Microbe-host interactions

Nov 15, 2006

Ch. 21

Science 307:1915-20, 2005.

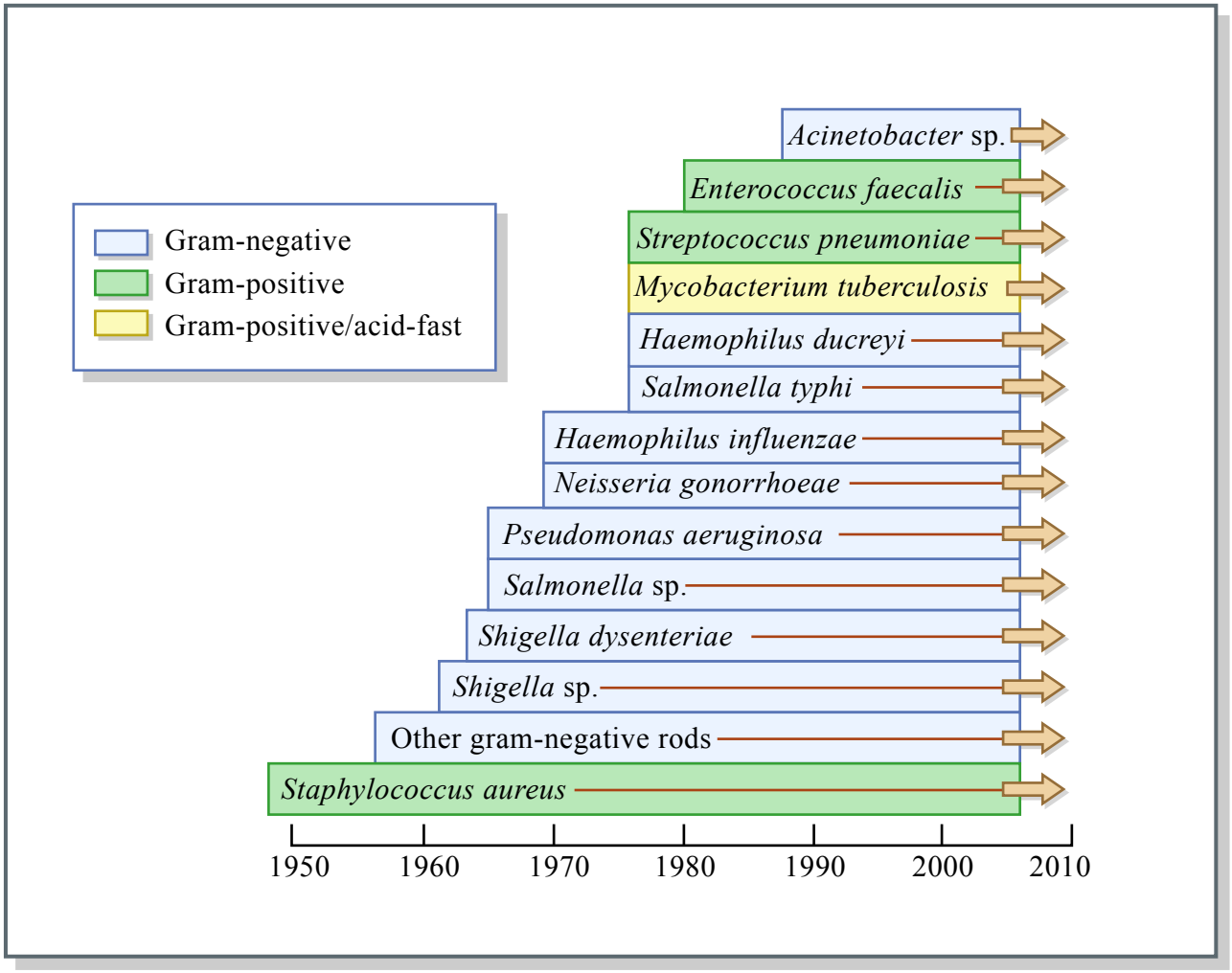
Antimicrobial drug resistance

- Acquired ability to resist effects of a chemotherapeutic to which it is normally susceptible
- Common mechanisms
  1. Lack structure drug targets
  2. May be impermeable to drug
  3. Organism may be able to modify drug to an inactive form
  4. Organism may modify the target itself
  5. Organism may develop a new pathway
  6. Organism may be able to pump out the drug

R factors

- Most drug resistant bacteria isolated from patients contain drug resistance genes on plasmids
- Many of these plasmids encode enzymes that inactivate drugs
- Multi-drug resistance plasmids predate medical use of antibiotics
- Widespread emergence of multi-drug resistance

Resistance to all known drugs…



- Methicillin-resistant *Staphylococcus aureus* (MRSA)
- Vancomycin-resistant *Enterococcus* (VRE)

Figure by MIT OCW.

