

# Resources for Influenza Research

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## Topics and Keywords

- Influenza | Flu
- Pandemic (Antigenic Shift) vs. Epidemic (Antigenic Drift)
- Epidemiology of Influenza
- Modeling Influenza
  - Transmission
  - Forecasting
- Surveillance of Influenza
- Ecology of Influenza
- Evolution of Influenza
  - Phylodynamics
  - Phylogeography

## Infectious Disease Epidemiology

### *Textbooks*

- Gordis, L. (2013). Epidemiology. Elsevier: Saunders.
  - [ ] Chapter 2 The Dynamics of Disease Transmission
- Nelson, K. E., & Williams, C. (2013). Infectious disease epidemiology. Jones & Bartlett Publishers.
  - [x] Chapter 6 Infectious Disease Dynamics
  - [ ] Chapter 7 Geographic Information Systems
  - [x] Chapter 15 Epidemiology and Prevention of Influenza

## Modeling Infectious Diseases

### *Textbooks*

- Anderson, R. M., & May, R. M. (1991). *Infectious Diseases of Humans: Dynamics and Control*. Oxford: Oxford university press.
- Keeling, M. J., & Rohani, P. (2008). *Modeling Infectious Diseases in Humans and Animals*. Princeton University Press.
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- Diekmann, O., & Heesterbeek, J. A. P. (2000). *Mathematical epidemiology of infectious diseases: model building, analysis and interpretation*. John Wiley & Sons.
- Sattenspiel, L. (2009). *The Geographic Spread of Infectious Diseases: Models and Applications*. Princeton University Press.
- [x] Vynnycky, E., & White, R. (2010). *An Introduction to Infectious Disease Modelling*. Oxford University Press.
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- Fine, P. (1981). *Influenza Models: Prospects for Development and Use*. Proceedings of a Working Group on Epidemiological Models of Influenza and Their Practical Application.

### *Review Papers*

- Metcalf, C. J. E., & Lessler, J. (2017). Opportunities and challenges in modeling emerging infectious diseases. *Science*, 357(6347), 149-152.
- [x] Heesterbeek, H., Anderson, R. M., Andreasen, V., Bansal, S., De Angelis, D., Dye, C., ... & Viboud, C. (2015). Modeling Infectious Disease Dynamics in the Complex Landscape of Global Health. *Science*, 347(6227), aaa4339.
- A Special Issue of *Epidemics* on Challenges in Modelling Infectious Disease Dynamics.
- [x] Grassly, N. C., & Fraser, C. (2008). Mathematical Models of Infectious Disease Transmission. *Nature Reviews Microbiology*, 6(6), 477-487.
- McCallum, H., Barlow, N., & Hone, J. (2001). How should pathogen transmission be modelled?. *Trends in ecology & evolution*, 16(6), 295-300.
- Hethcote, H. W. (2000). The Mathematics of Infectious Diseases. *SIAM review*, 42(4), 599-653.

## Ecology and Evolution of Influenza

### *Textbook*

- Webster, R. G., Monto, A. S., Braciale, T. J., & Lamb, R. A. (2014). *Textbook of Influenza*. John Wiley & Sons.

### *Review Papers*

- Nelson, M. I., & Holmes, E. C. (2007). The Evolution of Epidemic Influenza. *Nature reviews genetics*, 8(3), 196-205.
- [x] Earn, D. J., Dushoff, J., & Levin, S. A. (2002). Ecology and Evolution of the Flu. *Trends in ecology & evolution*, 17(7), 334-340.
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- [x] Cox, N. J., & Subbarao, K. (2000). Global Epidemiology of Influenza: Past and Present. *Annual review of medicine*, 51(1), 407-421.
- Webster, R. G., Bean, W. J., Gorman, O. T., Chambers, T. M., & Kawaoka, Y. (1992). Evolution and Ecology of Influenza A Viruses. *Microbiological reviews*, 56(1), 152-179.

## Seasonality of Influenza

### *Key Paper*

- [x] Dushoff, J., Plotkin, J. B., Levin, S. A., & Earn, D. J. (2004). Dynamical resonance can account for seasonality of influenza epidemics. *Proceedings of the National Academy of Sciences of the United States of America*, 101(48), 16915-16916.
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- Tamerius, J., Nelson, M. I., Zhou, S. Z., Viboud, C., Miller, M. A., & Alonso, W. J. (2011). Global influenza seasonality: reconciling patterns across temperate and tropical regions. *Environmental health perspectives*, 119(4), 439.
- [x] Fuhrmann, C. (2010). The Effects of Weather and Climate on the Seasonality of Influenza: What We Know and What We Need to Know. *Geography Compass*, 4(7), 718-730.
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- Lofgren, E., Fefferman, N. H., Naumov, Y. N., Gorski, J., & Naumova, E. N. (2007). Influenza Seasonality: Underlying Causes and Modeling Theories. *Journal of virology*, 81(11), 5429-5436.

