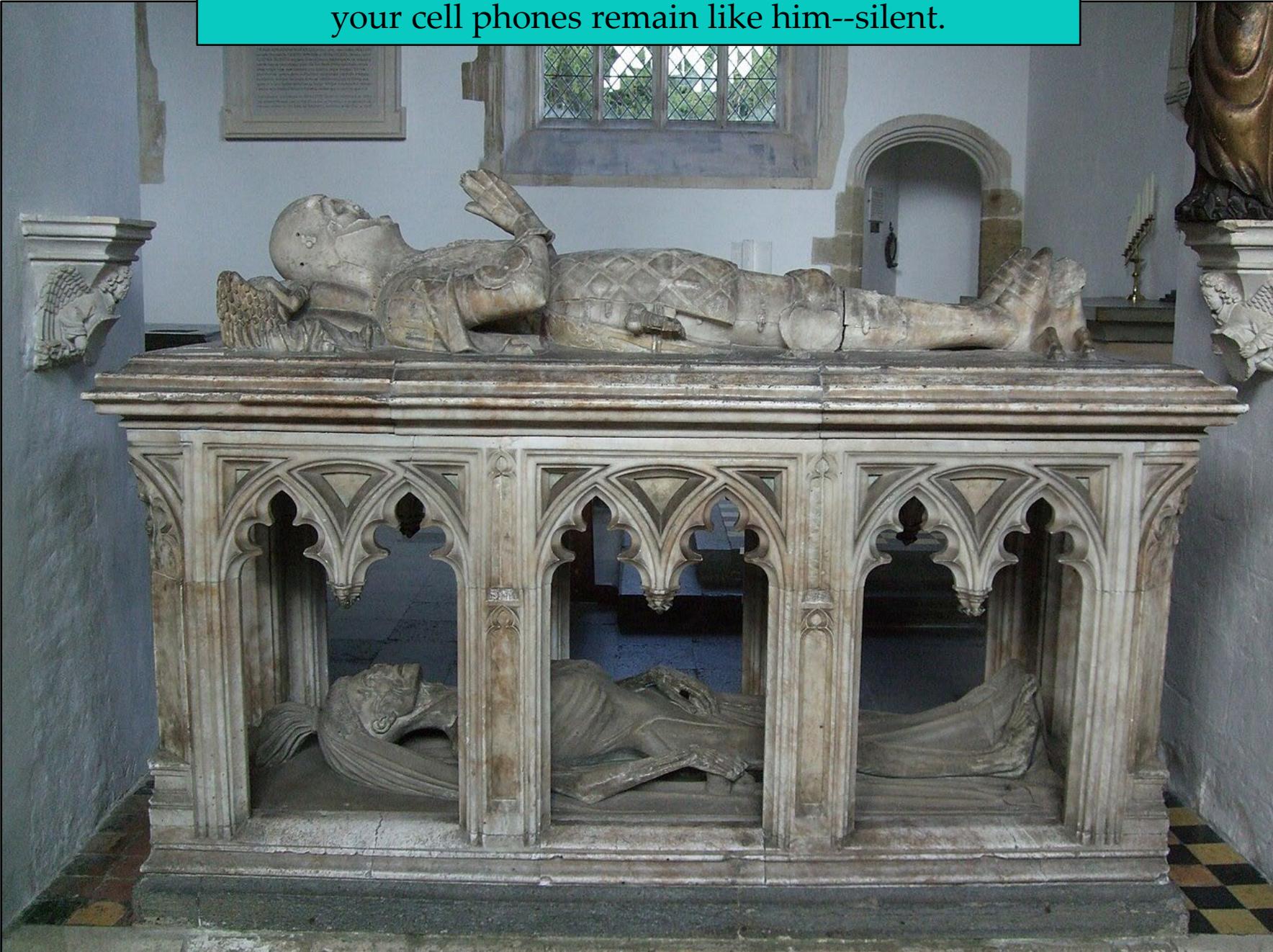


Earl John Fitzalan, 7th Earl of Arundel, requests that
your cell phones remain like him--silent.

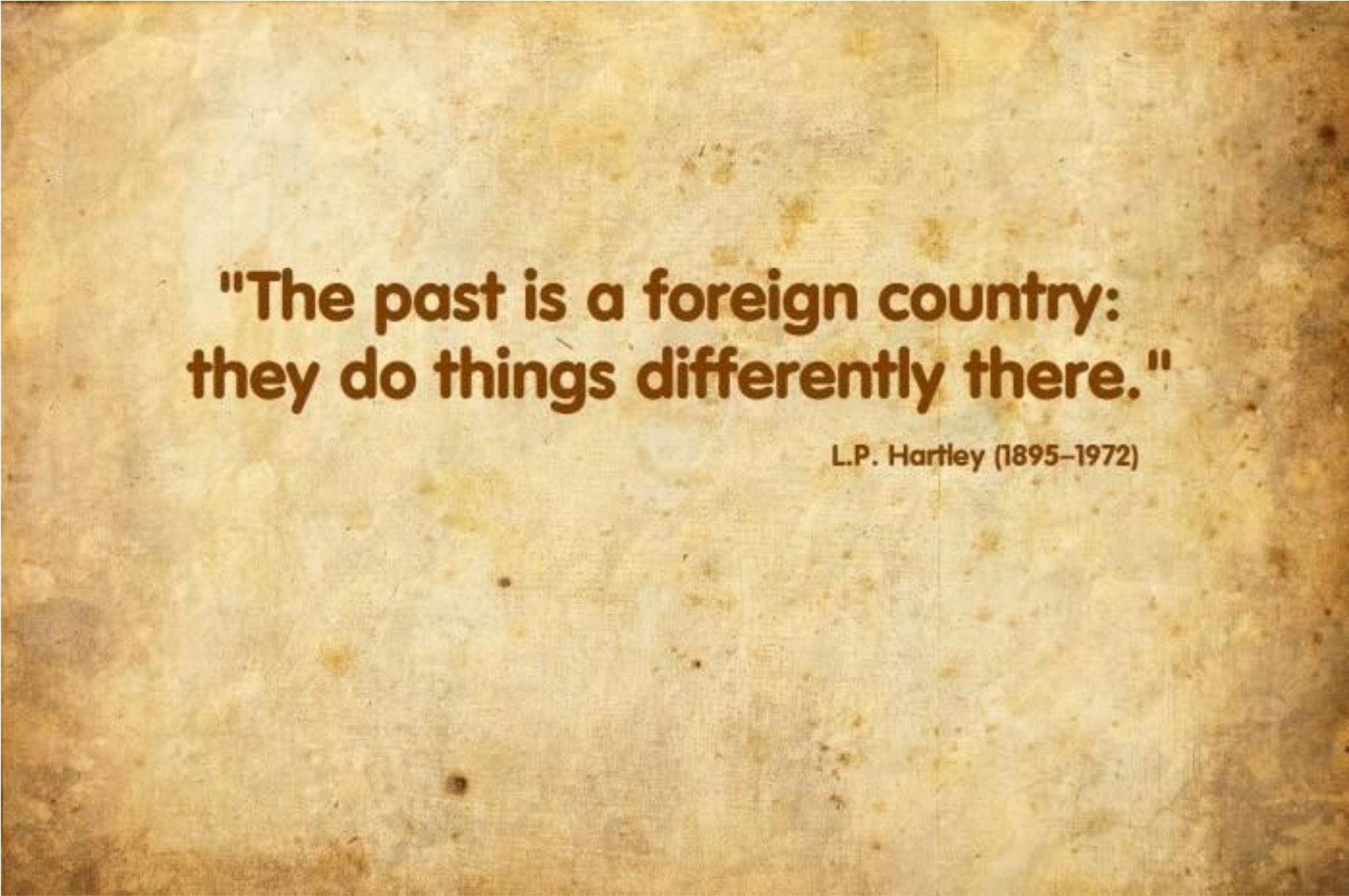




All Because of a Flea: The Plague in a Historical Context

Day One: Epidemiology and Early Plagues Martin Cox





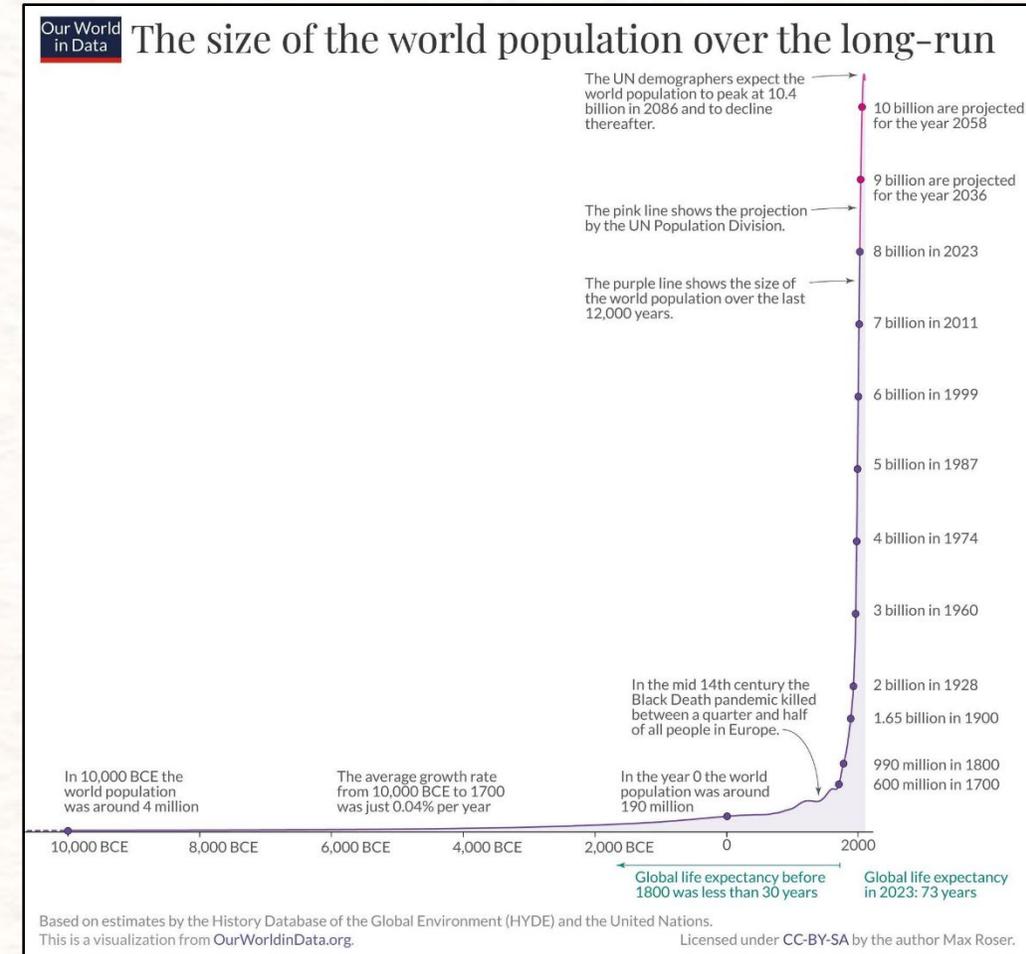
**"The past is a foreign country:
they do things differently there."**

L.P. Hartley (1895–1972)



Why Should We Care?

