Biodiversity of Pathogens

Guest Lecture: Joel Wertheim

10/23/08

Review Session for Exam #2

Tuesday October 28th

Starts at 5:15 pm

BioSciences West 219

Bring Questions!

Today

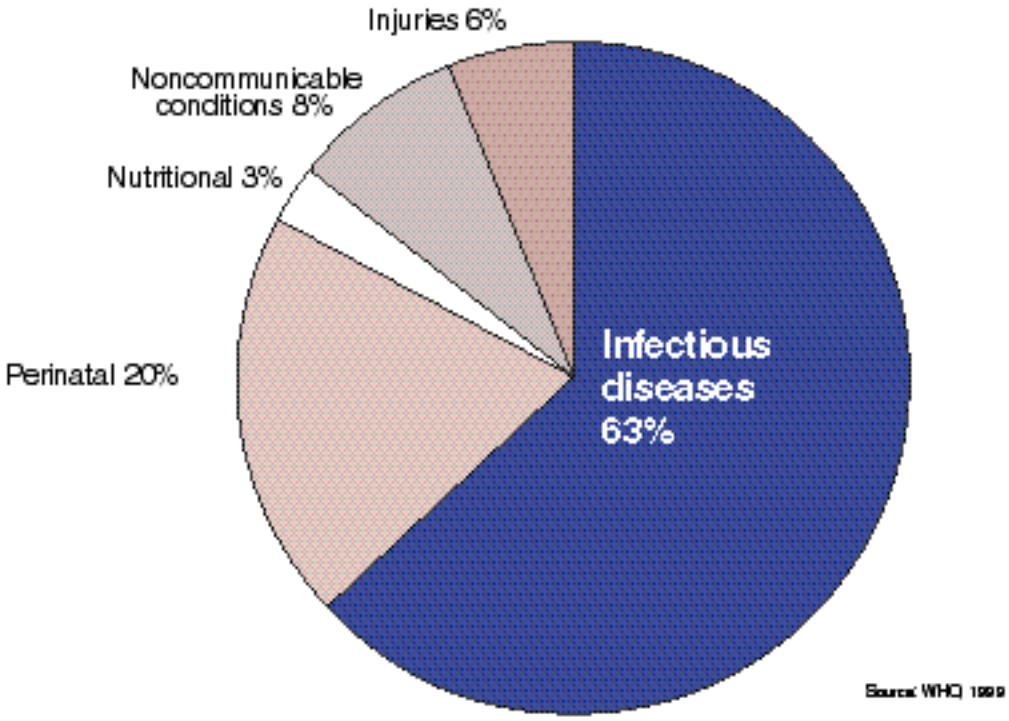
Pathogens in context: the diversity of life on Earth

- Bacteria
- Viruses
- Parasites

Along the way, we'll try to look at some pathogens that have been important in human evolution

Main causes of death among children

Ages 0 to 4 years
Estimates for 1998, worldwide

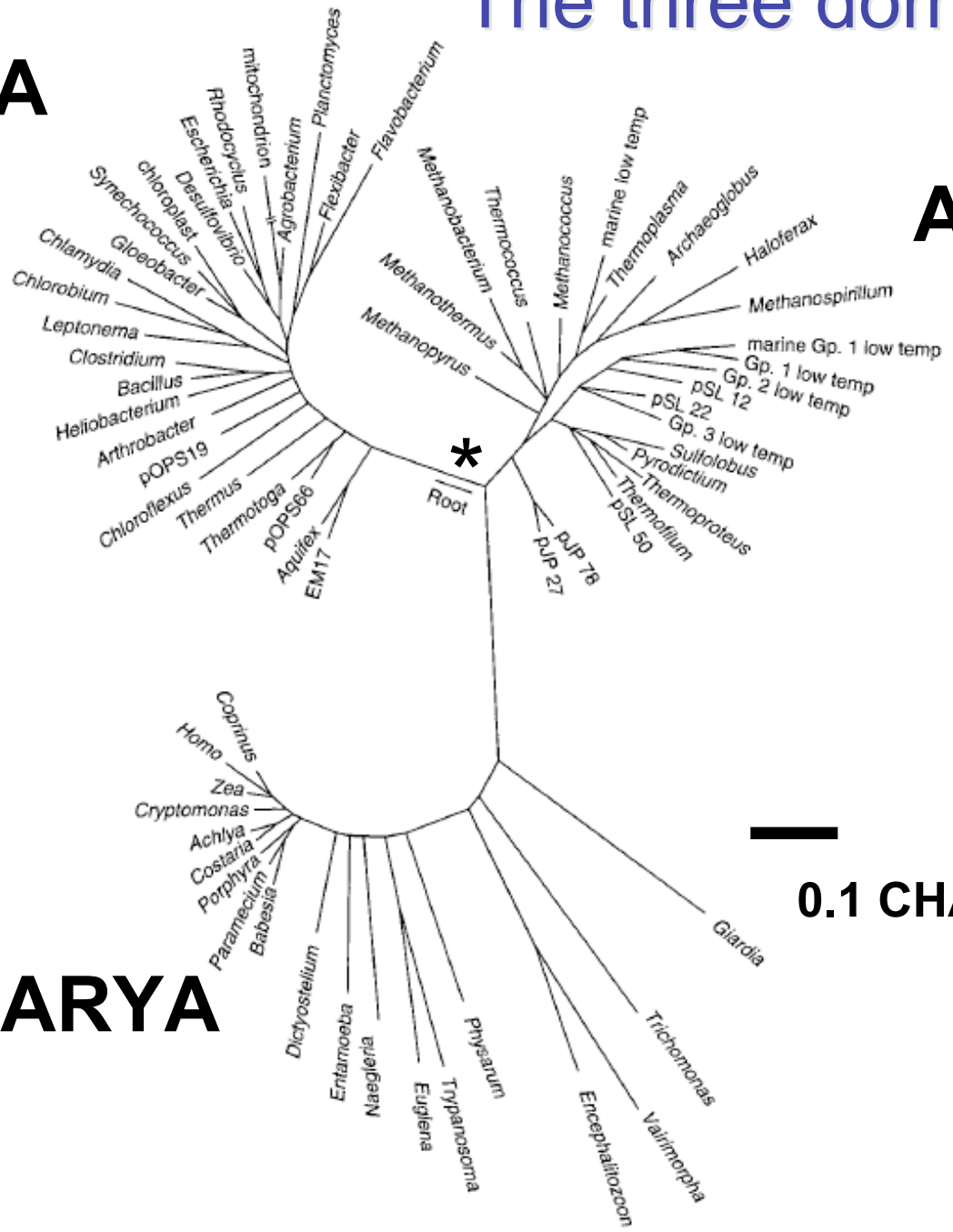


The three domains of life

BACTERIA

ARCHEA

EUCARYA



How do we find bacteria?

