

Mathematics and Statistics $\int_{M} d\omega = \int_{\partial M} \omega$

Mathematics 747 / 5GT3 Topics in Mathematical Biology

Instructor: David Earn

Lecture 4 Plague Pandemics Thursday 8 October 2020

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Daily SARS-CoV-2 in 2020 (Worldwide)



Daily SARS-CoV-2 (Worldwide) exponential growth fits



What does "plague" mean?



plague





NOUN

 (usually the plague) A contagious bacterial disease characterized by fever and delirium, typically with the formation of buboes (see bubonic plague) and sometimes infection of the lungs (pneumonic plague).
See also bubonic plague

+ Example sentences

1.1 Any contagious disease that spreads rapidly and kills many people. https://en.oxforddictionaries.com/definition/plague

Plague is caused by the bacterium Yersinia pestis

Scanning electron micrograph depicting a mass of Yersinia pestis bacteria in the foregut of the flea vector

https://en.wikipedia.org/viki/Yersinia_pestis

Transmission of Plague

How do humans get plague?

 Normally present at low levels in rodents

(e.g., rats, prairie dogs)

- Occasional large outbreaks
- Spread by insect vector (typically fleas)
- Infected fleas may bite humans
- ► If it enters the lungs, can spread human-to-human ⇒ pneumonic



How Y. pestis manipulates the flea



- Bacteria plug up the stomach of the flea.
- It starves and constantly tries to feed.
- When it tries to swallow, it regurgitates Y. pestis into the wound of the host.

Clinical Nature of Disease

Clinical nature of disease depends on parts of body infected

Normally begins with flu-like symptoms: high fever, chills, malaise







Cartoon credit: https://www.emaze.com/@ACFTLRFL/The-Black-Plague

Clinical nature of disease depends on parts of body infected

Symptoms of Septicemic Plague



Hence "black death"...

Probability of death from plague infection

Bubonic: ~ 66% if untreated ~ 11% with antibiotics

\blacktriangleright Pneumonic: \sim 100% if untreated

Bubonic < Septicemic < Pneumonic</p>

https://www.cdc.gov/plague/faq/

Plague in of History



Plague in History

- Plague of Justinian
 - Began 541 CE
 - Continued \sim 200 years
 - \blacktriangleright ~ 25 million deaths
- Black Death
 - Began 1334, China
 - ▶ Continued \sim 350 years
 - \blacktriangleright ~ 60% Europe killed in 1300s
- Modern Plague
 - Began ca. 1860, China
 - 2–10 million deaths
- Causative agent identified by Alexander Yersin in 1894 (bacterium later named Yersinia pestis).

How do we know historical outbreaks were caused by *Y. pestis* ?

Actually, *do we know* historical "plagues" were caused by *Y. pestis* ???

Hendrik Poinar

a.k.a. "Indiana Bones"

Bos et al. 2011, Nature 478:506

The Nature of Things Season 2013–14, Episode 12

BLACK DEATH GENOME Reconstruction from fourteenth-century DNA is

close match to modern pathogen PAGES 444, XXX & 506

Do we know historical "plagues" were caused by Y. pestis?

Second pandemic: Black Death: YES

Bos et al. 2011, Nature 478:506

Plagues following the starts of these pandemics? Probably! (Many now confirmed.)

First pandemic: Plague of Justinian: YES

Wagner et al. 2014, Lancet Infectious Diseases 14:319-326

Third pandemic: Modern Plague: YES

What data exist that allow us to quantify the temporal and spatial patterns of plague outbreaks?

A variety of sources for the <u>second</u> pandemic.





Isaac Newton

- Cambridge University closed for fear of plague in August 1665.
- Newton developed calculus, optics, and universal law of gravitation while away from Cambridge.



Plague Science

To describe the spread of plague in a human population, we need:

- Written records that survive in archives today
- Systematic record keeping over the course of an epidemic
- Ideally, death certificate for each person who died of plague
- What can we obtain in practice?

Where should we look for useful data?

London, England

London, England, 1630





THE

BRIDGE

-

J. Alhallows barking

London, England 1670

Data Source

Weekly Bills of Mortality (London, England)