Healthcare-associated infections

- Healthcare-associated infections (HAIs) are infections that patients acquire during the course of receiving treatment for other conditions
- In hospitals alone, HAIs account for an estimated 2 million infections, 90,000 deaths, and $4.5 billion in excess health care costs annually

http://www.cdc.gov/ncidod/dhqp/healthDis.html

Changing patterns for HAIs

- 1950s to 1960s gram positive bacteria were a major problem (*Streptococcus pyogenes* and *Staphylococcus aureus*)
- 1970s and 1980s gram negative bacteria became a major problem (*E. coli* and *Pseudomonas* spp.)
- Currently, gram positive bacteria are again emerging as a major problem (*S. aureus* and *Enterococcus* spp.)

Methicillin-resistant *Staphylococcus aureus* N315

Image removed due to copyright restrictions.

Hiramatsu et al. Trends Microbiol 9:486, 2001

Terminology

- Normal microbial "flora" or "microflora"
  - Better term is microbiota
  - Commensal (at the same table)
- Pathogen
  - Infection versus disease
- Virulence
- Opportunistic pathogen

Indigenous microbiota

- Microorganisms that inhabit body sites in which surfaces and cavities are open to the environment
- Skin, oral cavity, upper respiratory tract, gastrointestinal (GI) tract, and vagina
- Each habitat can be considered a separate ecosystem
- For every cell in human body (10^{13}) there are 10 viable indigenous bacteria in the GI tract
- The GI tract (10^{14}) harbors 100-fold more bacteria than the skin (10^{12})

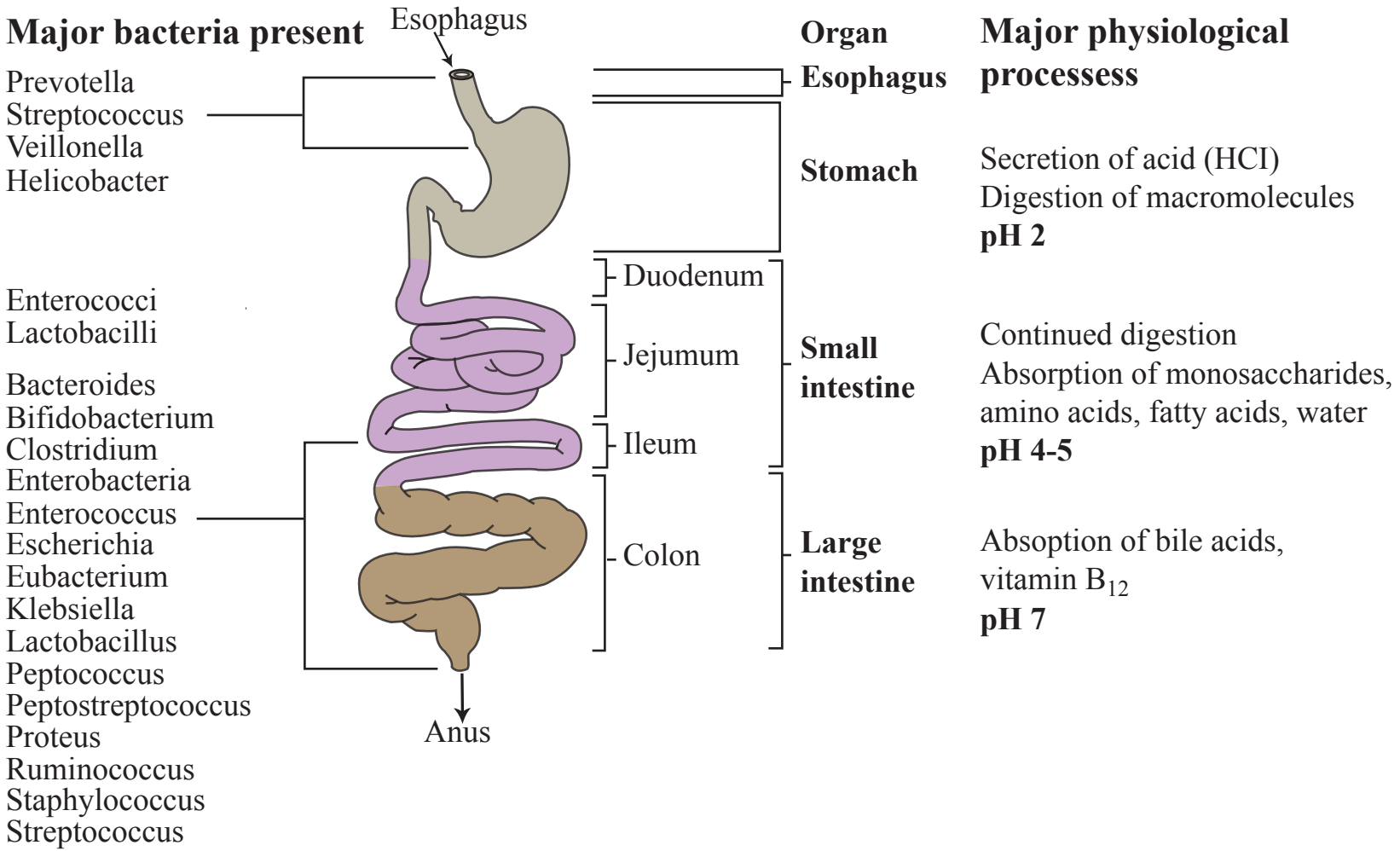


Figure by MIT OCW.

