Introduction:

Infections and Infectious diseases

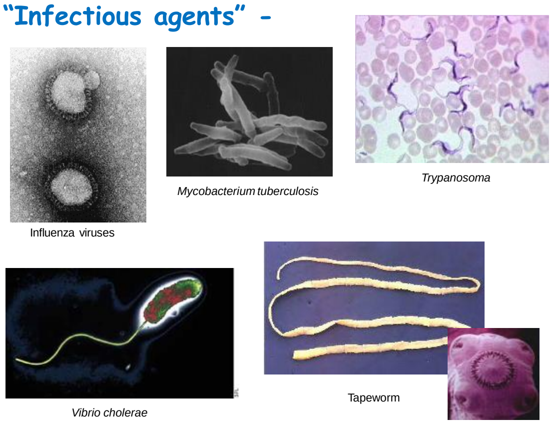
Introduction to Infectious Disease Modelling and its Applications
June - 2018

PEM Fine
LSHTM

What is an infectious disease ?

- Involves a "living" "infectious" agent (prion, virus, bacterium, protozoan, helminth….) or a toxin produced by a microbe as a necessary (though not always sufficient) cause
- Note the "microbiome" and its implications

"Infectious agents" -



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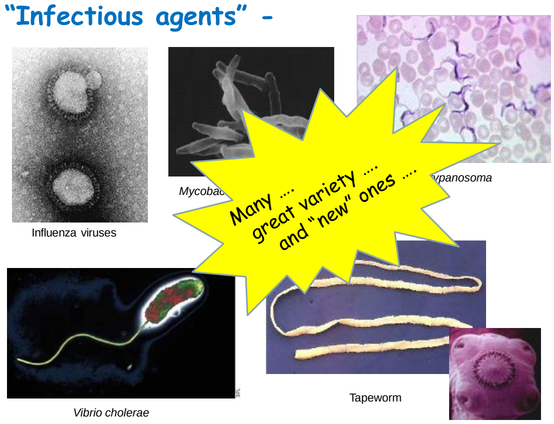

Who ? "Natural history of infection"

Susceptible (*vs* resistance, immunity….) *
Exposure (type of "contact", dose….) **
Infection (abortive, persistent, subclinical ….)***
Infectiousness (varies greatly)
Disease (a "case", severity….) ****
Recovery (+/- immunity ?), or death

* May not be "yes-or-no" binary
** Note odd use of term in epidemiology *and modelling* literatures !
*** Not a synonym for disease !
**** Diseases are not transmitted ! *thus STIs, not STDs, etc*

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Time course

Incubation period – from infection to disease
typically has a right-skew distribution

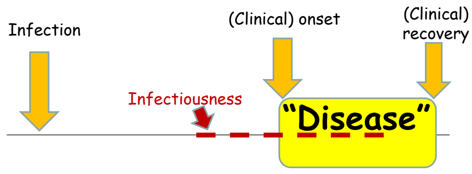
Pre-infectious period -- from infection to infectiousness
(sometimes called the "latent period" but this is a poor term as it also means various other things)

Serial interval -- from clinical onset to clinical onset

Generation time -- from infection to infection
(difficult to observe directly)

Time course

Much variation between infections and individuals



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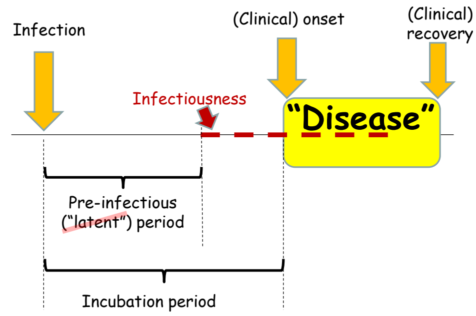
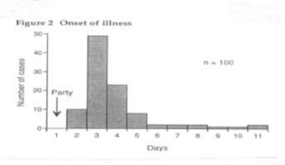


Common source epidemics

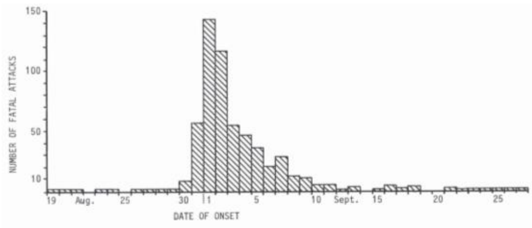
***Point source* epidemic curves reflect distribution of incubation periods**

- Distributions are typically "right skew" or "log-normal" (thus median or geometric mean may be the best measure – but range is preferable)
- Why this variation ?