## Dynamics of Influenza

### **Influenza Transmission**

#### *Classical Paper*

- [x] Rvachev, L. A., & Longini, I. M. (1985). A Mathematical Model for the Global Spread of Influenza. *Mathematical biosciences*, 75(1), 3-22.

### **Influenza Forecasting**

#### *Review Papers*

- Nsoesie, E. O., Brownstein, J. S., Ramakrishnan, N., & Marathe, M. V. (2014). A Systematic Review of Studies on Forecasting the Dynamics of Influenza Outbreaks. *Influenza and other respiratory viruses*, 8(3), 309-316.
- [x] Chretien, J. P., George, D., Shaman, J., Chitale, R. A., & McKenzie, F. E. (2014). Influenza Forecasting in Human Populations: a Scoping Review. *PloS one*, 9(4), e94130.

#### *Projects*

- FluSight 2016-17 from Epidemic Prediction Initiative
  - flusight: a static influenza forecasts visualizer created by the Reich Lab at UMass-Amherst. source code
- The Delphi group at Carnegie Mellon University focuses on developing the theory and practice of epidemiological forecasting.
  - ILI-Nearby: Geographically detailed real-time estimates (nowcasts) of Influenza-Like-Illness.

- Delphi’s forecasts: Weekly forecasts of Influenza-Like-Illness nationally and in 10 U.S. regions.

## Surveillance of Influenza

### *Review Paper*

- [x] Unkel, S., Farrington, C., Garthwaite, P. H., Robertson, C., & Andrews, N. (2012). Statistical methods for the prospective detection of infectious disease outbreaks: a review. *Journal of the Royal Statistical Society: Series A (Statistics in Society)*, 175(1), 49-82.

## Digital Detection of Influenza

### *Review Paper*

- Salathe, M., Bengtsson, L., Bodnar, T. J., Brewer, D. D., Brownstein, J. S., Buckee, C., ... & Vespignani, A. (2012). Digital Epidemiology. *PLoS computational biology*, 8(7), e1002616.

### *Classical Paper*

- [x] Ginsberg, J., Mohebbi, M. H., Patel, R. S., Brammer, L., Smolinski, M. S., & Brilliant, L. (2009). Detecting Influenza Epidemics using Search Engine Query Data. *Nature*, 457(7232), 1012-1014.

### *Projects*

- Google Flu Trends: using aggregated Google search data to estimate flu activity.
- HealthMap: flu & Ebola map | virus & contagious disease surveillance.

## Databases for Influenza Research

- WHO FluNet: a global tool for influenza virological surveillance.
- WHO FluID: a data collection tool to collect defined epidemiological indicators and data on seasonal and pandemic Influenza from national, regional and global systems on a weekly basis. It complements the existing virological data collection tool FluNet.
- Weekly U.S. Influenza Surveillance Report
  - FluView: influenza-like illness (ILI) activity level indicator determined by data reported to ILINet.
  - FluView: national and regional level outpatient illness and viral surveillance.
  - FluView: age group distribution of influenza positive specimens reported by public health laboratories.
  - FluView: pneumonia and influenza (P&I) mortality surveillance from the National Center for Health Statistics (NCHS) mortality surveillance system.
  - FluView: influenza-associated pediatric mortality.
  - FluView: laboratory-confirmed influenza hospitalizations preliminary cumulative rates and preliminary data.
  - The R package `cdcfluview` can retrieve the U.S. flu season data from the CDC FluView portal.
- Weekly influenza reports from Chinese National Influenza Center
- Estimated flu activity from Google Flu Trends. Google is no longer publishing estimates of disease activity (as of August 20, 2015), but it continue to provide signal data for research purposes. See details on the next chapter for Google Flu Trends (Ginsberg et al., 2009; Butler, 2013; Lazer et al., 2014).
- HealthMap Flu Trends (see Freifeld et al., 2008 for details)
- FluWeb Historical Influenza Database: free access to a number of rare and valuable sources of data concerning past influenza outbreaks.
- Project Tycho®: currently including data from all weekly notifiable disease (containing **influenza** and **pneumonia**) reports for the United States dating back to 1888 (see Panhuis et al., 2013 for details).