Defining the GI microbiota

- Autochthonous microbiota
  - Present during the evolution of an animal and therefore present in every member of a species
- Normal microbiota
  - Common and perhaps even present in every individual in a given geographic area/community, but not in every member of the species
- True pathogens
  - Acquired accidentally and therefore not normally present in all members of a community of an animal species

Dubos et al. J Exp Med 122:67-76, 1965

Ecological principles

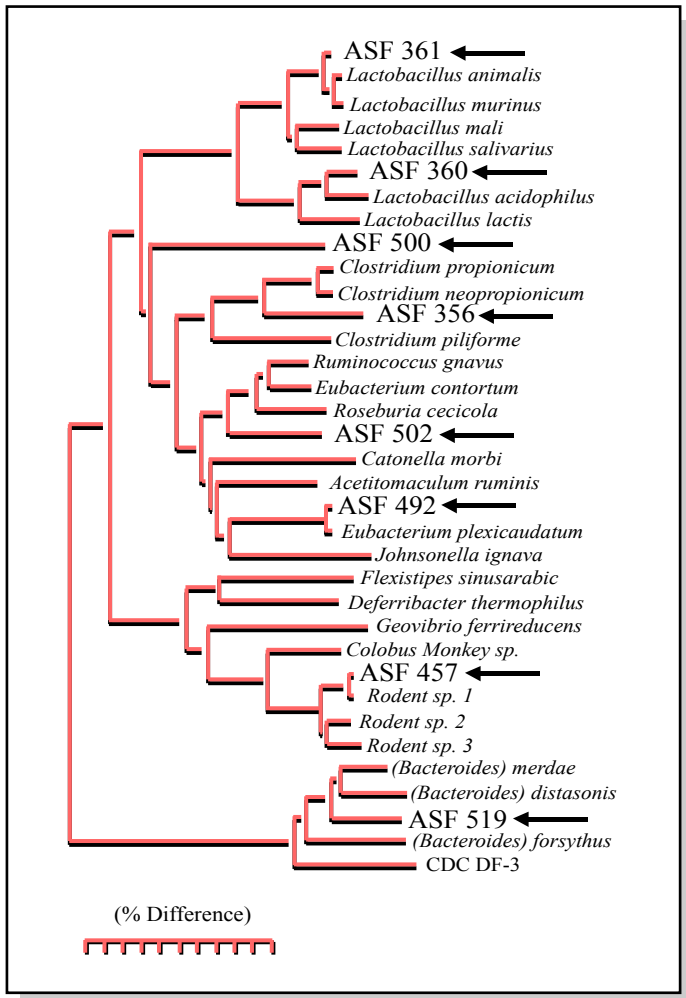
- In a stable GI ecosystem, all available habitats are occupied by indigenous microbiota
- Transient species derived from food, water, or even another part of the GI tract or the skin will not establish (colonize)
- Habitats are physical spaces in the GI tract normally occupied by a climax community of indigenous microbiota
- Population levels and species composition are stable and not easily disrupted

