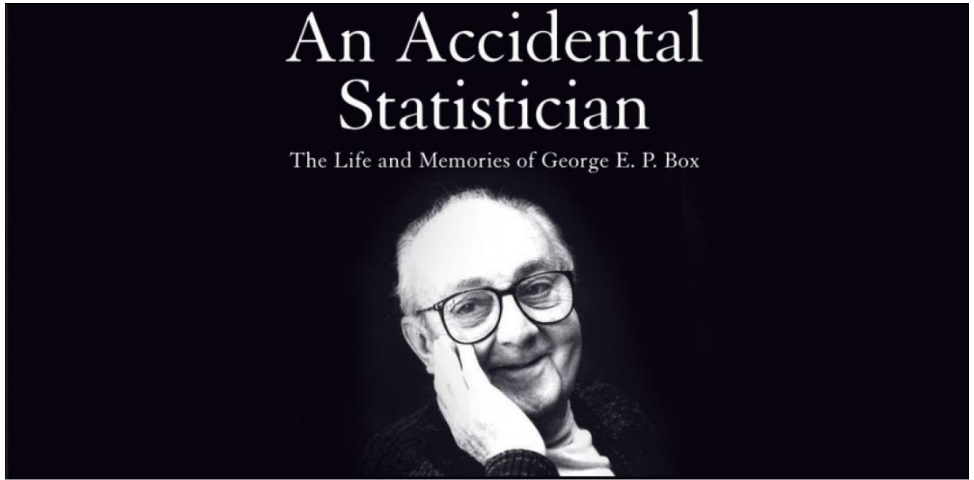
מודלים מתמטיים בחקר מגיפות

הרצאת מבוא

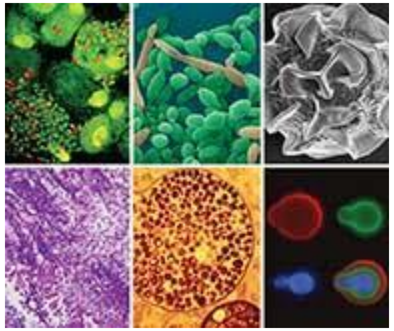
עמית הופרט מכון גרטנר

All models are wrong, but some are useful!

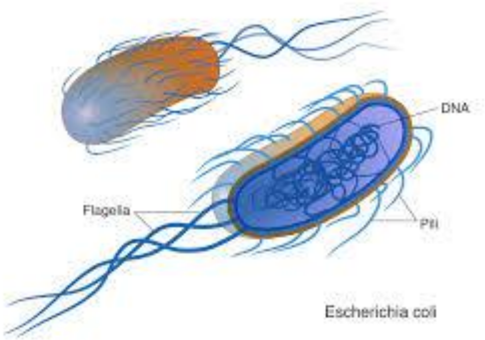


Introduction to Infectious Diseases

- Infectious diseases are disorders that are caused by organisms, usually microscopic in size, such as bacteria, viruses, fungi, or parasites that are passed, directly or indirectly, from one person to another. Humans can also become infected following exposure to an infected animal that harbors a pathogenic organism that is capable of infecting humans.

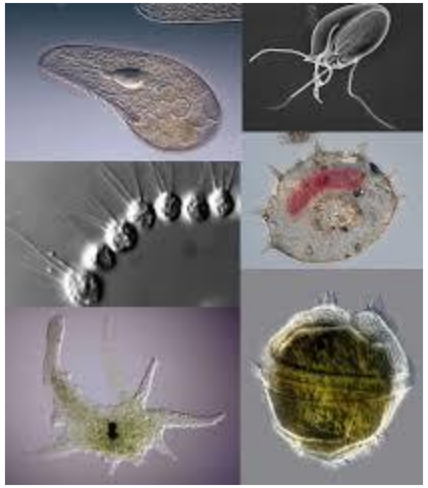


Fungi



Bacteria

Viruses



Protozoa

Parasites

- Infectious diseases are a leading cause of death worldwide, particularly in low income countries, especially in young children.

- Three infectious diseases were ranked in the top ten causes of death worldwide in 2016 by the World Health Organization. They are:
- Lower respiratory infections (3.0 million deaths)
- Diarrheal diseases (1.4 million deaths)
- Tuberculosis (1.3 million deaths).
- HIV/AIDS, which was previously on the list, has dropped from the global list of the top ten causes of death (1.0 million deaths in 2016 compared with 1.5 million in 2000), but it is still a leading cause of death in low income countries.
- Malaria, accounts for a top cause of death in low income countries.

Pathogens

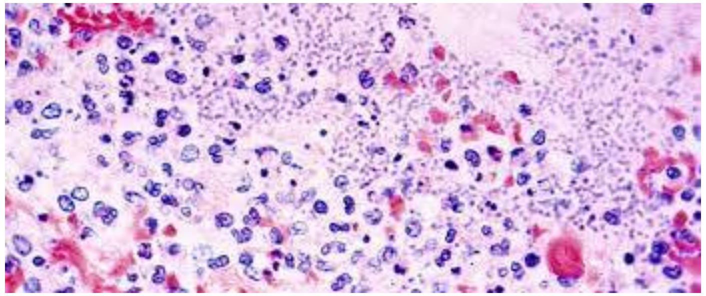
- Bacterial
  - About 1 million on the head of a pin
  - Salmonella, botulism, anthrax
- Viral
  - About 230 million HIV on the head of a pin.
  - Not affected by antibiotics
- Chemical toxins
  - Organic and inorganic
  - Allergens, carcinegens, neurotoxins, teratogens
- Parasitic (multi-cell)
  - tapeworms, trichinosis, schistosomes
- Fungal
  - yeast infections, Candida
- Protozoa
  - Single cell organisms
- Prions
  - Relatively new discovery,Infectious agent with protein-like qualities
  - Thought to be responsible for BSE (mad cow disease) and vCJD
  - Difficult to disinfect

Historical Overview

- Traditionally, infectious disease was the biggest health threat to human civilization.
- As medical technology and public health reduced the threat of infectious diseases, lifespans increased to the point of making chronic diseases more prevalent.

Infectious Diseases in History

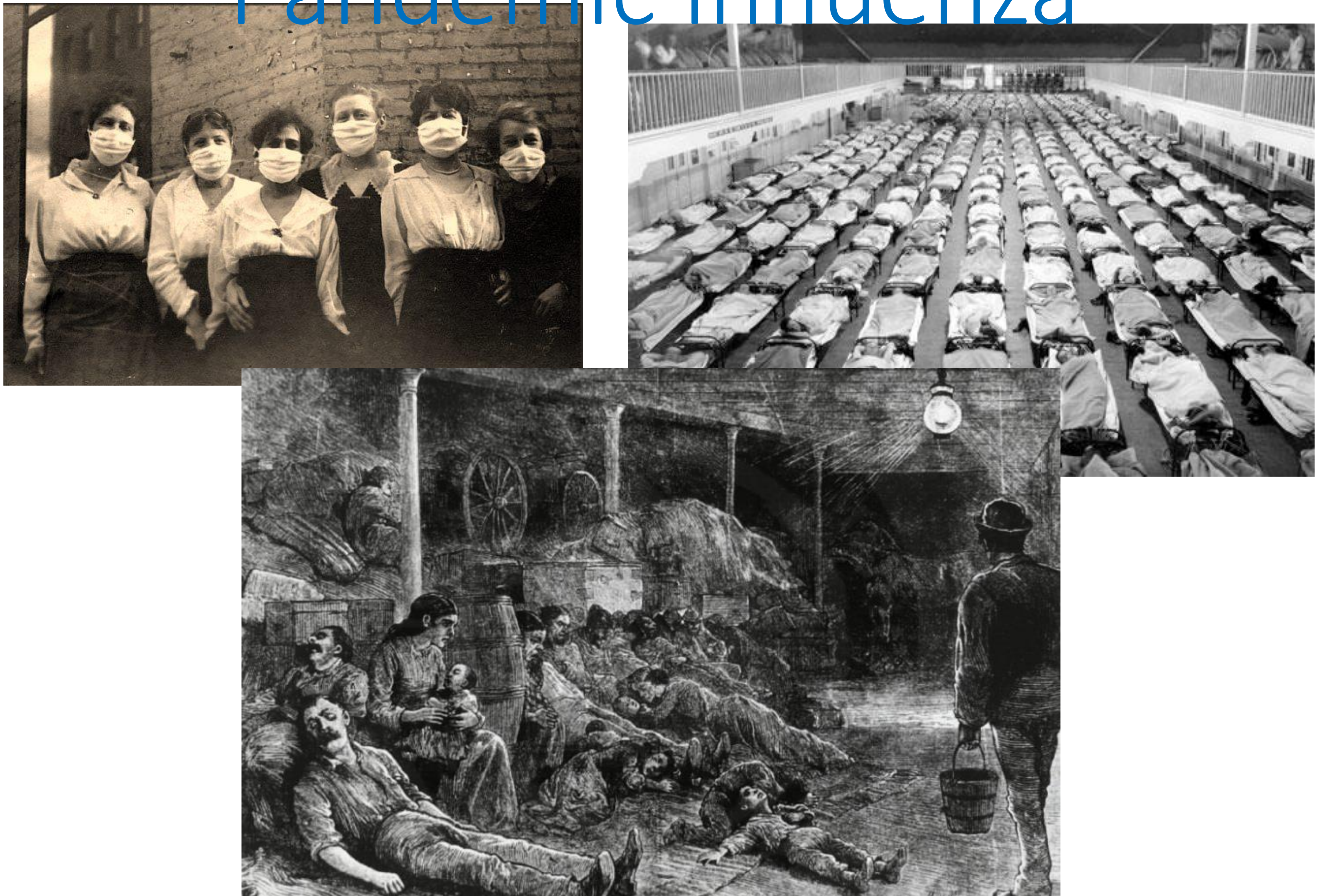
- In the mid-1300’s about 23 million people in Europe died from plague.
  - Plague-related deaths represented 10-15% of each new generation for a period of about 100 years.
  - The population shifts changed the cultural and political makeup of Europe