- Influenza Research Database (IRD): global public database and analysis resource for the study of influenza viruses (see Squires et al., 2012 for details).
- NCBI Influenza Virus Resource
- Global Initiative on Sharing Avian Influenza Data (GISAID)
- EMPRES Global Animal Disease Information System (EMPRES-i)
- Social contact data: a website for sharing social contact data and data analysis methods between researchers in infectious diseases modelling.

## Software Packages for Influenza Research

### *R Packages*

- `cdcfluview`: Retrieve U.S. Flu Season Data from the CDC FluView Portal.
- `EpiDynamics`: Dynamic Models in Epidemiology. Currently, the R package **EpiDynamics** implements the computer programs written in other programming languages and available in the web page of the book written by Keeling & Rohani (2008). Python Programs for this book can also be found here.
- `epidemics`: An R package to define seasonal influenza epidemic onset and duration.
- `EpiModel`: Mathematical Modeling of Infectious Disease.
- `epitools`: Tools for training and practicing epidemiologists including methods for two-way and multi-way contingency tables.
- `epinet`: An R package to analyze epidemics spread across contact networks. Details are described in Groendyke & Welch (2018).
- `fitR`: Provides functions for model fitting and inference.
- `mem`: The Moving Epidemic Method, created by Tomás Vega and José E. Lozano (see details in Vega et al. (2013) and Vega et al. (2015)), allows the weekly assessment of the epidemic and intensity status to help in routine respiratory infections surveillance in health systems.
- `R0`: Estimation of  $R_0$  and Real-Time Reproduction Number from Epidemics. Details are described in Obadia et al. (2012).
- `socialmixr`: Provides methods for sampling contact matrices from diary data for use in infectious disease modelling, as discussed in Mossong et al. (2008).
- `tsiR`: An implementation of the time-series Susceptible-Infected-Recovered (TSIR) model described by Finkenstädt & Grenfell (2000) using a number of different fitting options for infectious disease time series data.
- `Projects of R Epidemics Consortium (RECON)`: lists released projects and packages, up-and-coming packages, and related packages that authored by RECON members and relevant for infectious disease epidemiology. The precursor of RECON is The R-epi project, which will eventually be replaced by the RECON website.

### *Python Packages*

- `pypfilt`: Bootstrap particle filter for epidemic forecasting.
- `epifx`: Epidemic forecasting with mechanistic infection models.

## Workshops and Conferences

- Multinational Influenza Seasonal Mortality Study (MISMS) Workshop
- Options for the Control of Influenza Conference
- International Conference on Emerging Infectious Diseases
- Epidemics: International Conference on Infectious Disease Dynamics
- Annual Ecology and Evolution of Infectious Disease Conference

## Courses

### *Massive Open Online Courses (MOOCs)*

- Epidemics - the Dynamics of Infectious Diseases: a course provided by the Pennsylvania State University discusses about the dynamics of Malaria, HIV/AIDS, Influenza, Measles - how they emerge, how they spread around the globe, and how they can best be controlled.
- Epidemics: a course provided by the University of Hong Kong covers these four topics: origins of novel pathogens; analysis of the spread of infectious diseases; medical and public health countermeasures to prevent and control epidemics; panel discussions involving leading public health experts with deep frontline experiences to share their views on risk communication, crisis management, ethics and public trust in the context of infectious disease control.

### *Short courses*

- Introduction to Mathematical Models of the Epidemiology & Control of Infectious Diseases: an interactive short course taught by leading researchers who advise policy-makers internationally. Topics include HIV, TB, malaria, Ebola, pandemic influenza, health economics, vaccination programmes, stochastic models & more.
- Introduction to Infectious Disease Modelling and Its Applications: a two week course organised jointly between the London School of Hygiene & Tropical Medicine (LSHTM) and Public Health England.
- [x] Model Fitting and Inference for Infectious Disease Dynamics (MFIIDD): a short course taught by members of the Centre for the Mathematical Modelling of Infectious Diseases (CMMID) at the London School of Hygiene & Tropical Medicine (LSHTM). MFIIDD 2016 course materials can be found [here](#).
- Model-based Inference in Ecology and Epidemiology: an introduction to ecological and epidemiological stochastic dynamical systems models using a series of examples with real data.
- Network Modeling for Epidemics: a 5-day short course at the University of Washington that provides an introduction to stochastic network models for infectious disease transmission dynamics, with a focus on empirically based modeling of HIV transmission.