- Plague has killed an estimated 200 million people worldwide, with no pandemic claiming as many as the Great Mortality
- On the Foster scale of a disaster's impact, only World War II produced more death, destruction, and human suffering than the Black Death
- Population drop of up to 50% in areas struck by the plague; a modern demographic disaster on scale of Black Death would claim 1.9 billion lives
- **During the Cold War, the US Atomic Energy Commission used the Black Death to model the consequences of global nuclear conflict, stating that "of all recorded human events, the Black Death comes closest to mimicking nuclear war in geographic extent, abruptness of onset, and scale of casualties"**



Course Themes

Course Outline

- Day One: Epidemiology and Early Plague
 - Biochemistry, bacteriology, epidemiology
 - The three types of plague
 - Possible neolithic plague pandemic
 - First Plague Pandemic (Plague of Justinian)
- Day Two: The Great Mortality (aka The Black Death)
 - Pre-pandemic Europe
 - 1347-1353 “Great Mortality”
 - Continued medieval outbreaks
 - Societal, economic, religious, and artistic effects of the Great Mortality
- Day Three: Modern Plague
 - Plague in early modern era (Great Plague of London)
 - Third Plague Pandemic
 - Plague in the modern world
 - Biowarfare/bioterrorism implications
 - Plague deniers

Epidemiology of Plague

Endemic, Epidemic, and Pandemic

- Endemic: When a disease is consistently present but limited to a particular region, making disease spread and infection rates predictable. Example: Malaria in tropics, dengue fever in tropics, hantavirus in US southwest, **plague**
- Epidemic: When an unexpected increase in the number of disease cases occurs in a specific geographic area. The disease does not necessarily have to be highly contagious or particularly severe. Examples: Ebola, smallpox, measles, polio, **plague**
- Pandemic: When a disease's growth is exponential, with skyrocketing growth rate covering a wide area affecting multiple regions and populations. Again, the disease does not necessarily have to be particularly severe. Examples: COVID-19, Influenza (1918 and subsequent recurrences), **plague**
- **A pandemic cuts across global boundaries, potentially leading to large-scale social disruption, economic loss, general hardship, and (potentially) mortality. An epidemic can spread into a pandemic once it is international and out of control**

Enzootic and Epizootic

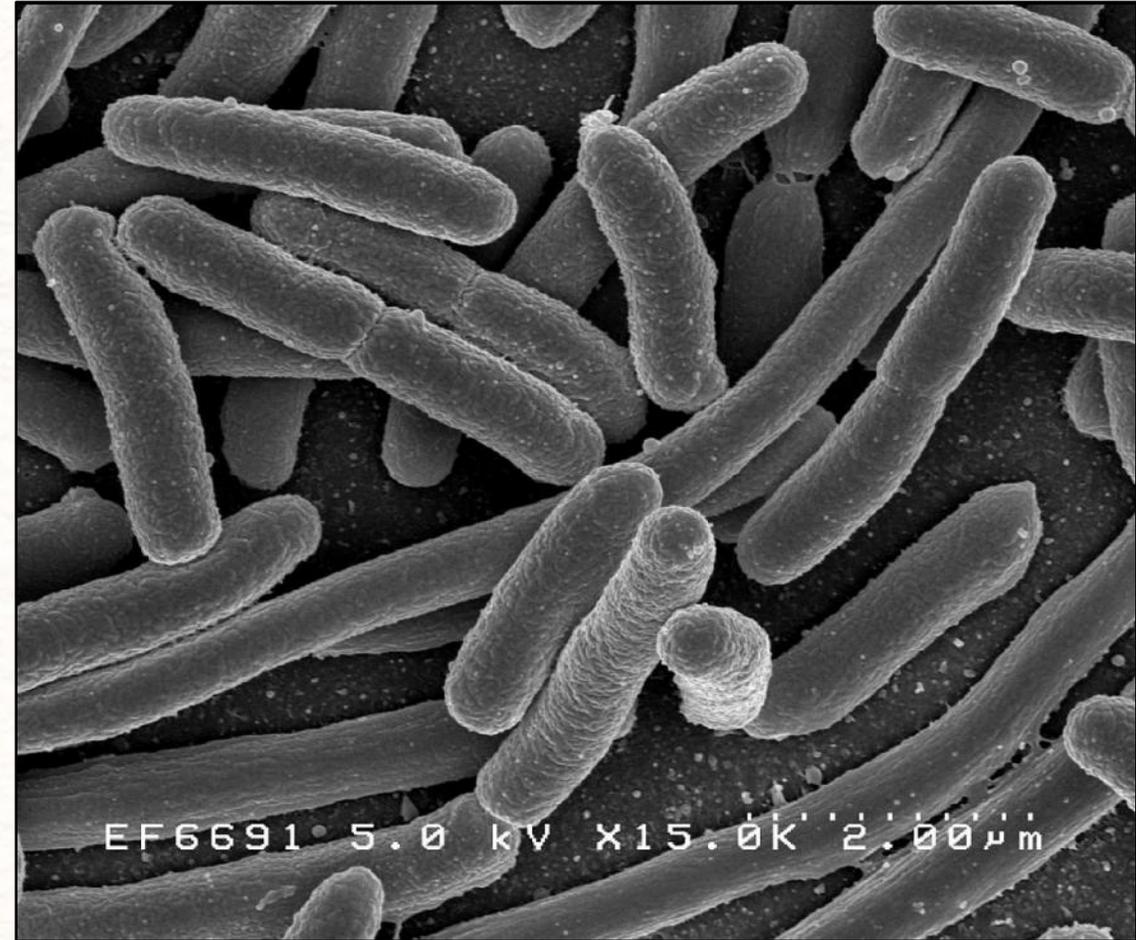
- **Enzootic:** When a disease is continuously present in an animal population, but at a low to moderate level. Often localized within a specific geographic area or group of animals, affecting only a small number of individuals at a given time. Similar to term “endemic”. Examples: Avian influenza, Ebola, **plague**
- **Epizootic:** A disease event in a nonhuman animal population analogous to epidemic in humans, with high population density a major contributing factor. Examples: Rinderpest, TSE (Mad Cow Disease), **plague**
- **An enzootic disease can become an epizootic outbreak and the disease can sometimes make a jump to human populations, creating epidemics or pandemics.**

Bacteria

- Earth's first lifeforms, originating ~4 billion years ago (along with Archaea)
- Prokaryotic organisms – utilize cell walls and lack centralized nucleus
- Poor mechanics but master chemists; bacteria solve evolutionary problems by altering their biochemistry
- Eukaryotic cells utilizing cell membranes and centralized nucleus for DNA appear much later
- Multicellular life evolved relatively late
 - Since then, bacteria and animals have been involved in an evolutionary arms race
 - Bacteria win, lose, and draw

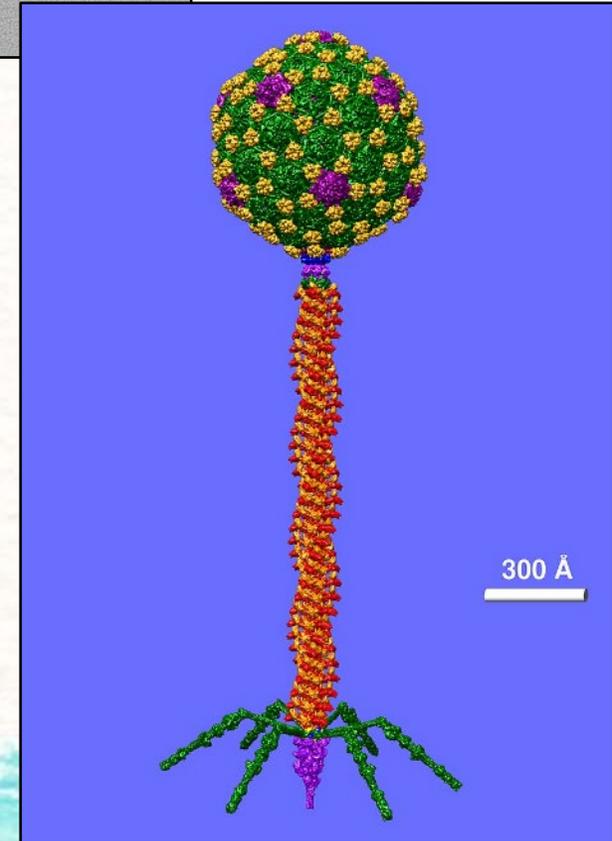
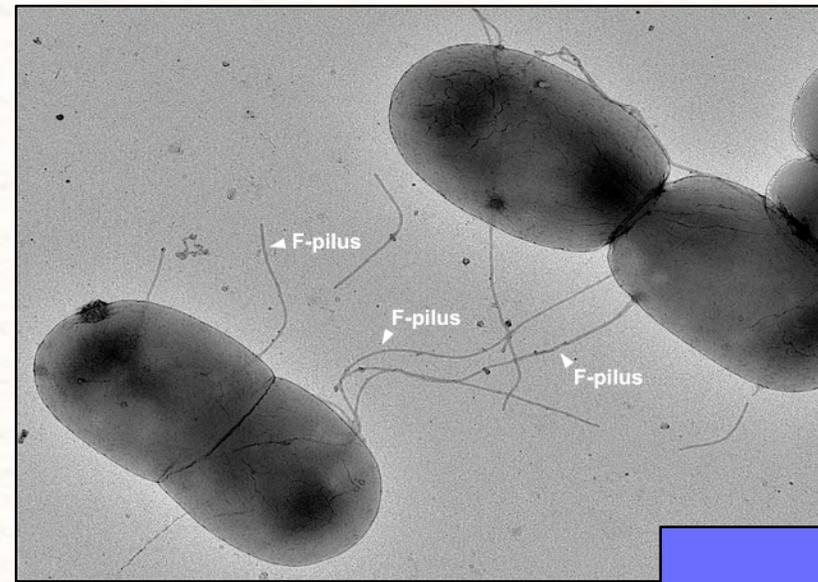
“On any possible, reasonable, or fair criterion, bacteria are and have always been the dominant form of life on Earth”