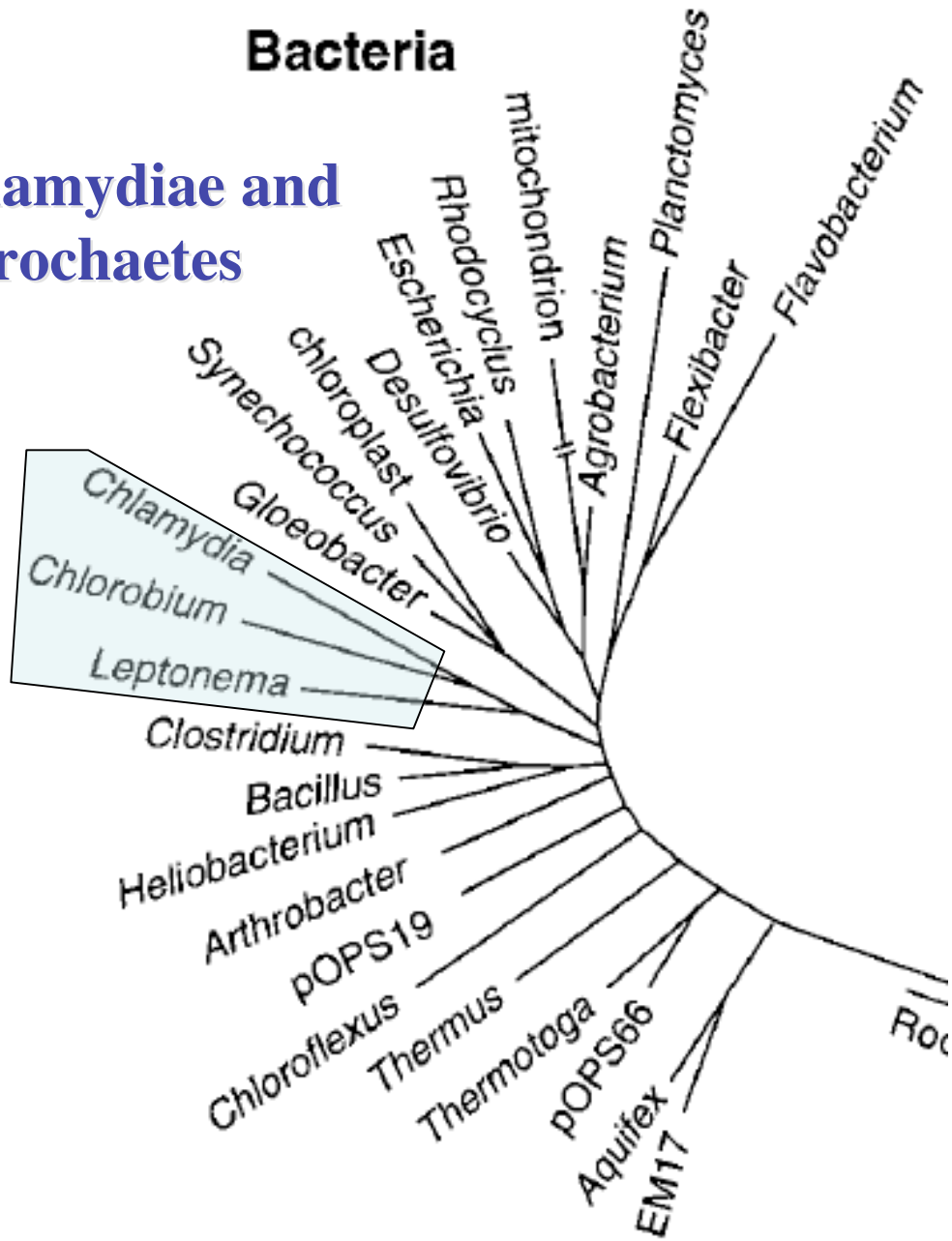
- Classical microbiology relied on observing bacteria through a microscope
- Have to be able to culture them in the laboratory
- Now we use conserved sequences such as 16s rRNA to find new species
- It turns out that most all bacteria are not easily cultured, and we were ignoring them

Extremely brief history of life

- Fossil evidence for prokaryotic life 3.5 billion years ago
- It took another 2 billion years or so for the appearance of eukaryotic cells that could give rise to larger animals and plants
- Archea may be the most diverse and massive domain, but few are known to cause infectious disease, so we'll ignore them

- Only very few bacteria of the innumerable species are pathogenic
- Of the roughly 400 genera less than 40 contain species that regularly cause disease in humans
- Other animals have different suites of pathogens
- But there is overlap: **zoonoses** are diseases that occasionally jump into humans from from some "natural" non-human host
- E.g. plague from rats, HIV/AIDS from chimps/sooty mangabeys, rabies from many tetrapods, Lyme's disease from deer ticks

Chlamydiae and Spirochaetes



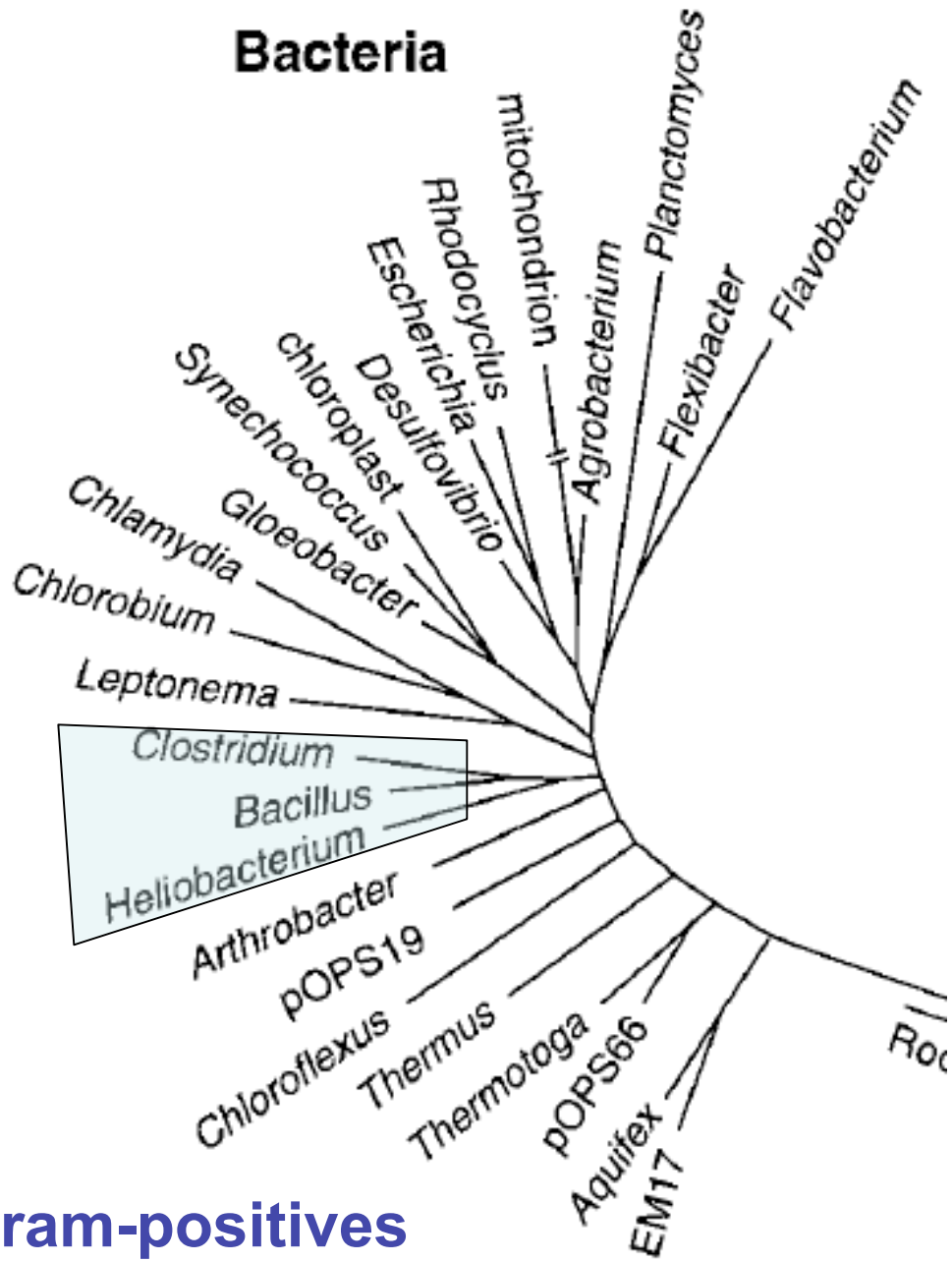
- Chlamydiae and sprirochaetes are obligate **intracellular** parasites of animals

- *Chlamydia* infection is often asymptomatic

- Most common bacterial STD in USA, with about 3 million new infections/year

- Can cause reproductive problems, pneumonia in newborns

- Spirochaetes include the agents of syphilis (*Tryponema pallidum)* and yaws and the agent of relapsing fever and Lyme disease (*Borrelia burgdorferi)*



Gram-positives

- Gram-positive bacteria include the agents of tuberculosis, *Mycobacterium tuberculosis,* and leprosy. *M. leprae*
- These are both “high G-C” Gram-positives
- What is “high G-C”?
- Lots of G’s and C’s relative to A’s and G’s in their DNA

Gram-Positive?