Influenza

- By many estimates, major flu outbreaks occur about every 11 years.
- The 1918 flu pandemic killed 50-100 million people within about 18 months.
  - More people died worldwide than in all of the wars of the 20th century, combined.
- The 1976 swine flu scare resulted in a national immunization program.
  - The fear was that the swine flu was a close variant of the 1918 virus and would trigger another pandemic.

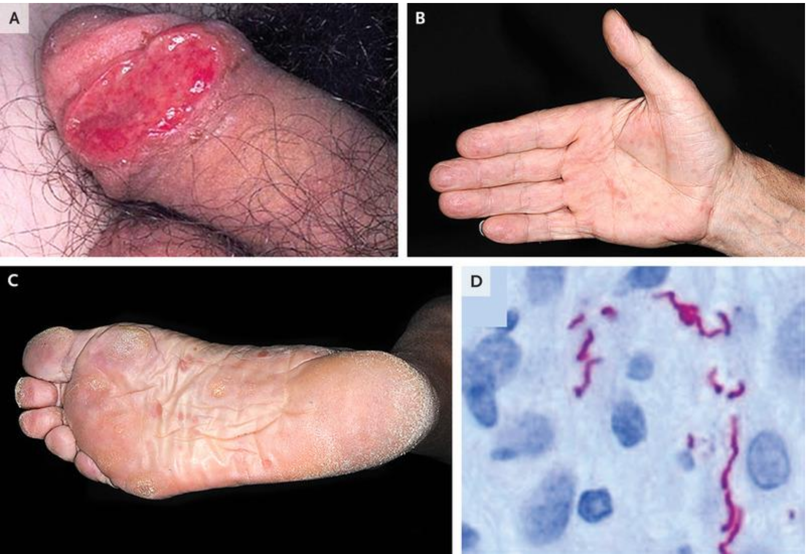
Pandemic Influenza



Syphilis; HIV/AIDS

- Is thought to have been brought back by Columbus’ crew from the New World to Europe.
  - Often treated with mercury, which resulted in many individuals with mercury poisoning.

- Human Immunodeficiency Virus was first detected in 1980.
  - Confirmed index patient was a Canadian flight steward.
  - The earliest known case may date back to 1958.



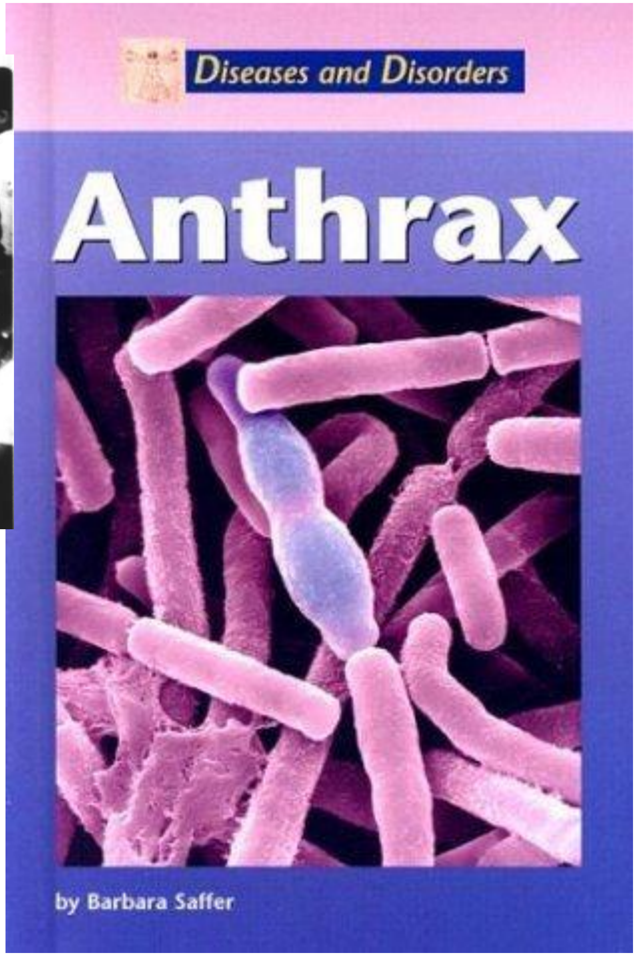
New Concerns

- Increased frequency of travel combined with short travel times mean that pathogens are no longer geographically isolated
  - One reason that Ebola has never spread has been the remote areas in which it is found.
- MDRs – Multiple drug resistant bacterial strains.
  - A variety of bacteria no longer respond to traditional antibiotics as they have begun to mutate and adapt.
  - Partially due to inappropriate antibiotic use.