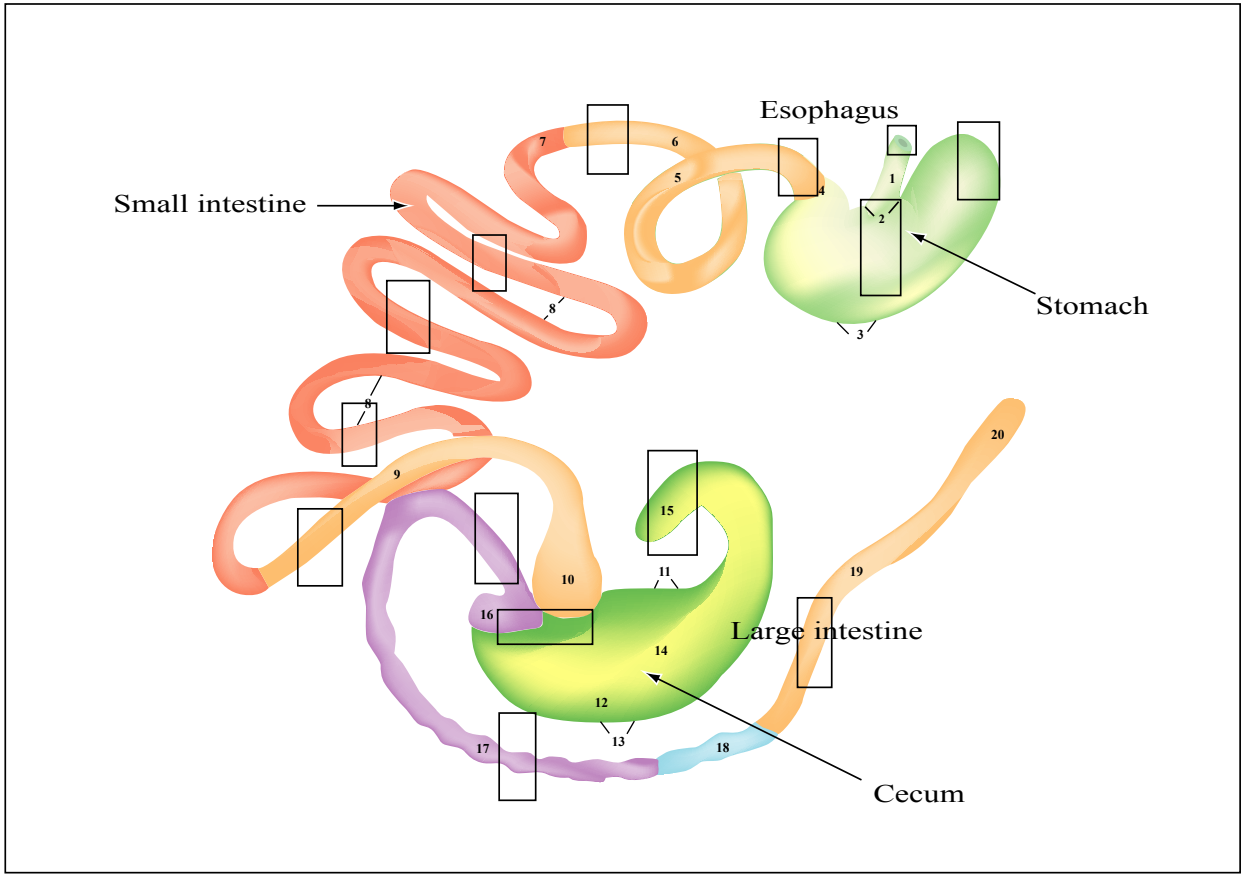
Succession & climax populations

- Lactic acid bacteria and coliforms predominate in infant human and animal GI tracts
- During weaning the microbiota changes drastically and obligate anaerobic bacteria become predominant
- The indigenous GI microbiota of adults consists of climax communities that are remarkably stable
- Each region of the GI tract has a characteristic population of microbes, in terms of complexity and population density

Model systems

- Germ free animals