Shigella sonnei
Incubation period: "12 to 96 hours (usually 1 - 3 days)"
CDR 26/02/93

Onsets of fatal cases of cholera near Golden Square in Soho, London, 19 August – 30 September, 1854



Point source ?

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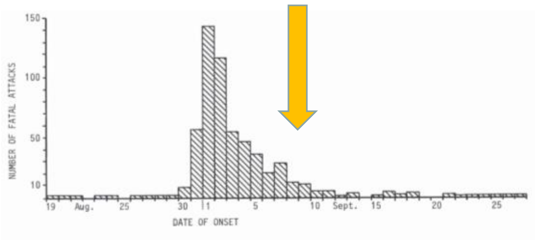

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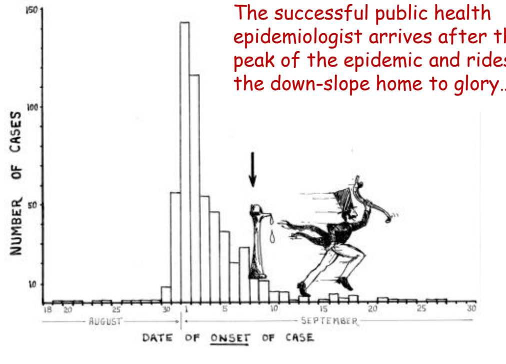
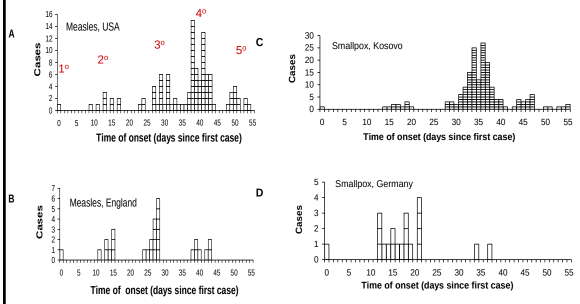


"Snow's Law":
The successful public health epidemiologist arrives after the peak of the epidemic and rides the down-slope home to glory….

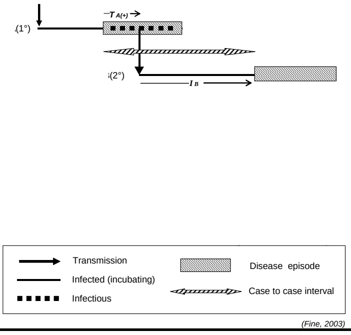
"Propagated" epidemics

Successive "generations" of cases



Refs in Fine 2003

"Serial interval": time between successive *onsets* in a chain of transmission



$SI = T_A + I_B$

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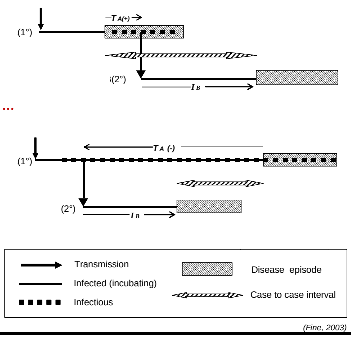
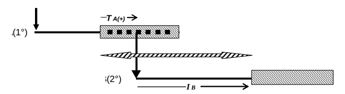


$SI = T_A + I_B$

But …

!