Great concern about the deliberate introduction of diseases by bioterrorists

- Bioterrorism

- Anthrax
- Smallpox



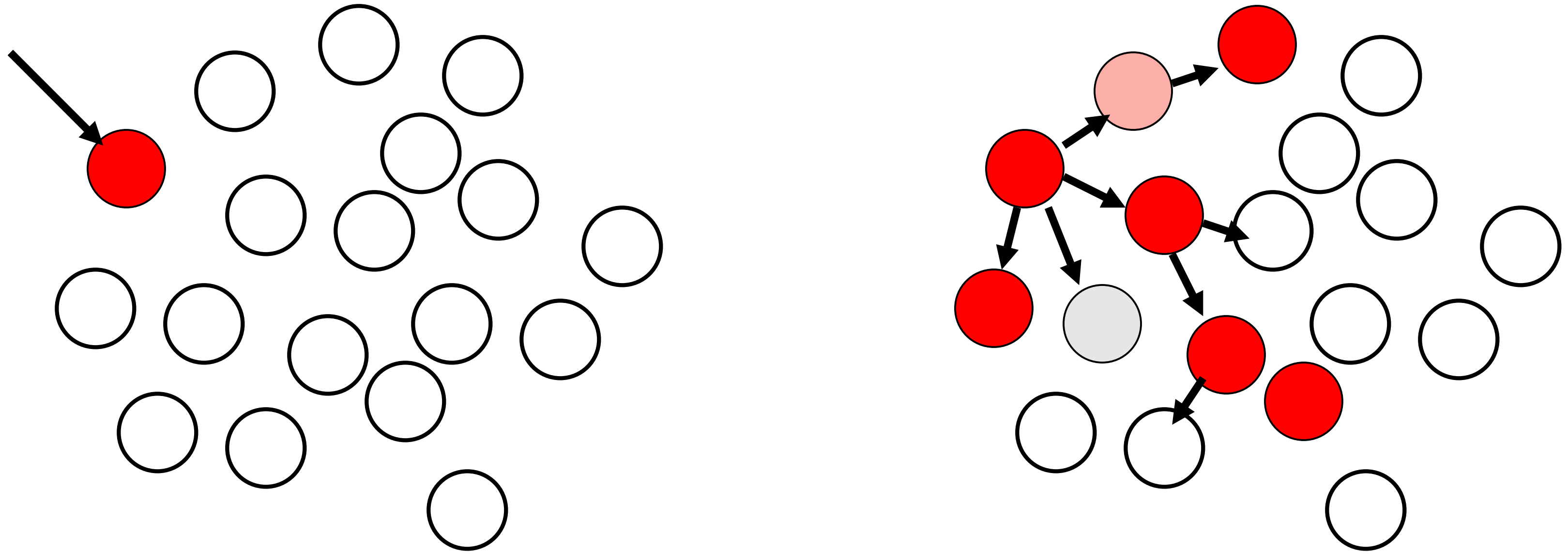
Diseases and Disorders

Anthrax

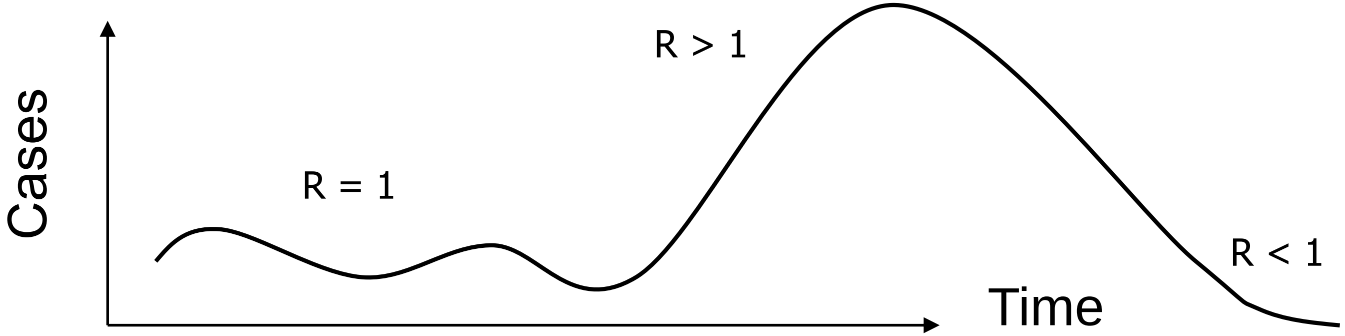
by Barbara Saffer

What is *infectious disease epidemiology?*

- A case is a risk factor …
  - Infection in one person can be transmitted to others



Endemic - Epidemic - Pandemic



- **Endemic**
  - **Transmission occur, but the number of cases remains constant**
- **Epidemic**
  - **The number of cases increases**
- **Pandemic**
  - **When epidemics occur at several continents – global epidemic**

Reproductive Number, R_0

A measure of the potential for transmission

***The basic reproductive number*, R_0**, the mean number of individuals directly infected by *an infectious case* through the total infectious period, when introduced to a susceptible population

probability of transmission per contact

$$R_0 = p \cdot c \cdot d$$

duration of infectiousness

contacts per unit time

Infection will …..	disappear, if	$R < 1$
	become endemic, if	$R = 1$
	become epidemic, if	$R > 1$

Reproductive Number, R_0

- If $R_0 < 1$ then infection cannot invade a population
  - implications: infection control mechanisms unnecessary
- If $R_0 > 1$ then (on average) the pathogen will invade that population
  - implications: control measure necessary to prevent (delay) an epidemic

What determines R_0 ?

$$R_0 = p \cdot c \cdot d$$

p, transmission probability per exposure – depends on the infection

- HIV, p(hand shake)=0, p(transfusion)~1, p(sex)=0.001
- interventions often aim at reducing *p*
  - use gloves, screene blood, condoms

c, number of contacts per time unit – relevant contact depends on infection

- same room, within sneezing distance, skin contact,
- interventions often aim at reducing *c*
  - Isolation, sexual abstinence