- Delivered by Cesarean section into sterile plastic-film isolators
- Maintained free of all bacteria, fungi, protozoa, viruses, and other detectible life forms
- Introducing microorganisms is called association or colonization
- Contamination is accidental introduction of unwanted microorganisms
- Germ free animals can be monoassociated with a singe species or poly associated with multiple species





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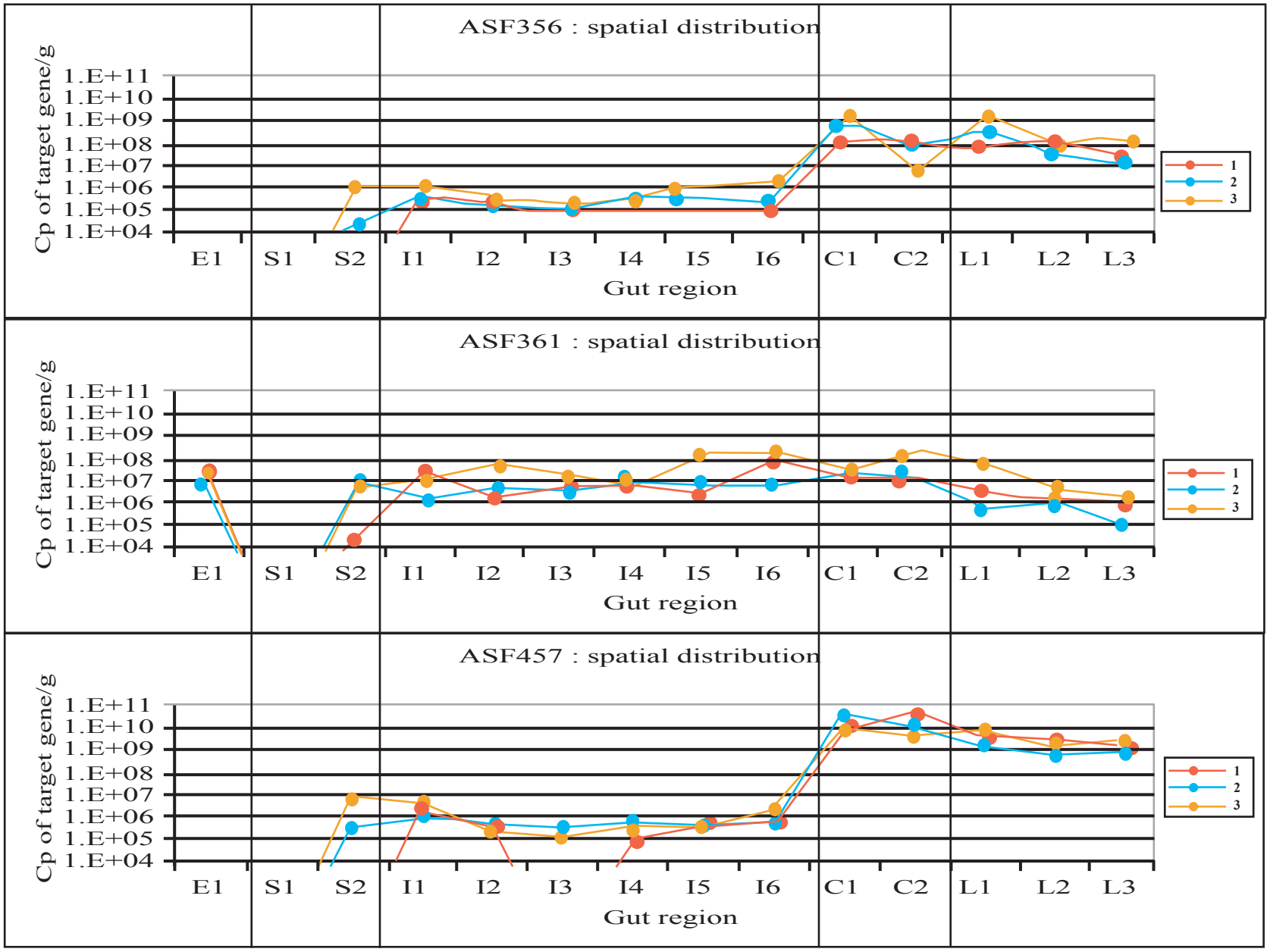

