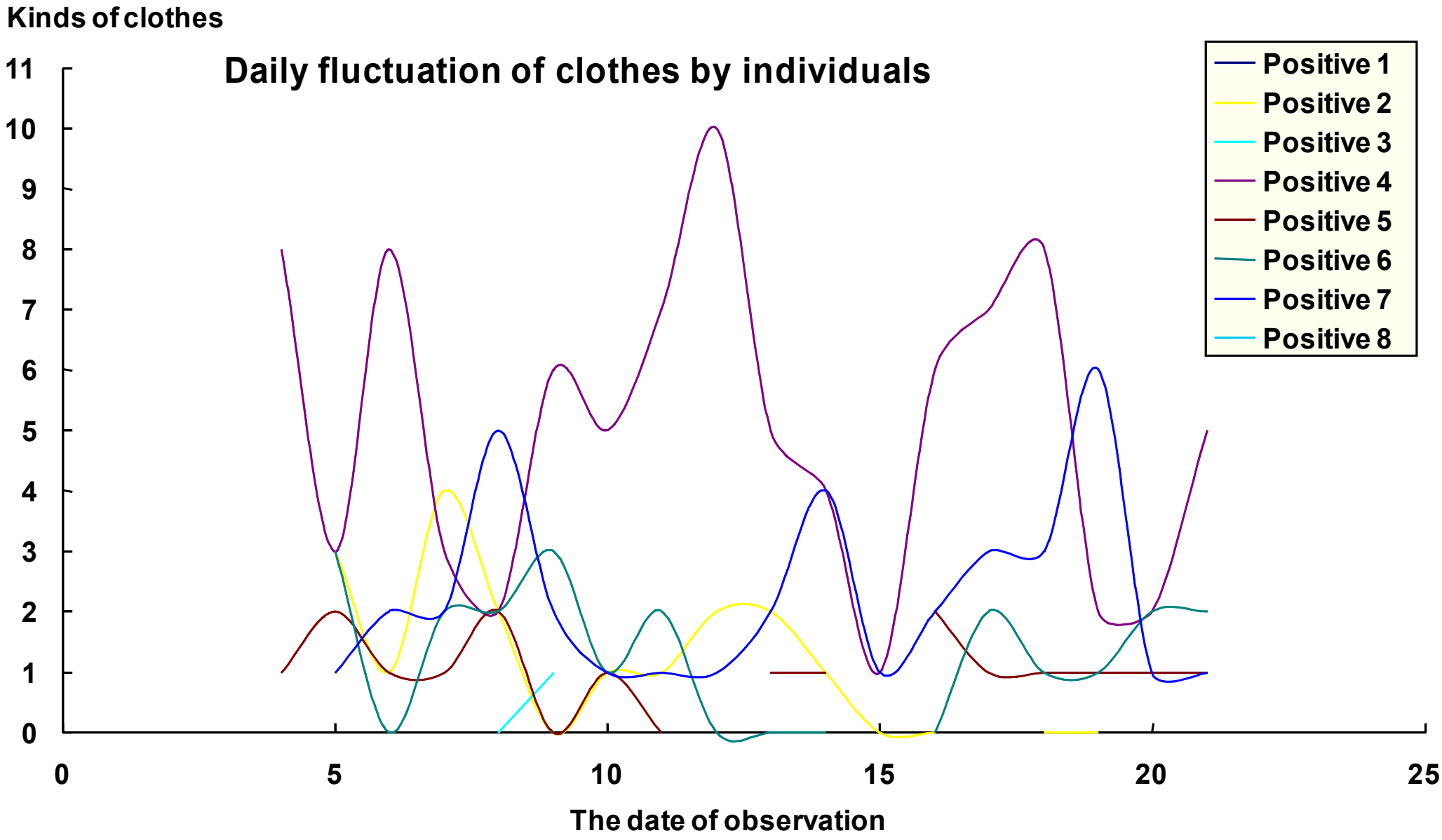
People stay outside during night

Bare foot

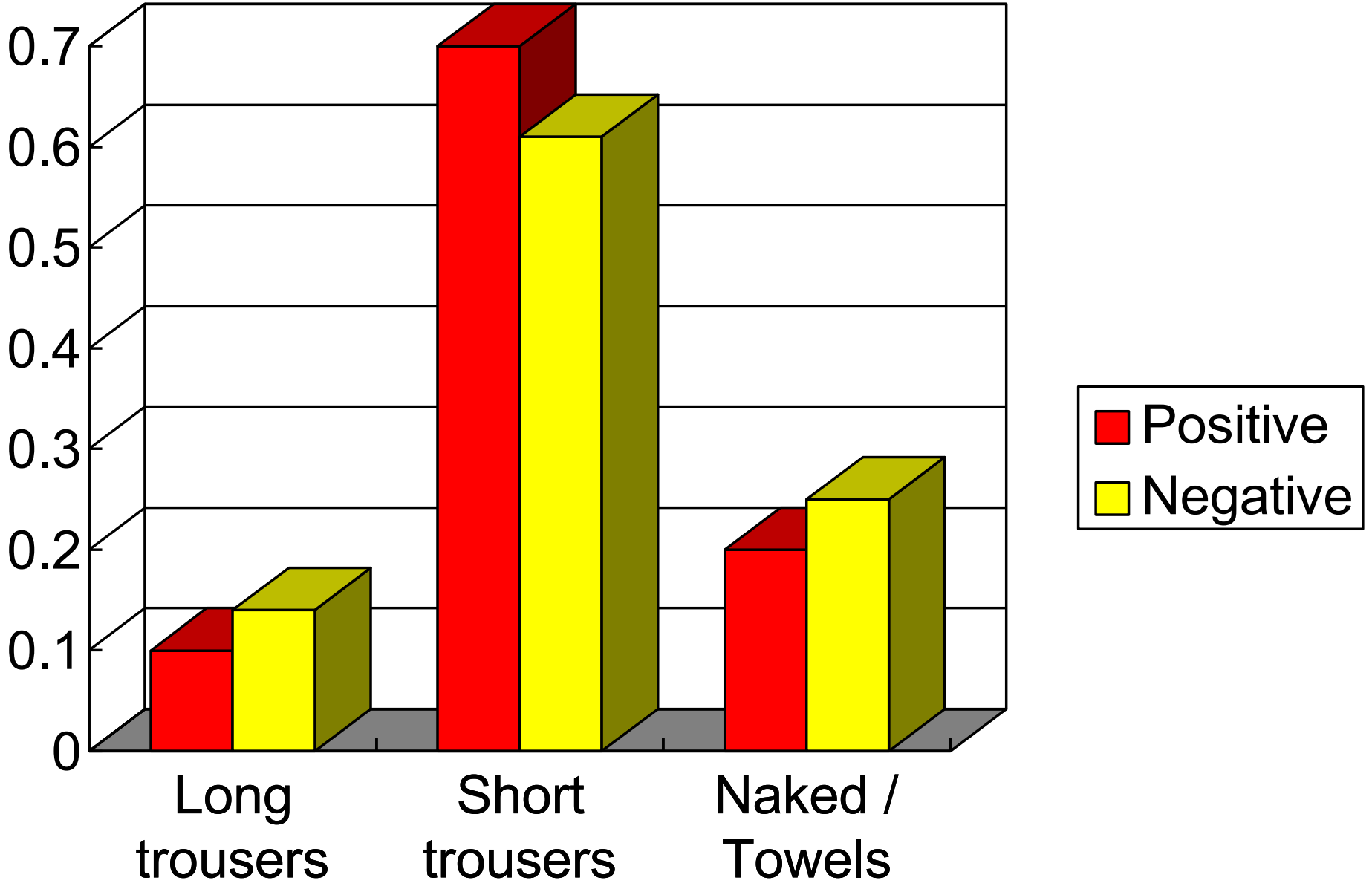
Place to stay and malaria infection



Clothes change everyday



Clothes were significantly related with malaria infection



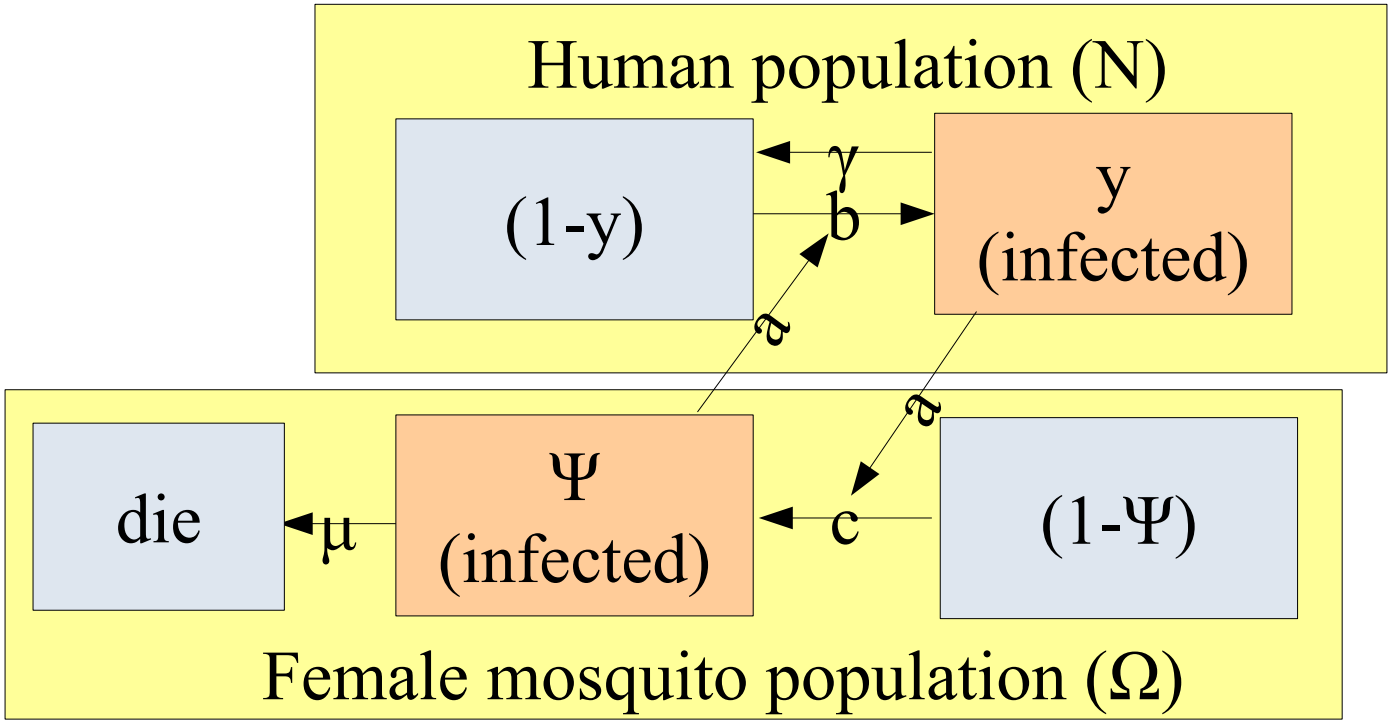
Predicting the effect of behavioral change on malaria infection

- Using simulation model
- Based on the differential equations
  - Kermack-McKendrick model for epidemic
  - Ross-Macdonald model for malaria
  - Dietz-Molineaux-Thomas model (SEIR)
- Implementing stochastic fluctuation of human behavior into SEIR

Mathematical models of malaria transmission

- Basic formulation was "Ross-MacDonald"
- Dietz-Molineaux-Thomas (DMT) included the factors of immunity after recovery
- Other extensions were more heterogeneity, intervention, drug-resistance, transmission-blocking vaccine, multi-strain effects, ...
- But host factors such as human and/or mosquito behavior (as well as genetic diversity) were less included (But zooprophylaxis papers exist)
- My model is unique because it includes stochastic human behavioral protection