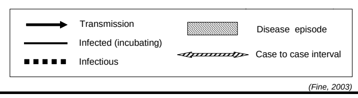
"Serial interval": time between successive *onsets* in a chain of transmission



$SI = T_A + I_B$

Generation interval = time between successive infections, or transmissions

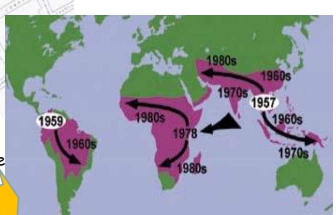
rarely "observed", but important concept in modelling



Place …

John Snow's map of Cholera deaths in Soho, August – September 1854

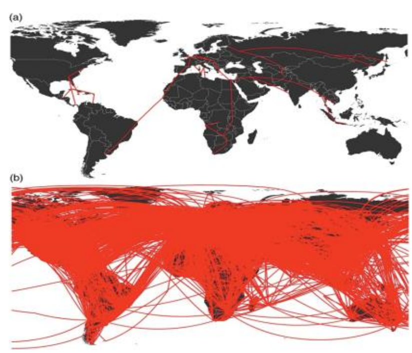
Pattern driven by source, population distribution and behaviour



Spread of Cloroquine resistance In *Plasmodium falciparum*

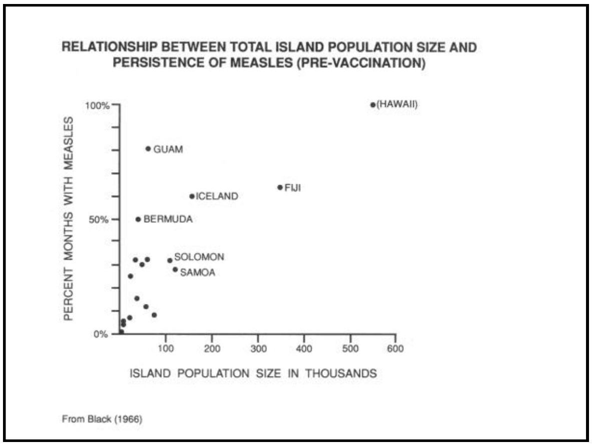
Pattern driven by population movement, treatment, genetics

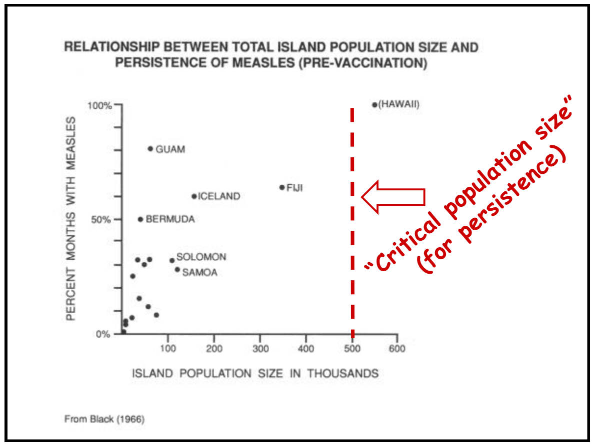
Global spread of infection a function of air travel networks ….