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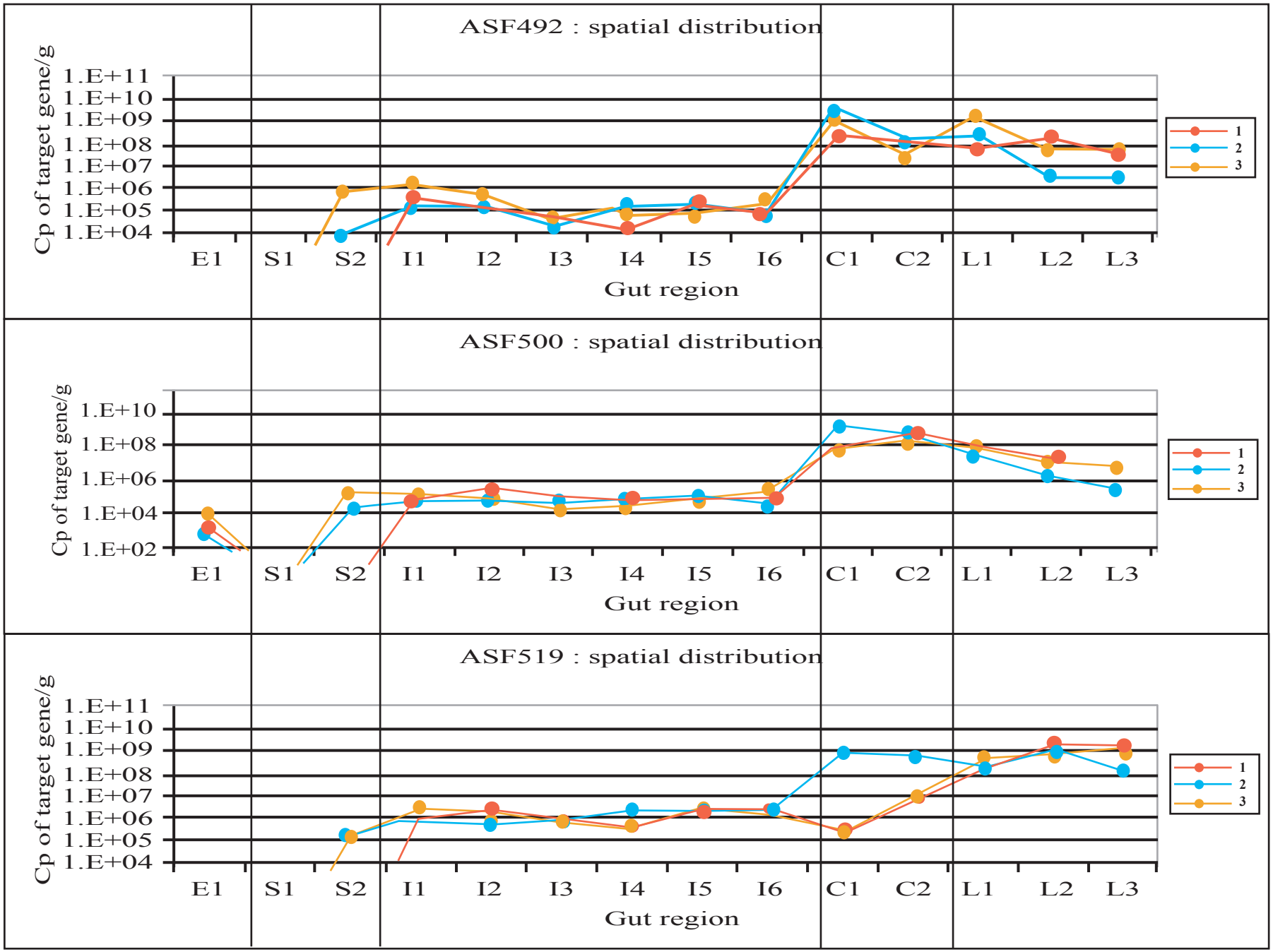
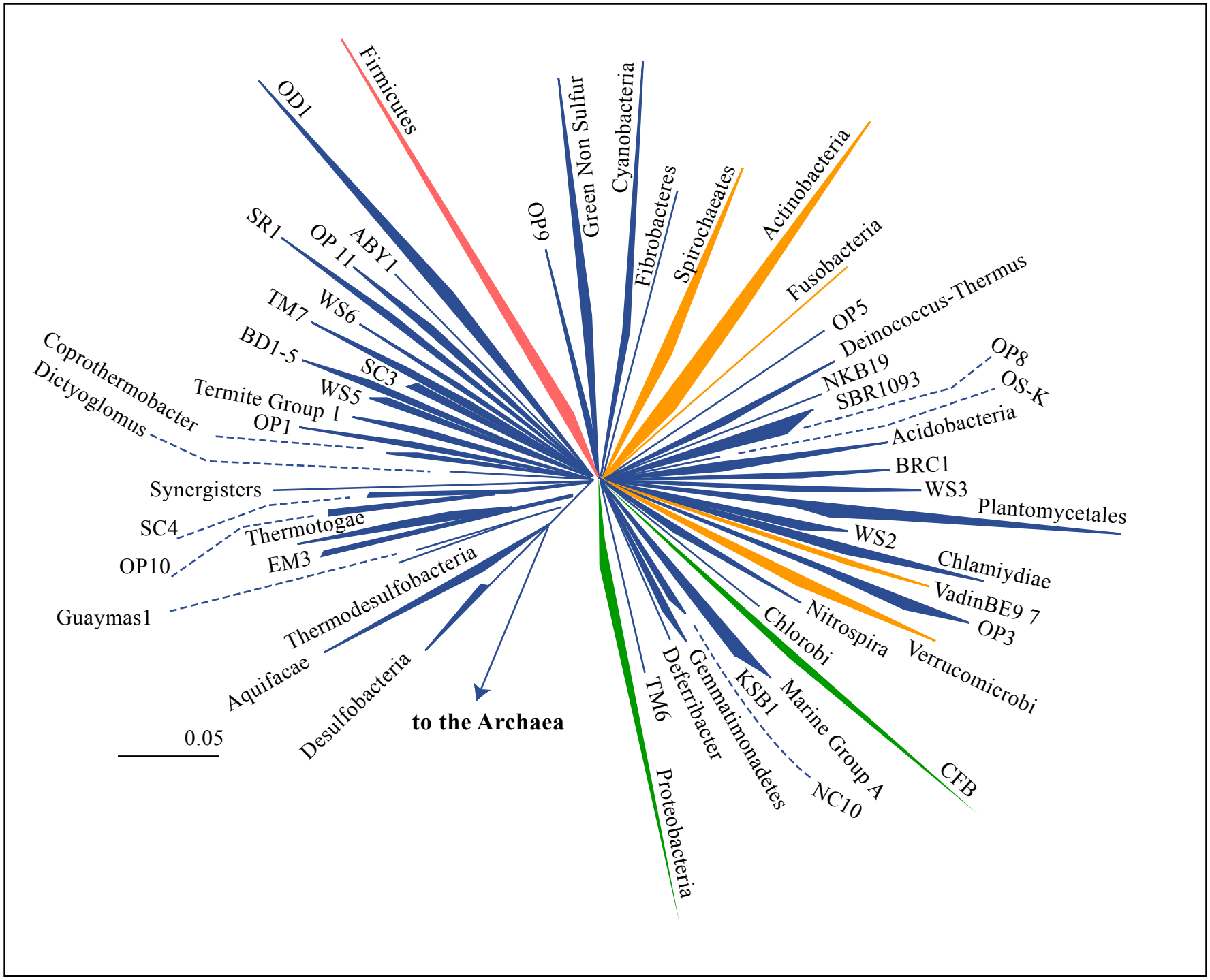