Ross-Macdonald Model



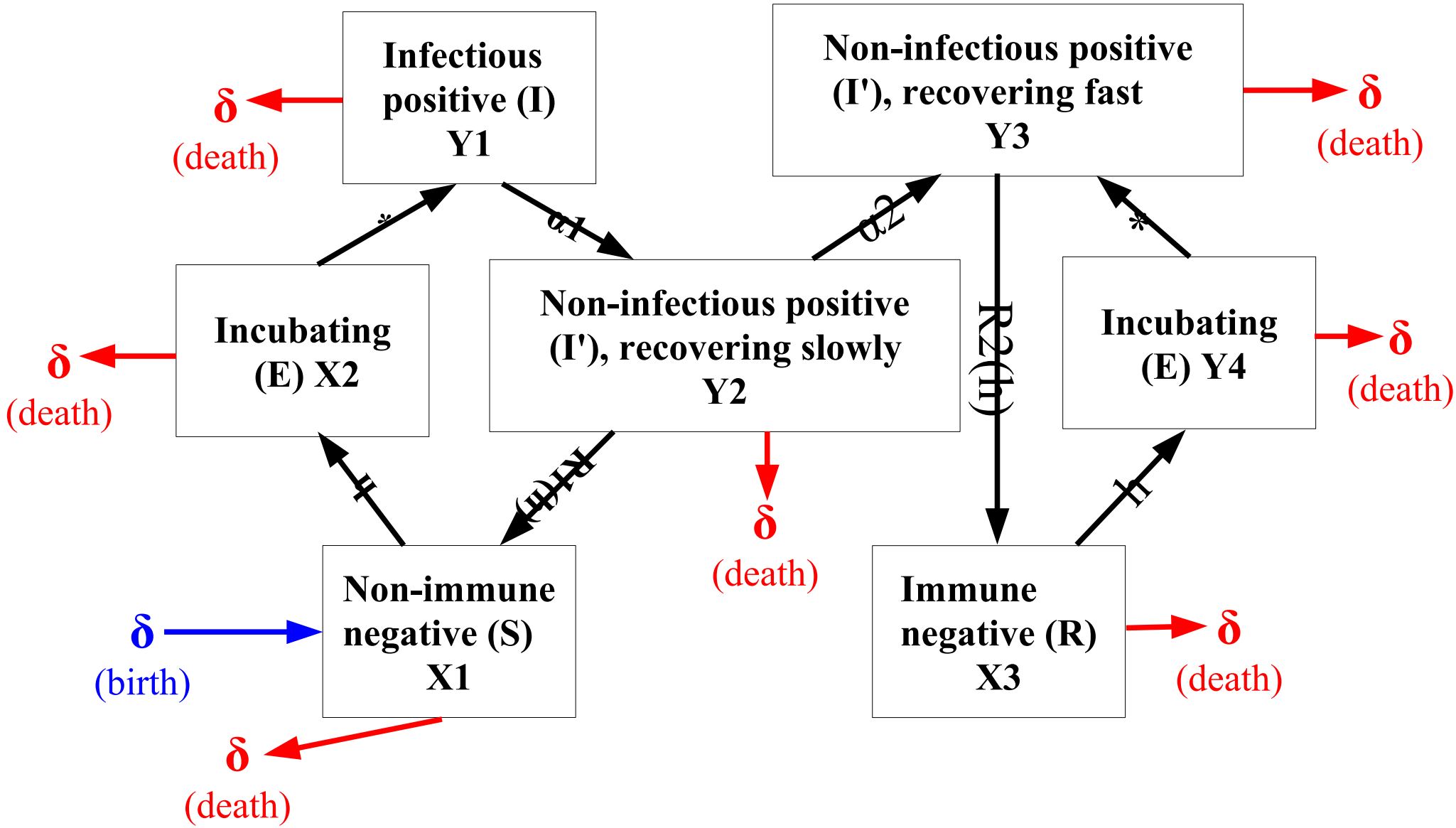
$$\frac{dy}{dt} = \frac{ab\Omega}{N}(1-y)\psi - \gamma y$$

$$\frac{d\psi}{dt} = acy(1-\psi) - \mu\psi$$

Ross R (1916) An application of the theory of probabilities to the study of *a priori* pathometry --- Part I. *Proceedings of the Royal Society of London: Ser A*, 92: 204-230. Macdonald G (1950) The analysis of infection rates in diseases in which superinfection occurs. *Tropical Diseases Bulletin*, 47(10): 907-915. Macdonald G (1955) The measurement of malaria transmission. *Proceedings of the Royal Society of Medicine*, 48: 295-301.

Dietz-Molineaux-Thomas model

Dietz K, Molineaux L, Thomas A (1974) A malaria model tested in the African savannah. *Bulletin of the World Health Organization*, 50: 347-357.



* Assuming all X2 move Y1 after incubation period, unless they die.