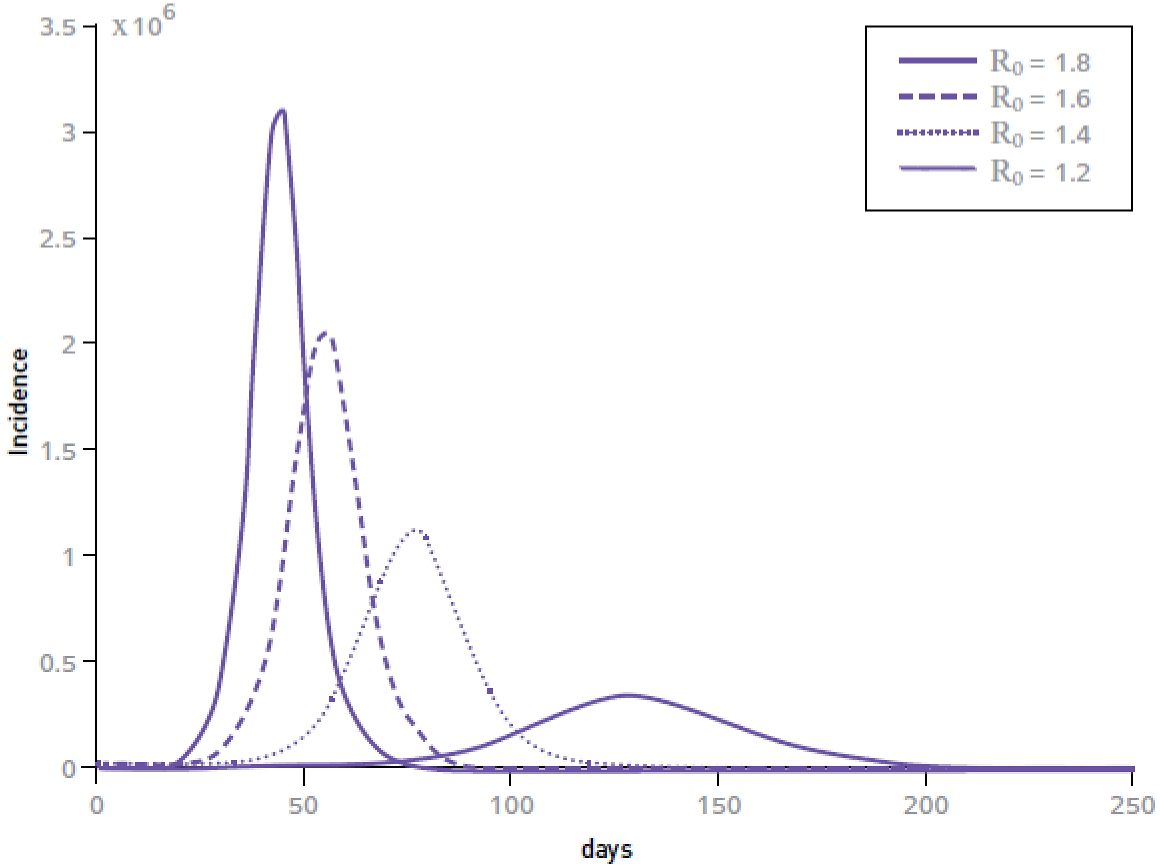
d, duration of infectious period

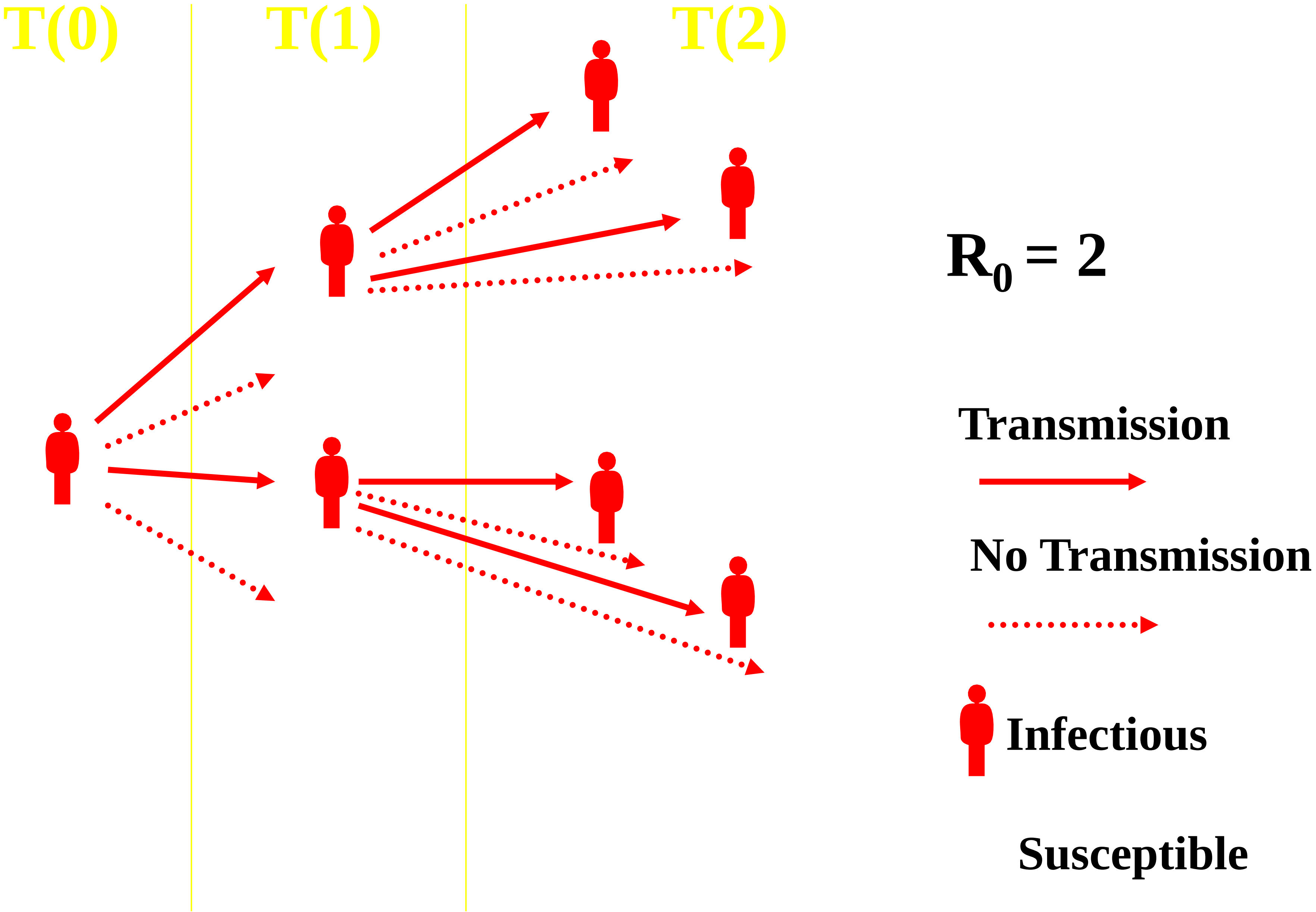
- may be reduced by medical interventions (TB, Flu)