1933

2010


RELATIONSHIP BETWEEN TOTAL ISLAND POPULATION SIZE AND PERSISTENCE OF MEASLES (PRE-VACCINATION)
PERCENT MONTHS WITH MEASLES
100%
50%
0%
(HAWAII)
GUAM
FIJI
ICELAND
BERMUDA
SOLOMON
SAMOA
100 200 300 400 500 600
ISLAND POPULATION SIZE IN THOUSANDS
From Black (1966)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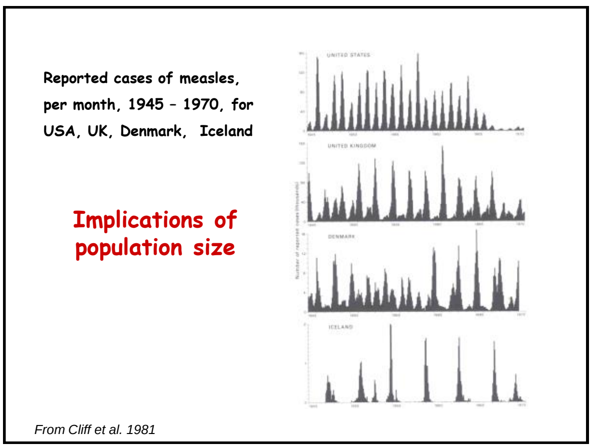
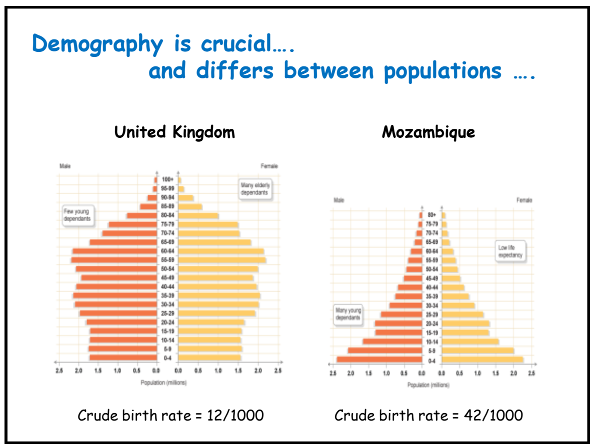
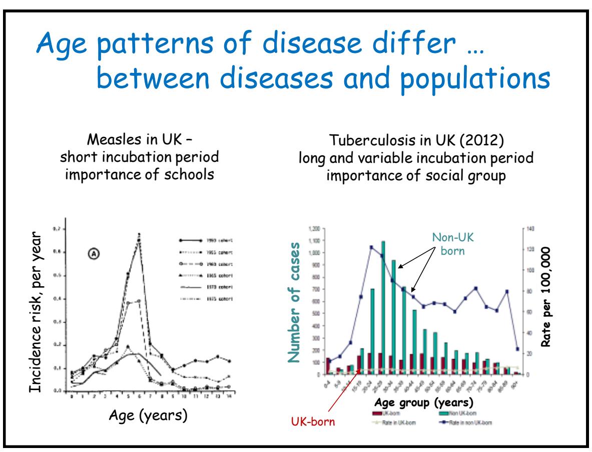
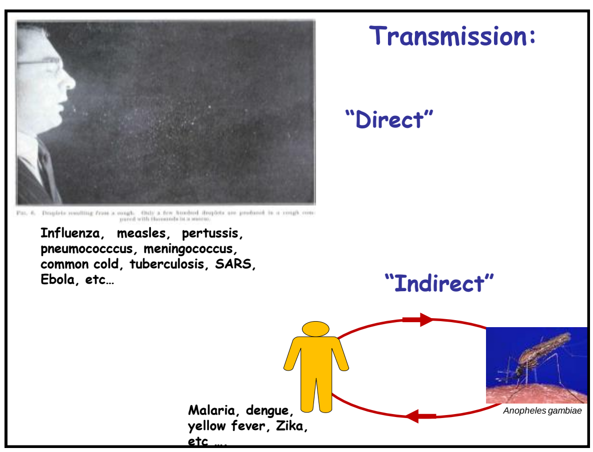
ISLAND POPULATION SIZE IN THOUSANDS
"Critical population size" (for persistence)
From Black (1966)

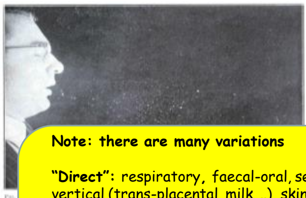

Reported cases of measles, per month, 1945 – 1970, for USA, UK, Denmark, Iceland
Implications of population size
From Cliff et al. 1981


Demography is crucial….
and differs between populations ….
United Kingdom
Mozambique
Crude birth rate = 12/1000
Crude birth rate = 42/1000


Age patterns of disease differ …
between diseases and populations
Measles in UK –
short incubation period
importance of schools
Tuberculosis in UK (2012)
long and variable incubation period
importance of social group
Incidence risk, per year
Age (years)
Non-UK born
Number of cases
Rate per 100,000
Age group (years)
UK-born


Transmission:
"Direct"
Influenza, measles, pertussis, pneumococcus, meningococcus, common cold, tuberculosis, SARS, Ebola, etc…
"Indirect"
Malaria, dengue, yellow fever, Zika, etc ….
Anopheles gambiae

Transmission:



"Direct"

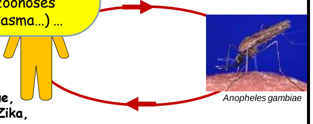
Note: there are many variations

"Direct": respiratory, faecal-oral, sexual, vertical (trans-placental, milk …), skin ….