### *Summer School*

- [x] Computational Biology for Infectious Diseases (CBID): The summer school is for students, researchers and professionals working on infectious diseases and wishing to acquire knowledge and practice in quantitative analyses or, on the contrary, working in modeling sciences (mathematics, informatics) and wishing to acquire knowledge in health sciences applications.
- Summer Institute in Statistics and Modeling in Infectious Diseases (SISMID): The summer institute is designed to introduce infectious disease researchers to modern methods of statistical analysis and mathematical modeling and to introduce statisticians and mathematical modelers to the statistical and dynamic problems posed by modern infectious disease data.
  - Materials for SISMID 2016 Module 4: Introduction to R
  - Lectures 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 for SISMID 2016 Module 5: Stochastic Epidemic Models with Inference
  - Materials for SISMID 2016 Module 7: MCMC I for Infectious Diseases
  - Materials for SISMID 2016 Module 9: Simulation-based Inference for Epidemiological Dynamics
  - Materials for SISMID 2016 Module 10: Statistics and Modeling with Novel Data Streams
  - Materials for SISMID 2016 Module 11: MCMC II for Infectious Diseases
  - Materials for SISMID 2016 Module 15: Pathogen Evolution, Selection, and Immunity
  - Materials for SISMID 2016 Module 16: Spatial Statistics in Epidemiology and Public Health

## Channels

- Disease Forecasting & Surveillance: a global forum for disease forecasting and surveillance research.
- RECON learn: a free, open platform for training material on epidemics analysis.

## Glossary

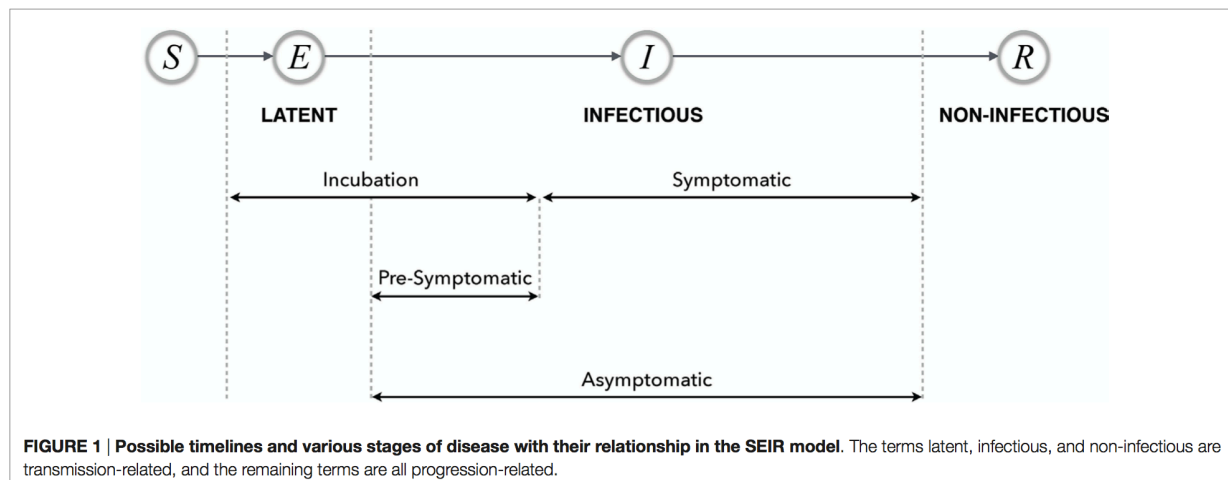
### *Review Papers*

- Moghadas, S., & Laskowski, M. (2014). Review of terms used in modelling influenza infection. NCCID, 1-39.
- Moghadas, S., & Laskowski, M. (2014). A Logical Modelling Framework for Influenza Infection. NC-CID, 1-24.
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### *Terms*