Reproductive Number, R_0

Useful summary statistic

Measure of the intrinsic potential for an infectious agent to spread





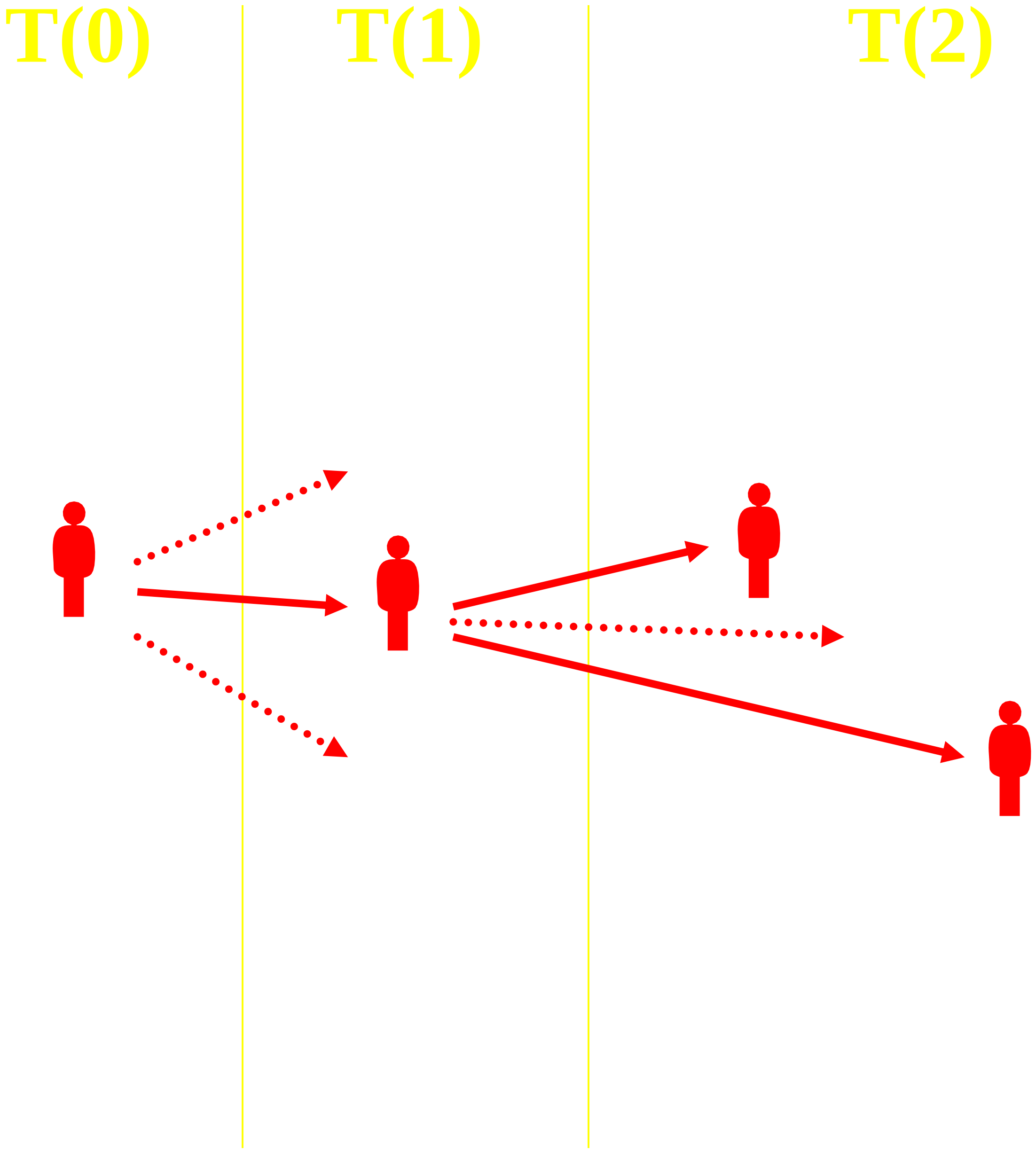
$R_0 = 2$

Transmission

No Transmission

Infectious

Susceptible



$R_0 = 1.5$

Transmission

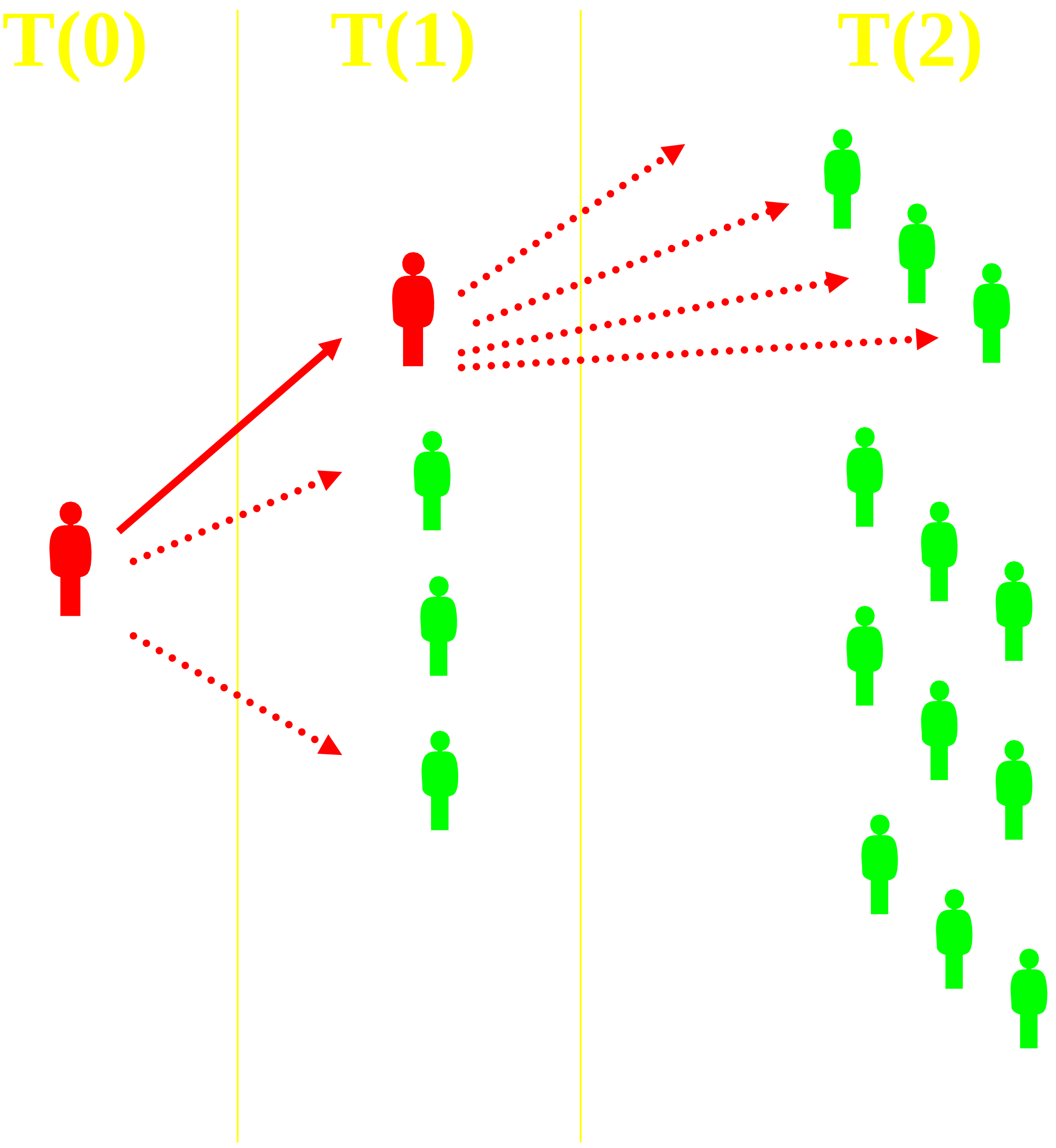
→

No Transmission

⇢

Infectious

Susceptible



$R_0 = 2$

Transmission

→

No Transmission

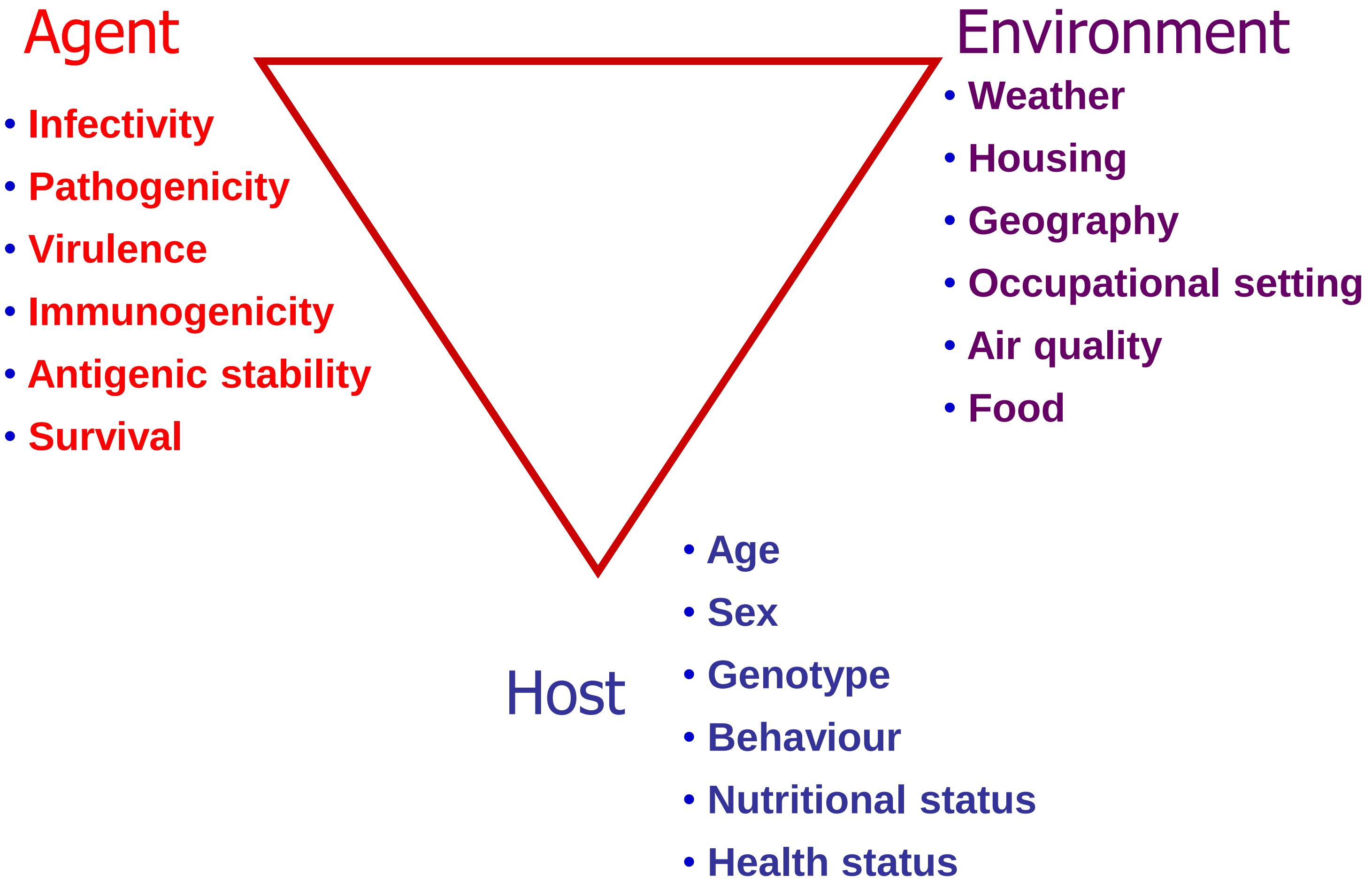
⇢

🟥 **Infectious**

Susceptible

🟩 **Immune**

Factors Influencing Disease Transmission



Agent

- Infectivity
- Pathogenicity
- Virulence
- Immunogenicity
- Antigenic stability
- Survival

Environment

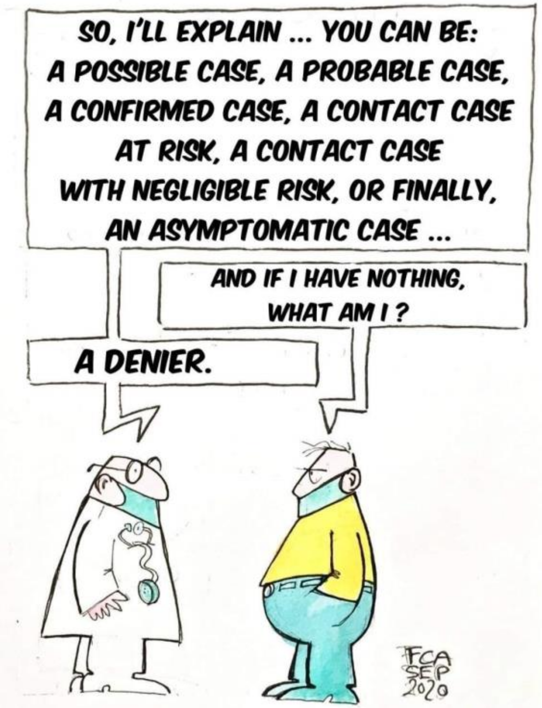
- Weather
- Housing
- Geography
- Occupational setting
- Air quality
- Food