London, 1630





The Difeases and Casualties this Week. fondon 41 From the 26 of september to the 3 of October Bur Pise (Frighted _____ A Linn WoodRress 16 12 St George Borolphiane- 1 1 Albalions Barking 40 34 St Gregory by St Pauls 26 25 St Martin Ludgates St Martin Organs Iballows Breadftreet- I St Martin Outwitch Alhallows Great 42 41 St Tames Dukes place-27 Griping in the Gurs -----St Martin Vintrey-St James Garlickhithe-16 12 Laundies----St John Bautift-Tohn Evangelift ---Impolthame St Maudlin Oldfilm Altuliows Staining 21 18 St Michael Baffifhay 10 Infants Alhallows the Wall-33 St Katharine Coleman-20 16 Kingfevil----Stalplinge Se Katharine Crechurch -34 29 St Michael Crookedlane St Andrew Hubbard St Lawrence Jewry-Mcagrome-St Michael Queenhithe- 2 St Andrew Underfhaft-16 14 St Lawrence Pountney-14. 10 Michael Quern Bortive Plague -----Michael Royal-Aged-Lemard Fofterlane-16 12 Puroles St Michael Woodftreet St Mildred Breadfir Rickets-St Mildred Poultrey -Apoplexie -Rifing of the Lights-St Margarer Newfilhftreet 1 S 1 3 Childbed-St Nicholas Coleabby-St Nicholas Olayes-Rupture-St Rennet Fynck-St Margares Pattons-4 Chrifomes-St Benner Gracechurch Scurvy -Cold-St Benner Paulfwhart- IS 7 Spotted Feaver----St Olave Jewry ----St Bennet Sherehog 2 St Botolph Billingigate - 8 Confumption-St Mary Aldermary -4 St Olave Silverfreet--Stilborn ---Convultion---St Mary le Bow ---Chrifts Church--44 39 St Mary Bothaw _____ 6 St Mary Colechurch ____ 3 Stone St Peter Cheap-Cough-St Chriftophers-4 St Clement Eaftcheap-1 St Dionis Backchurch-9 St Peter Cornhil St Mary Hill Droplic-St Peter Paulfwharf-St Mary Mounthaw-Drownd at St. Martin in the Suddenly ----St Peter Poor-St Mary Sommerfer-44 St Dunftan Eaft-28 24 Surfeit-St Steven Colemanftr St Edmund Lumbardftr. 13 St Mary Stayning ---Fields _____ St Ethelborough-----St Steven Walbrook_ Feaver ----Teeth-St Mary Woolchurch St Mary. Woolnorh-Fiftula Thru(h -St Thomas Apoffic-St Martin Iremongerlane 2 Flox and Small-pox-Tiffick Trinity Parifi-St Gabriel Fenchurch- 2 Vomiting-Finy-Found dead in the Fields at Winde-St.Mary Iflington Wormes S' Bligger - 23 23 S' Giles Cripplegate - 126 151 Innity Minories S' Borolph Alderfate - 71 64 S' Olave Southwark - 378 281 (Males ---- 9212) (Malestheiftned in the 1.6 Periffer withow the Walls-45 Buried, and at the Peffourte-2258 Platue-Chriftned Females-Buried Females 3248 > Plague-5533 g Gile in the hald 25 178 Lambein Baugh 29 19 S Mary Hingson inclusy Parthin 21 S Laouard Stored (c) 05 Mary With and 05 Mar (In all ---- 6460) In all---- 146 Decreafed in the Burials this Week-Parifhes clear of the Plague ---- 7 Parifhes Infe ded ----- 122 Christered in the 12 cast Parifless in Middlefer and Surry-40 Baried - 1613 Plague-The ABize of Bread les forsh by Order of the Lord Mator and Cours of Aldermen. A penny Wheaten Loaf to contain Nine Ounces and a half, and three S' Paul Covene Garden 235 124 St Mary Savoy _____ 19 16 Werren at the Perbouthalf-penny White Loaves the like weight " White Loaves

1665

Frighted Gowt Grief Griping in the Gurs 3 Jaundies-Impolthame Infants-Kingfevil Meagrome Plague. 5533 Purples Rickets









~ 20% of the total population is reported to have died in each of these 16th and 17th century plague epidemics

Registration of baptisms, weddings and burials began in London in 1538.

How can we quantify earlier epidemic patterns?
Data Source

Last Wills and Testments (London, England)

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Data from Last Wills and Testaments in London

We assume the *temporal pattern* of wills written reflects *deaths from plague* throughout the population

Similar to how Google searches for flu symptoms can predict the patterns of flu epidemics today Ginsberg et al (2009, Nature 457:1012)

 Google recently scanned a 19th century "calendar" of wills probated by the Court of Husting and made pdfs freely available online.

In the summer of 2017 I entered the dates of 1113 wills that were probated between 1346 and 1378.

Much further work on Husting wills in Alex Bushby's 2019 McMaster MSc thesis





Date of Will









Is it OK to compare results based on wills with results from mortality data?

The London Metropolitan archives has created an <u>online index</u> of wills probated by the Court of Canterbury since 1384...



How can we use these time series to learn about the disease?

A mathematical model will help...

The SIR model



Rates of change of numbers of individuals who are:

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

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

Removed
$$\frac{dR}{dt} = \gamma I$$

The SIR model





The Great Plague of London, 1665



SIR Model Fit to the Great Plague of London



What can we estimate confidently from the data?

- Fitting an SIR model to these data yields:
 - transmission rate
 - recovery rate

but implicitly assumes human-to-human transmission.

- Hard to justify SIR fit given:
 - All we have is mortality time series.
 - We do not know the precise transmission process that generated these data (*e.g.*, bubonic vs. pneumonic).
- What can we estimate from the data alone that will facilitate meaningful <u>comparisons</u> of epidemics ?

Initial epidemic growth rate?