DMT's differential equation

Susceptible: $$\frac{dS}{dt} = -\beta SI + \phi R$$

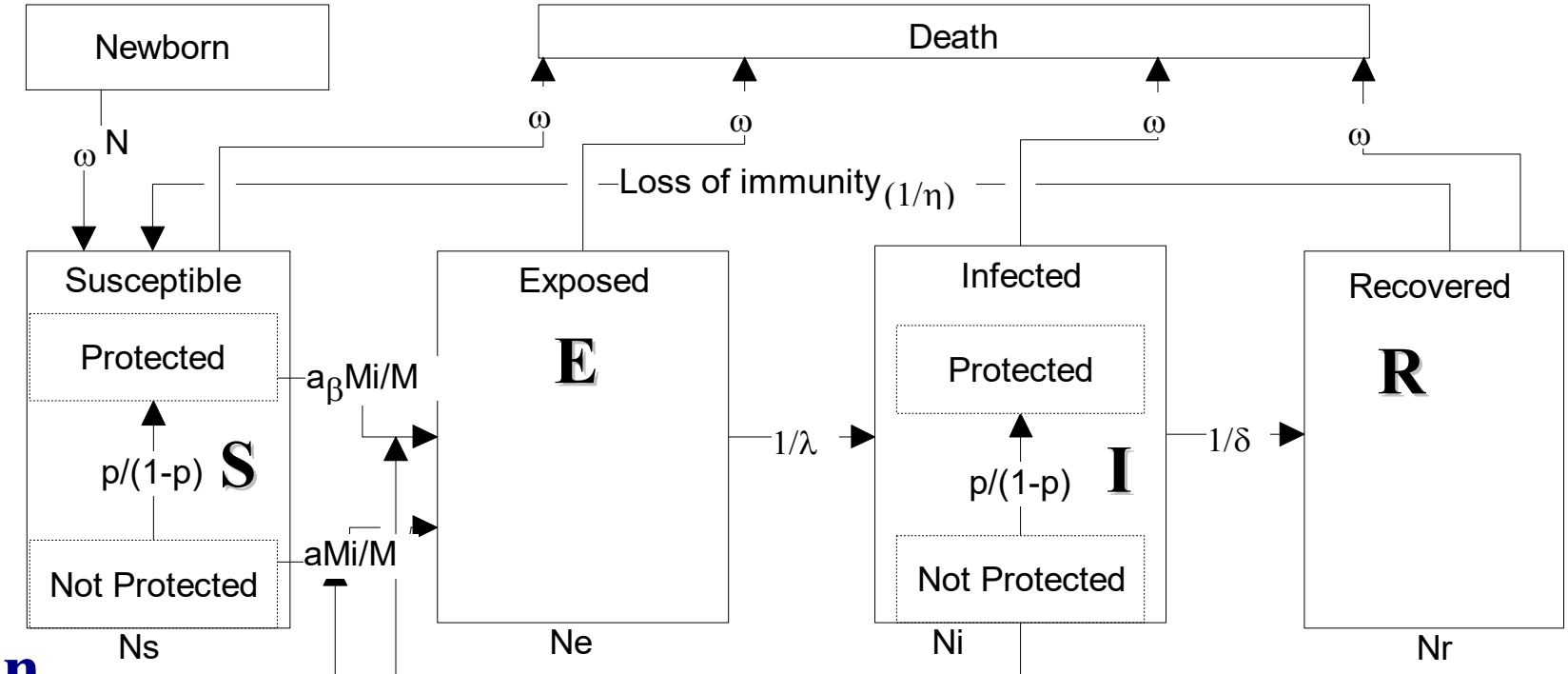
Exposed: $$\frac{dE}{dt} = \beta SI - \tau E$$

Infectious: $$\frac{dI}{dt} = \tau E - \gamma I$$

Recovered: $$\frac{dR}{dt} = \gamma I - \phi R$$

Nakazawa's model framework

Nakazawa M, Ohmae H, Ishii A, Leafasia J (1998) Malaria infection and human behavioral factors: A stochastic model analysis for direct observation data in the Solomon Islands, *Am. J. Human Biol.*, 10: 781-789.



Nakazawa's differential equations

$$\frac{dN_s}{dt} = -\frac{M_i}{M}\alpha B(N_s, 1-p\beta) + \omega(N - N_s) + \frac{1}{\eta}N_r$$

$$\frac{dN_e}{dt} = \frac{M_i}{M}\alpha B(N_s, 1-p\beta) - \frac{1}{\lambda}N_e - \omega N_e$$

$$\frac{dN_i}{dt} = \frac{1}{\lambda}N_e - \frac{1}{\delta}N_i - \omega N_i$$

$$\frac{dN_r}{dt} = \frac{1}{\delta}N_i - \frac{1}{\eta}N_r - \omega N_r$$

$$\frac{dM_s}{dt} = -\frac{\alpha}{M}B(N_i, 1-p\beta)M_s + \mu(M - M_s)$$

$$\frac{dM_e}{dt} = \frac{\alpha}{M}B(N_i, 1-p\beta)M_s - \frac{1}{\tau}M_e - \mu M_e$$