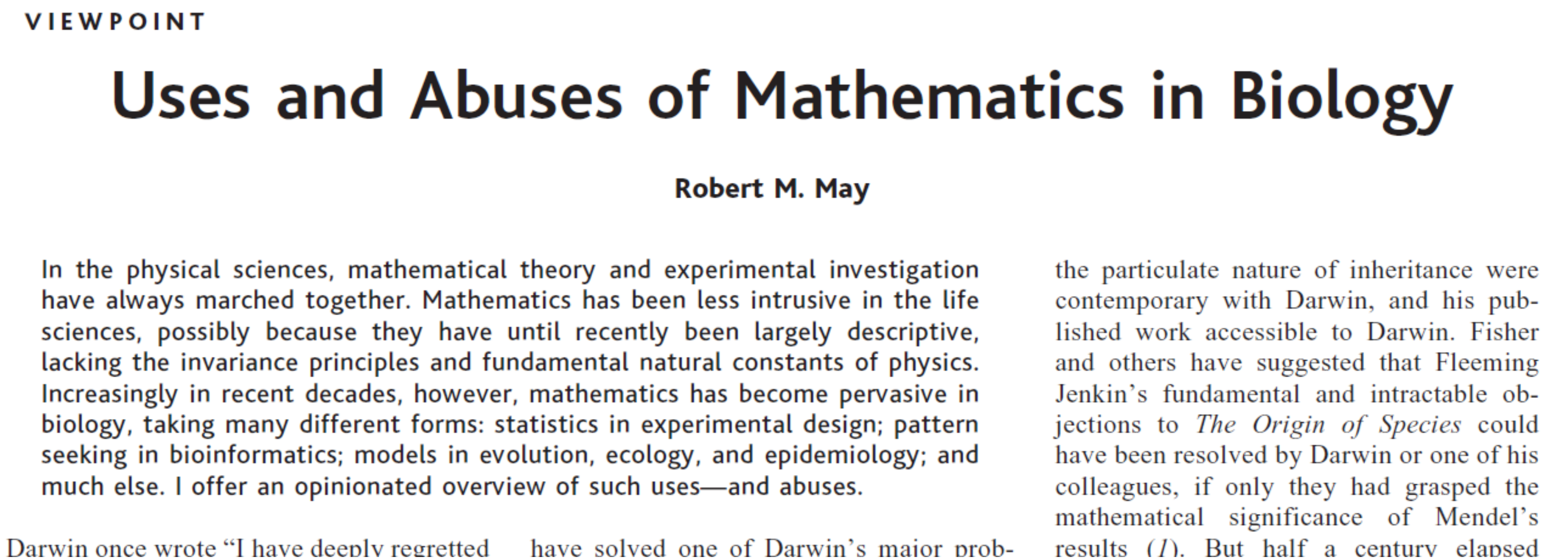
Host

- Age
- Sex
- Genotype
- Behaviour
- Nutritional status
- Health status

What is the role of a statistician?

- A **statistician** gathers numerical data and then displays it, helping to make sense of quantitative data and to spot trends and make predictions. Typical responsibilities of the job include: designing data acquisition trials. ... applying statistical methodology to complex data.





VIEWPOINT

Uses and Abuses of Mathematics in Biology

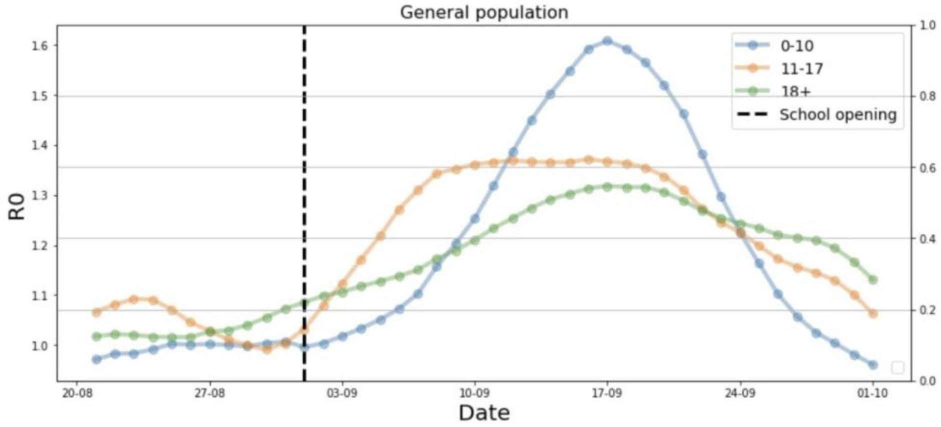
Robert M. May

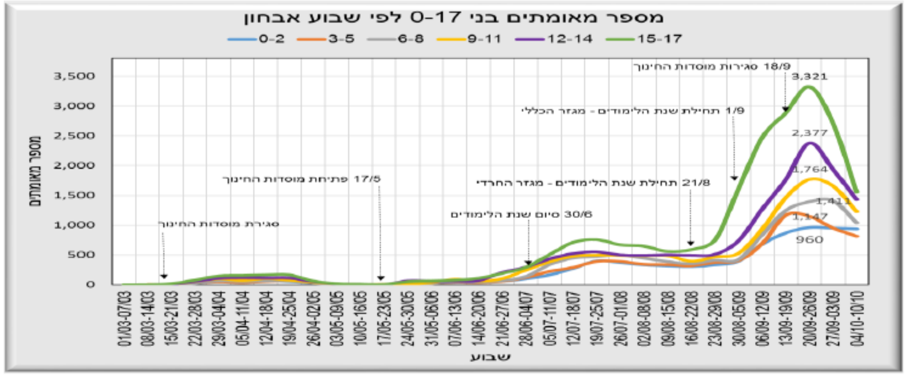
In the physical sciences, mathematical theory and experimental investigation have always marched together. Mathematics has been less intrusive in the life sciences, possibly because they have until recently been largely descriptive, lacking the invariance principles and fundamental natural constants of physics. Increasingly in recent decades, however, mathematics has become pervasive in biology, taking many different forms: statistics in experimental design; pattern seeking in bioinformatics; models in evolution, ecology, and epidemiology; and much else. I offer an opinionated overview of such uses—and abuses.

Darwin once wrote “I have deeply regretted

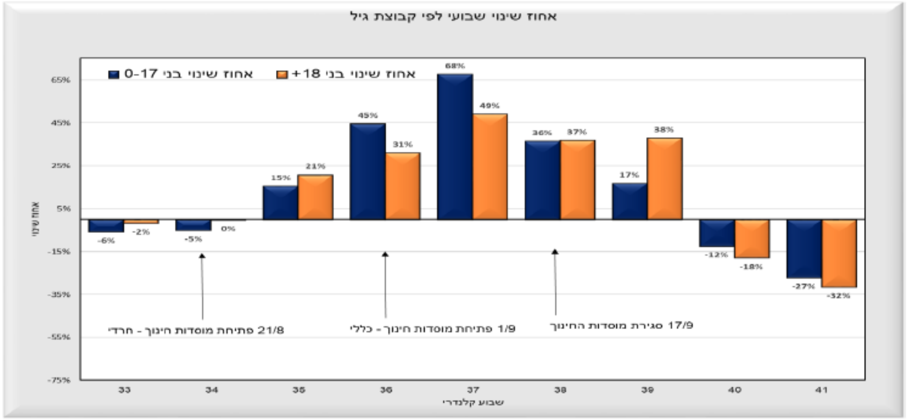
have solved one of Darwin’s major prob-

the particulate nature of inheritance were contemporary with Darwin, and his published work accessible to Darwin. Fisher and others have suggested that Fleeming Jenkin’s fundamental and intractable objections to *The Origin of Species* could have been resolved by Darwin or one of his colleagues, if only they had grasped the mathematical significance of Mendel’s results (*1*). But half a century elapsed





תרשים 7א. שרשרת ההדבקה לפי קבוצות גיל



בתרשים 11 ניתן לראות איך פתיחת השנה הביאה קודם לעליה בילדים ואיך הסגירה הביאה קודם לירידה בילדים. אחר כך המבוגרים עוקבים אחרי מגמה זו.