"Indirect": insect vectors, water, food, various objects ("fomites"), soil (eg various helminths)….

From environment reservoirs: zoonoses (rabies, brucella….), soil (histoplasma…) …

"Indirect"



Malaria, dengue, yellow fever, Zika, etc ….

Measures of transmissibility

nb: Standard incidence measures (new cases per population per time) do not measure this

Particularly important for "emerging" infections

1. **"Secondary attack rate"**
   Risk (proportion "attacked", among contacts)

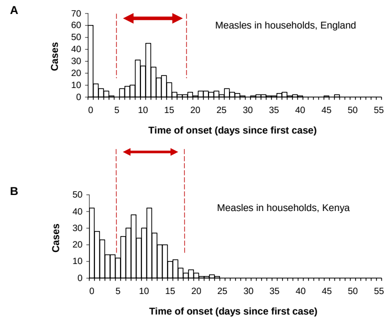
2. **Reproduction number**
   Number of transmissions per source
   Demographic analogy (number of progeny)
   Implications for infection maintenance / persistence

Secondary attack rate

Definition: The proportion "attacked" among individuals "in contact" with a (single) primary case

- The "classic" measure of transmissibility
- "Attacked" should mean *infected*, not just diseased
- Typically defined for households (to standardise)
- 2°AR higher in household than in community
- Need to enumerate (susceptible) contacts, and secondary "cases"

Identifying secondary cases in households (Measles)



Refs in Fine 2003

Household secondary attack rates of measles, by age and population

Age group	Providence USA (1929 – 1934)	Cirencester UK (1947 – 1951)
<1	41 %	40 %
1 – 14	81 %	80 %
>14	17 %	16 %

WHY ?

Data from Wilson (1939) and Hope-Simpson (1952)

(refs in Fine 2003)

Reproduction numbers

R = Average number of transmissions per "case"

Reproduction numbers

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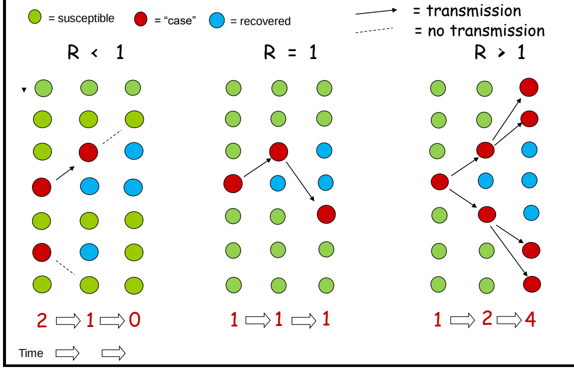
Crucially important word !

- Needs precise definition, always
- In this context:
  = an infected individual

Reproduction numbers

R = Average number of transmissions per "case"



Reproduction numbers

R_n = *Net number* of "successful" transmissions per "case"

Depends upon:

1. Agent ("transmissibility", biology)
2. Host population (numbers, contact, hygiene,….)
3. Proportion immune (*maximum when zero immunes*)

"R_0" = **(Average) number of transmissions from a single "case" introduced into a totally susceptible population**

= **"Basic reproduction number"**
(must exceed unity for infection to persist)

Estimation of R_0

1. **Simple concept** $R_0 = \beta\ n\ D$

where β = per contact risk of transmission

n = number of contacts per day

D = Duration of infectiousness

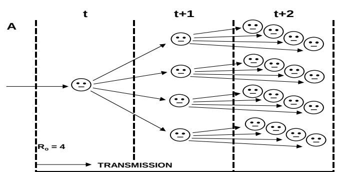
This is intuitively OK, but difficult to use, as "contacts" vary in type (β varies) and are often repeated (multiple contacts with same individuals), and there is in reality great heterogeneity….