- **Index case**
  - Definition: The first case in a family or other defined group to come to the attention of the investigator (Porta, 2014).
  - Chinese: 指示病例
- **Primary case**
  - Definition: The individual who introduces the disease into the family or group under study. Not necessarily the first diagnosed case in a family or group (Porta, 2014).
  - Chinese: 原发病例
- **Secondary case**
  - Definition:
  - Source:
  - Chinese: 二代病例, 继发病例, 续发病例
- **Latent period**
  - Definition: The latent period refers to the period of time between exposure to a disease with successful transmission and the onset of **infectiousness** (Milwid et al., 2016).
  - Chinese: 潜伏期
- **Incubation period**
  - Definition: The incubation period is defined as the period of time between exposure to the disease (if transmission occurs) and the onset of **clinical symptoms** (Milwid et al., 2016).
  - Chinese: 潜育期
- **Infectious period**
  - Definition: The infectious period is defined as the time interval in which the infected individual is capable of transmitting the disease (Milwid et al., 2016).
  - Chinese: 传染期

The relationship of periods: latent, incubation, and infectious in the SEIR model is illustrated in Figure 1 of Milwid et al. (2016).



- **Generation time (interval)**
  - Definition: In modeling, the generation interval refers to the period of time between the onset of **the infectious period** in a primary case to the onset of **the infectious period** in a secondary case infected by the primary case (Wallinga & Teunis, 2004; Milwid et al., 2016).
  - Chinese: 世代时间
- **Serial interval**
  - Definition: In epidemiology, the serial interval is defined as the period of time between the onset of **symptoms** in a primary case to the onset of **symptoms** in a secondary case infected by the primary case (Fine, 2003; Milwid et al., 2016).
  - Chinese: 传代间期
- **Morbidity (rate)**
  - Definition: Morbidity is another term for illness.
  - Source: <https://www.health.ny.gov/diseases/chronic/basicstat.htm>
  - Chinese: 发病率
- **Mortality (rate)**
  - Definition: Mortality is another term for death.
  - Source: <https://www.health.ny.gov/diseases/chronic/basicstat.htm>
  - Chinese: 死亡率
- **Incidence**
  - Definition: Disease incidence is defined by both epidemiologists and modelers as the number of **new** cases in a population generated within a certain time period (Milwid et al., 2016).
  - Chinese: 发病率
- **Prevalence**
  - Definition: Disease prevalence is defined as the number of cases of a disease at a single time point in a population (Milwid et al., 2016).
  - Chinese: 患病率
- **Attack rate**
  - Definition: The attack rate describes the proportion of the population that becomes **infected** over a specified period of time (Milwid et al., 2016).
  - Chinese: 罹患率
- **Clinical attack rate**
  - Definition: The clinical attack rate measures the proportion fo the population that develops disease **symptoms** as a result of an infection (Milwid et al., 2016).
  - Chinese: 临床罹患率
- **Secondary attack rate**
  - Definition: The secondary attack rate (SAR) is the probability that infection occurs among susceptible persons within a reasonable incubation period following known contact with an infectious



- person or another infectious source (Altman et al., 2005).
  - Chinese: 续发率
- **Basic reproduction/reproductive number/ratio**
  - Symbol:  $R_0$
  - Definition: the expected number of secondary cases produced by a typical primary case in an **entirely susceptible population** (Wallinga & Teunis, 2004).
  - Chinese: 基本再生数
- **Effective reproduction/reproductive number/ratio**
  - Symbol:  $R_t$
  - Definition: A population will rarely be totally susceptible to an infection in the real world. The effective reproductive number estimates the average number of secondary cases per infectious case at time  $t$  in a population made up of both susceptible and non-susceptible hosts.
  - Source: <http://www.healthknowledge.org.uk/public-health-textbook/research-methods/1a-epidemiology/epidemic-theory>
  - Chinese: 有效再生数
  - Remark: Wallinga & Teunis (2004) proposed a method that is generic and requires only case incidence data and the distribution of the serial interval to estimate effective reproduction number over the course of an epidemic. However, the approach has several drawbacks. First, estimates are **right censored**, because the estimate of  $R$  at time  $t$  requires incidence data from times later than  $t$ . Approaches to correct for this issue have been developed by Cauchemez et al. (2006). Furthermore, when the data aggregation time step is small (e.g., daily data), estimates of  $R$  can vary considerably over short time periods., producing substantial negative autocorrelation. For more details we refer the reader to Cori et al. (2013).
- **Case reproduction number**
  - Definition: The case reproduction number is a property of individuals infected at time  $t$ , and is the average number of people someone infected at time  $t$  can expect to infect. It is sometimes called the **cohort reproduction number** because it counts the average number of secondary transmissions caused by a cohort infected at time step  $t$  (Fraser, 2007; Cori et al., 2013).
  - Chinese: 病例再生数
  - Remark: The case reproduction number is denoted  $R_c(t)$  in Fraser (2007) while  $R^c(t)$  in Cori et al. (2013). Essentially, It is the widely used effective reproduction number. The case reproduction number is the quantity estimated in the Wallinga and Teunis-type approaches.
- **Instantaneous reproduction number**
  - Definition: The instantaneous reproduction number is a property of epidemic at time  $t$ , and is the average number of people someone infected at time  $t$  could expect to infect should the condition remain unchanged (Fraser, 2007; Cori et al., 2013).
  - Chinese: 瞬时再生数
  - Remark: In both Fraser (2007) and Cori et al. (2013), the instantaneous reproduction number is denoted  $R(t)$ , which is usually used as the notation for effective reproduction number. The instantaneous reproduction number is the only reproduction number easily estimated in real time. Moreover, effective control measures undertaken at time  $t$  are expected to result in a sudden decrease in the instantaneous reproduction number and a smoother decrease in the case reproduction number. Hence, assessing the efficiency of control measures is easier by using estimates of the instantaneous reproduction number.
- **Household reproduction number**
  - Definition: The household reproduction number is defined as the number of households infected by each infected household (Fraser, 2007).
  - Chinese: 家庭再生数
- **Vaccine efficacy**
  - Definition: In epidemiological and clinical studies, vaccine efficacy refers to the percentage reduction in the attack rate of the vaccinated cohort compared to the unvaccinated cohort as observed in randomized controlled (field) trial (Milwid et al., 2016).
  - Chinese: 疫苗效能
- **Vaccine effectiveness**