פרויקט התפרצות הקורונה בישראל ובעולם

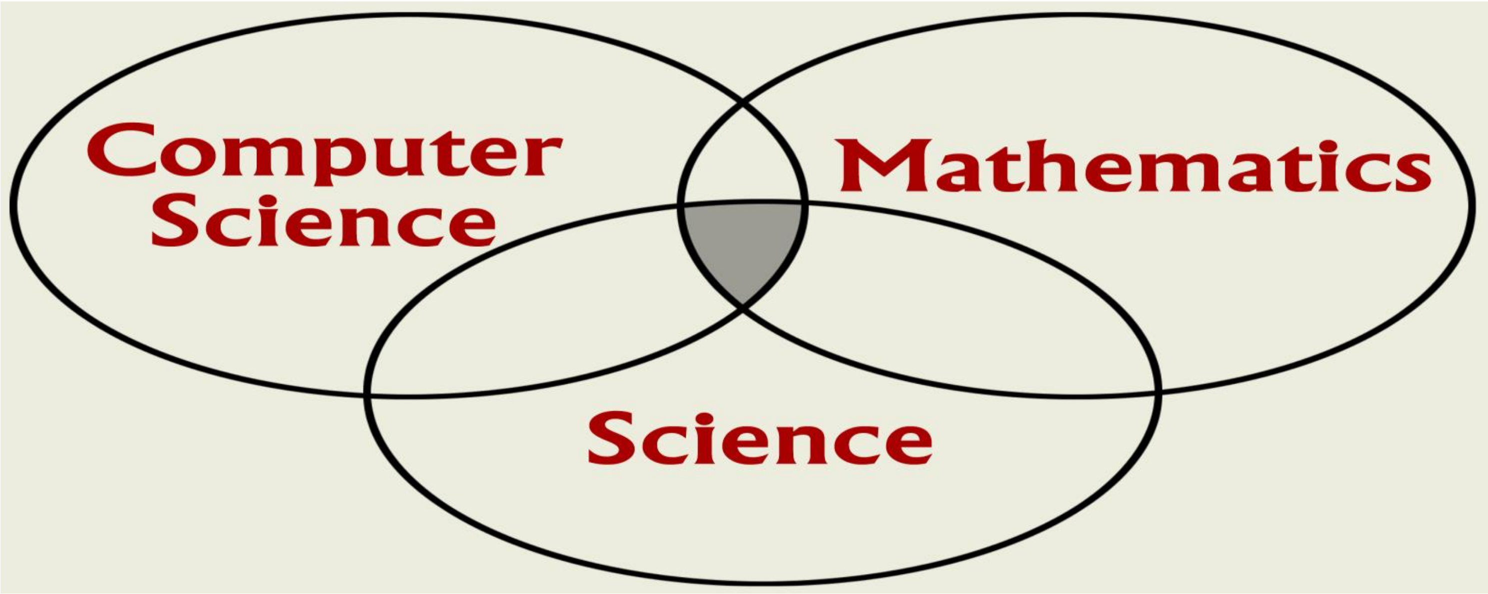
רשימת פעילויות	
• בניית תרחישי ייחוס להתמודדות עם הקורונה (רכש, כוח אדם, הכנת תשתיות)	• בניית מדגם לסקר סרולוגיה לאומי בישראל
• בניית מודל התפשטות של קורונה בישראל	• ניתוח נתונים על צוות רפואי שנחשף לקורונה
• אמידת פרמטרים בזמן אמת של ההתפרצות ובפרט של R0 בישראל	• שימוש ברצפים גנטיים ומידע אפידמיולוגי למידול התפשטות הקורונה בישראל
• דינמיקת הדבקות ילדים בקרב משפחות	• כתיבת מסמך אסטרטגית היציאה
• מגן אבות ואמהות	• כתיבת מסמך מתווה חזרה ללימודים
• חיזוי מצב הדרדרות להנשמה בקרב חולי קורונה	• אפיון ומודלים לקיטוע שרשראות הדבקה
• תיקוף בדיקות סרולוגיות	• בניית דוחות לצורך שיתוף מידע בין מדינות COVID-19 Data Sharing System
• תכנון, ייעוץ, אפיון וניתוח נתוני סקר סרולוגי בבני ברק	• בניית מערך תחקור ומידול אירועי התפרצות בבתי ספר, מקומות ציבוריים ומקומות עבודה
• בניית מודל מבוסס סוכנים (agent base model)	• בניית מודלים מרחבים

Why Modeling?

- Fundamental and quantitative way to understand and analyse complex biological systems and phenomena
- Complement to Theory, Data and Experiments, and often can help Integrate between them

Mathematical Modeling?

Mathematical modeling seeks to gain an understanding of science through the use of mathematics, statistics and computer science.



The Challenge

Understanding infectious systems requires being able to reason about highly complex biological systems, with hundreds of demographic and epidemiological variables.

Intuition alone is insufficient to fully understand the dynamics of such systems.

Experimentation or field trials are often prohibitively expensive or unethical and do not always lead to fundamental understanding.

Therefore, ***mathematical modeling*** becomes an important experimental and analytical tool.

Mathematical models have become important tools in analyzing the spread and control of infectious diseases.

The Role of the Mathematical Modeling in Epidemiology

Emergence of new infectious diseases:

- Ebola
- HIV/AIDS
- Hepatitis C
- West Nile Virus

Evolution of antibiotic-resistant strains:

- tuberculosis
- pneumonia
- gonorrhea

What Can Models Do For Us?

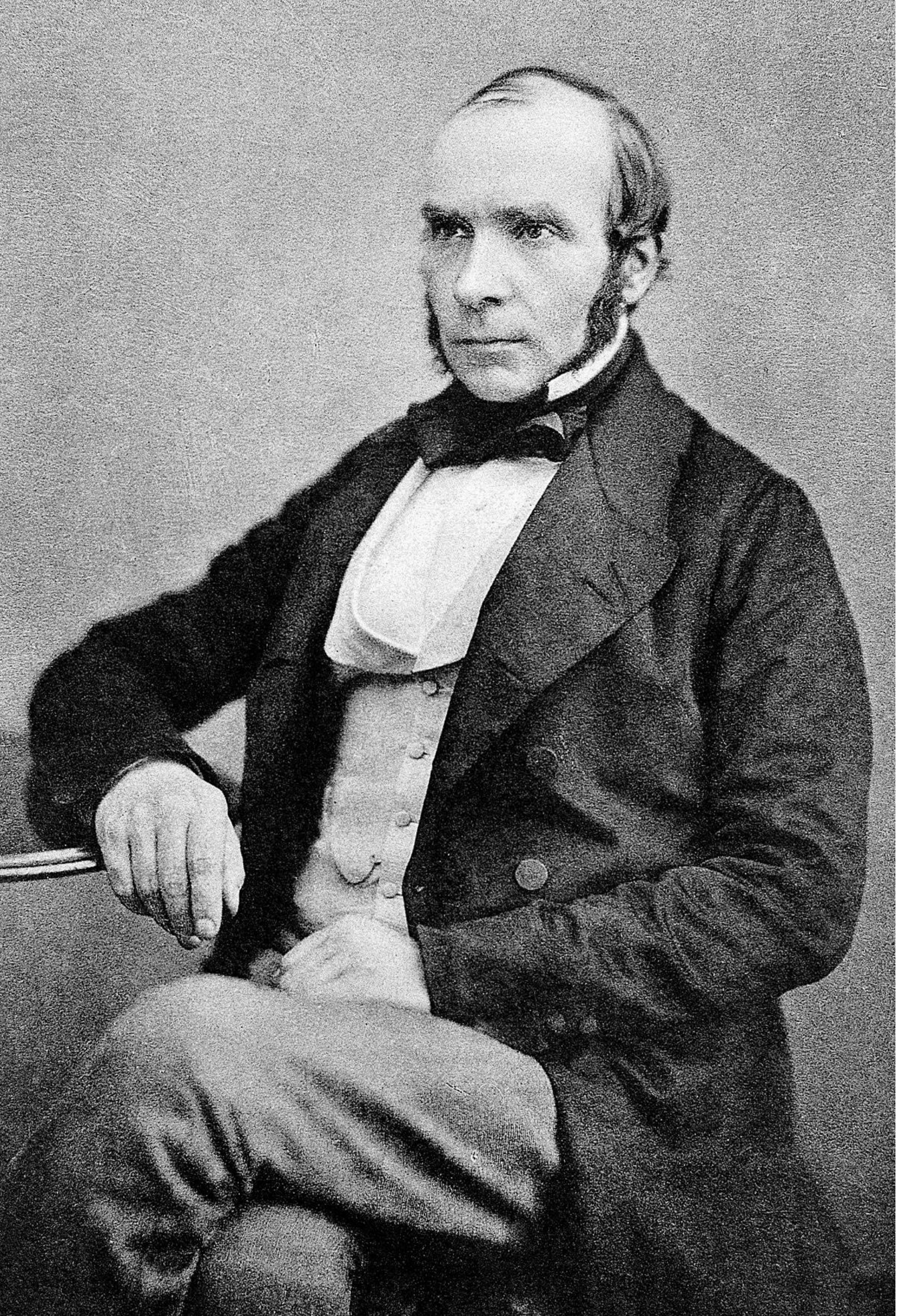
- Sharpen our understanding of fundamental processes.
- Compare alternative policies and interventions.
- Help make decisions.
- Prepare responses to bioterrorist attacks.
- Provide a guide for training exercises and scenario development.
- Guide risk assessment.
- Predict future trends.