Most commonly used in context of sexually transmitted infections

Estimation of R_0

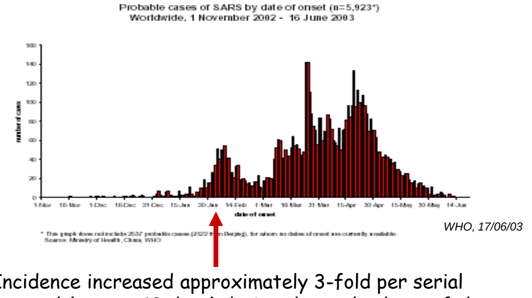
2. From incidence increase in early epidemic

In theory, incidence trend after introduction into a totally susceptible population should begin as a geometric progression, multiplying by R_0 in each successive "generation" (ie in each successive serial interval ….)



Exponential increase, × R_0 (= 4) each generation, until immunes build up….

Example : How transmissible was the SARS agent ?

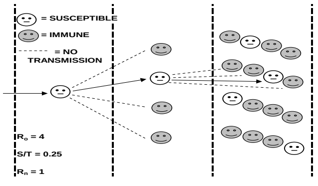


Incidence increased approximately 3-fold per serial interval (approx 10 days) during the early phase of the epidemic, before control measures introduced. So R_0 ~ 3.

Estimation of R_0

3. Ubiquitous immunising infections

Once such an infection is established in a population, its R_0 should be (roughly) the inverse of the proportion susceptible in the population (assuming homogeneous mixing)



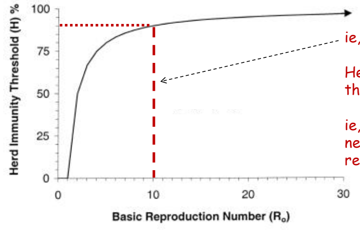
If proportion susceptible = $1 / R_0$,
Look what happens !

NB: That's when proportion immune = $1 - 1/R_0$,
$= (R_0 - 1) / R_0$

(Called the "herd immunity threshold")

Herd immunity threshold:

$$H = 1 - 1/R_0 = (R_0 - 1) / R_0$$



ie, if $R_0 = 10$,

Herd immunity threshold is 90 %

ie, more than 90 % need to be immune to reduce transmission

Estimation of R_0

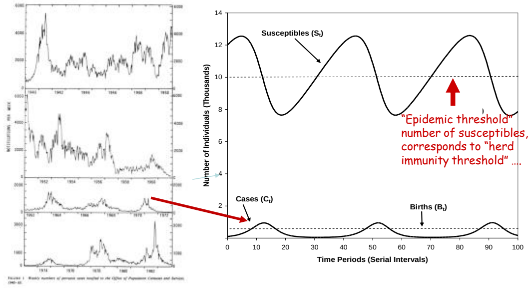
3. Ubiquitous immunising infections, cont..

If R_0 is the reciprocal of the proportion susceptible to an ubiquitous immunising infection, then it can be estimated roughly by a simple trick:

If everyone lives, on average *L* years, and becomes infected on average at age *A*, then a proportion *A/L* of all lives is spent susceptible, and that should be the average proportion susceptible in the population: so

$$R_0 \sim 1 / (A/L) = L/A$$

The "balance" of susceptibles, cases and immunes… can explain non seasonal cycles



Pertussis in England and Wales

Examples of transmissibility measures ("Rough" !)

Infection	Population	H/hold 2° AR	R_0 *	Herd Imm. threshold
Monkeypox	Zaire	c. 10 %	c. 0.8	n.a.
Smallpox	India	c. 40 %	c. 5	c. 80 % **
Measles	Europe	c. 80 %	c. 15	c. 93 % **
Influenza	USA	c. 15–30 %	c. 2	c. 50 % **
Malaria	W Africa	Not applic	c. 100 !	c. 99 % **

* Considerable variation between (and within) populations

** Nice in theory ($1-1/R_0$), but underestimates because of heterogeneity

Special characteristics of infections and infectious disease epidemiology

- Importance (c.25 % of DALYS, > 50 % in Africa, 2010)
- Novelty (emerging infections)
- Biological understanding (to the molecule….)
- Dynamic interaction of two or more populations
  (thus appropriate for modelling)
- Dependency (cases are sources of new cases)
- Immunity (historical record)
- Urgency (because of potential for spread)
- Potential for eradication (not uncontroversial !)