- Gram stain is a purple stain that gets caught in the peptidoglycan layer
- Gram-positive bacteria have thicker layer
- Penicillin disrupts formation of peptidoglycan layer, therefore effective against gram-positive bacteria

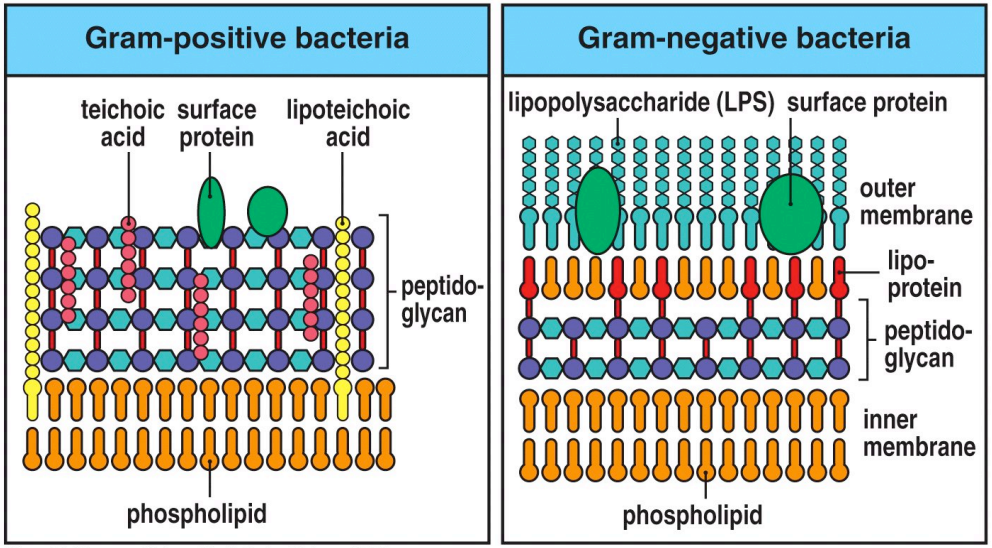


Figure 15-3 Immunobiology, 6/e. (© Garland Science 2005)

What's wrong with the term gram-negative?

Tuberculosis

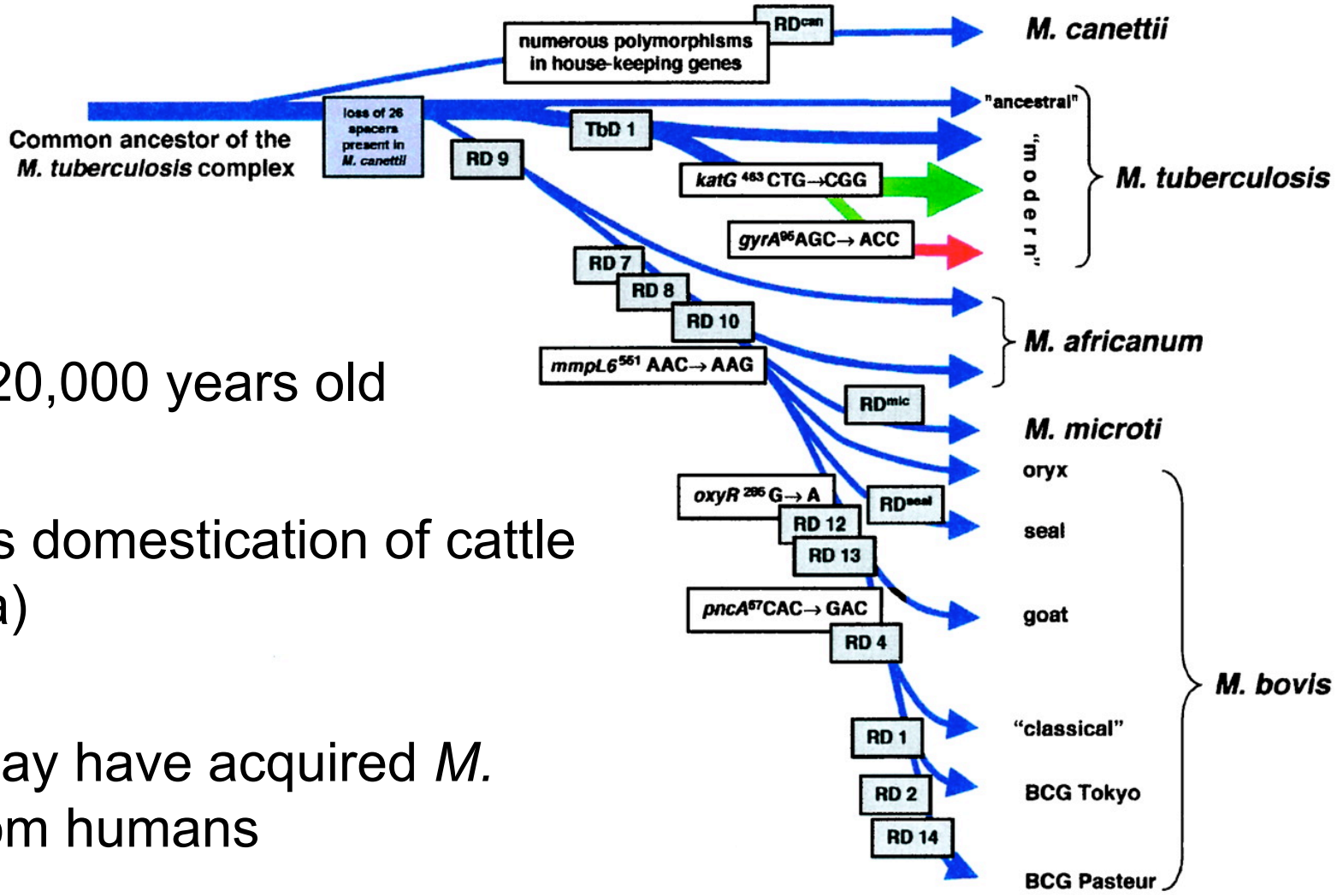
- The singlemost important bacterial pathogen of humans right now (around 2 million deaths/year)
- Most deaths in developing world, but by no means solely there
- A.k.a. ‘consumption’: used to kill 5/1000/year in Britain
- Accounted for many of those pale, coughing Victorians
- Caused by *Mycobacterium tuberculosis*, a very tough bacterium that is resistant to most host defense mechanisms

Mycobacterium tuberculosis

- Produces a chronic infection (is difficult to clear even with the contemporary use of antibiotics)
- Is increasing along with HIV/AIDS
- High level of associated mortality
- Documented ancient association
  - Egyptian mummies (5000 years ago)
  - South American mummies (1000 years ago)

Mycobacterium tuberculosis

- 15,000-20,000 years old
- Predates domestication of cattle (~10 kya)
- Cattle may have acquired *M. bovis* from humans