Evolutionary biologist Stephen Jay Gould



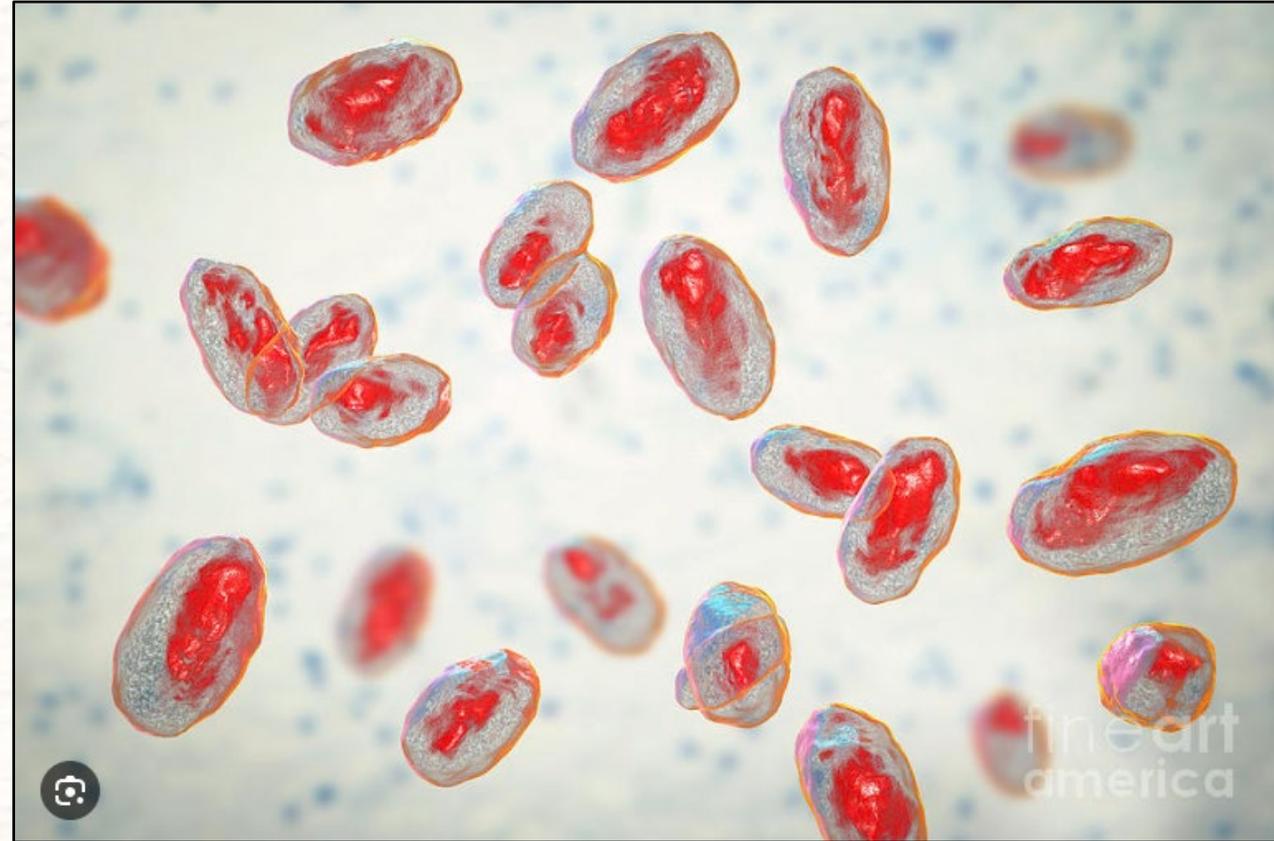
Bacterial Evolution

- Adept at DNA transfer for obtaining new genes
 - Conjugation via organelle called a pilus
 - Transduction via virus
 - Transformation by absorbing and incorporating loose DNA strands
 - Widespread DNA transfer across strains renders traditional taxonomy almost useless
- Bacterial evolution is rapid
 - Bacterial pool is enormous
 - Reproduces every 20 minutes
 - Sloppy DNA replication
- Bacteria didn't stop evolving when their descendants showed up, and they haven't stopped yet



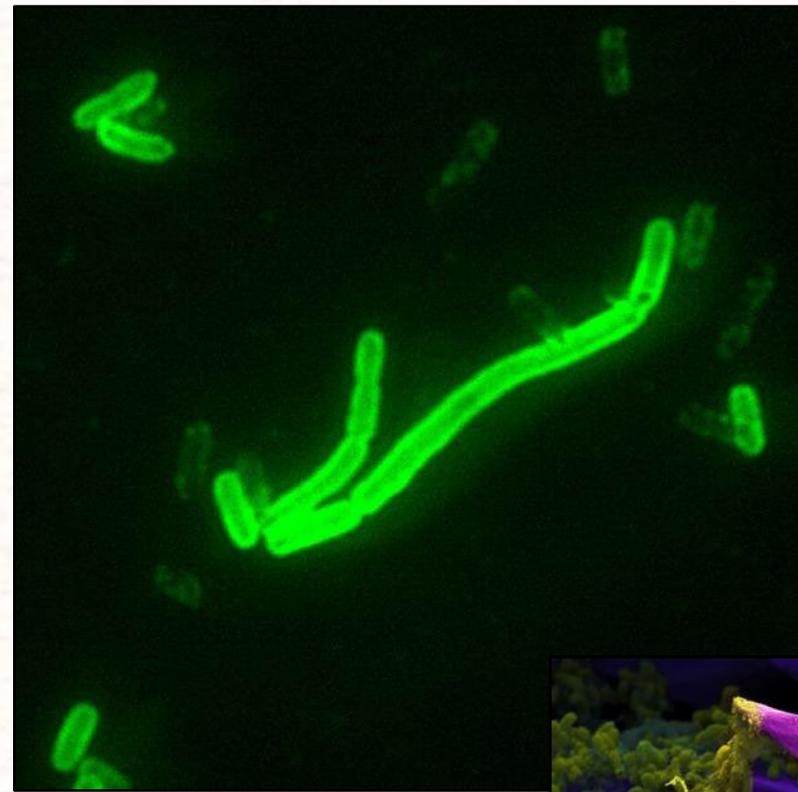
Yersinia pseudotuberculosis

- Gram-negative, non-motile bacterium
 - Widespread distribution across the planet
 - Existed for long time
- A trouble-maker, not a killer
 - Mostly innocuous
 - Can cause a variety of infections, most of which are mild to moderate unless patient is immunocompromised
 - Usually gastrointestinal
- Spreads via animal and human fecal waste
 - An inefficient way to spread long-distance
 - *Y. pseudotuberculosis* doesn't appear to care that much.....
 -but its evil child certainly does.....



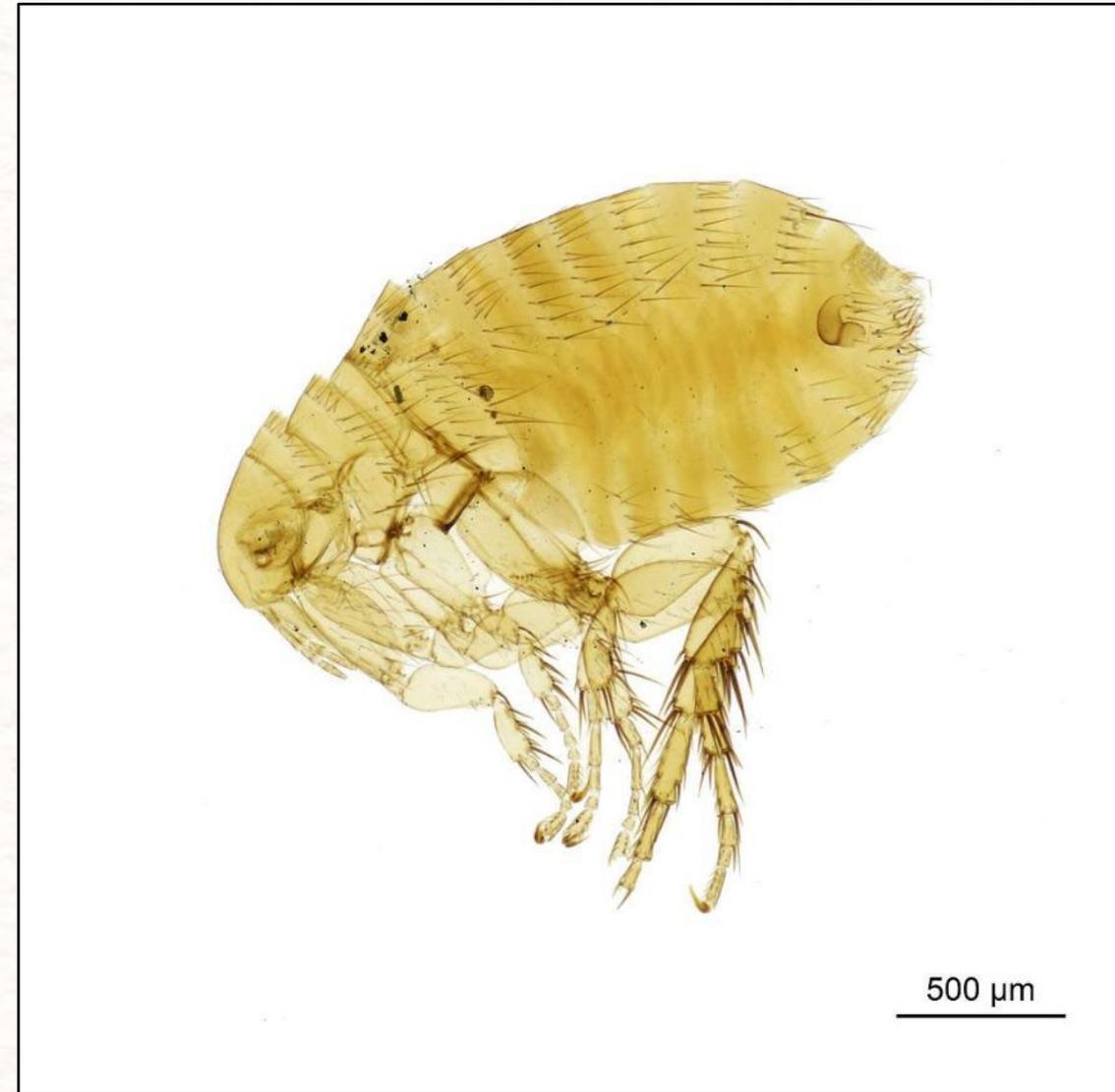
Yersinia pestis

- Gram-negative, non-motile coccobacillus bacterium
 - Isolated in 1894 by Swiss/French bacteriologist Alexandre Yersin
 - Believed to have evolved from *Y. pseudotuberculosis* between 1500-20,000 years ago
 - Genetically quite similar to its ancestor; only a few dozen genes and plasmids are different
- Several strains of pathogen
 - West Europeans and Americans classify as *Antiqua*, *Medievalis*, and *Orientalis* (after pandemics)
 - Russian scientists divide by host—marmot, gerbil, rat, and ground squirrel
- **Evolution has driven *Y. pestis* to almost certainly be the deadliest pathogen in human history**



Enter the Flea

- *Y. pestis* figured out how to evade the most effective defense system you have—the skin—and enter directly into blood and lymphatic systems
- At first, fleas are not an expected vector
 - Fleas spend most of their life on a single host; parasitic but rarely more than a nuisance
 - Arthropods that don't leave host are less effective vectors
- Settled on *Xenopsylla cheopsis* as favorite flea
 - But how to get the flea to leave the host?