$$\frac{dM_i}{dt} = \frac{1}{\tau}M_e - \mu M_i$$

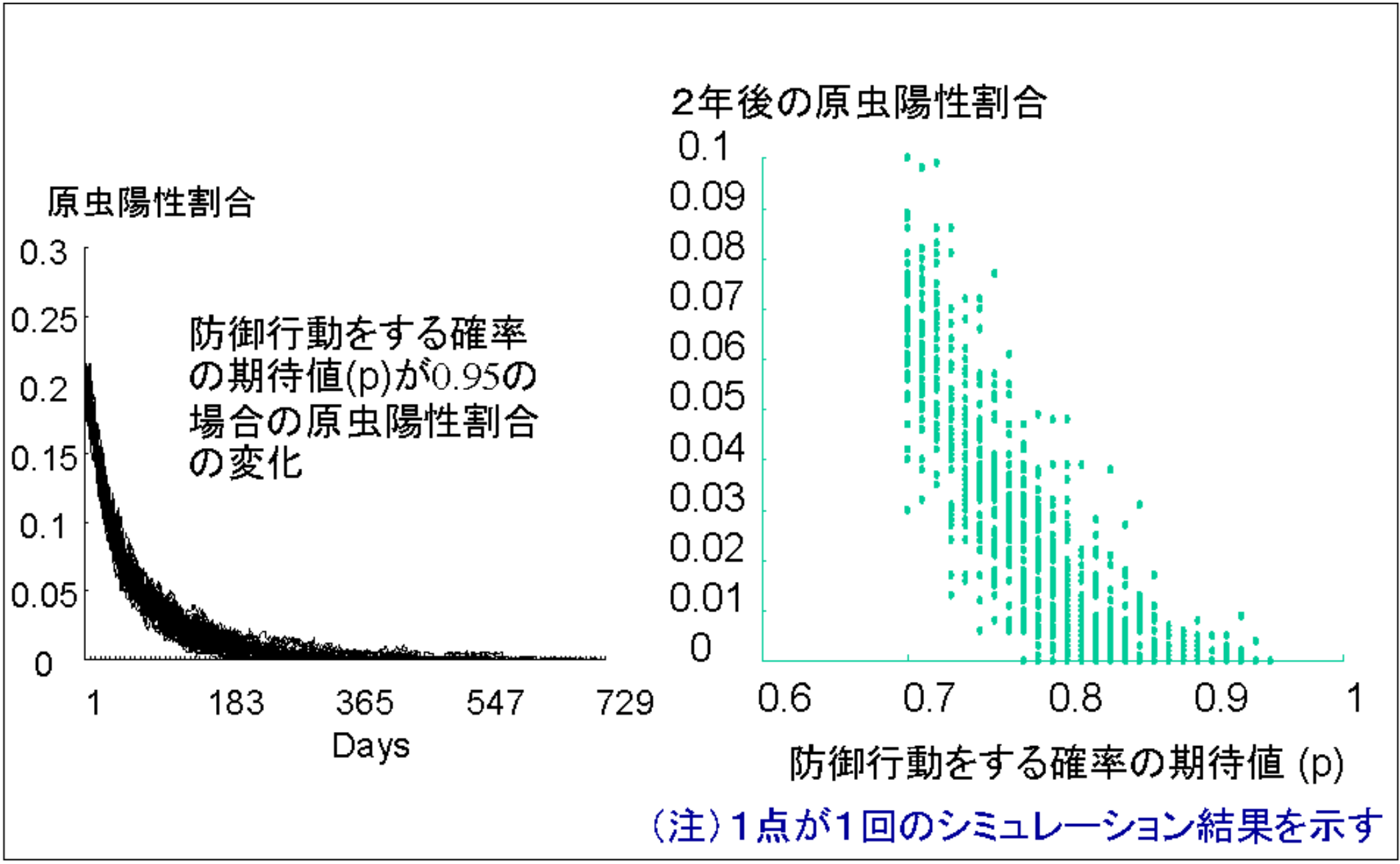
Simulation program in R

```
Mer <- 0.016242; Mir <- 0.008238; maxdate <- 365*2; PI <- rep(0,maxdate)
a <- 5.0; delta <- 14.0; eta <- 14.0; r <- 5.0; omega <- 0.0001
mu <- 0.2; tau <- 10.0; phi <- 5.0; lambda <- 14.0

simexec <- function(px,beta) {
            ZI <- rep(0,maxdate)
            Ns <- 400; Ne <- 200; Ni <- 200; Nr <- 200
            N <- Ns+Ne+Ni+Nr
            M <- floor(N*(1-px*beta)*r*a*((1-mu)^phi)/mu)
            Me <- floor(M*Mer); Mi <- floor(M*Mir); Ms <- M - Me - Mi
            for (j in 1:(maxdate-1)) {
                        ZI[j] <- Ni/N
                        IB <- rbinom(1,rbinom(1,Ns,(1-px*beta)),a*Mi/M)
                        if (!is.na(Ms)) { if (a*Ms/M < 1) {
                         EB <- rbinom(1,rbinom(1,Ni,(1-px*beta)),a*Ms/M) } else {
                         EB <- rbinom(1,Ni,(1-px*beta)) }} else { EB <- 0 }
                        dNe <- rbinom(1,Ne,omega); dNi <- rbinom(1,Ni,omega); dNr <- rbinom(1,Nr,omega)
                        nNs <- dNe + dNi + dNr
                        Fever <- rbinom(1,Ne,1/lambda)
                        Recover <- rbinom(1,Ni,1/delta)
                        LI <- rbinom(1,Nr,1/eta)
                        Ns <- Ns - IB + nNs + LI
                        Ne <- Ne + IB - dNe - Fever
                        Ni <- Ni - dNi + Fever - Recover
                        Nr <- Nr - dNr + Recover - LI
                        GI <- rbinom(1,Me,1/tau)
                        dMe <- rbinom(1,Me,mu); dMi <- rbinom(1,Mi,mu)
                        nMs <- dMe + dMi
                        Ms <- Ms - EB + nMs; Me <- Me + EB - GI - dMe; Mi <- Mi + GI - dMi
            }
            ZI[maxdate] <- Ni/N
            ZI
}

PI <- simexec(0.7,0.8)
plot(1:maxdate,PI,type="l",ylim=c(0,0.4),xlab="days",ylab="parasite rate",
 main="Change of parasite rates as the result of simulation\n [p=0.7, beta=0.8]")
for (i in 2:50) {
            PI <- simexec(0.7,0.8)
            lines(1:maxdate,PI)
}
```