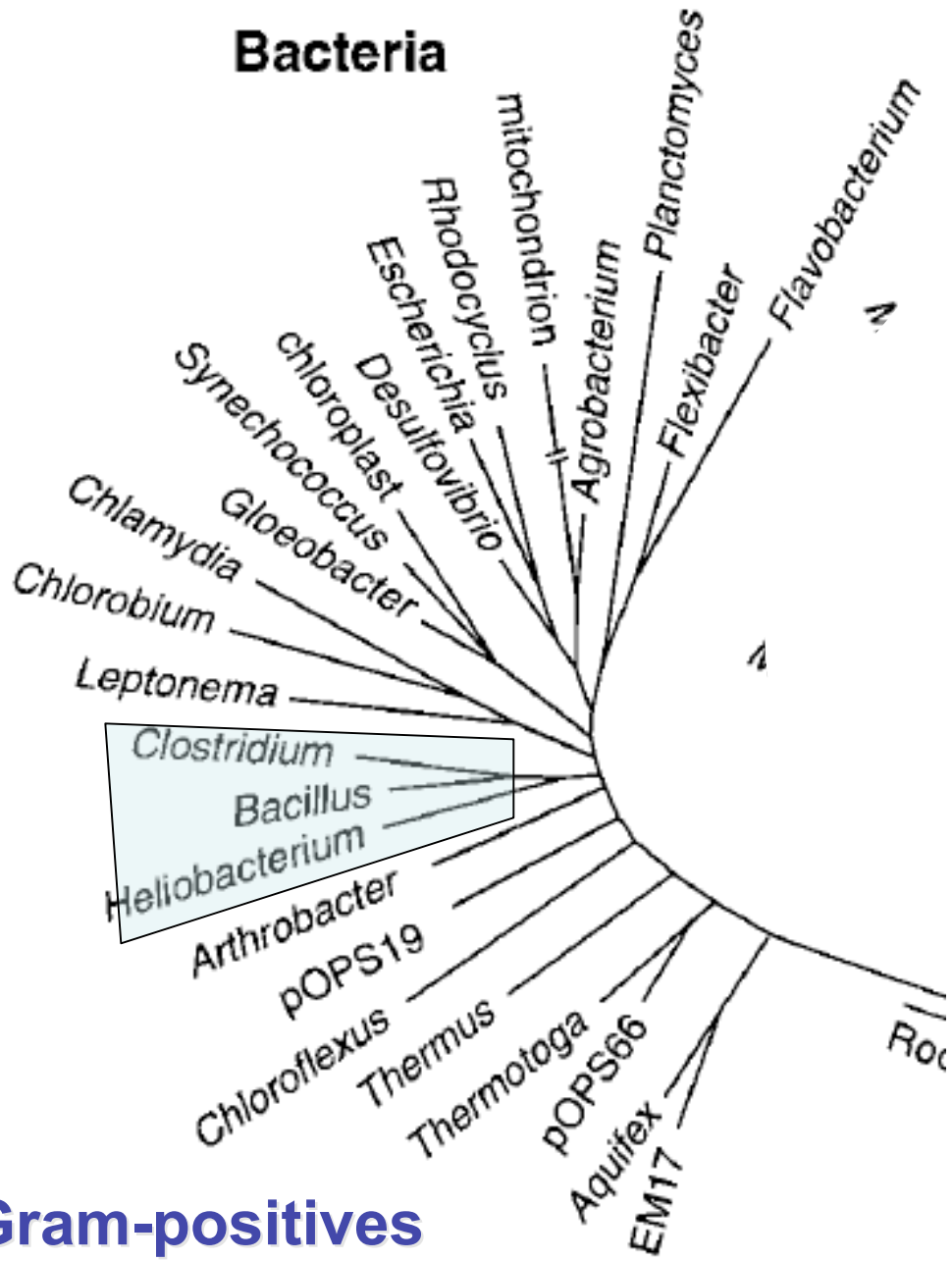


Cystic Fibroris Link?

- Cystic Fibrosis (CF) is the most common single locus genetic disorder
- The most common allele (ΔF508) arose ~600 generations ago and may have increased rapidly
- Those afflicted with CF cannot produce an enzyme (arylsulphatase B) needed by *M. tuberculosis* to produce cells walls
- Heterozygotes have a 2% selective advantage
- High levels of ΔF508 in Europeans have been attributed to a 16th century TB epidemic

Mycobacterium leprae

- Causative agent of Leprosy
- Does not actually cause body parts to fall off, rather it deadens nerve cells with allow for skin damage
- Resides in macrophages (like *M. tuberculosis*)
- Immune response can go in two directions: T_h1 vs. T_h2
  - T_h1 stimulates macrophages to destroy bacteria and disease is less serious
  - T_h2 stimulates B-cells to make antibodies which are not as effective against intracellular pathogens and disease is more severe



Gram-positives

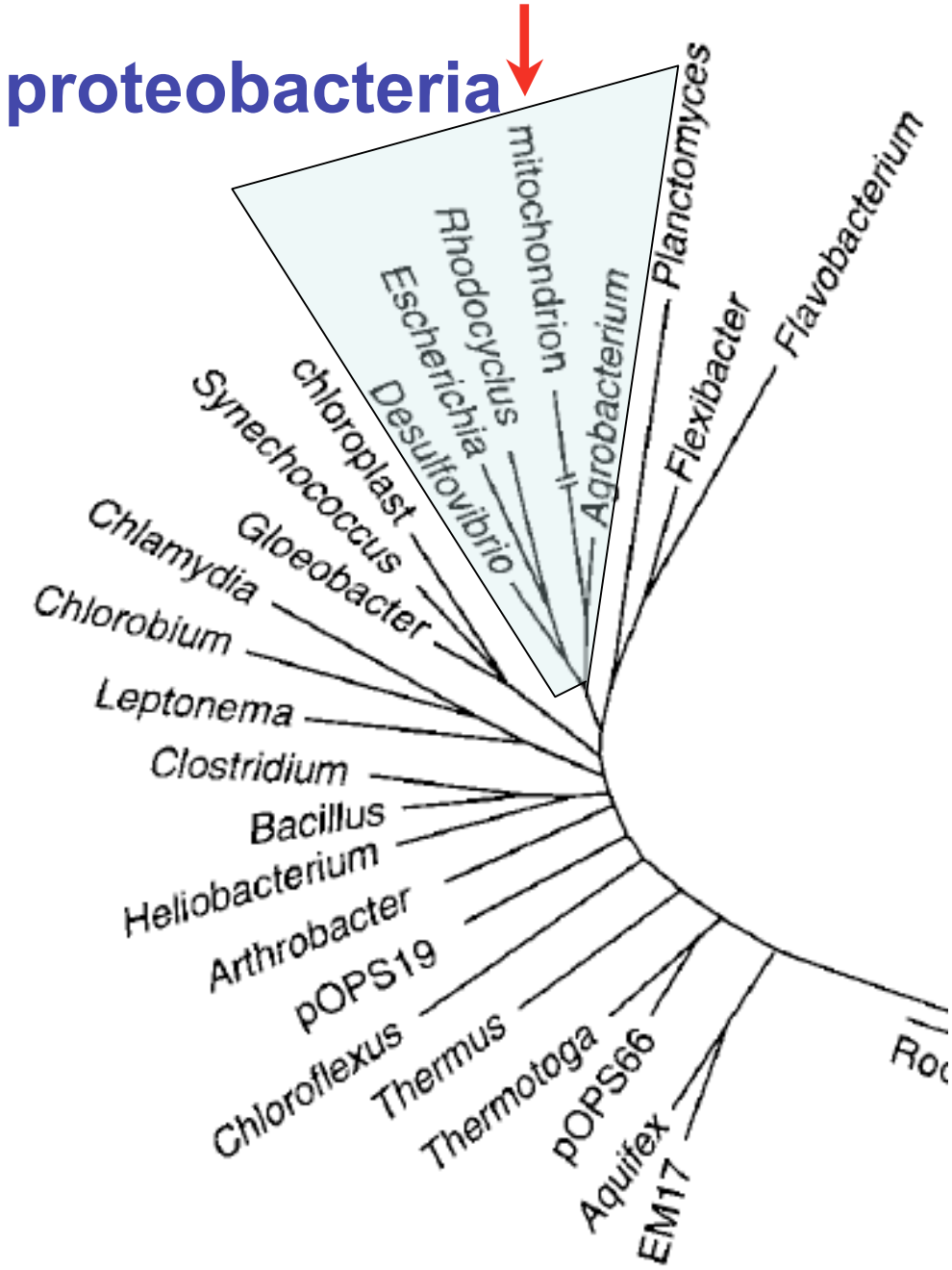
•Among the “low G-C” ones are
-*Bacillus anthracis* (anthrax)

-*Staphylococcus aureus* (what you don’t want to get after surgery)

-*Streptococcus pneumoniae* (pneumonia, bacterial meningitis)

-*Clostridium spp.*(anaerobic, spores resist boiling; causes botulism, gas gangrene, tetanus, among other pathologies)

Practical advice:
Don’t eat from bloated cans
Don’t feed honey to infants
Don’t step on rusty nails