Figure by MIT OCW.

Human colonic microbiota

- Highest cell densities recorded for any ecosystem
- Diversity at the division level is among the lowest
- Only 8 of the 55 known bacterial divisions have been identified in colonic bacteria to date
- 2 division dominate
- Cytophaga-Flavobacterium-Bacteroides (CFB)
- Firmicutes (genera *Clostridium* and *Eubacterium*)
- Proteobacteria are common, but not dominant
- Compare to many soil communities, where ≥ 20 bacterial division can be present

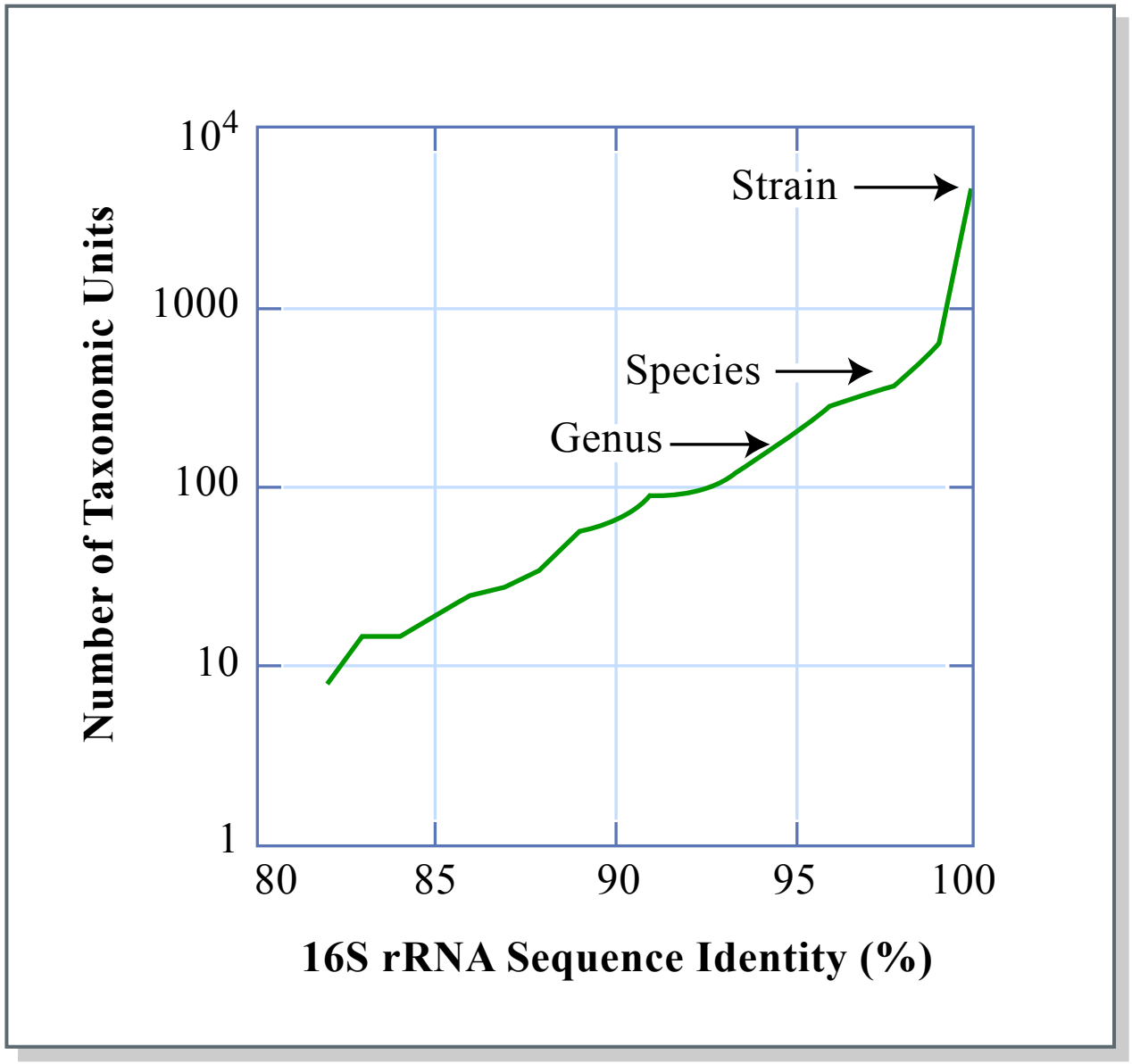


Bäckhed et al. Science 307:1915-19, 2005

Figure by MIT OCW.

Diversity

- > 200,000 16S rRNA sequence in GenBank
- 1,822 from human gut
- 1,689 are uncultured
- Look at 495 with length > 900 bp
- ~ 800 species
- > 7,000 strains



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Helicobacter pylori

Photographs of Barry J. Marshall and J. Robin Warren removed due to copyright restrictions.Marshall and Warren won the 2005 Nobel prize in medicine for their discovery of Helicobacter pylori
and its role in gastritis and peptic ulcer disease.