Enter the Flea

- Biochemical changes enable spread
 - Modified its chemistry to live in the flea midgut as opposed to a mammalian digestive system
 - Uses a protein called YMT to turn off the flea's defenses
 - Then evolved a protein called HMS to create a biofilm out of blood
- This biofilm blocks the midgut; the flea thinks it's starving and feeds frantically
 - Eventually the flea figures out that its midgut is blocked and it regurgitates the mass of blood — into the bloodstream of the mammalian victim
- *Y. pestis* also utilizes flea species that don't block as reservoirs and sometimes as vectors
 - Including *Pulex irritans*, the human flea



Mammalian Vectors

- *Y. pestis* loves burrowing rodents
 - Live, love, kill
- Multiple rodent vectors in the pathogen's Central Asian origination area
 - Tarbagan marmot native to modern-day Mongolia, Siberia, western China, and eastern Eurasian steppes
 - Russian scientists absolutely convinced that marmot plague is more virulent than other types; they appear to be right
 - Eurasian hunters to this day are wary of sick-looking marmots
 - Population appears to have undergone cycles of population boom followed by plague-driven mass death
- Marmots are a well-established source of human plague outbreaks
 - Marmots are only rodent to routinely develop pneumonic plague

"I want only one strain — marmot plague!"
-- MG Nikolai Urakov, head of USSR biological weapons program



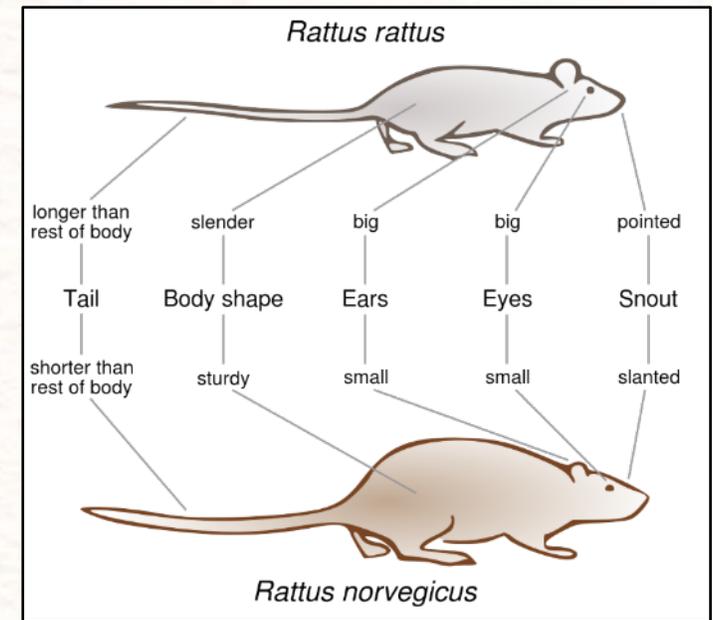
Black Rat

- Aka *Rattus rattus*
- South Asian origin, worldwide distribution
 - Comfortable in close proximity to humans
 - Sedentary; rarely moves more than a few hundred meters in its life
 - Adept hitchhiker on wagons, carts, and ships following maritime commerce and Roman roads
- Often lives in high densities, which pathogens love
- Highly omnivorous
 - Loves grain gathered by humans
 - 50 pounds per rate per annum, spoils twice as much



Brown Rat

- Aka *Rattus norvegicus*
- Chinese origin, now global in distribution
 - Larger than *R. rattus*
 - Slightly less comfortable in close proximity to humans
 - Sedentary; rarely moves more than a few hundred meters in its life
 - Also adept hitchhiker on wagons, carts, and ships
- Highly omnivorous
 - Also loves grain gathered by humans
- Displaced *R. rattus* as dominant rat in Eurasia
 - Also vector for plague, but less so than *R. rattus*
- **Sedentary nature of *X. cheopsis* and *R. rattus*/*R. norvegicus* almost forces *Y. pestis* to become a killer**



The Killer Emerges

- Pathology is similar in marmots and rats
 - Needs the host to stay alive long enough for pathogen to reproduce
- Coordinated juggling
 - Uses a protein to make Lipid A poison less lethal at mammalian body temperature than room temperature
 - Rat remains asymptomatic for 5-6 days
 - In latter stage of disease bacterial population grows enough to block bile duct causing death
- Fleas flee dead rats, spreading the disease
- **Bubonic plague in humans is a sideshow; we aren't intended victims**
 - **This removes normal evolutionary tendency for pathogens to become less virulent over time**



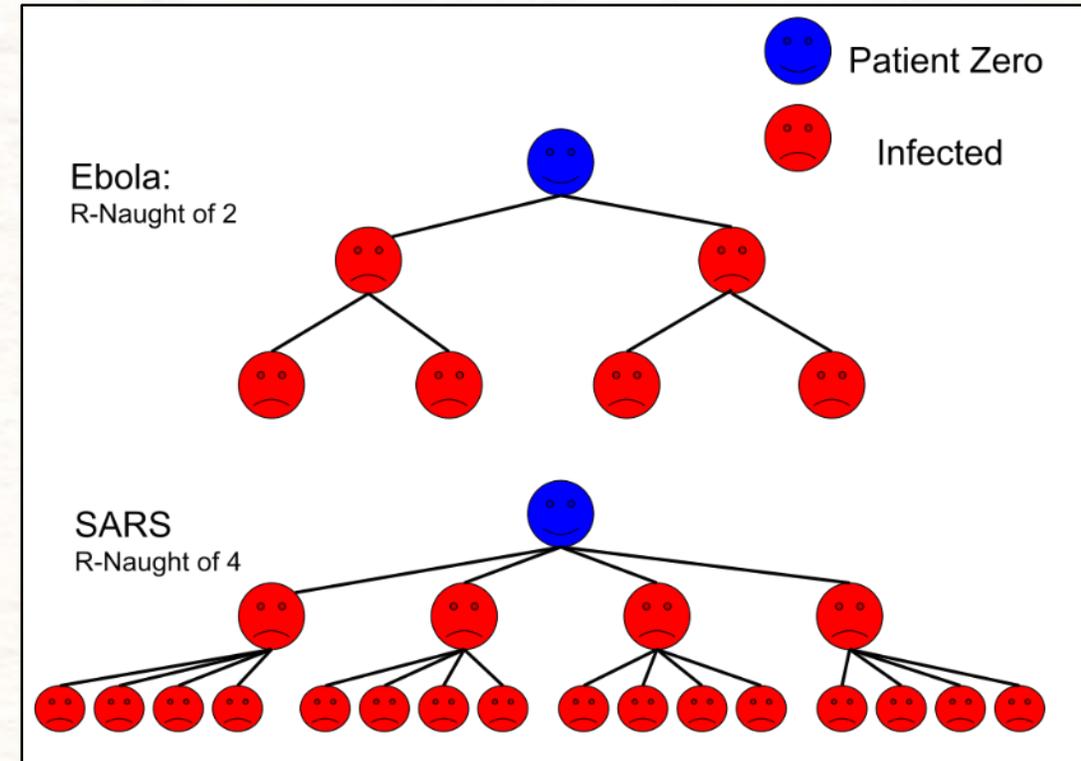
The Numbers Game

- Likelihood of plague outbreak dependent upon rodent density – more rodents, more risk
 - Low temperatures and increased rain increases rat population
 - High temperature and low precipitation lowers it
- Rodent susceptibility
 - Each rat home to hundreds or thousands of fleas
 - 1 in 8 are carrying *Y. pestis*
 - Not all are susceptible due to variety of reasons
- If less than 50% susceptible, jump to humans doesn't happen
 - If more than 80% are susceptible, jump becomes inevitable
- **More infection leads to population crash**
 - **Starving fleas move to other mammals, including humans**



Epidemiological Probability Statistics

- Epidemiology is a statistical numbers game centered on Basic Reproduction Number, or R_0 ,
- Three variables
 - Rate of contacts, or c
 - Duration of infectiveness, or d
 - Probability that pathogen will transfer to susceptible host, or p
- $R_0 = c * d * p$
 - If $R_0 < 1$, disease dies out
 - If $R_0 = 1$, disease is endemic
 - If $R_0 > 1$, disease spreads (epidemic or pandemic)
- **It takes a surprisingly small increase in R_0 to lead to quickly-spreading epidemic/pandemic**
 - **Increase c , d , or p slightly and mass outbreak occurs**



Spreading the Disease

- *X. cheopsis* active in a narrow temperature range (59-68F)
- But blocking tends to fall when temperature goes above 75F
- These narrow ranges normally kept *Y. pestis* geographically confined
 - Changing climate can allow pathogen to escape its geographic jail
- **Two of the three plague pandemics were preceded by a changing climate**
 - **Climate in both early 6th and 14th Centuries became colder and wetter (crop failures, malnutrition)**
 - **This allowed rodent populations to explode**
 - **Trade networks allowed disease to spread into vulnerable populations**