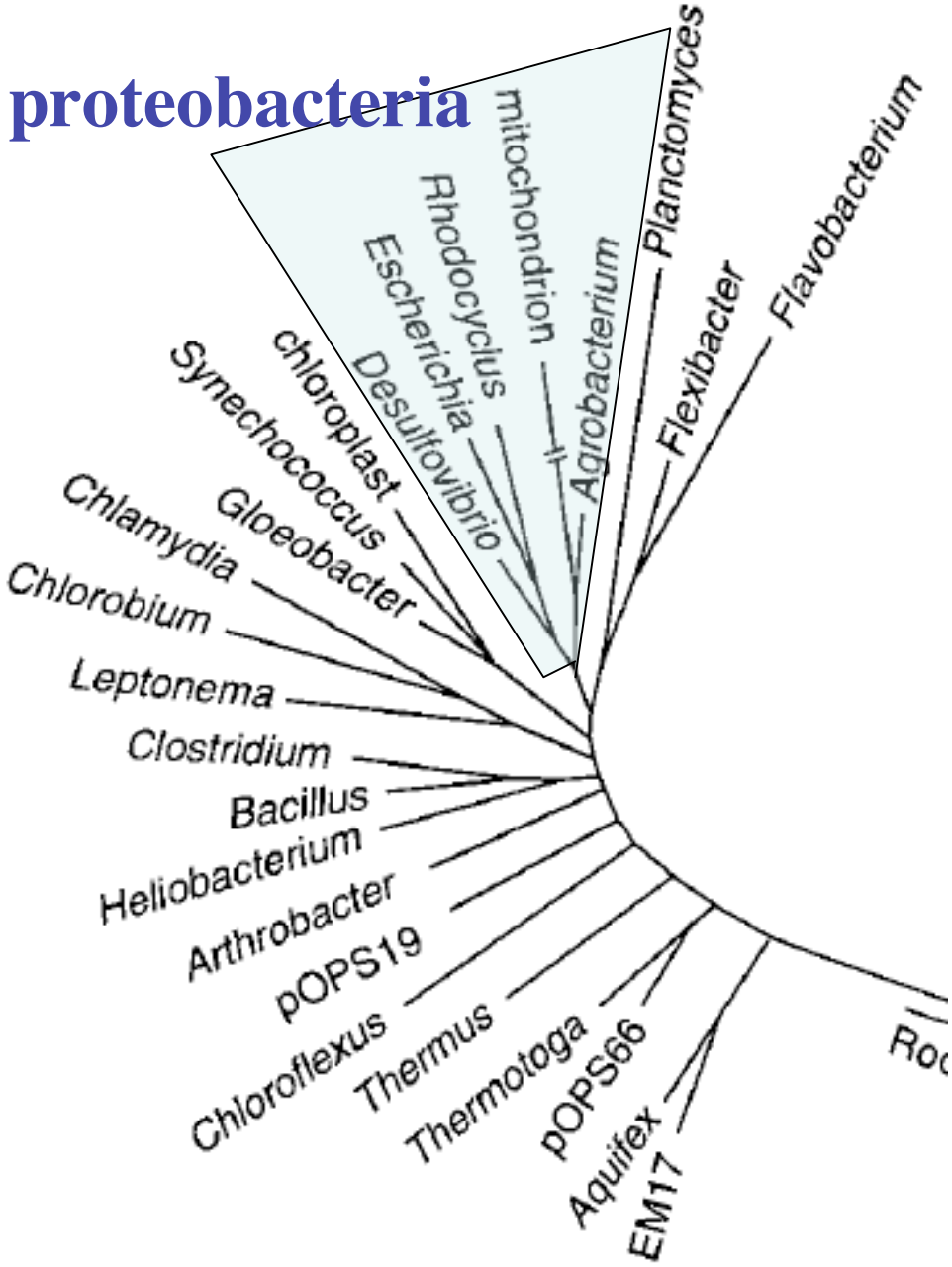
•Proteobacteria are a diverse and important group also known as **purple bacteria**

•Mitochondria are endosymbiotic proteobacteria obtained by an ancestral eukaryote

•Traditionally divided into alpha, beta, gamma, delta

•Epsilon has now been added

•Many proteobacteria practice photosynthesis that is distinct from other bacteria

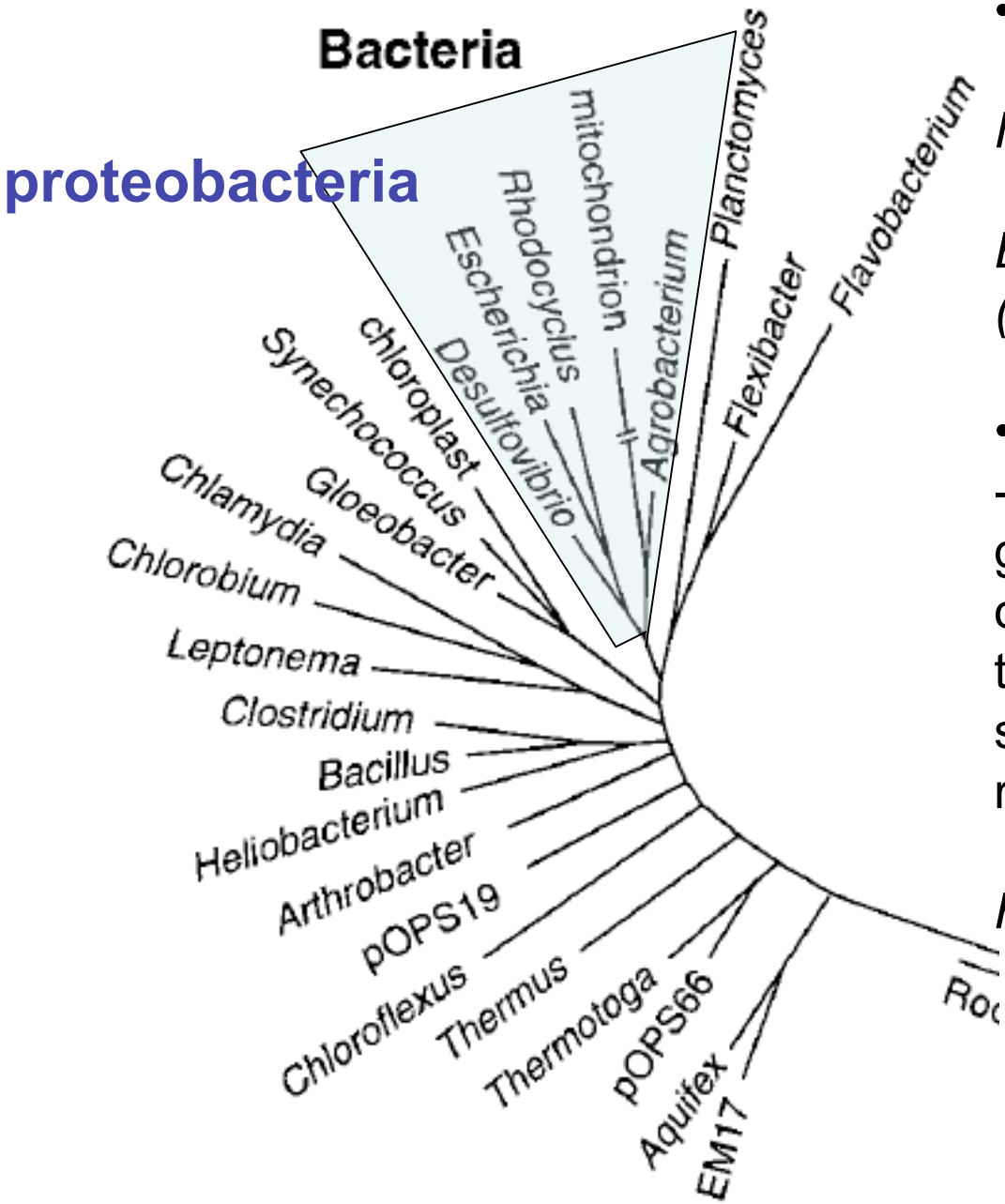


•Various **alpha proteobacteria** form close association with eukaryotes
Rhizobium fix nitrogen in root nodules

•*Agrobacterium* is closely related and is a plant pathogen

•Rickettsias are intracellular pathogens of animals (e.g. typhus*/Rickettsia prowazekii)*

•Rickettsias dwell within cells and it's not surprising that mitochondria, which also dwell intimately in eukaryotic cells, are closely related