Major results of Nakazawa's model



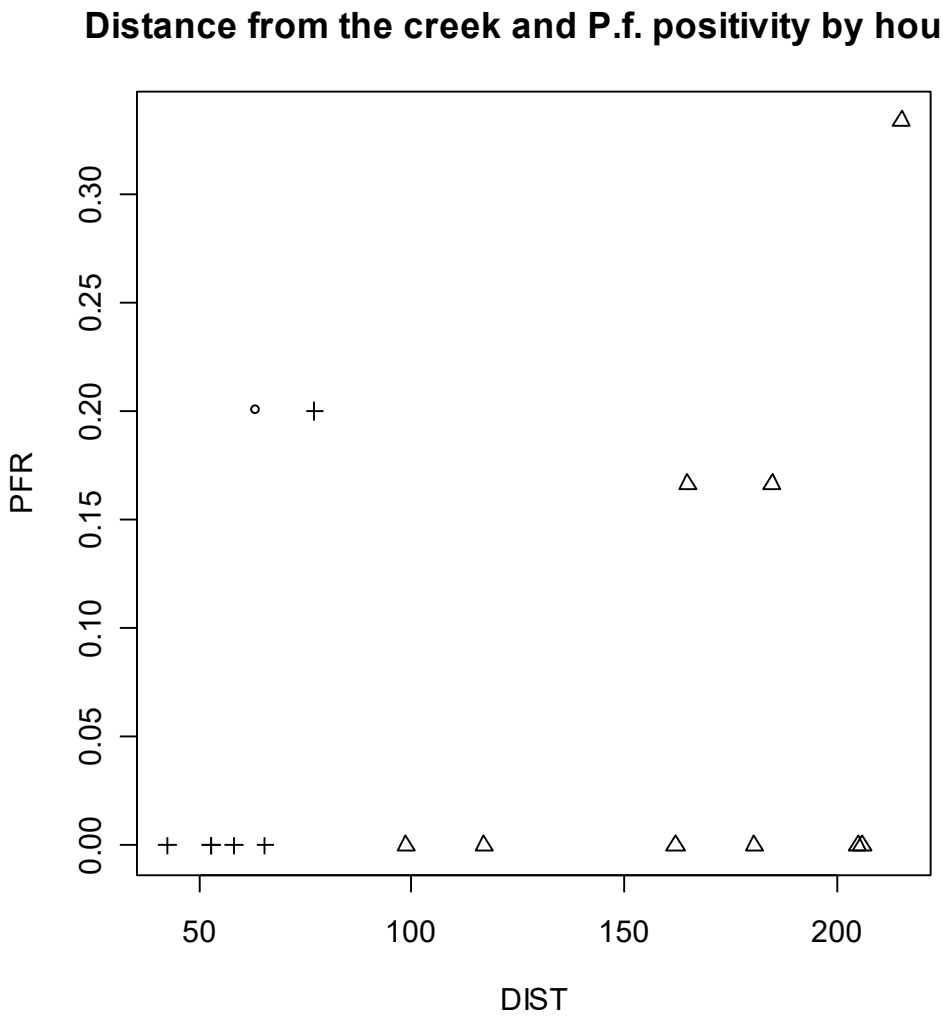
Recent changes

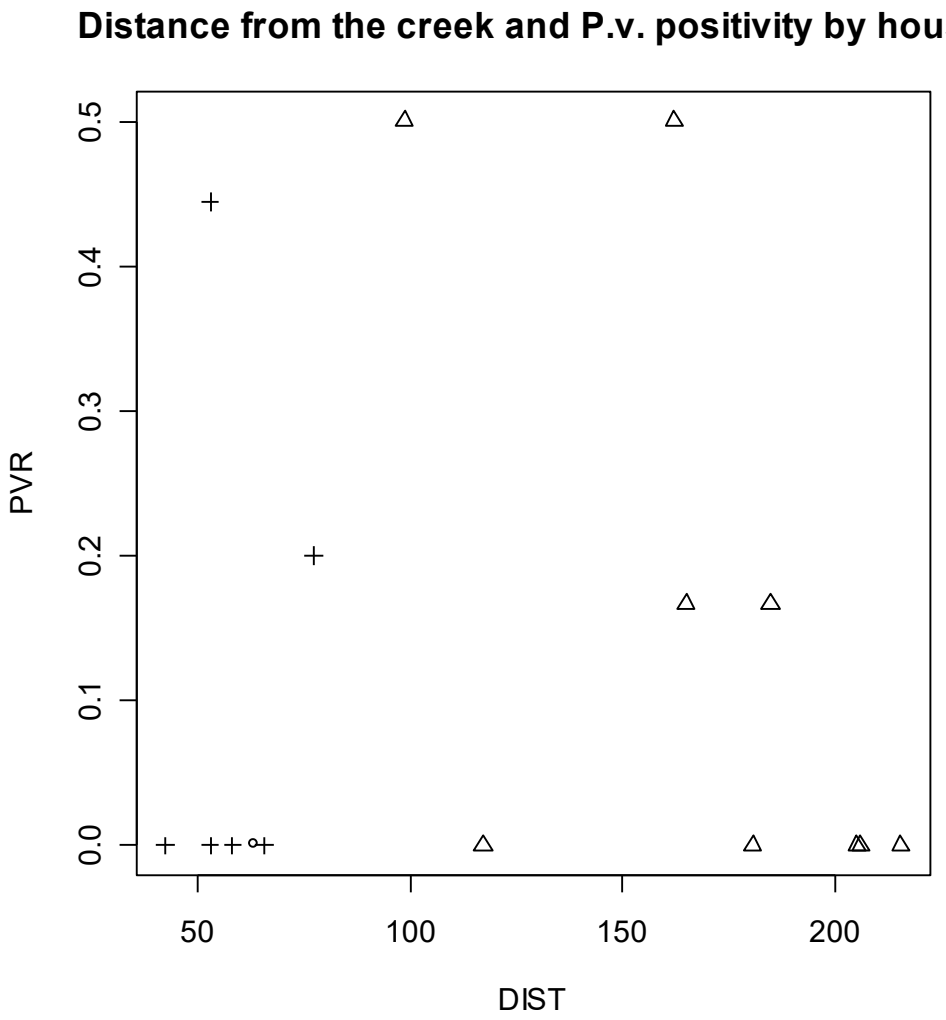
- Baby wears socks
- Screening and ACT every half year
- Repeated infection still remains for geographically restricted areas' residents

Low parasite rates and dominance of *P.v.* ?

The houses marked by circles have more than two malaria patients.

Relationship of the distance from creek and positive/house





OIL PALM PLANTATION
"GPPOL"s

New habitat for mosquitoes?

+ Market economy oriented behavior, less compliance?

RICE FIELD, supported by TAIWAN