Defeating the Immune Systems

IMMUNITY

INNATE IMMUNITY

Physical Barriers



Chemical Barriers



Cellular Defences



ADAPTIVE IMMUNITY

Active Immunity



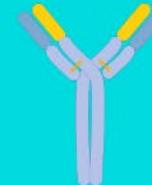
Natural



Vaccination



Passive Immunity



Maternal

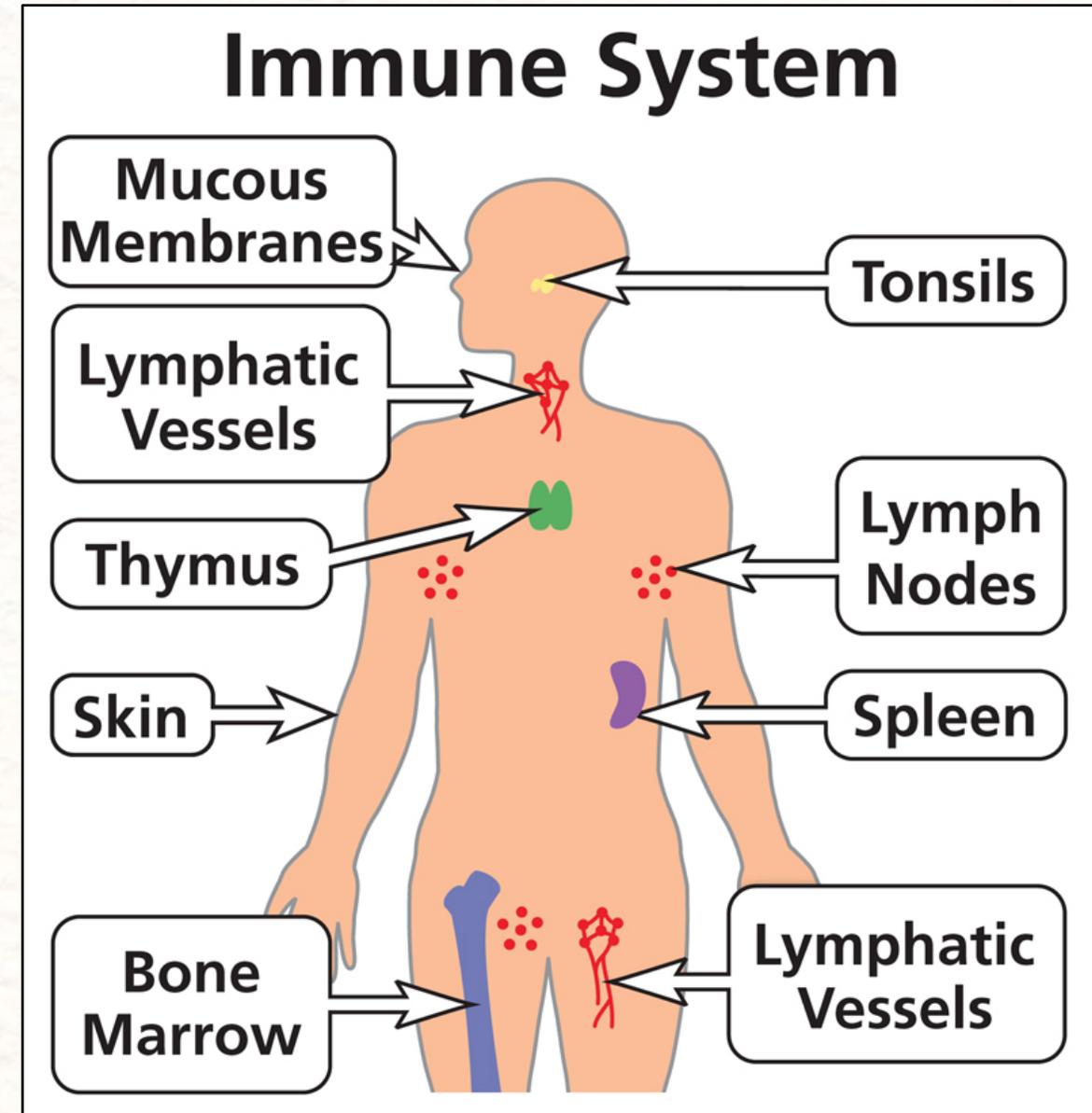


Artificial



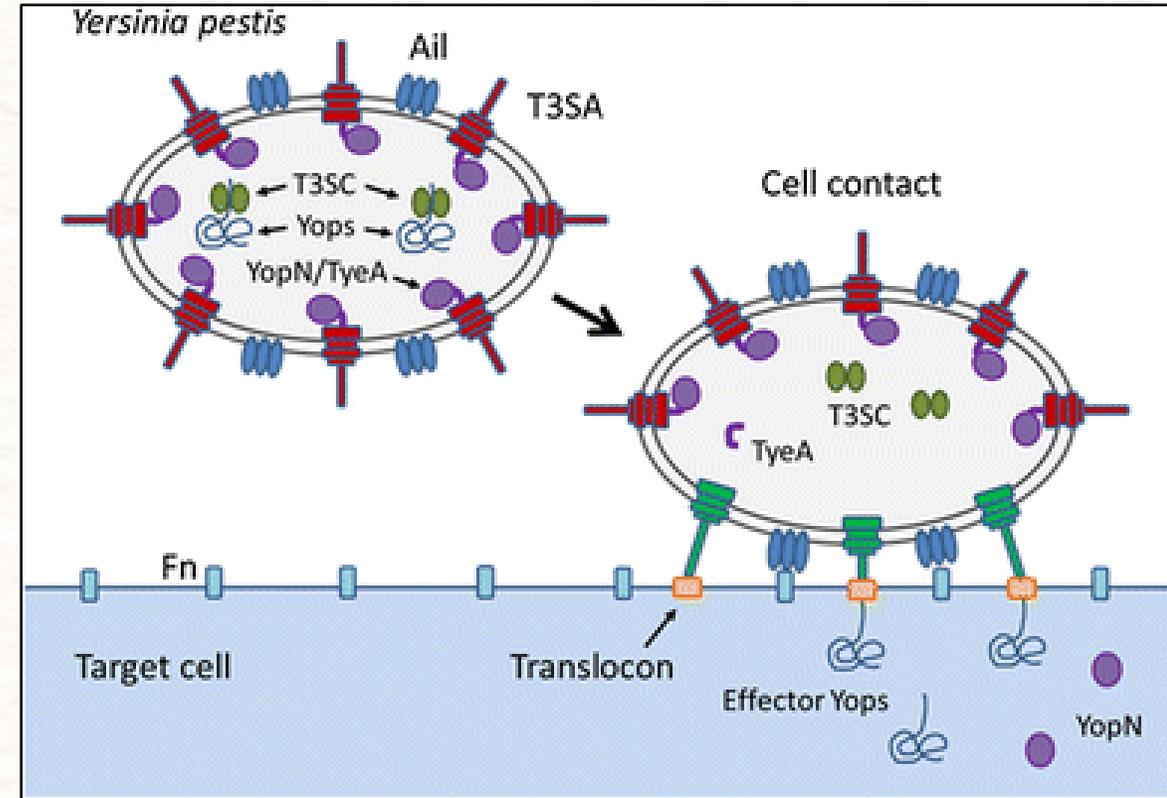
Human Immune System

- Body utilizes a “defense in depth” strategy
 - Barriers such as skin, caustic acid in stomach
 - Toll-like receptors and mast cells summon proteins known as cytokines
 - Cytokine individual shapes binds it to proteins in invading bacterium
- Cytokine binding calls in additional specialized cells
 - B-lymphocytes produce antibodies to attack invading cell
 - T-lymphocytes punch holes in invading cell wall
 - B- and T-lymphocytes “remember” the invader and are prepared to respond to additional infections
- Highly effective when it works
 - *Y. pestis* doesn't want it to work, and has evolved to defeat it



Y. pestis Weapon Systems

- Biting flea allows pathogen to avoid skin barrier
- Biochemical warfare as *Yersinia* Outer Proteins (Yops) counter defense mechanisms
 - YopJ prevents cytokine production
 - YopH deactivates white blood cells
 - YopM binds thrombin
- Simultaneously, plasminogen activator protease digests fibrin, preventing blood from clotting
 - Creates both thromboses and hemorrhaging, leading to gangrene



Y. pestis Weapon Systems

- Lymphatic system is attacked and fooled
- Lymph nodes swell and cells rupture, creating buboes (bubonic plague)
- *Y. pestis* also creates several endotoxins
 - Lipid A directs cells to destroy themselves
 - Waits until the bacteria is ensconced in the lymph system
- By the time the victim's immune system fully responds and patient begins to feel sick, they already well on the way to death