•Beta proteobacteria include

Neisseria gonorrhea

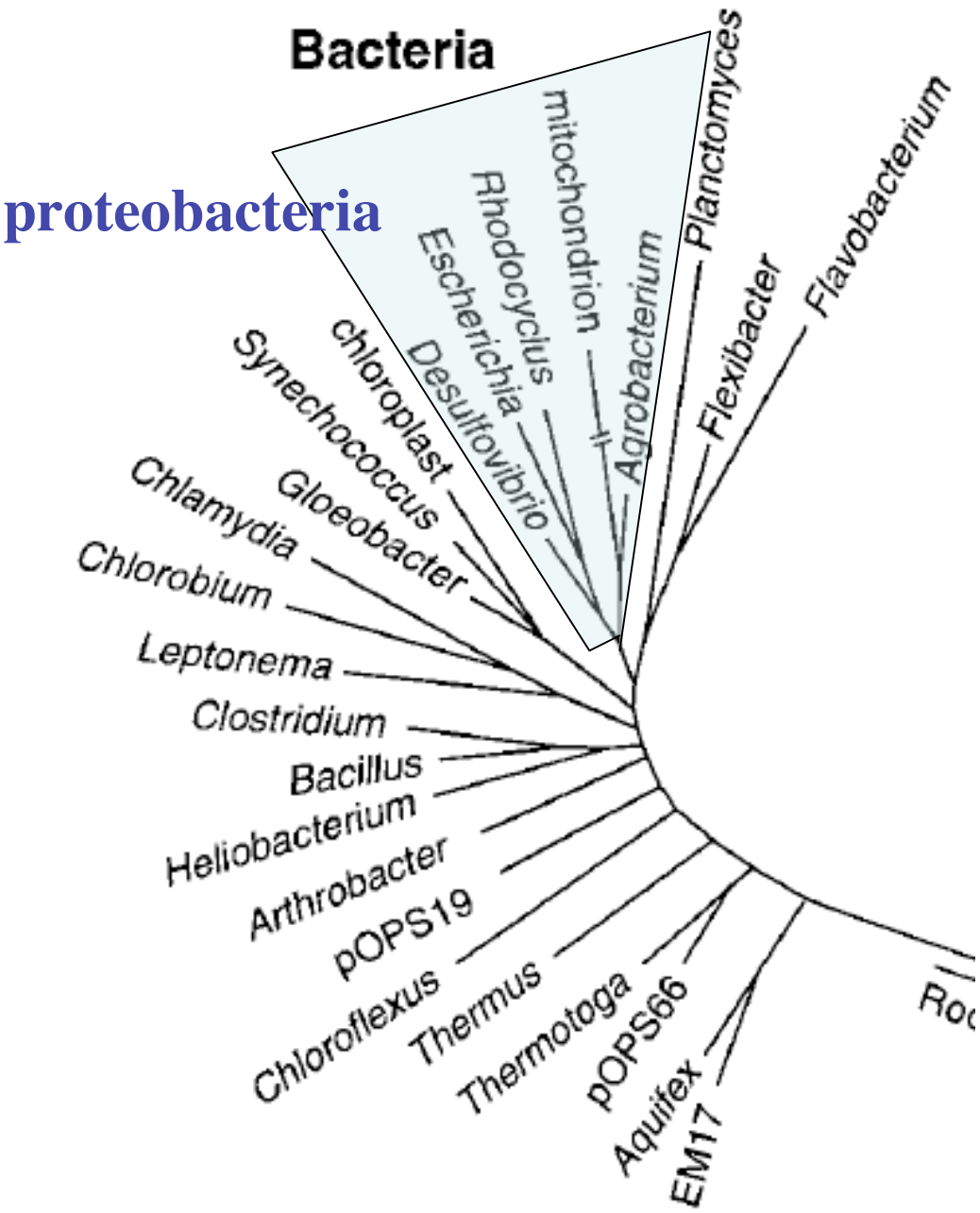
Bordetella pertussis (whooping cough)

•Deltas/epsilons include -*Bdellovibrioi* which acts like a guided missile and attacks other bacteria by rushing at them at 100 cell lengths per second and boring in at 6000 rpm

Helicobacter pylori

Heliobacter pylori

- It's not the stress that's getting to you, it's *H. pylori*
- Causes stomach ulcers (Nobel Prize in Medicine, 2005)
- Can build *H. pylori* phylogeny to track human migration out of Africa and across Asia/Europe
- Might be a selective force for the different ABO blood types (different types have different susceptibility)



•Gamma proteobacteria include several important pathogens, including:

-*Escherichia coli*

-*Shigella*

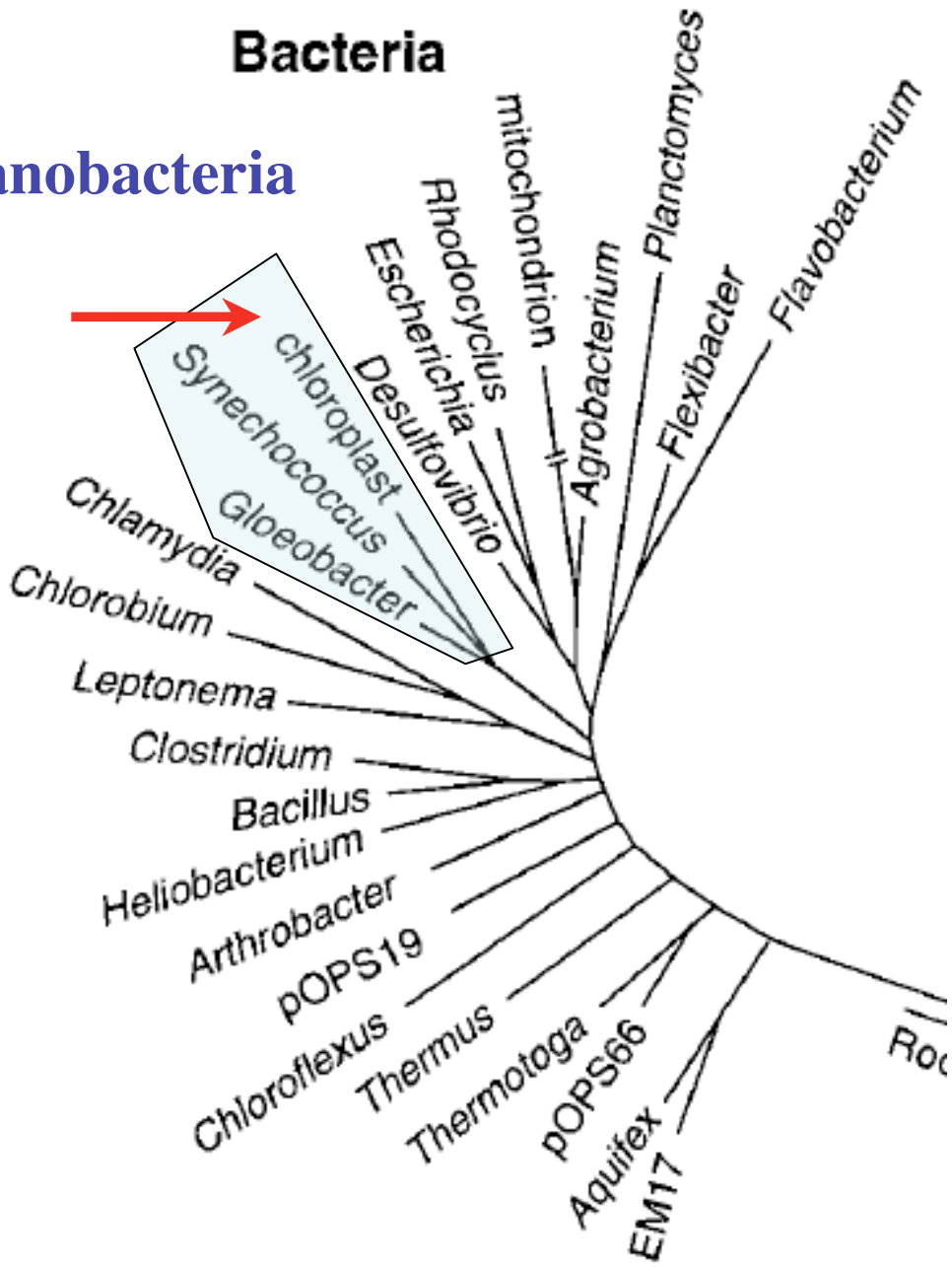
-*Salmonella*
(Typhoid fever)

-*Vibrio*
(Cholera)

-*Legionella*

-*Yersinia pestis*
(plague)

-*Haemophilus influenzae*
(pneumonia)



- Supremely important ecologically
- Used to be called "blue-green algae"
- Ubiquitous green scum responsible for a lot of the world's photosynthesis
- Chloroplasts are endosymbiotic cyanobacteria

Types of Viruses

dsDNA

ssDNA

dsRNA

ssRNA (-)

ssRNA (+)

RNA retroviruses

DNA retroviruses

Are there evolutionary links amongst any or all viruses?
What about relation to cellular life?

How do we detect viral diversity?