- Definition: Vaccine effectiveness refers to the ability of a vaccine to prevent infection or related outcomes in the population in real-world conditions (Milwid et al., 2016).
- Chinese: 疫苗有效性
- **Herd immunity**
  - Definition: a form of indirect protection from infectious disease that occurs when a large percentage of a population has become immune to an infection, thereby providing a measure of protection for individuals who are not immune.
  - Source: [https://en.wikipedia.org/wiki/Herd\\_immunity](https://en.wikipedia.org/wiki/Herd_immunity)
  - Chinese: 群体免疫
- **Herd immunity threshold, Eradication fraction**
  - Symbol:  $S_h$
  - Definition: Under a compartmental framework with homogenous mixing, the minimum fraction of susceptibles that must be immune (or vaccinated at birth (assuming 100% vaccine efficacy)) to reduce  $R_t$  below 1 and eradicate infection; that is, by the removal of susceptible hosts (Mishra et al., 2010).
  - Chinese: 群体免疫阈值
- **Epidemic**
  - Definition: The occurrence of more cases of disease, injury or other health condition than expected in a given area or among a specific group of persons during a particular period. Usually, the cases are presumed to have a common cause or to be related to one another in some way (Orbann et al., 2017).
  - Chinese: 流行病
- **Epidemic final size**
  - Definition: TODO
  - Source: A Note on the Derivation of Epidemic Final Sizes, Generality of the Final Size Formula for an Epidemic of a Newly Invading Infectious Disease, Epidemic final size calculation
  - Chinese: TODO
- **Epidemic threshold**
  - Definition: TODO
  - Source: TODO
  - Chinese: TODO
- **Epidemic curve**
  - Definition: the frequency of new cases over time based on the date of onset of disease.
  - Source: [http://sphweb.bumc.bu.edu/otlt/MPH-Modules/EP/EP713\\_DescriptiveEpi/EP713\\_DescriptiveEpi3.html](http://sphweb.bumc.bu.edu/otlt/MPH-Modules/EP/EP713_DescriptiveEpi/EP713_DescriptiveEpi3.html)
  - Chinese: 流行曲线
- **Emerging Infectious Disease (EID)**
  - Definition: an infectious disease whose incidence has increased in the past 20 years and could increase in the near future.
  - Source: [https://en.wikipedia.org/wiki/Emerging\\_infectious\\_disease](https://en.wikipedia.org/wiki/Emerging_infectious_disease)
  - Chinese: 新发传染病
- **Seasonal threshold**
  - Definition: TODO
  - Source: TODO
  - Chinese: TODO
- **Alert threshold**
  - Definition: TODO
  - Source: TODO
  - Chinese: TODO

## Films and TV Series

- CNN documentary film Unseen Enemy

- BBC documentary Contagion! The BBC Four Pandemic
- Contagion from U.S.
- Flu from South Korea
- 亚洲英雄 from Hong Kong, based on the SARS outbreak in 2003

## Contributing

Your contributions are always welcome!

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