Y. pestis Limitations

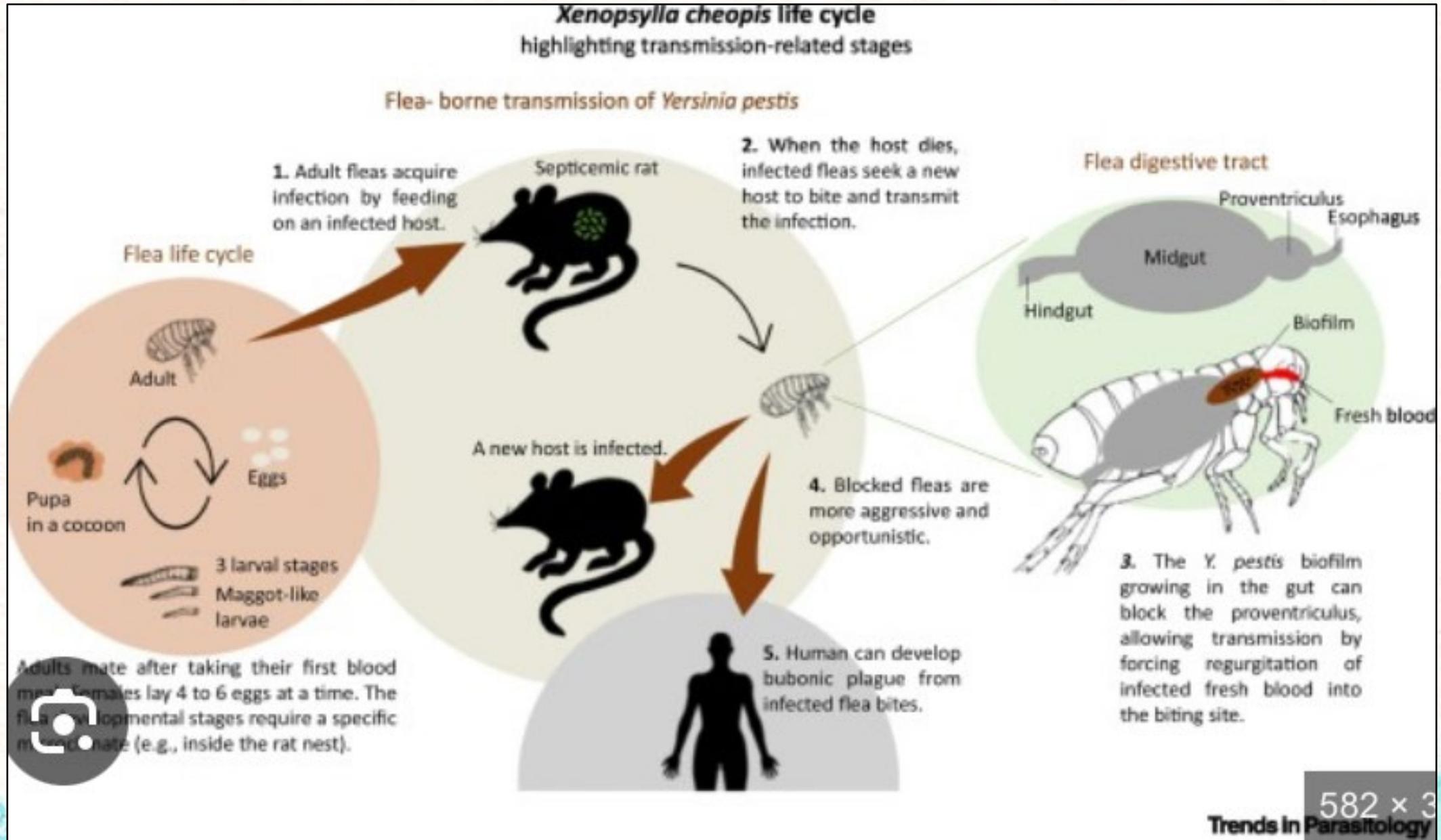
- *Y. pestis* is an adaptable pathogen that can kill almost everything put in front of it
 - Marmots, rats, gerbils, squirrels, prairie dogs, camels, chickens, pigs, dogs, cats, HUMANS
- But it does have limitations
 - Doesn't survive long on surfaces
 - Some animals appear to have resistance to bacillus—skunks, polecats, black bears, and coyotes
- Rodents sometimes exhibit resistance
 - Most of time enzootic
 - Changes in environment, virulence, or demographic changes can tip into epizootic outbreak
 - Theories of surge years where rodent population surges into classic Malthusian dilemma
 - Surge years also drive rodents into greater contact with people



Thomas the Tarbagan Says “Time for a Break”



The Plague Cycle



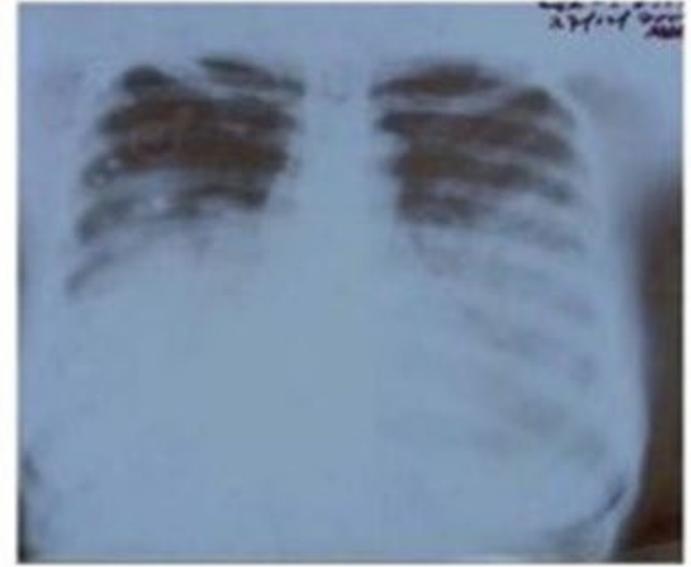
The Three Forms of Plague



Bubonic plague



Septicemic plague



Pneumonic plague

Bubonic Plague

- Spread primarily via flea bites
- Pathogen spreads to lymph nodes
 - Typically appear in groin; also in neck and armpit
- Non-specific symptoms (until bubo appears)
 - High fever, chills, muscle cramps
 - Can develop into gangrene and sepsis
- High mortality
 - 30-90% throughout history
 - Still 10% even with modern medical treatment



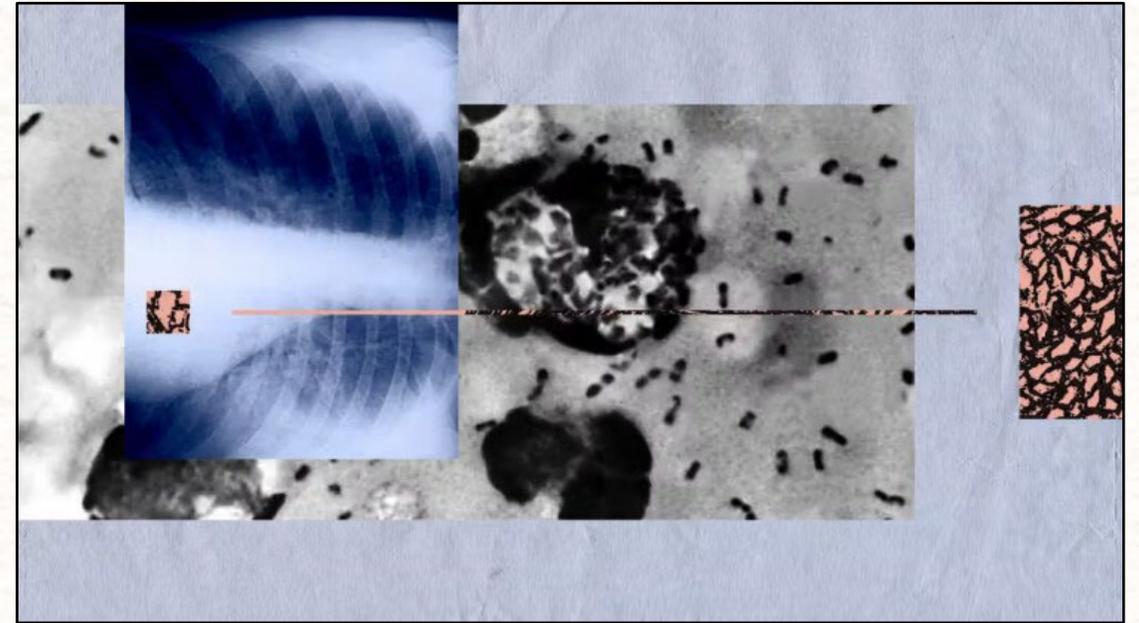
Septicemic Plague

- Spread primarily via flea bites; often a complication of bubonic plague
- Spreads into bloodstream, creating sepsis
- Bubonic symptoms, plus:
 - Bleeding under skin, gangrene, organ failure
 - Nausea and bloody vomiting and diarrhea
- Lethal
 - Death within 24-48 hours absent modern treatment
 - 4-15% *if* diagnosed and treated early
 - Still highly lethal if treatment delayed 24 hours



Pneumonic Plague

- Pathogen enters the pulmonary system
 - Can now spread via sputum and airborne droplets
 - **The only form that can be spread directly from victim to victim**
- Severe but non-specific symptoms (at first)
 - Initially, fever, weakness, headaches and nausea
 - Proceeds to severe pneumonia
 - Hemoptysis (coughing blood)
 - Respiratory shock
- Lethal
 - Death within 36-72 hours absent modern treatment
 - 7% fatality rate even with treatment
- **Lengthy incubation period allows victim to travel widely, spreading the disease**

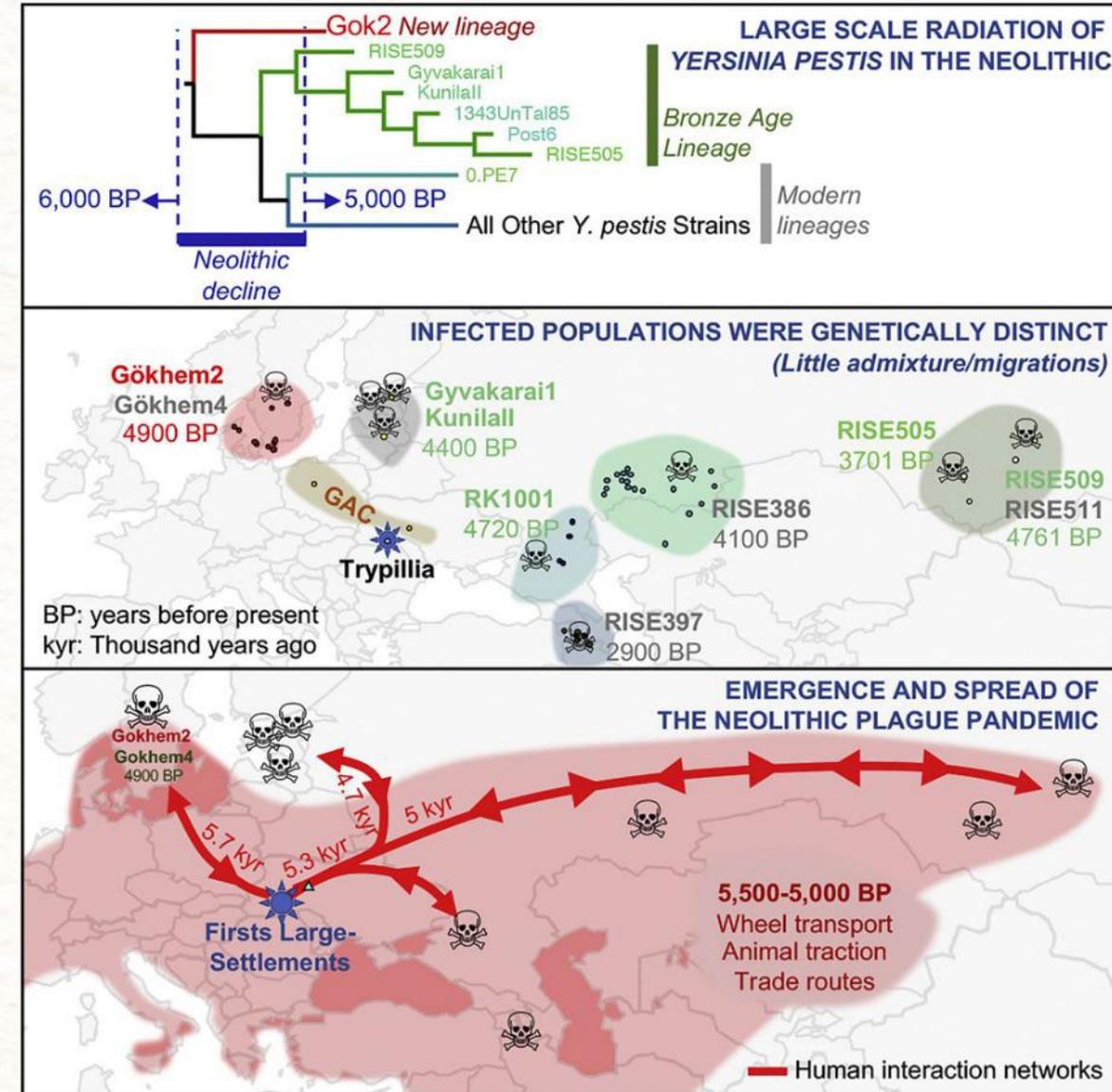


DO NOT WAIT FOR DIAGNOSTIC TEST RESULTS IF YOU SUSPECT PLAGUE

A confirmatory diagnosis can be established later using specialized laboratory tests. Never delay or withhold treatment pending the receipt of laboratory test results. The decision to initiate antibiotic therapy for plague should be made based on [clinical signs and symptoms](#) and a careful patient history. A recent flea bite, exposure to areas with rodents, or contact with a sick or dead animal are risk factors for plague in endemic areas.