- Viruses are too diverse to use a single gene (one conserved gene doesn't even exist)
- We can look for genes conserved in a viral family, such as Lentiviruses (e.g., *pol* in HIV)
- We can also use array technology to look for all viral families at the same time
- SARS virus was discovered using a "chip" that contained sequences from ALL known viral families

http://www.nytimes.com/2008/10/07/health/research/07conv.html

dsDNA Viruses

Can be extremely large (>100 kb in length) containing hundreds of genes

Less reliant on host-cell machinery

- Poxviridae
  - Variola virus (smallpox)
  - Vaccinia virus (cowpox)
  - Camelpox virus
- Herpesviridae
  - HSV-1 & 2
  - Varicella Zoster Virus (chickenpox)
  - Epstein Barr Virus (mononuleosis)
  - CMV

Herpesviruses

- Herpes Simplex Virus (HSV 1 & 2)
- Varicella Zoster Virus (VZV, Chickenpox)
- Epstein Barr Virus (EBV, Mononucleosis and Burkitt's Lymphoma)

All of these viruses go latent and can reemerge in individuals

They cause moderate levels morbidity and mortality, often dependant on age of infection

Chickenpox/Shingles (HHV-3)
(not a poxvirus)

- VZV phylogeny corresponds to human migratory patterns our of Africa
- Lethal in post-adolescents
- Reemerges as shingles in adults, therefore is maintained in populations
- Has been shown to persist in small populations

Epstein-Barr Virus (HHV-4)

- Modern hygienic practices delay infection until later in life, resulting in Mononucleosis
- Goes latent in B-lymphocytes and can cause Burkitt's Lymphoma, especially in the presence of malarial infection
- Example of human ecology changing the type of disease resulting from the same pathogen

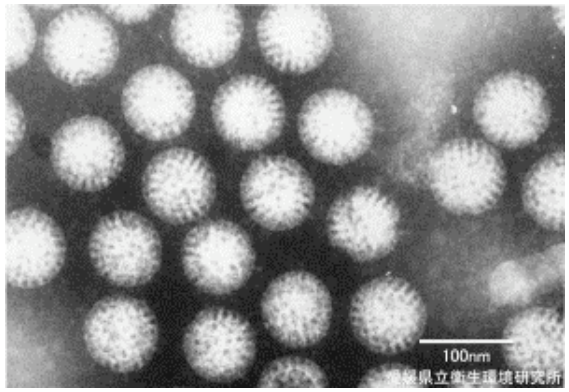
ssDNA Viruses

Not many human pathogens in this group

- Parvovirus is the cause of Fifth Disease
  - Causes the 5th of the “childhood rashes”
  - Can cause abortions in pregnant females

dsRNA Viruses

- Rotavirus (the most important virus you've never heard of)
- Causes the death of >600,000 children worldwide via diarrhea
- 2 new vaccines are available (old vaccine had rare side-effects, so use was discontinued)
- Rota (=wheel), keeps its segmented genome in the spokes. These spokes hide the dsRNA from the immune system, preventing the interferon response (**PAMP**).



ssRNA (+ stranded)

Smaller genomes (up to 30kb, SARS), often coding for one giant polyprotein

- Poliovirus (poliomyelitis)
- Rhinovirus (common cold)
- Hepatitis A virus
- Hepatitis C virus
- Dengue fever virus
- West Nile virus
- SARS virus

Poliovirus

- Fecal-oral transmission (small hardy virus)
- Virus that enters the CNS and causes disease (paralysis/death) is a dead-end

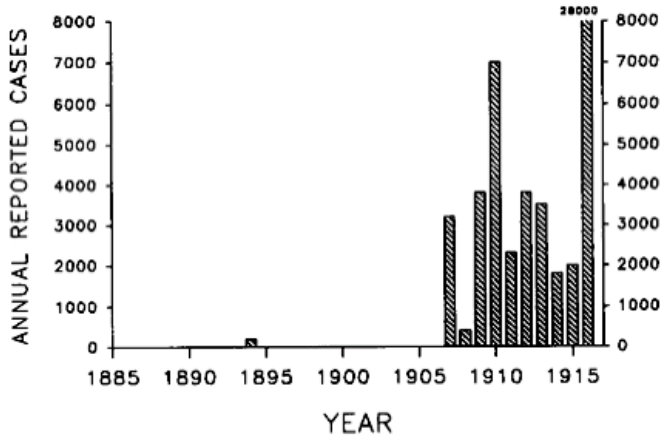


Fig. 1. The appearance of epidemic poliomyelitis in the United States, 1885–1916. Based on reported cases, most of which were paralytic, during an era when reporting was estimated at about 50%. After Lavinder et al. (1918).

TABLE 1

Poliomyelitis attack rates and age distribution in the European and Moroccan populations of Casablanca during 1947–1953 (after Horstmann and Paul, 1955)

	European	Moroccan
Population	125,000	530,000
Paralytic cases	117	25
Annual attack rate per 100,000	13.4	0.7
1953 cases by age (years)		
0–1	8	9
2–9	15	2
10–39	5	

Hygiene May Have Brought About the Polio Epidemic

Fig. 2. Age-specific proportion of native Moroccans with type 1 poliovirus neutralizing antibody at a 1:10 titer or greater, Casablanca, 1953. After Paul and Horstmann (1955).

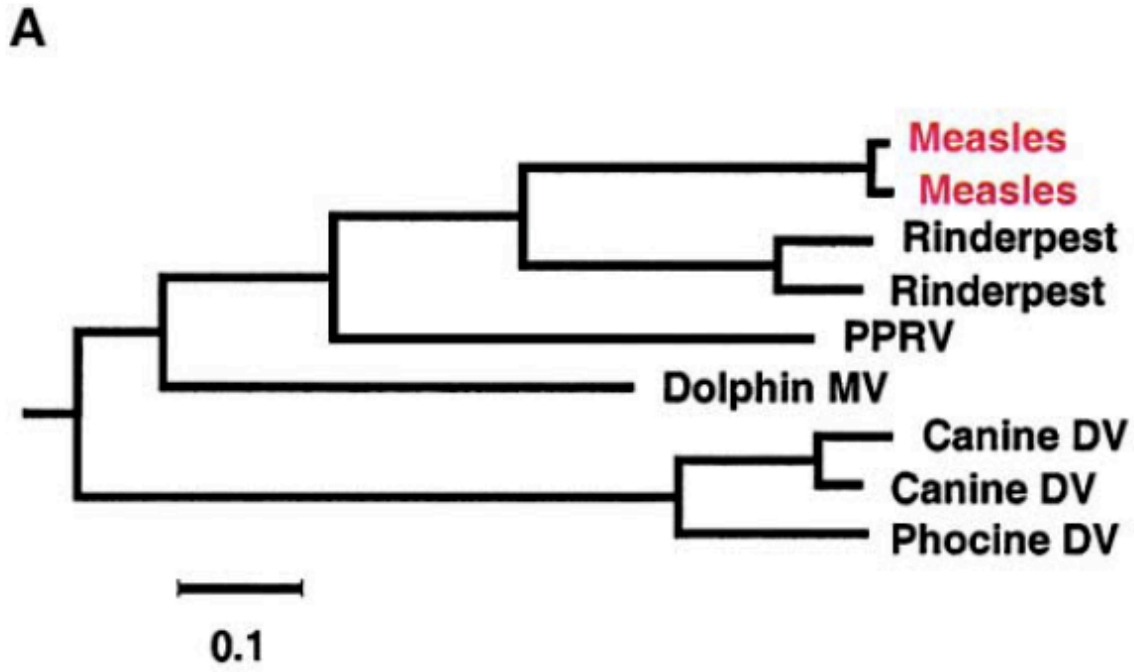
Most Moroccans get the disease earlier on in life than pre-vaccine era Americans

ssRNA (- stranded)

Smaller genomes (~10kb)

- Influenza virus
- Measles virus
- Mumps virus
- Ebola virus
- Human respiratory syncytial virus
- Rabies virus

Measles: Zoonosis



- Measles is a crowd disease that probably could not have maintained itself until recently in human populations
- Related viruses are found in a range of mammals
- Most closely related is Rinderpest, from bovids
- Did we acquire measles after settling down and domesticating cattle?

Somewhere in the Middle-East Around 10,000 Years Ago

Rabies virus

- Zoonosis: transmission to humans from animals under natural conditions (skunks, dogs, bats)

- Mortality rate = 100%

Follows nerve cells to brain. How can this help explain the high mortality rate?