- This is a property of the epidemic curve.
- We can estimate it <u>without</u> making assumptions about the processes that generated the data.

Exponential growth at rate r



 Naïvely, we just fit a straight line to the log of the mortality time series.



Naïvely, we just fit a straight line to the log of the mortality time series.



Naïvely, we just fit a straight line to the log of the mortality time series.



A number of thorny issues:

- How do we determine the *time window* during which growth was exponential?
 - "By eye" is <u>not</u> robust: different people choose different windows, yielding very different growth rates.
- How does saturation ("running out of susceptibles") affect our estimates? Growth is truly exponential <u>only briefly</u>.
- How do we estimate a meaningful *confidence interval* (CI) for an estimated growth rate?
 - To compare different epidemics, we need to have CIs for each epidemic individually.

All these thorny issues can be addressed by fitting a **saturating** rather than a **purely exponential** curve.



Both curves have same initial exponential growth rate r.

Test extensively using simulated epidemics for which we know the correct answer. Ma, Dushoff, Bolker, Earn (2014, Bull. Math. Biol. 76:245–260)

Application to Plague

Plague Epidemics in London, 1348–1665



Earn, Ma, Poinar, Dushoff, Bolker (2020, PNAS, in press)

Fits to Plague Epidemics in London, 1348-1665



Earn, Ma, Poinar, Dushoff, Bolker (2020, PNAS, in press)

Initial growth rates for plague in London, 1348-1665



Earn, Ma, Poinar, Dushoff, Bolker (2020, PNAS, in press)

Initial growth rates for plague in London, 1348–1665

Later plagues grew <u>4× faster</u> than early plagues!

Intuition is better for *doubling time* than growth rate.

First vs. last outbreak:

- ▶ 1348: ~ 56 days (95% CI: 41–74 days)
- ▶ 1665: ~ 11.4 days (95% CI: 10.8–12.0 days)

Early vs. late epoch:

- 14th c. wills: ~ 43 days (95% CI: 26–73 days)
- ▶ 17th c. wills: ~ 11 days (95% CI: 5.6–21.5 days)

Puzzles in the Patterns of Plagues...

- Why were plague epidemics in London four times faster in the 16th and 17th centuries than in the 14th century?
 - Pathogen evolution?
 - increased infectiousness?
 - Ionger infectious period?
 - Host population changes?
 - increased population density?
 - different social structure / contact patterns?
 - effects of selection on hosts in 1300s?
 - Weather or other environmental changes?
 - "Little Ice Age" circa 1300–1850 (minimum in 1600s)
 - Bubonic vs pneumonic plague?
 - Other ideas?

Bubonic or pneumonic plague?

Suppose pneumonic plague during second pandemic was exactly like modern pneumonic plague.

• Pneumonic in 14th century London? $\implies \leq 20\%$ of population infected

 $\underline{\text{BUT}}\sim 30\text{--}50\%$ of total population died in 1348

- \implies early plagues probably <u>not</u> (primarily) pneumonic
- A remarkable inference to be able to make based on counting wills! (and a little mathematical modelling)

Spatial Dynamics of Plague in London, England

Why study spatial dynamics of plague?

Is there evidence of spatial spread? or did plague enter the whole city roughly simultaneously?

- Fitting spatial transmission models to observed data may allow us to estimate:
 - disease properties (e.g., latent and infectious periods);
 - patterns of contact within host population;

Some preliminary work in Karsten Hempel's 2018 PhD thesis



plausibility of bubonic vs pneumonic plague.

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1665

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When graphics professionals get involved...

CBC was not satisfied with that animation...

So they made their own version:

The Nature of Things Animation

Dec 21, 166

EpiVis Animation



Another Plague Puzzle...

Why did plague disappear in London after 1666?

We can speculate that the distance between humans and rats generally increased. For example:

... Thatch roofs, in particular, offered ready refuge for rats; and it was easy for a flea to fall from such a roof onto someone beneath. When thatch roofs were replaced by tiles, as happened generally in London after the Great Fire of 1666, opportunities for this kind of transfer of infection drastically diminished. Hence the popular notion that the Great Fire somehow drove the plague from the city probably had a basis in fact.

- McNeill 1978, "Plagues and Peoples", p. 153

Plague in Our Time

The Global Distribution of Plague



https://www.cdc.gov/plague/maps/



https://www.cdc.gov/plague/maps/

Human Plague Cases and Deaths - United States, 2000-2017



Year



plague





NOUN

 (usually the plague) A contagious bacterial disease characterized by fever and delirium, typically with the formation of buboes (see bubonic plague) and sometimes infection of the lungs (pneumonic plague).
See also bubonic plague

+ Example sentences

1.1 Any contagious disease that spreads rapidly and kills many people. https://en.oxforddictionaries.com/definition/plague



plague

- Example sentences

'The pneumonic plague would be the form most likely implicated in the event of an intentional attack.'

'At first, bioterrorism – whether it's inhalation anthrax, smallpox, pneumonic plague or something else entirely – will probably feel like the flu.'