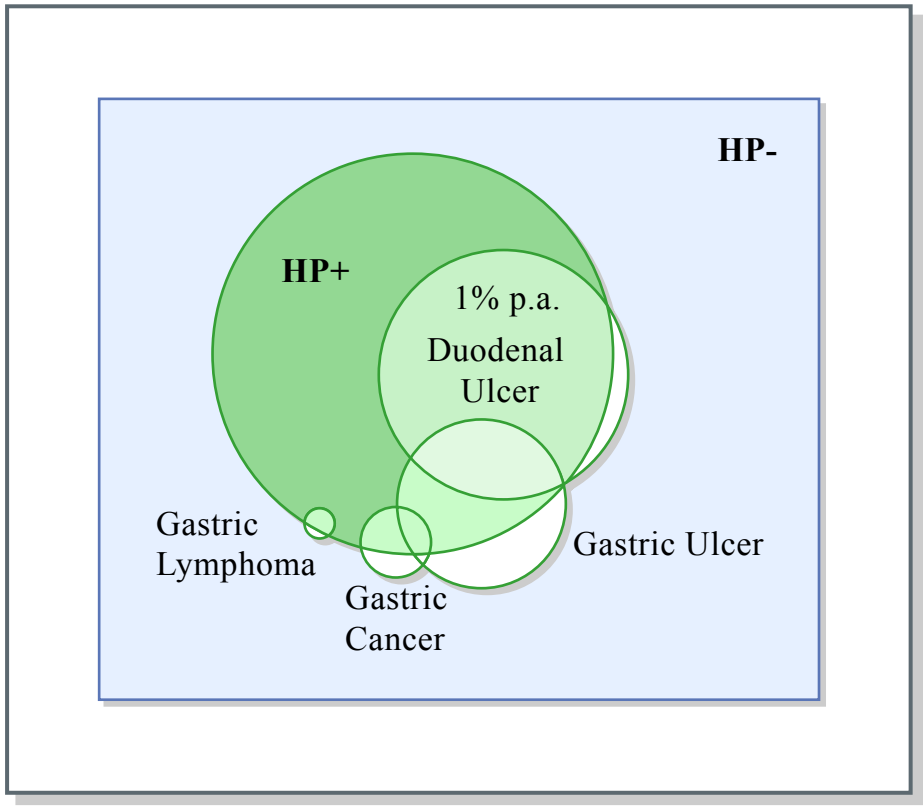

Figure by MIT OCW.

Incidence diagram of *Helicobacter pylori* disease in the world today

Gastritis and peptic ulcer

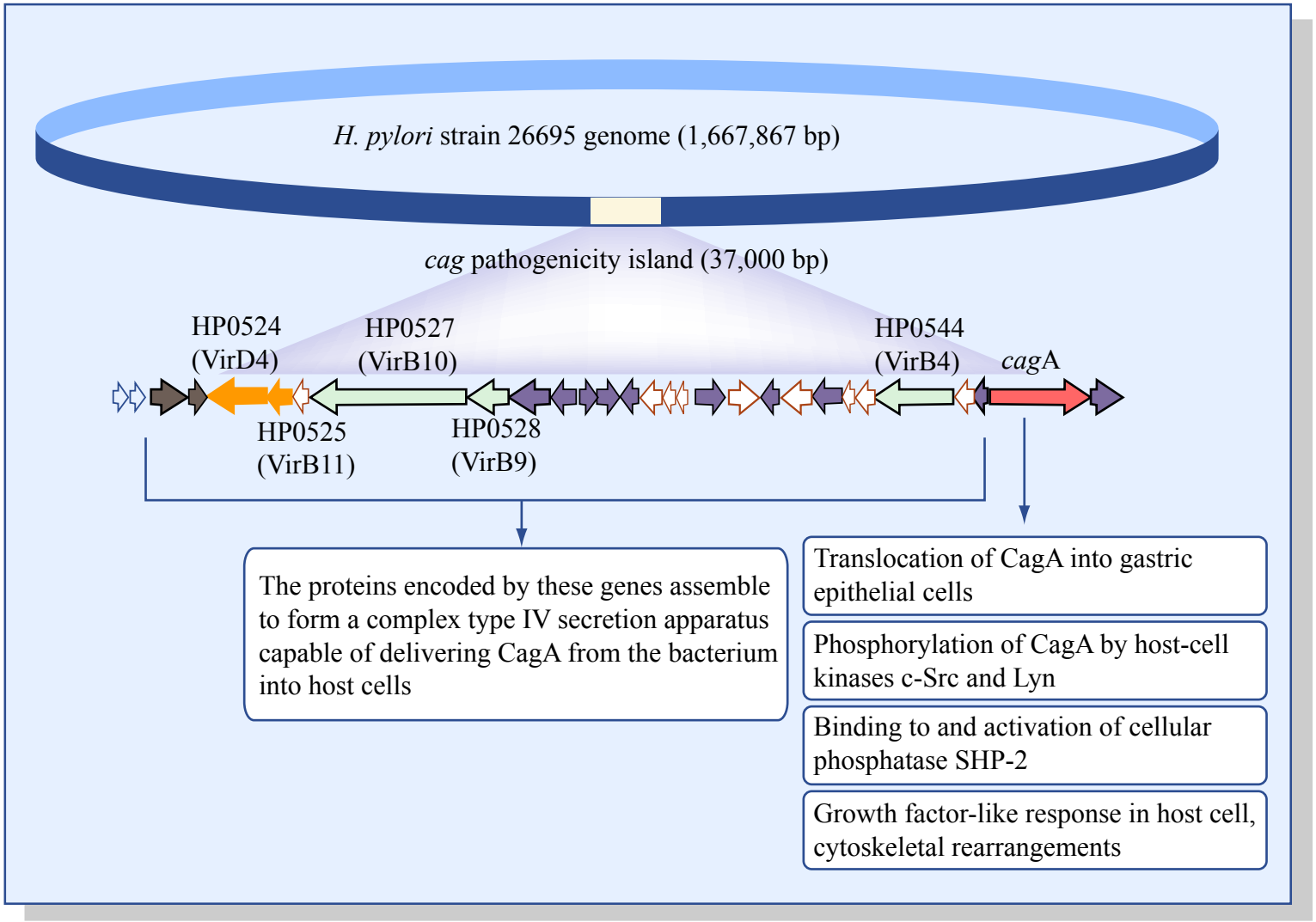

Figure by MIT OCW.

http://www.cdc.gov/ulcer/

H. pylori and gastritis

Images of *Helicobacter pylori* removed due to copyright restrictions.

Helicobacter pylori on gastric epithelial cells (false-color SEM)

Suerbaum & Michetti N Eng J Med 2002