Retroviruses and Retroelements

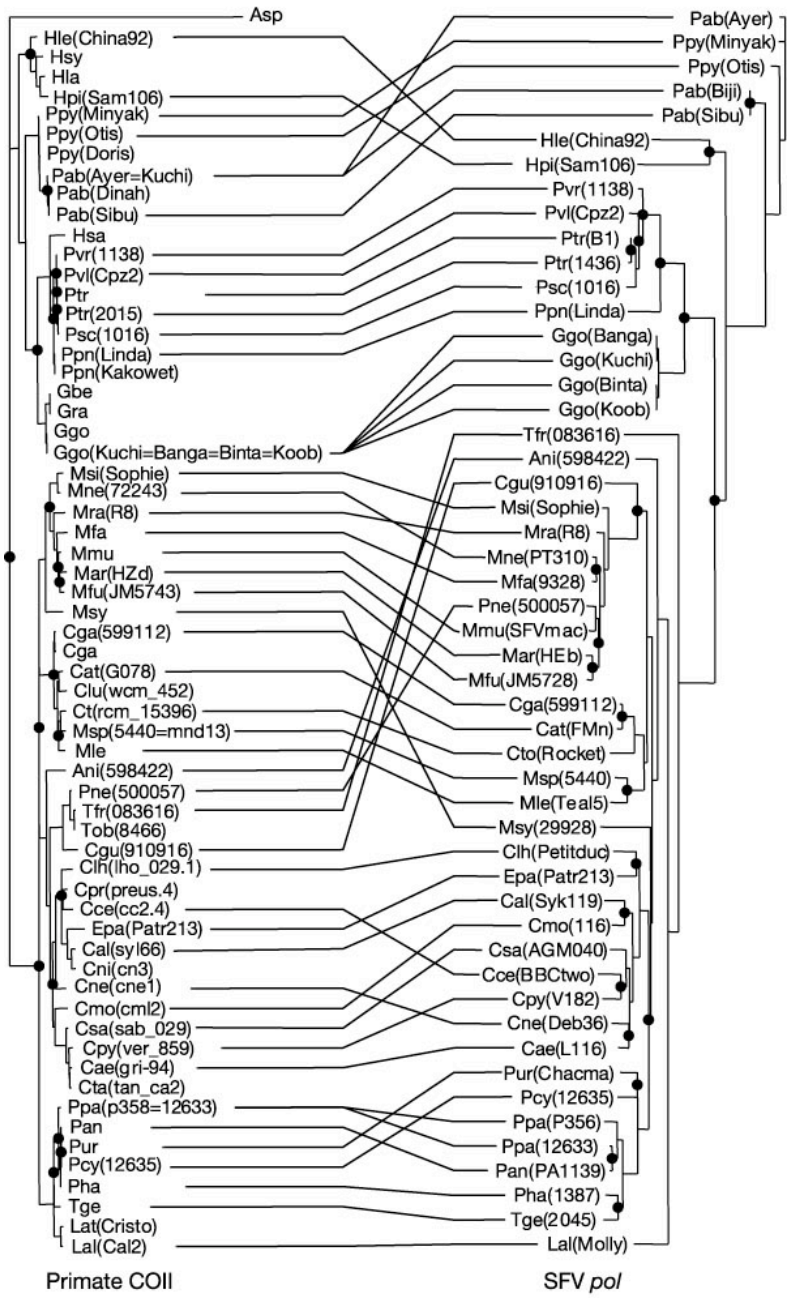
Small compact genomes (10kb) with many overlapping genes

- RNA Genomes
  - HIV
  - Foamy virus
  - HTLV
- DNA Genomes
  - Hepatitis B virus

Ancient co-speciation of simian foamy viruses and primates

William M. Switzer[1], Marco Salemi[2], Vedapuri Shanmugam[1], Feng Gao[3], Mian-er Cong[1], Carla Kuiken[4], Vinod Bhullar[1], Brigitte E. Beer[5], Dominique Vallet[6], Annie Gautier-Hion[6], Zena Tooze[7], Francois Villinger[8], Edward C. Holmes[9] & Walid Heneine[1]

Simian foamy virus (SFV) tree is very similar to host tree suggesting that the ancestral primate was infected with a retrovirus over 30 million years ago



Retroviruses and Retroelements

- >45% of the human genome is composed of retroelements including active and inactive retroviruses
- Non-human primates are all infected with many retroviruses, some of which can persist via vertical transmission
- Some of the strongest positive selection in the human genome is attributable to these viruses
- Common ancestor with retroviruses
- Can disrupt genes and their expression

Defenses against retroelements

- **APOBEC** proteins
  - Related to **AID** (the enzyme responsible for **somatic hypermutation** and **affinity maturation** of immunoglobulins)
  - Was discovered because of hypermutated HIV (riddled with G to A mutations)
  - Can also function against Hepatitis B virus and retroelements

- **TRIM5-alpha**
  - Can disrupt capsid formation of retroviruses and some retroelements

Controlling lentiviruses: Single amino acid changes can determine specificity

- Species-specific APOBEC3G blocks infection with virus from other species
- Not even have the chance to evolve in the new host

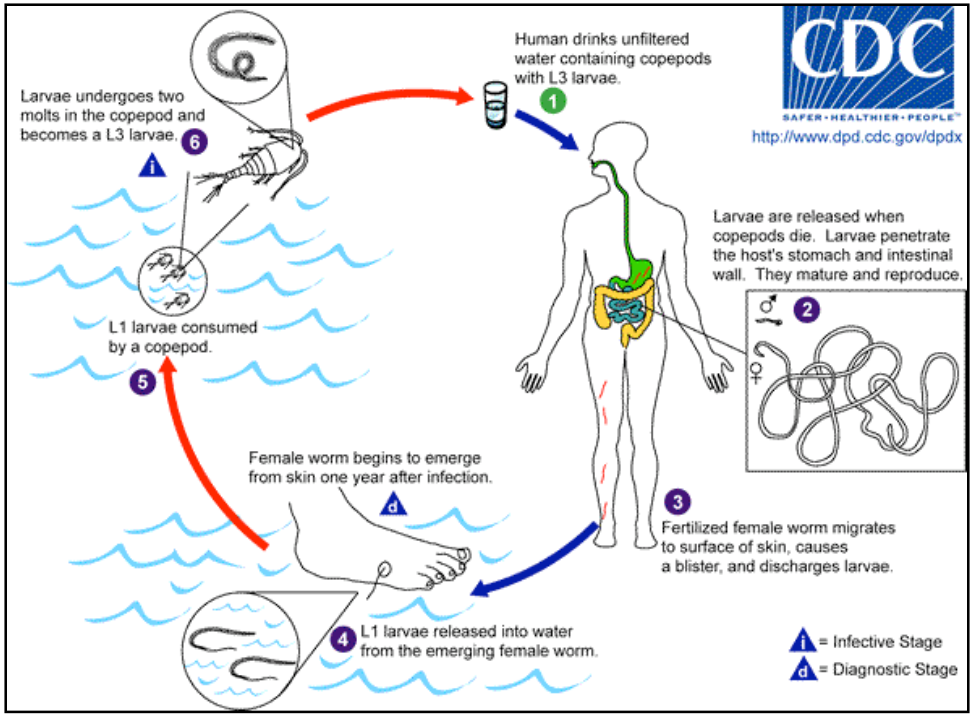
Kaiser, Shari M. and Emerman, Michael (2004) Proc. Natl. Acad. Sci. USA 101, 3725-3726

Rod of Asclepius & Caduceus

Where did these symbols come from?

Worms

Guinea Worm



Tapeworm

River Blindness

Carter Center

Taenid Worms

- Human tapeworms are most closely related to those infecting domesticated animals (e.g. cattle & swine)
- Tapeworms may have been acquired from African carnivores just under 1 mya
- Likely a **tradeoff** between nutrition from an omnivorous diet and morbidity

Hygiene Hypothesis

- Mast cells
- Eosinophiles
- IgE

What are they doing in the absence of worms? (More later in the semester)

Plasmodium falciparum

- It has likely been infecting humans since our divergence from chimpanzees
- Most adaptive evolution has occurred in the last 10,000 years along with the transition to an agrarian lifestyle
- It is unclear whether *P. falciparum* has become more prevalent, more virulent, or both

Evidence of Selection

- **Heterozygote Advantage**
  - Sickle-cell anemia (HbS mutant)
  - G6PD A-
- **Directional Selection**
  - MHC-I alleles increased in West Africa
  - MHC-II alleles that are rare in Europe

These selective forces appear in the last 10,000 years

P. vivax

- The Duffy blood group (FY) is an antigen found on red blood cells (RBC)
- *P. vivax* uses this FY receptor to gain entry into host RBC
- FY*O, the absence of a surface protein, is very common in sub-Saharan Africa, but is rare in Europe
- This selective regime may have begun 60,000 years ago, coinciding with *P. vivax* infection in humans
- FY*O is currently at an elevated level in Papua New Guinea, where *P. vivax* is also present

Which of these pathogens were most important in human evolution?

- Pathogens would:
  - Be able to persist in small populations
  - Have fitness effects without extremely high virulence
  - Need to exert selective force before reproduction

- Strategies
  - Latency
  - Vector-borne (or maintained in resevoir)
  - Low virulence (or sterilizing)

Conclusions

- Most modern-day infectious diseases are relatively recent scourges
- Many pathogenic infections had different outcomes just centuries ago (e.g. poliovirus, EBV)
- The pathogens that were important to our ancestors are still prominent in many parts of the world today

http://www.cartercenter.org/news/multimedia/HealthPrograms/TamingtheFierySerpent.html