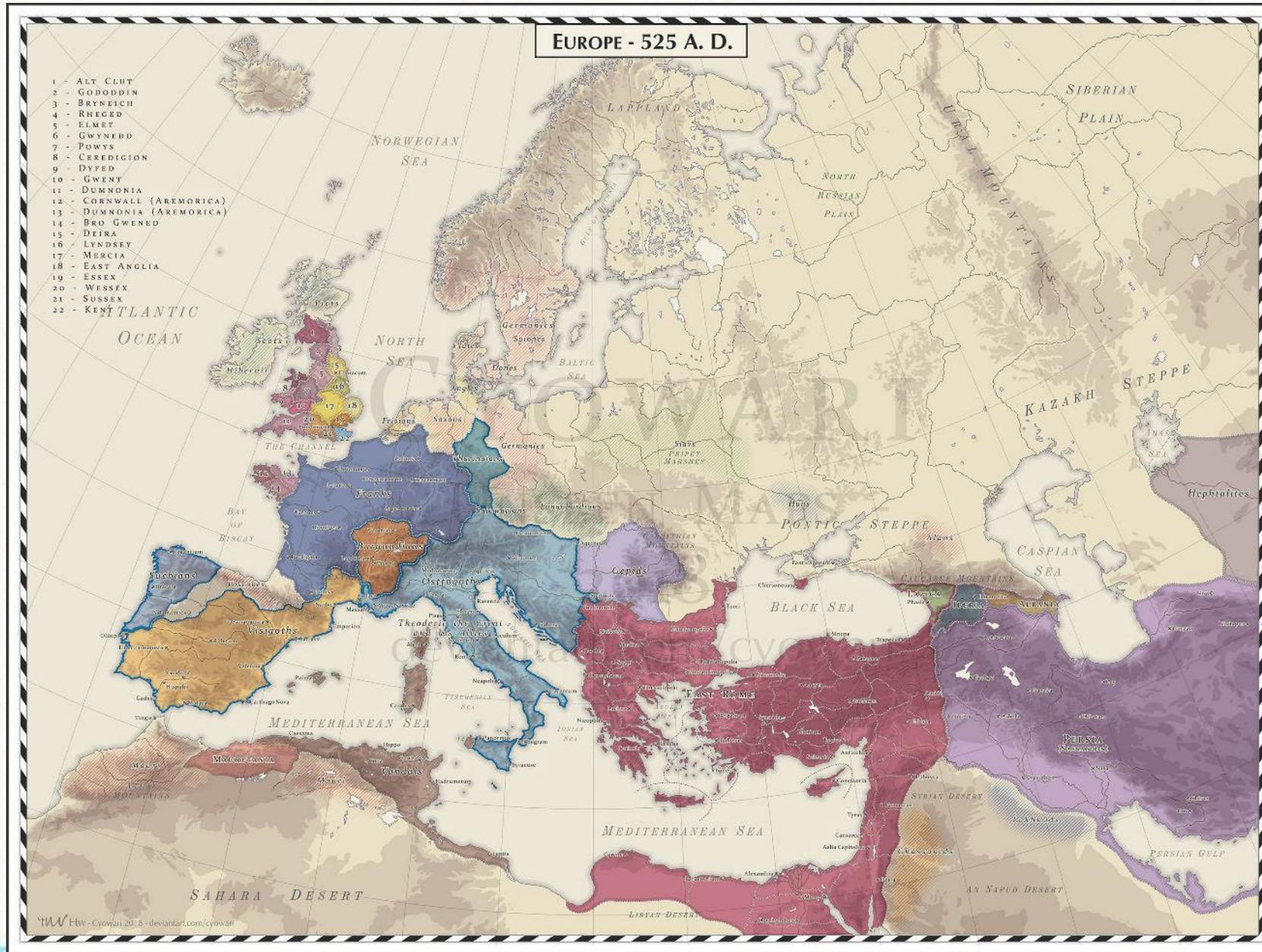
Neolithic Plague Pandemic?

- DNA evidence from skeletal remains shows that *Y. pestis* was circulating in Eurasia in late Neolithic and Early Bronze Age
 - Fragmentary
- Slight differences with later *Y. pestis*
 - Appears to lack gene to survive in fleas
 - Human to human pneumonic transmission?
- Timing coincides with Neolithic Decline
 - Late neolithic farmers replace hunter-gatherers ~4000BCE; population grows
 - Rapid population collapse ~3500-3000BCE
 - After collapse, Indo-European migration from Eurasian steppes occurs
- Replacement or virgin land?



First Plague Pandemic

First Plague Pandemic



535-545 — The Worst Decade to Be Alive

- At least three massive volcanic eruptions occur somewhere on the planet
 - Darkened skies across Europe and Asia
 - Summer temperatures dropped by 2.5C in Europe (biggest drop in 2300 years)
- Widespread crop failures and subsequent famines
 - Recorded in documents ranging from Ireland to China
 - Malnourished populations more susceptible to disease
- Subsequent eruptions in 539 and 547
 - Occurs during the backdrop of the Gothic Wars in Italy and the First Plague Pandemic
 - “Worst decade to be alive” isn’t actually a huge stretch

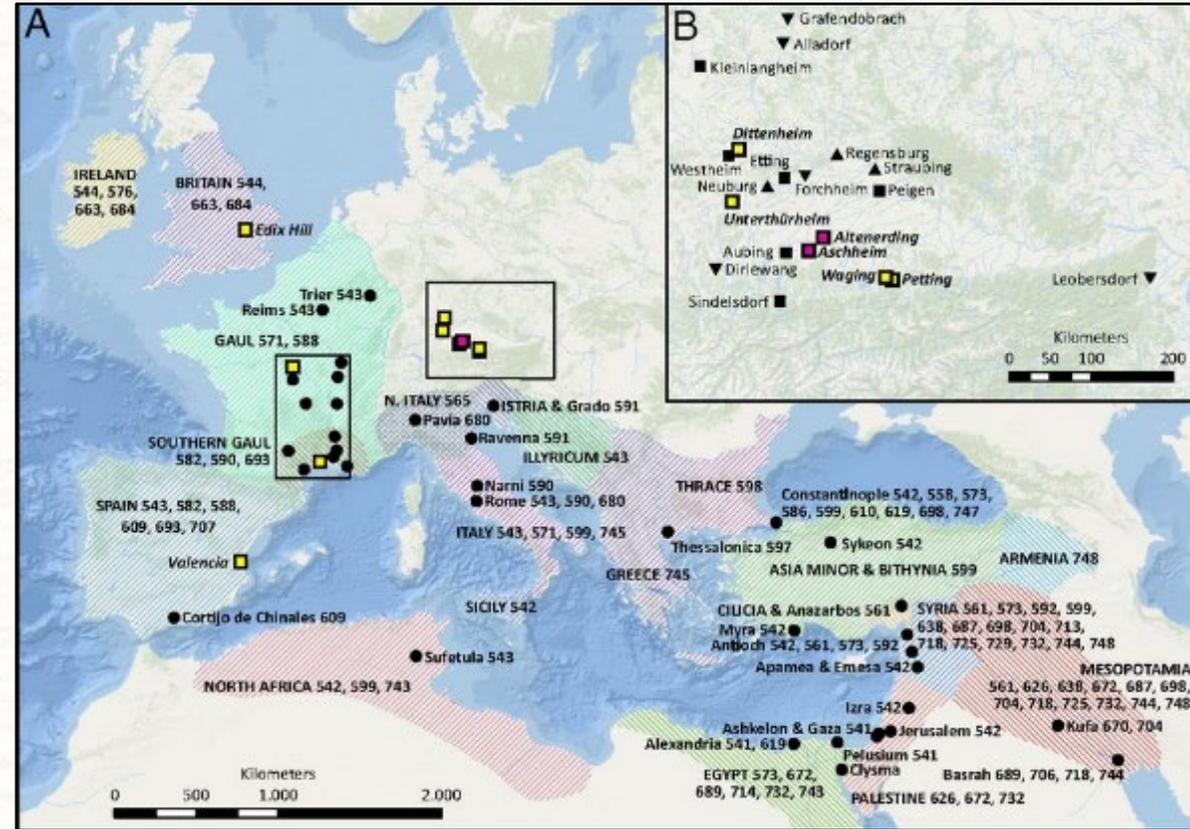
“The suns rays were weak and appeared bluish in color. At noon, no shadows were visible on the ground, and the heat from the sun was feeble. It was a winter without storms, a spring without mildness, and a summer without heat”

-- Cassiodorus, *The Letters of Cassiodorus*



First Plague Pandemic (541-549)

- Also known as the Plague of Justinian
 - Causative agent for long time was debated
 - Recent DNA evidence confirms that the pathogen was *Y. pestis*
- Death toll and impact debated
 - Procopius writes about the plague in almost apocalyptic terms; no reason not to accept his word
 - Some scholars argue that death toll and economic/societal impact was minimal
- Byzantine Emperor Justinian contracts the plague in 542
 - Falls into plague coma (typical for victims)
 - Survives and eventually recovers fully



First Plague Pandemic (541-549)