Increasing interest in epidemiology

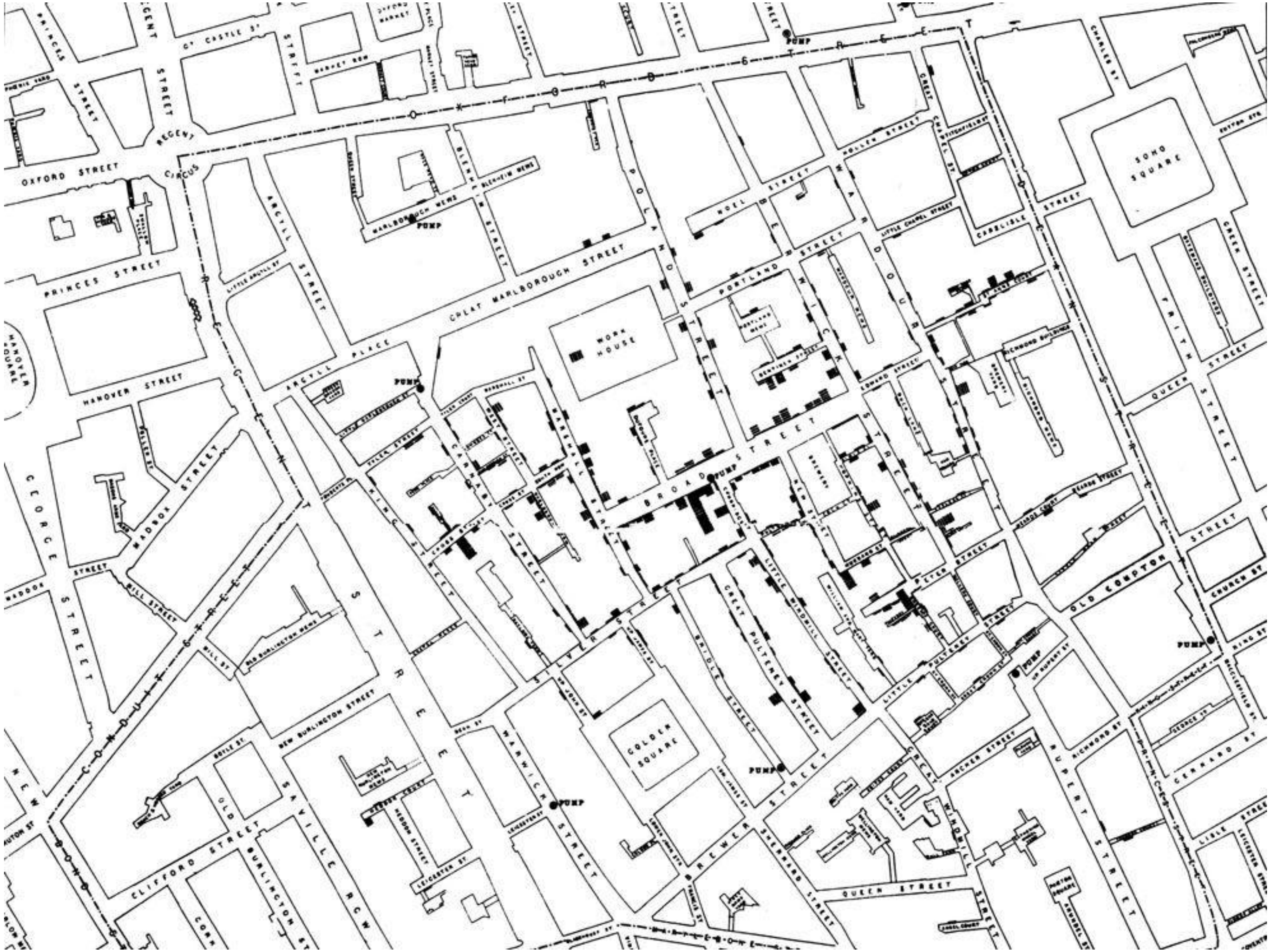
200 hundred years earlier…..
confronting the same problem.

1700-1782

- The very first known epidemiological model traces back to the 18'th century when Daniel Bernoulli, formulated equations describing the spread of smallpox and its eradication via inoculation.



in the 1840's and 1850's.
In what is widely regarded as the
birth of scientic epidemiology, Snow showed how clusters of cholera cases in London were related to the local water supply, and by eliminating this source (famously removing
the handle of the Broad Street water pump) helped bring the epidemic under control.



However, Snow's approach was predominantly statistical, looking for patterns in existing data.

What is a good model?

- The predictive power of these modelling techniques was first illustrated by work on Rubella using age-structured models when it was shown that although low levels of vaccination would reduce the overall prevalence of infection, it would delay infection to later in life so that more women would be infected during pregnancy.
- Hence a limited vaccination campaign would actually increase the amount of congenital rubella syndrome in unborn babies.

How are such models used?

- **Predictive mathematical models** were used to inform control of the Foot-and-Mouth outbreak in 2001 (one of the first times models were used during an epidemic).
- **Planning for pandemic outbreaks**
- **Cost-effectiveness** calculations before implementation of novel vaccine programes

The epidemiology of infectious diseases is a complex and multi-factorial subject

- Basic philosophy, using simple models to develop an intuitive understanding of infectious disease dynamics before describing the complexities that would need to be included to make such models practically useful.

- Focus largely on the population dynamics of infectious diseases { how the number of individuals infected changes dynamically over time}.

- Mathematical epidemiology relies heavily on tools from mathematics and theoretical physics (the theory of differential equations and dynamical systems, statistical mechanics, and stochastic processes)

- Statistics plays a vital role in both interpreting the observed infection data (accounting for the many biases in reporting) and in parameter inference when we attempt to fit models to data.

What should be included in models?

- Biology
  - Microbiology
  - Immunology
  - Ecology

- Sociology
  - Host and their interaction
  - Travel patterns
  - Behavior

- Psychology
  - Fear
  - Denial
  - Stigmatization

In recent years it has become apparent that other disciplines have a role to play:

Economics is vital to underpin cost- effctiveness studies that are key to assessing control programs;

Sociology and psychology help to explain and predict human response to outbreaks or new treatments;

Medical insights are needed to understand the link between the individual as a host for the pathogen and the individual as a patient that requires treatment.

The General Dynamic Of An Epidemic

- Individuals pass from one class to another with the passage of time.

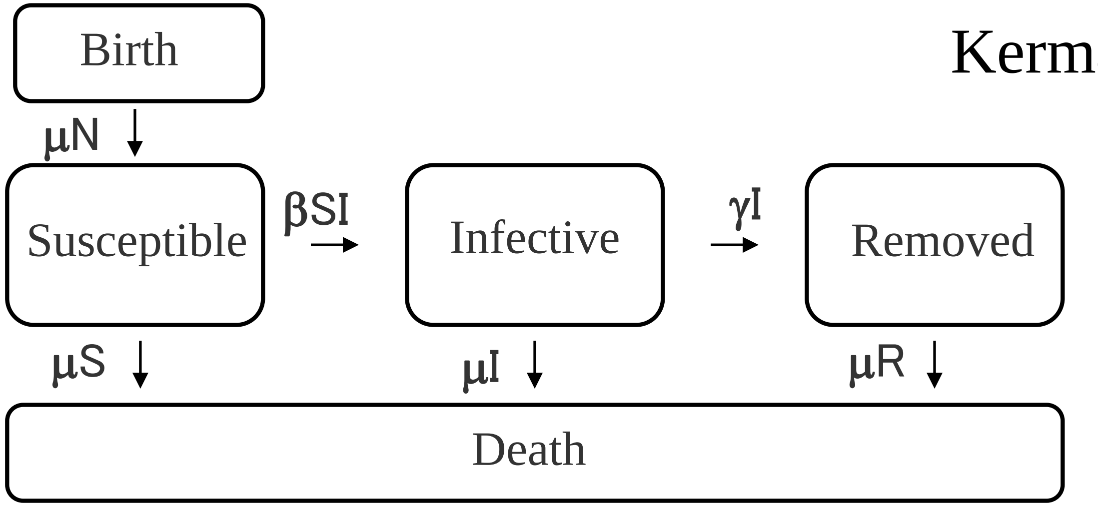
- Mathematical model tries to capture this flow by using compartments

The SIR Model

- Infectious disease dynamics can be modeled by considering simple systems of Ordinary Differential Equation (ODEs), their formulation may be motivated by considering the stochastic behaviour of individuals.

- In particular, one can consider the ODEs as the limit of a stochastic process where a large (infinite) number of individuals are moving between the various model compartments. In this limit of infinitely many individuals, the stochastic movement between compartments can be conceptualised as a continuous flow.

The SIR model


Birth

μN

Susceptible

βSI

Infective

γI

Removed

μS

μI

μR

Death

Kermack and McKendrick 1927


W. O. Kermack


A. G. McKendrick

$$\dot{S} = \mu - \mu S - \beta^{\pm} SI$$

$$\dot{I} = \beta^{\pm} SI - (\gamma + \mu) I$$

$$\dot{R} = \gamma I - \mu R$$