- DNA evidence suggests a Central Asian origin
 - Believed to have originated in Tian Shan region of Asia
- Emergence and spread from Egypt long suggested African origin
 - “Gerbil Belt” runs from Central Asia to Ethiopian highlands
 - Fragmentary reports of mass death in Yemen and Kush
 - At this time, Kingdom of Aksum controls Ethiopian highlands, Eritrea, coastal Sudan, and Yemeni coast
 - From Ethiopia, slowly follows trade routes to Egypt
- Once in Egypt, game on

“This disease always took its start from the coast, and then went up into the interior”
-- Procopius, *The History of the Wars*

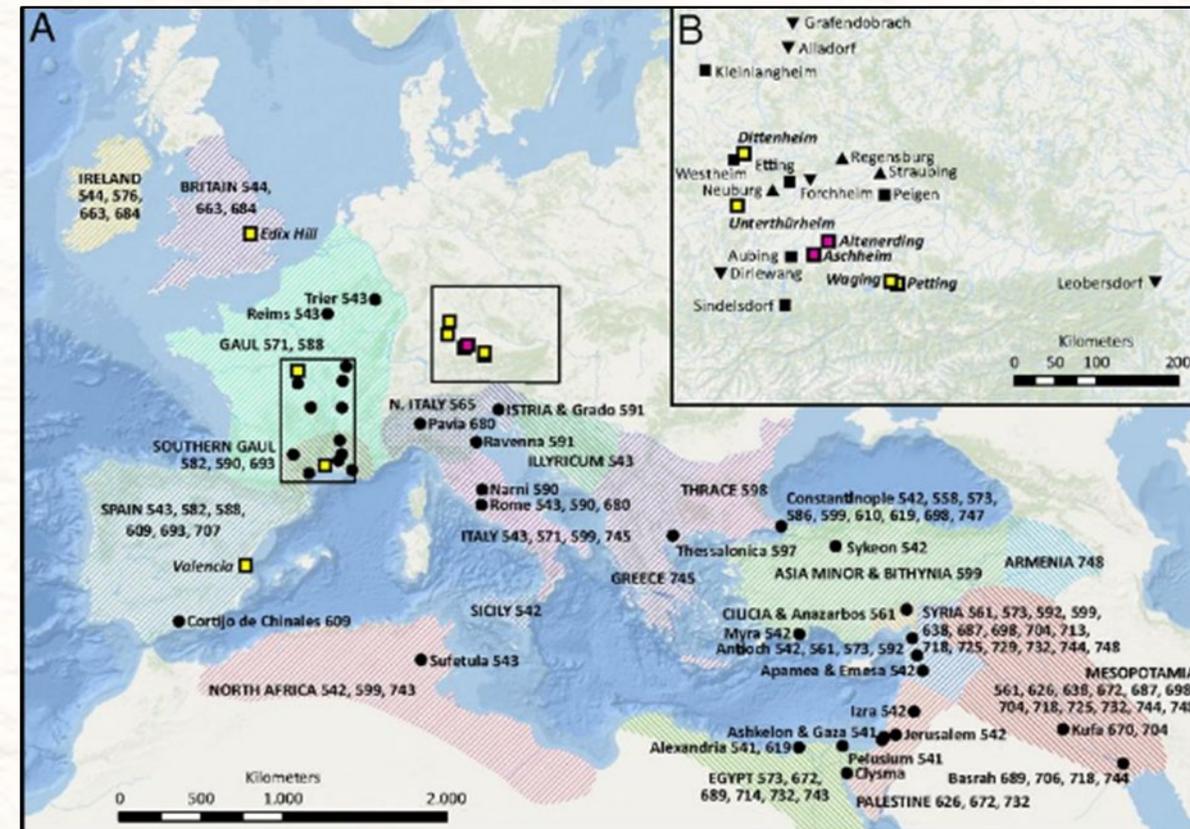


First Plague Pandemic (541-549)

- Disease rapidly spreads to major port cities, most importantly, Constantinople
 - DNA sampling suggests plague may have taken more than one pathway
- Procopius' observation, combined with symptom descriptions, suggests disease remained primarily bubonic
 - Some accounts suggest the septicemic form also occurred
 - Pneumonic form appears not to have been major factor

“This disease always took its start from the coast, and then went up into the interior...Victims had a sudden fever, within days a swelling developed and this took place not only in the groin but also inside the armpits...there ensued some with a deep coma, others a violent delirium...the swelling became mortified and the sufferer, no longer able to endure the pain, died ”

-- Procopius, *The History of the Wars*



First Plague Pandemic (541-549)

- Virulence and mortality highly debated
- Literary references argue strongly for catastrophic death toll
 - Procopius, John of Ephesus, Gregory of Tours and other chroniclers speak in almost apocalyptic terms
 - Constantinople runs out of burial space, begins burying corpses in consecrated towers and eventually dumping in the river
 - Pattern repeats across other cities
- Archaeological evidence much more sparse
 - No discovered plague pit mass graves
 - No clearcut evidence of demographic or economic decline (but this is the darkest of the Dark Ages)
- Most scholars emphasize literary sources, arguing for urban mortality of up to 40%

“Since soon no coffins or biers were left, six and even more persons were buried together in the same grave. One Sunday, three hundred corpses were counted in Saint Peter’s basilica in Cleremont alone”

-- Gregory of Tours, *The History of the Wars*

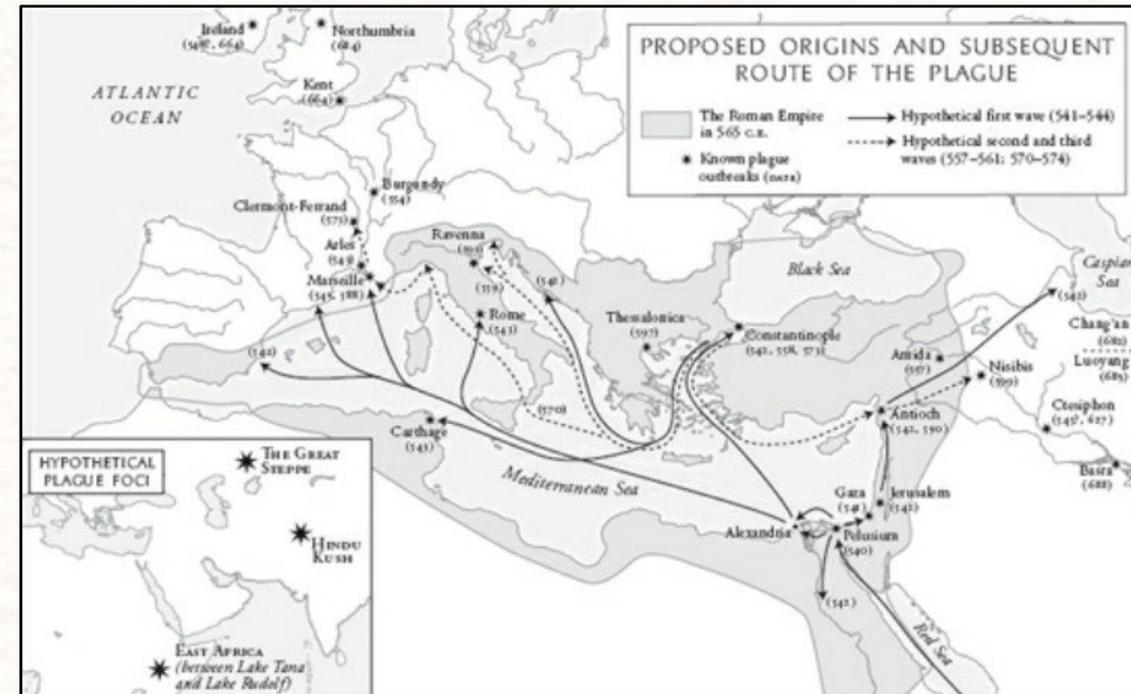


First Plague Pandemic (541-549)

- Plague also struck deep into Sassanid Persian Empire
 - Not a surprise, as it lies directly in the Silk Road
 - Grave sites and notarized wills provide evidence of spread, albeit slower
 - Accounts of symptoms and mortality similar to Byzantine
- Byzantine-Sassanid fighting slowed as armies died, but continued
- Later Arab records give greater precision
 - Specific word for bubonic plague—"ta'un"
 - Arabia itself remained relatively plague-free during the initial pandemic (temperature outside *X. cheopsis* tolerance)
 - After Arab conquests of early 7th Century, they would fall prey to the disease

"I lost many of my children, my wife and other relatives and numerous estate dwellers and servants...As I write this in the 58th year of my life I recently lost another daughter and the son she has produced."

-- Evagrius Scholasticus, *Ecclesiastical History*



Subsequent Returns

- After initial pandemic, plague recurred multiple times for more than two centuries
 - Rome (590), Sheroe (627-628), Amwas (638-639), Britain (664), regional (698-701, 746-747)
 - Accounts of symptoms and mortality similar to Byzantine
 - Struck the young disproportionately
- One possible account from China (610)
 - However, it's one account when Chinese were meticulous about reporting on many other diseases; unlikely to be plague
- Plague then (mostly) disappears from the records until 14th Century
 - Likely to have been periodic small outbreaks in Central Asian refuge

“The pestilence raged far and wide with fierce destruction, ravaging Britain and Ireland with cruel devastation”

-- St. Bede, *Ecclesiastical History of the English People* (731)



Medical Response

- Tied to Galen's humoral theory of disease
 - Thus, the "cures" often exacerbated the symptoms
 - Cold water, saintly relics, magical amulets offered harmless placebos
 - Not so true of mandrake and belladonna (atropine), verdigris (copper oxyacetate), opium poppy juice
- Attempts at primitive forms of quarantine
 - Late antiquity hospitals may have been some help in isolating individuals until they quickly became overwhelmed
- **Medical science (such that it was) was dealing with something it had never seen, did not understand, and was unprepared to face**
 - **This will be true for the Second Plague Pandemic as well**



Impacts of First Plague Pandemic

- Depopulated Europe, North Africa, Southwest Asia
- Fewer people to work land and in trades drives innovation
 - Inventory of arable land remains constant, but number of farmers was reduced
 - Moldboard plow makes its way from Asia and becomes more refined (excellent for heavy northern European soils)
 - Three-field system begins to replace two-field system; oats to feed livestock also becomes a cash crop
- Rich become poorer, the poor become richer
 - Landed elite (such as Justinian) try to freeze prices and wages, with expected result
 - Centuries before the previous ratio is restored
- By ~800, Europe is primed to begin population boom and economic expansion leading to the High Middle Ages



Justinian, looking forward to ruling over a prosperous Roman Empire:

Mother Nature:

