Evolutionary Medicine

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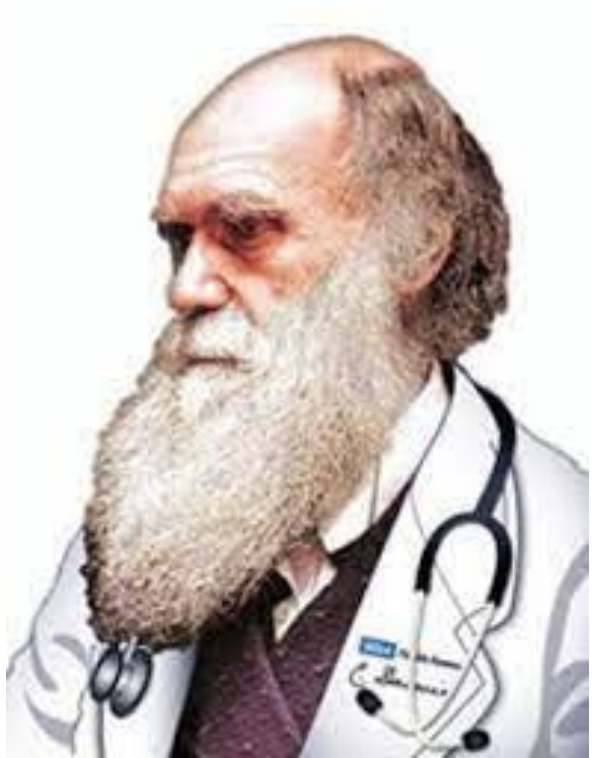
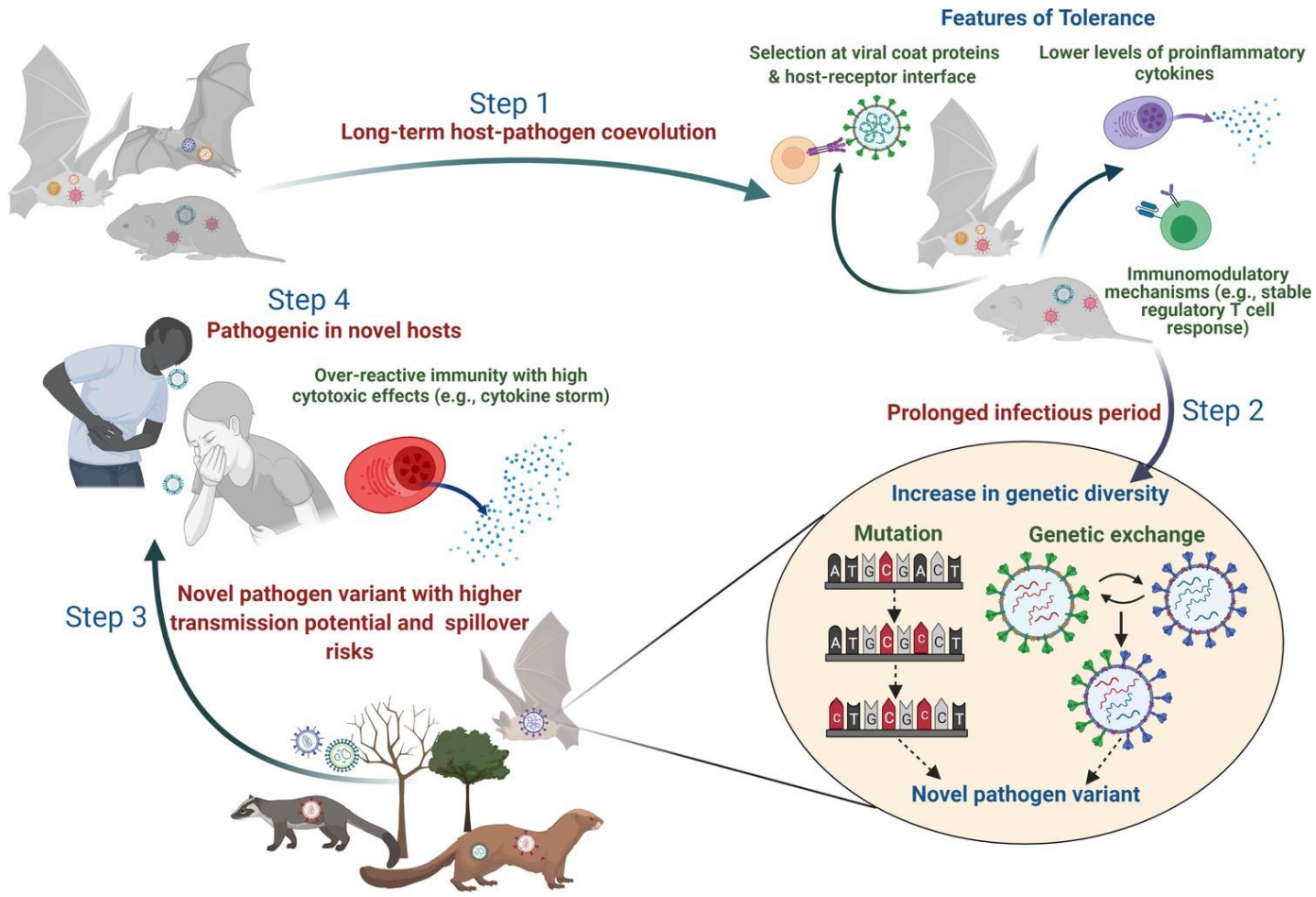
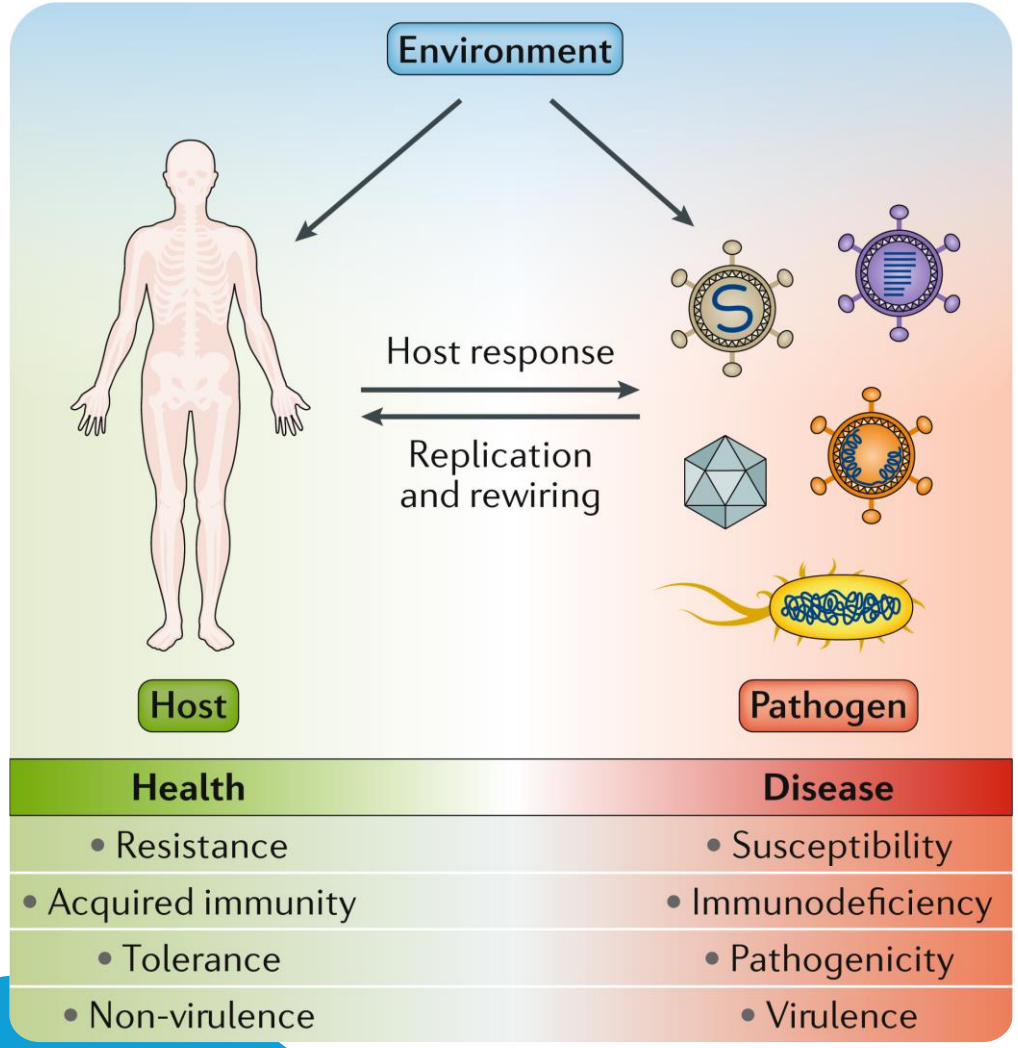


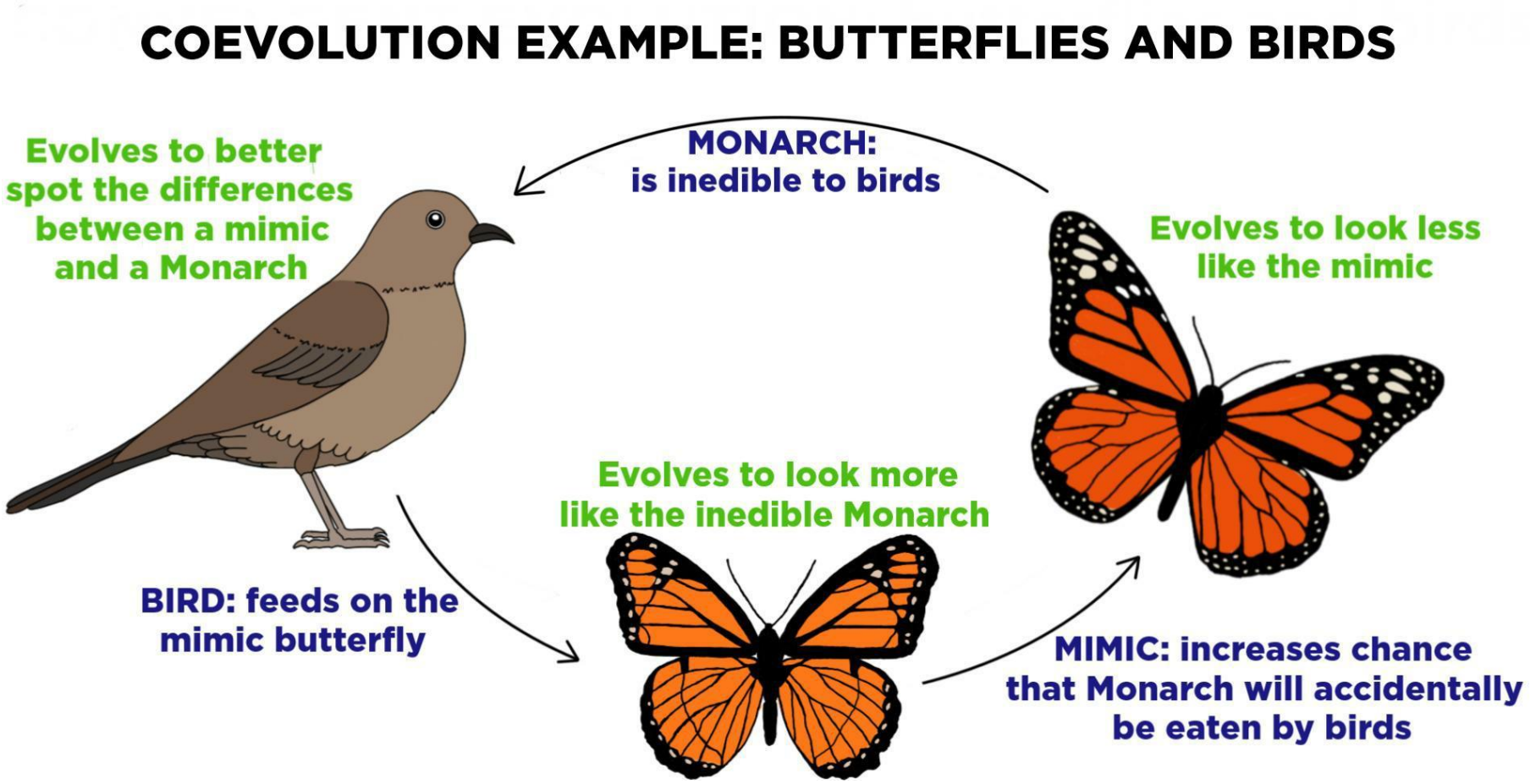
Coevolution, infection, and immunity

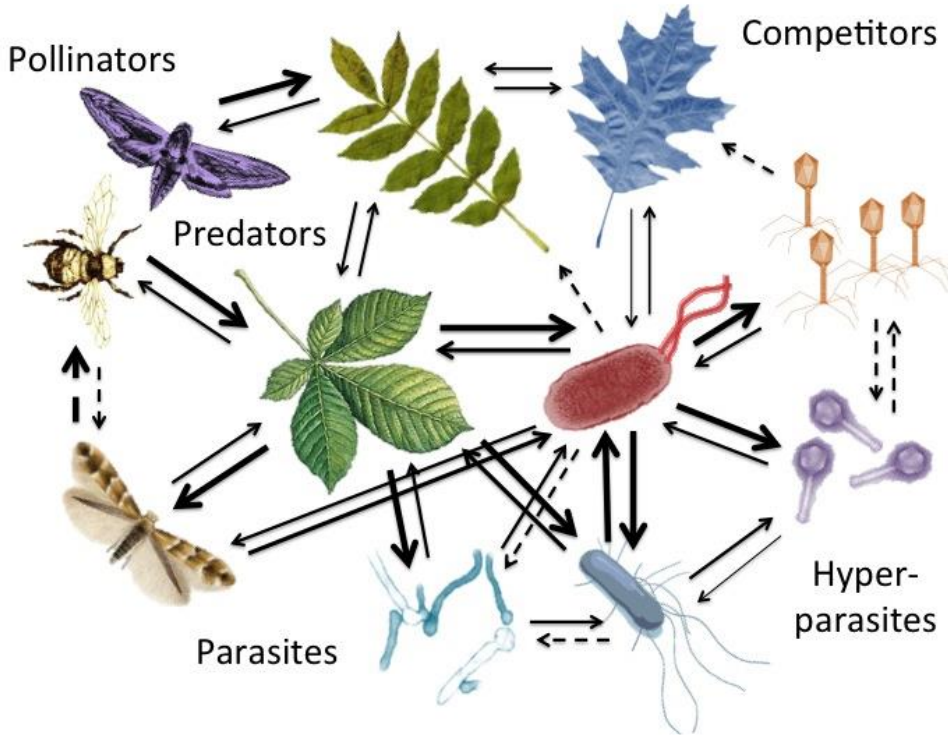




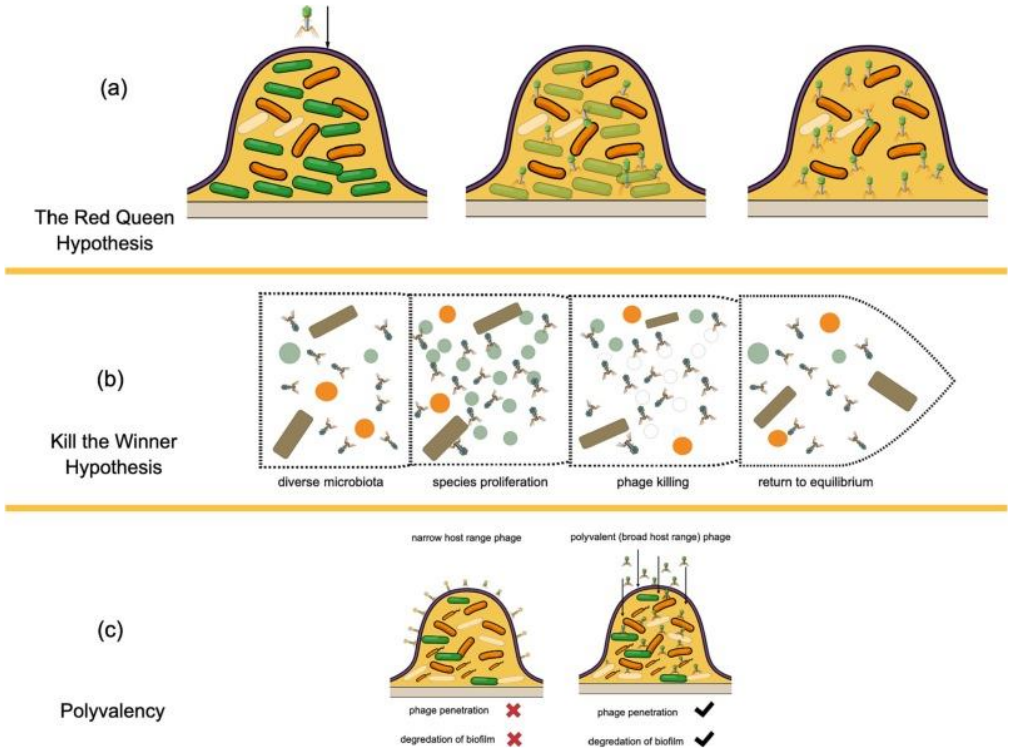
- Rates of extrinsic mortality (the risk of death as a result of environmental hazards) have had major effects on the evolution of life-history traits such as growth rate, timing of maturation, allocation of resources to repair and maintenance, and lifetime reproductive strategy. The major causes of extrinsic mortality are biotic, and include competition for nutrient supplies with other organisms of the same or different species, predation, infection by micro-organisms, many of which rely on a parasitic relationship for their own survival, and injury, which may be accidental or the result of conspecific competition and violence. This last cause is a particular feature of human biology. Human cultural evolution has resulted in mechanisms to ameliorate the risks of predation and accidental injury, and technological advances have reduced the impact of infection by micro-organisms in many parts of the world. Yet infectious disease still causes 25% of all deaths worldwide, with wide variations between high- and low-income countries. Evolved mechanisms to cope with the impact of infectious disease are a major feature of the human genome (Quintana-Murci et al. 2007). Not all human relationships with micro-organisms are deleterious to the host. Our associated microflora, principally in the gut, contribute to nutrition and metabolic regulation. Beneficial micro-organisms participate in controlling the growth of pathogens, and may have a role in the evolution and individual development of the host immune system. In this lecture we describe some fundamental aspects of coevolution and then apply them to the evolution of the relationship between humans and micro-organisms, discuss why and how some of those micro-organisms are pathogenic, and examine the benefits and occasional costs of our evolved defenses again micro-organisms through our innate and adaptive immune systems. Finally, we examine the three main types of human technological (cultural) response to the threat of infectious disease—public health measures, vaccination, and antimicrobial chemotherapy.

Coevolution



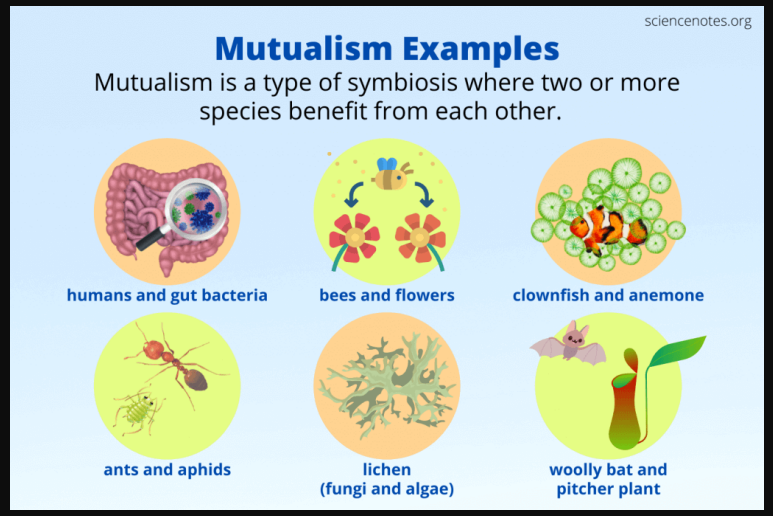


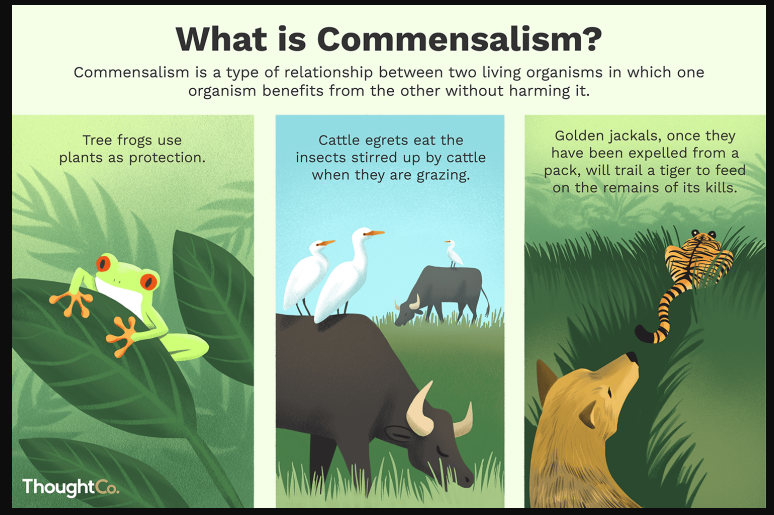
- Organisms live and evolve in environments that include other organisms. Coevolution occurs when one species reciprocally influences the evolution of another. A simple example is the evolution of a predator–prey relationship where the prey evolves a mechanism to evade the predator (perhaps running faster) and the predator, faced with the selection pressure of reduced food supply, responds by evolving a countering mechanism (perhaps running faster still or developing a new attack strategy). In turn, the prey evolves a response to the countering mechanism, and so on. Such processes of adaptation and counter-adaptation have been referred to as *evolutionary arms races*, by analogy with the desire by the military not to be left vulnerable to a potential enemy's developing arsenal.
- Modeling studies show that coevolution is an important driving force for evolution. A common metaphor in classical evolutionary theory suggests that species evolve "uphill" towards fitness peaks in their adaptive landscapes, where they are well adapted to their physical environment. As the physical environment generally only changes slowly, the rate of evolution is predicted to slow down as the peak is approached.

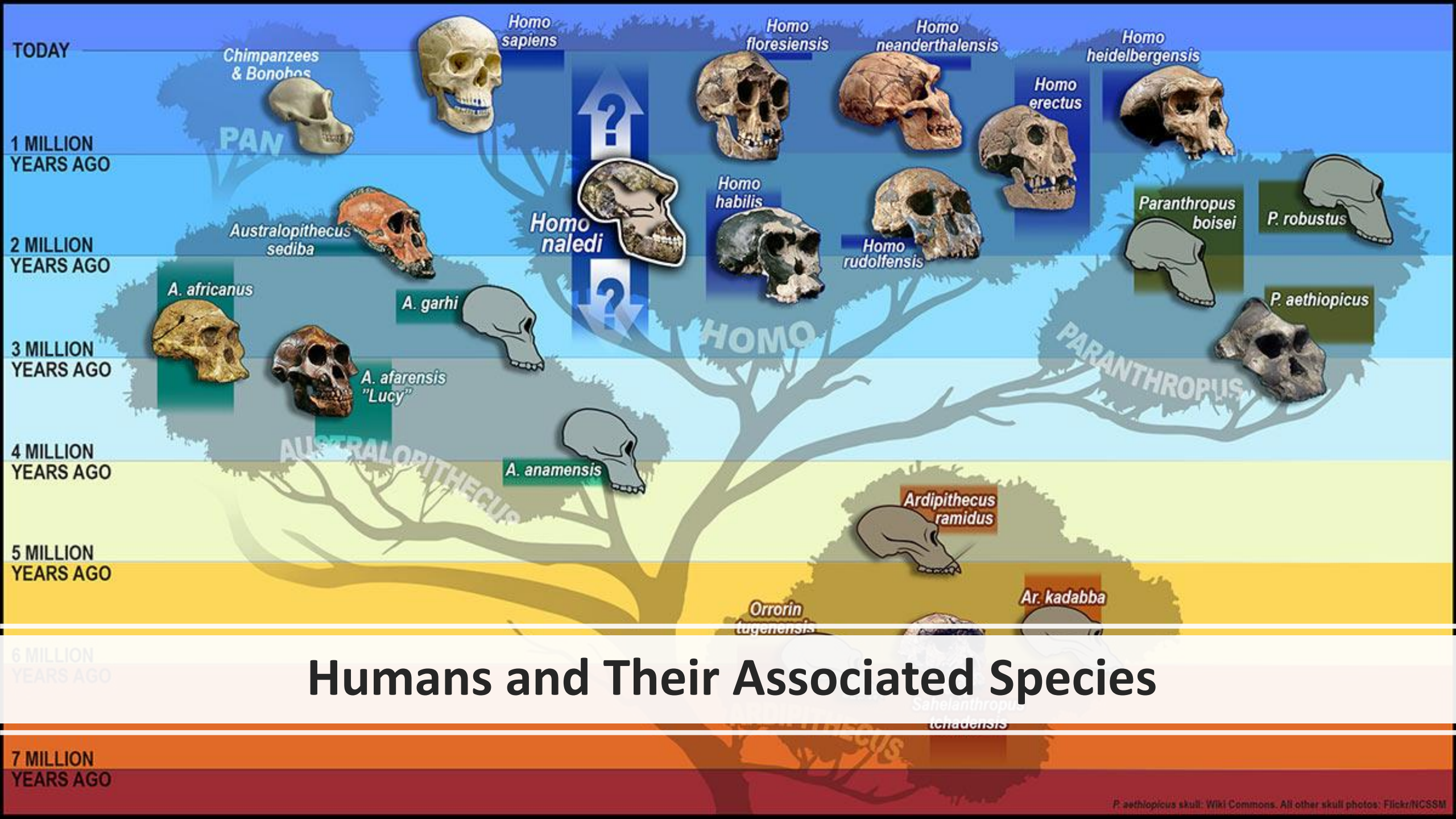


Inclusion of other species into the notion of “environment” changes this perspective, because other species, particularly micro-organisms, can evolve rapidly and this rapidly changing biological environment (which thus changes the shape of the landscape) requires equally rapid counter-adaptive change from the host species; this is then matched by a further adaptive response from the interacting species. Continuous adaptations by all species in the system are required for survival, although relative fitness as determined by classical measures of reproductive success does not increase. This concept was named the Red Queen hypothesis after the remark by the Red Queen in Lewis Carroll’s *Through the Looking Glass* that Alice needs to undertake “all the running you can do, to keep in the same place” (van Valen 1973). The Red Queen hypothesis as applied to host–parasite interactions has been proposed as an explanation for the evolution of sex. The argument is that the requirement for slowly evolving multicellular eukaryotes to compete with their more rapidly evolving parasites is facilitated by the continuous generation of new genotypes containing novel combinations of parasite resistence alleles, and that can only be achieved by meiotic recombination during the gametogenesis of sexual reproduction. There is some limited experimental evidence from organisms such as roundworms that can reproduce either sexually or by self-fertilization to suggest that the sexually reproducing forms do better when exposed to parasites (e.g., Morran et al. 2011).

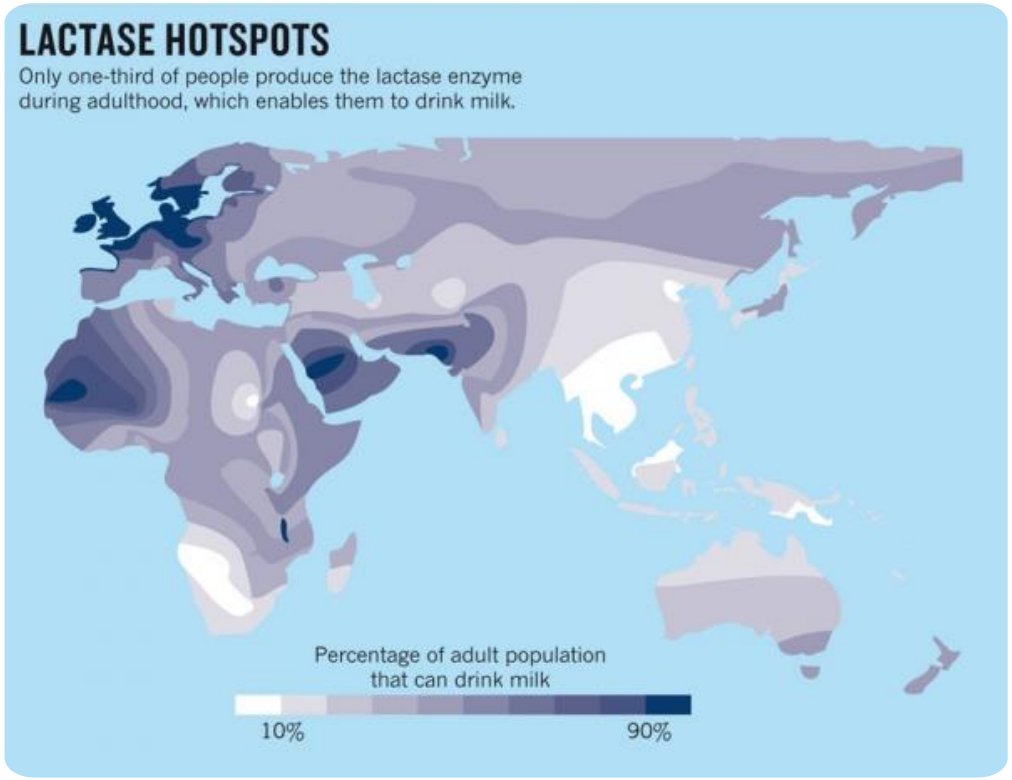
- Coevolution does not only occur in the context of parasite–host or predator–prey relationships, where one participant may be “running for its life, rather than just its dinner.” There are many different types of species interactions with different coevolved allocations of costs and benefits. *Symbiosis* refers to any long-term interactions between species: this can be subdivided into *mutualism* (where both participants benefit), *commensalism* (where one participant benefits and the other is unaffected), *parasitism* (where one participant benefits and the other is harmed by, e.g., reduced growth as the parasite extracts resources), and *predation* (where one participant benefits and the other reaches a sudden evolutionary dead end). Pathogens can be considered as a type of parasite with an evolved strategy of causing disease in their host. Some species with complex life cycles (such as the unicellular organism that causes malaria) may be parasites in a vector species (mosquitoes) but pathogens in an intermediate host during their life cycle (in this case humans). Some commensal species, such as certain micro-organisms in the human gut, may become opportunistic pathogens in their hosts when defenses such as epithelial barriers or the immune system are weakened.



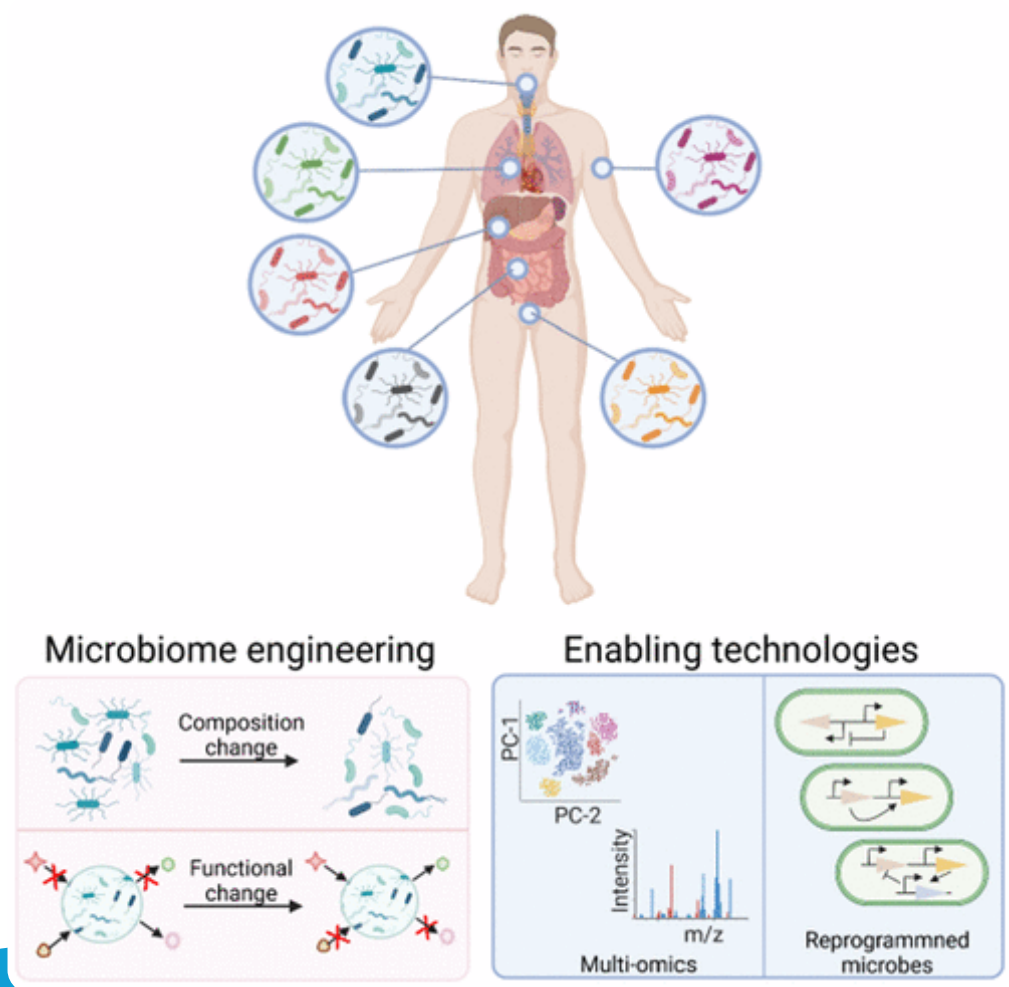




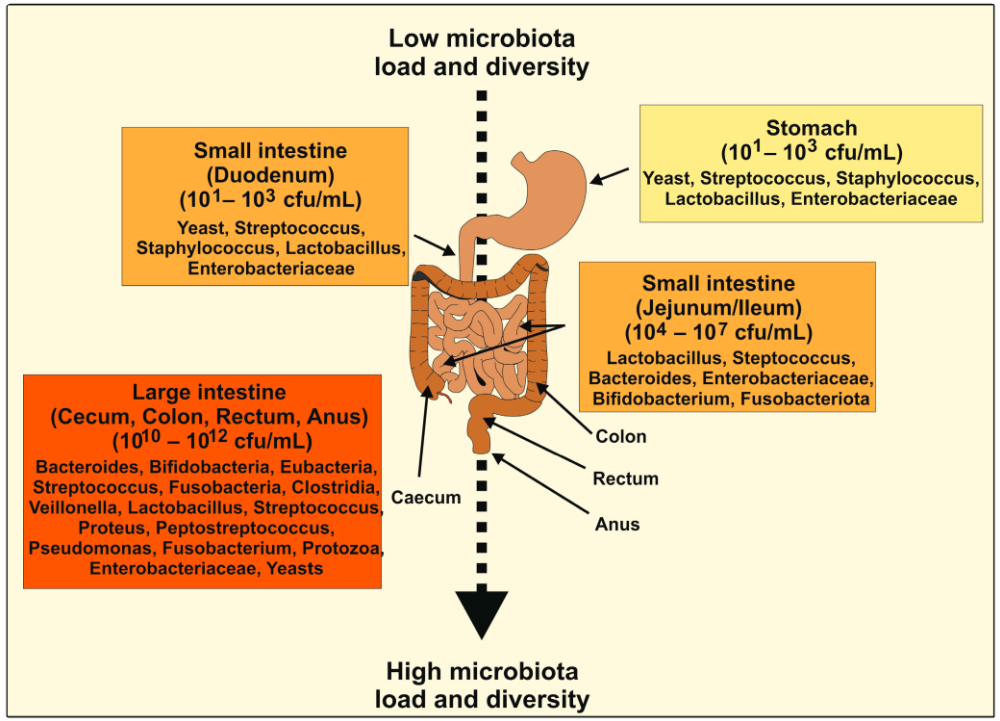
Humans and Their Associated Species



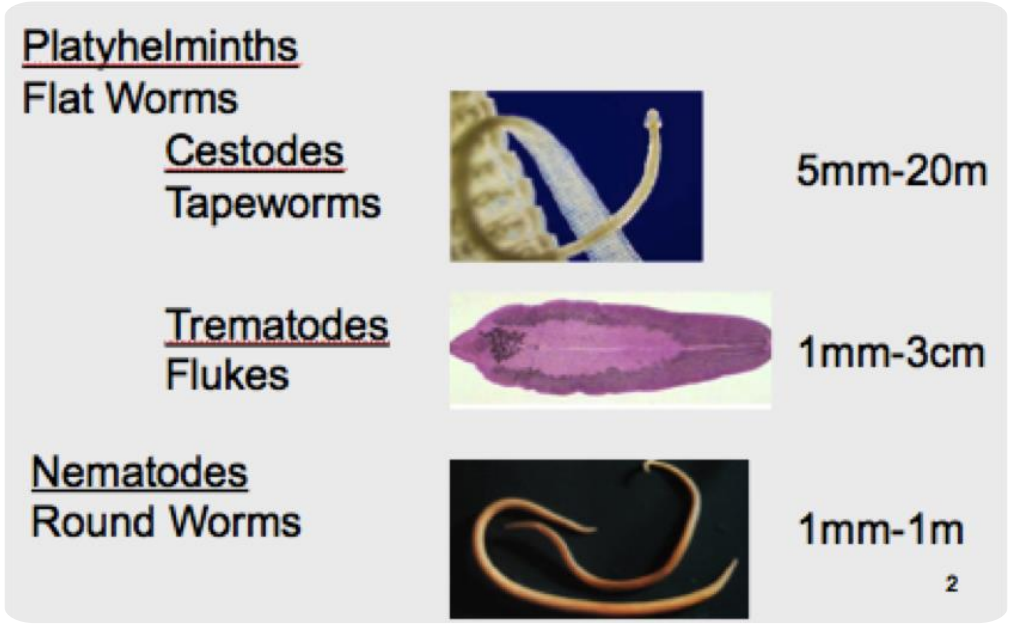
- Humans have coevolved with many species, ranging from large mammals to viruses. Coevolution of a mutualistic relationship of humans with domesticated animals is exemplified by cattle, where human-directed selection has resulted in multiple strains of animals selected for nutritionally and economically beneficial traits while the coevolved trait of lactase persistence in humans has spread as milk consumption and then dairy farmin became established practices.
- In this lectures, we are mostly concerned with the relationships between humans and their associated micro-organisms. Those relationships can be commensal (e.g., many skin and gut bacteria), mutualistic (many of the gut microbiota), parasitic (e.g., intestinal worms and body lice), or pathogenic (e.g., bacterial diseases such as cholera and tuberculosis and viral pathogens such as HIV and measles). Nevertheless, the distinction between a commensal and a pathogen is sometimes blurred, as for example when the normally harmless *Escherichia coli* acquires a virulence factor such as the bacteriophage-encoded Shiga toxin, giving rise to the pathogenic O157:H7 strain.



- It is only recently that the complexity and physiological importance of the community of symbiotic micro-organisms associated with humans (i.e., the microbiome) has come to be appreciated. The human body consists of about 1013 human cells, but this is outnumbered about ten-fold by the bacterial, archaeal, fungal, and protozoal cells found on all body surfaces (on the skin, in the mouth and nose, and in other orifices) and in particularin the lower gastrointestinal tract, which contains 1 to 2 kg of bacterial cells representing at least 500 species. However, most of the mass of the gut mikroflóra comes from 30 to 40 dominant anaerobic species, predominantly from the phyla Bacteroidetes and Firmicutes. The composition of the gut microbiome varies in type and diversity between individual humans according to factors such as age, geographical location, and diet. Families tend to share similar microbiomes, although this seems to be environmentally rather than genetically determined since monozygotic and dizygotic twins have similar levels of variability in their microbiomes and newborn infants take some months to achieve similar gut microbiomes to the rest of their family. The diversity of the microbiome, which is generally taken as an indicator of ecosystem health, is much higher in modern hunter- gatherer populations than in Westernized industrial populations.

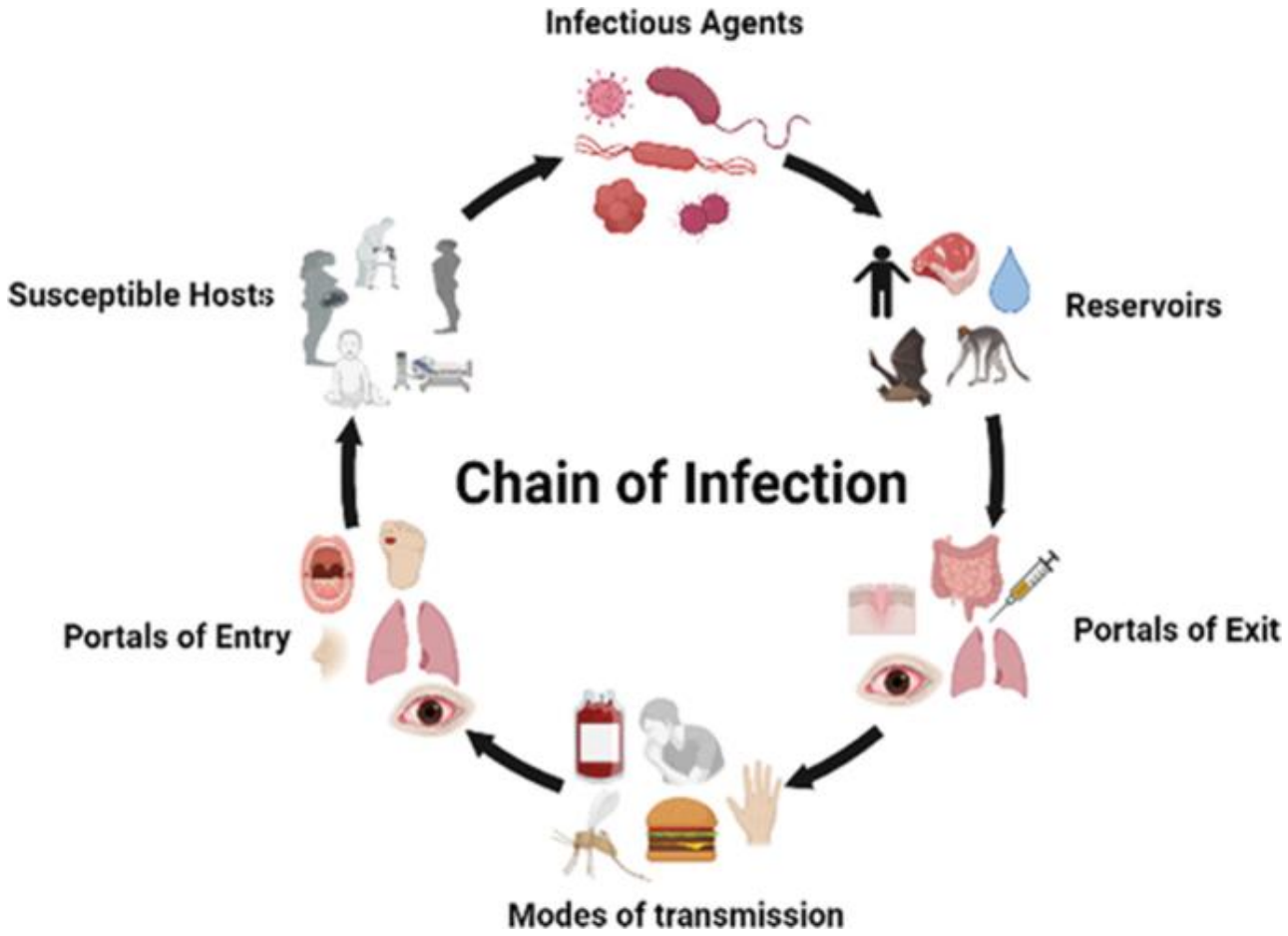


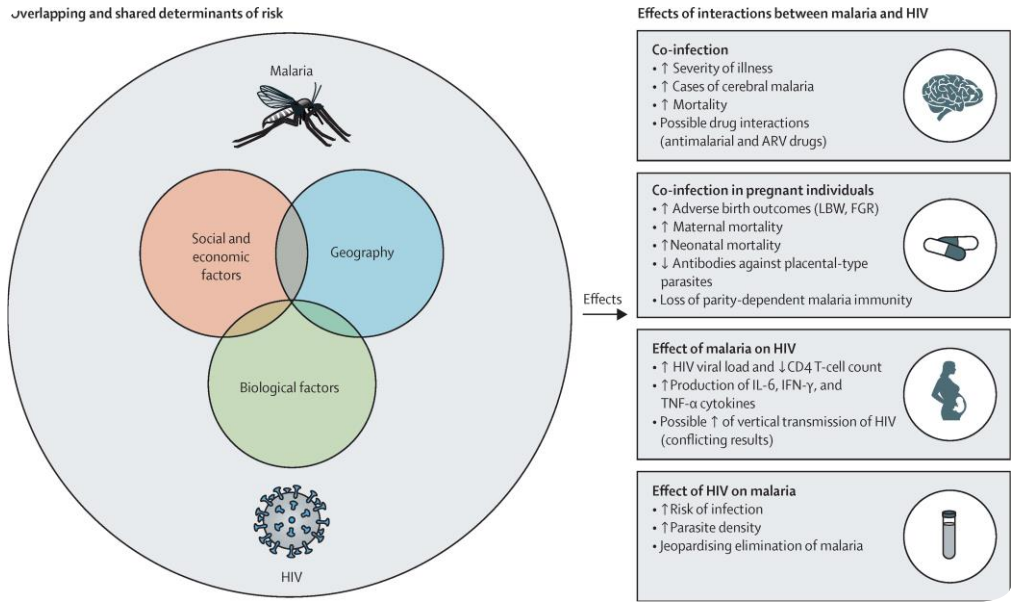
- The gut of the human neonate is generally sterile, but is rapidly colonized by maternal and environmental microflora; the composition matures during early life and then remains relatively stable, although subject to dietary and other environmental influences (Sekirov et al. 2010). Interestingly, establishment of the infant microbiome is promoted by, and the composition may be affected by, components of breast milk such as IgA and oligosaccharides, as well as by the tolerogenicity of the developing infant's immune system. Some studies have shown correlations between the composition of the microbiome in a mother and her offspring; this can be considered a further form of non- genomic inheritance. Infants born by cesarean section as opposed to a vaginal delivery have different gut microflora from each other, as do infants fed on formula as opposed to breast milk. It may be that these evolutionary novelties in childrearing have later consequences for health; for example, it is known that breastfed infants have a lower risk of obesity and metabolic disease and greater cognitive development than do formula- fed infants. The human gut offers an attractive environment to its microbial colonizers, being warm and damp and providing regular delivery of nutrients. Nevertheless, the relationship should be seen as mutual rather than commensal, since both parties derive benefit. The gut microflora provide numerous benefits to the host, including digestion of nutrients such as dietary fiber, synthesis of vitamins such as folate and biotin, and metabolism of potentially toxic food constituents. There is growing evidence for a link between the gut microflóra and the brain, affecting aspects of mood and behavior (see Sampson and Mazmanian 2015). Importantly the gut microflora also act to protect the host organism by preventing colonization of the gastrointestinal tract by pathogenic competitors and by modulating the development of the host's adaptive immune system.



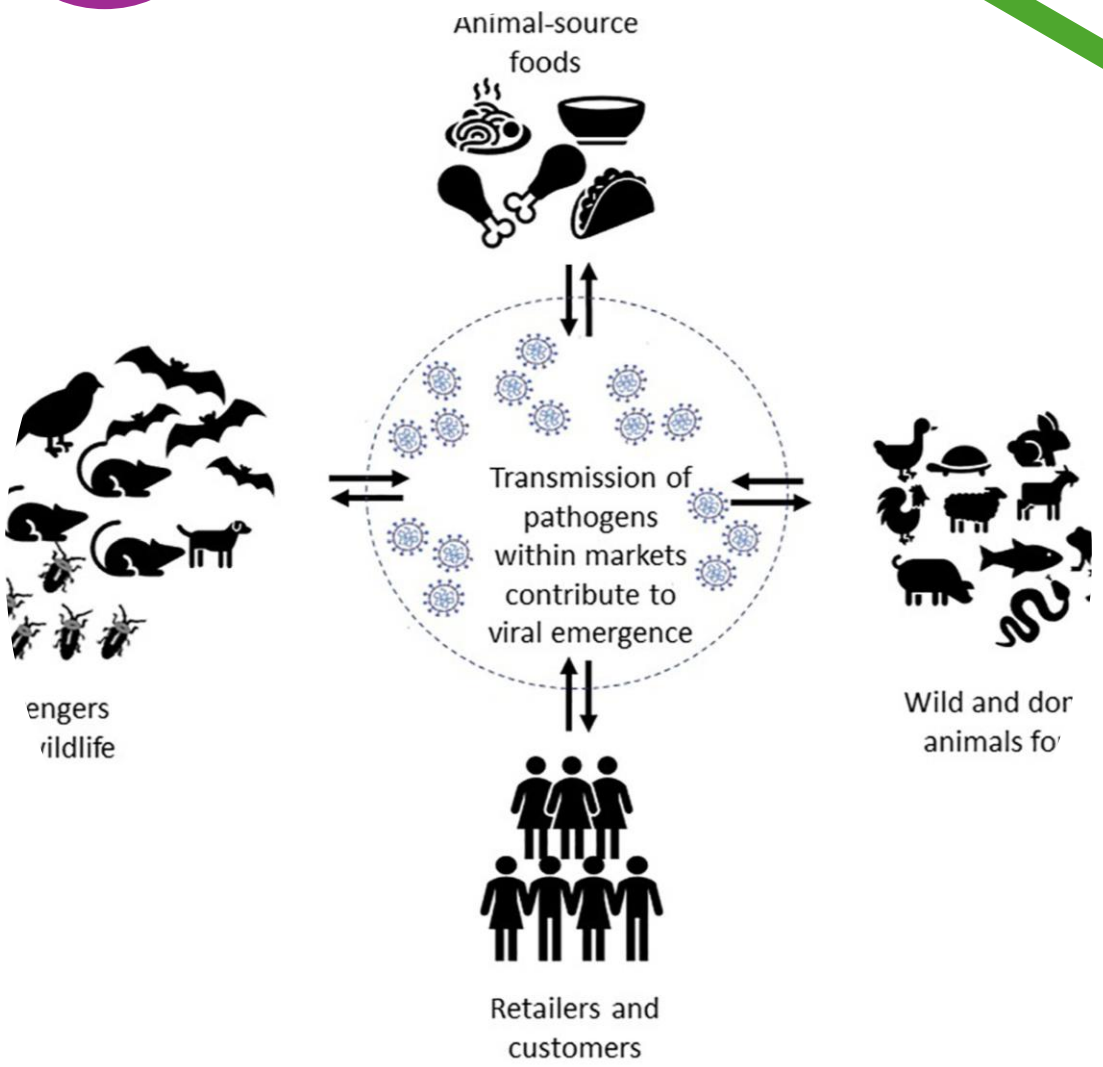
- On the other hand, some parasitic species use the human intestine as a host environment. Tapeworms, trematodes (flatworms or flukes), and roundworms pass their eggs/larvae to other hosts via human feces. Some infestation is direct, by contamination of water or vegetation, and sometimes it involves an intermediate host, for example the water snail in schistosomiasis. These parasites compete for nutrients and can cause considerable malnutrition in the host, with long-term consequences such as stunting, as well as abdominal disorders such as enlargement of the liver or spleen. Gut parasitism is particularly prevalent in low-income countries.

The Challenge of Infectious Disease

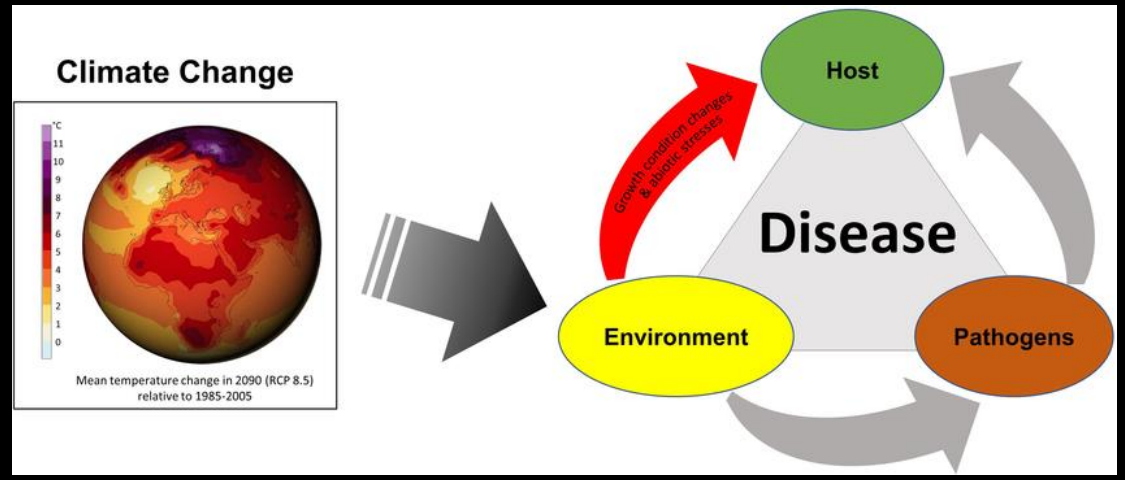




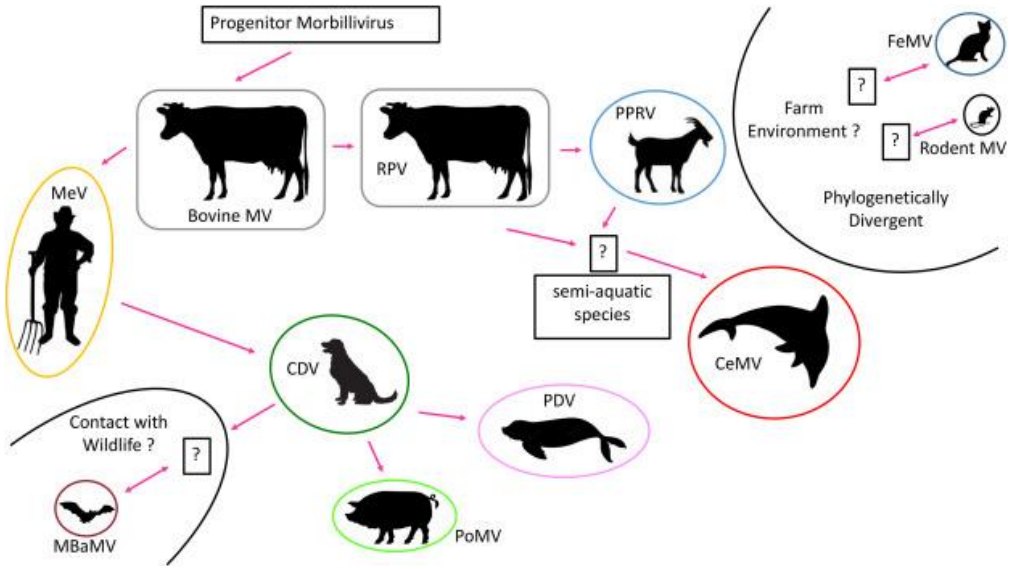
There are over 1200 species of recognized human pathogen, although the majority of infection-related mortality and morbidity is now caused by just a few of these, particularly malaria, HIV/AIDS, and tuberculosis. This multiplicity of threats imposes a continual interplay between our defense systems and the transmissibility and virulence of these organisms. Micro-organisms evolve in relation to their hosts and the vectors they rely on for their survival and fitness. There are great differences in population size and generation times between micro-organisms and humans, giving microbes the advantage of being able to evolve much more rapidly. Indeed, in bacteria, stress may produce an increase in their mutation rate (often termed the SOS response)- see Baharoglu and Mazel (2014) which makes it more likely that new variants will appear and that gene flow will be preserved. This difference in generation times is well demonstrated by the development of bacterial resistance to antibiotics, which is one of the best-characterized manifestations of evolutionary processes operating in real time. Humans with their long generation time must deal with this microbial challenge, and the biological complexity of vertebrates has allowed the evolution of a number of defensive strategies that can cope with faster-evolving organisms—in particular the innate and adaptive immune systems. In historical times humans have added additional strategies in the form of technologies such as vaccination and antimicrobial chemotherapy. Thus an evolutionary arms race is played out with different weapons employed on each side—rapid mutational change on one hand, and multivalent immune and defense mechanisms on the other



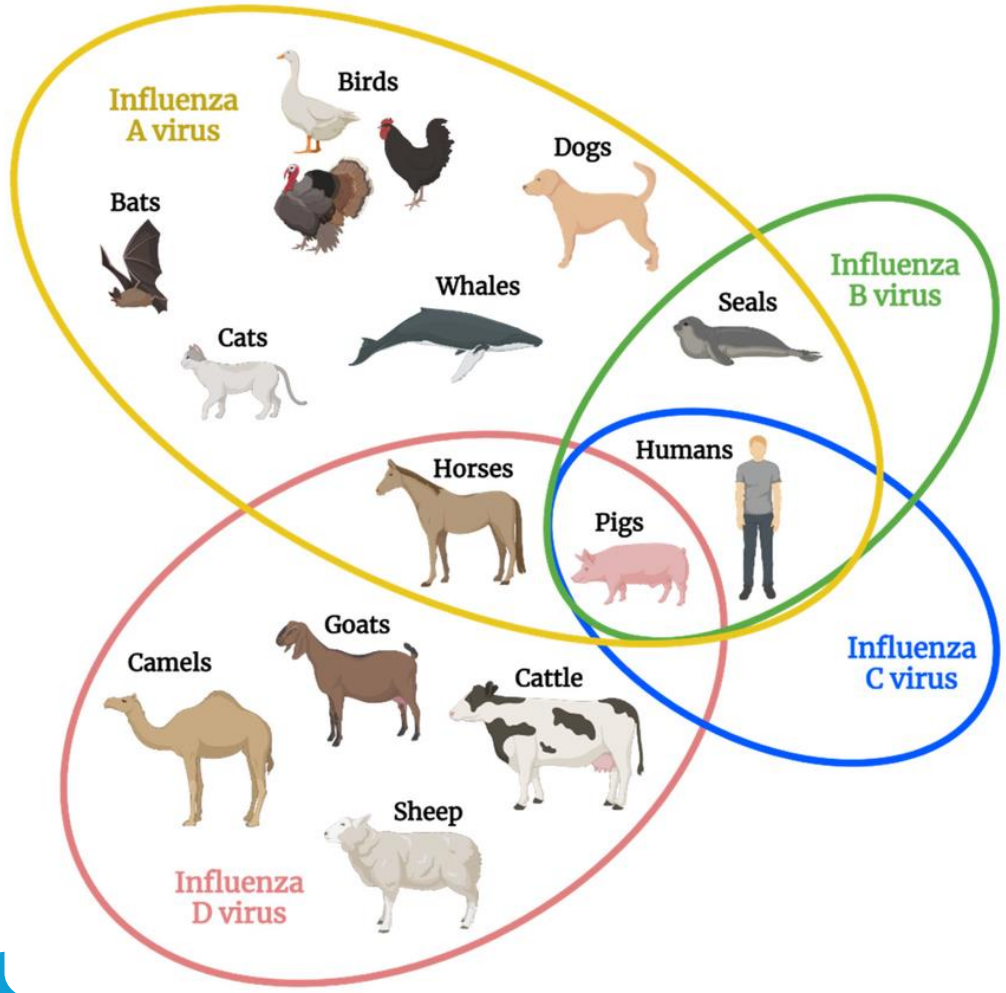
Pathogen Emergence



- During human evolution the risks of infection by many pathogens changed significantly. The development of animal husbandry, settlement, and increasingly larger aggregations of population allowed infectious agents to spread more easily. Problems of waste disposal and hygiene grew with settlement. Other human endeavors also increased the risk of infection. For example, alterations made in drainage and irrigation systems in Africa led to the spread of schistosomiasis. Thus, while humans have evolved alongside their microbiotic environment, the challenges have become greater in the past 10,000 years (see Cleaveland et al. 2007). Patterns of pathogen-induced disease are not the same across the globe. Environmental factors play a part in this; for example, the conditions suitable for mosquitoes to breed are confined to tropical and subtropical pools of water. Historically, malaria was endemic in southern Europe well into the twentieth century, and climate change may mean that the disease could well become widespread there again. However, historical considerations reveal that there may be more to explaining the patterns of disease. Why, for example, do the diseases of the tropics include chronic infections and infestations such as schistosomiasis and onchocerciasis and those of more temperate regions include infections such as smallpox and tuberculosis? One hypothesis is that the tropical pattern emerged through coevolution of the pathogens responsible in consort with ancestral hominins in Africa. Low population density and a nomadic lifestyle may have favored the evolution of chronic diseases with relatively low virulence and the need for intermediate vectors such as the mosquito, tsetse fly, and water snail. The more recent migration into temperate regions was accompanied by the development of settlements with a higher population density and of animal husbandry, favoring diseases with a zoonotic origin or with higher virulence and more direct person-to-person transmission. In addition to the adoption of a sedentary lifestyle, humans in temperate zones began to domesticate animals. Close proximity to such animals favored the transmission of their pathogens to humans, and this may be the origin of diseases such as tuberculosis. Interestingly, the overwhelming majority of human infectious diseases originated in the Old World (Africa and Eurasia) rather than in the Americas, possibly as a result of the geographical difference in the number of animals that were domesticated (see Wolfe et al. 2012).

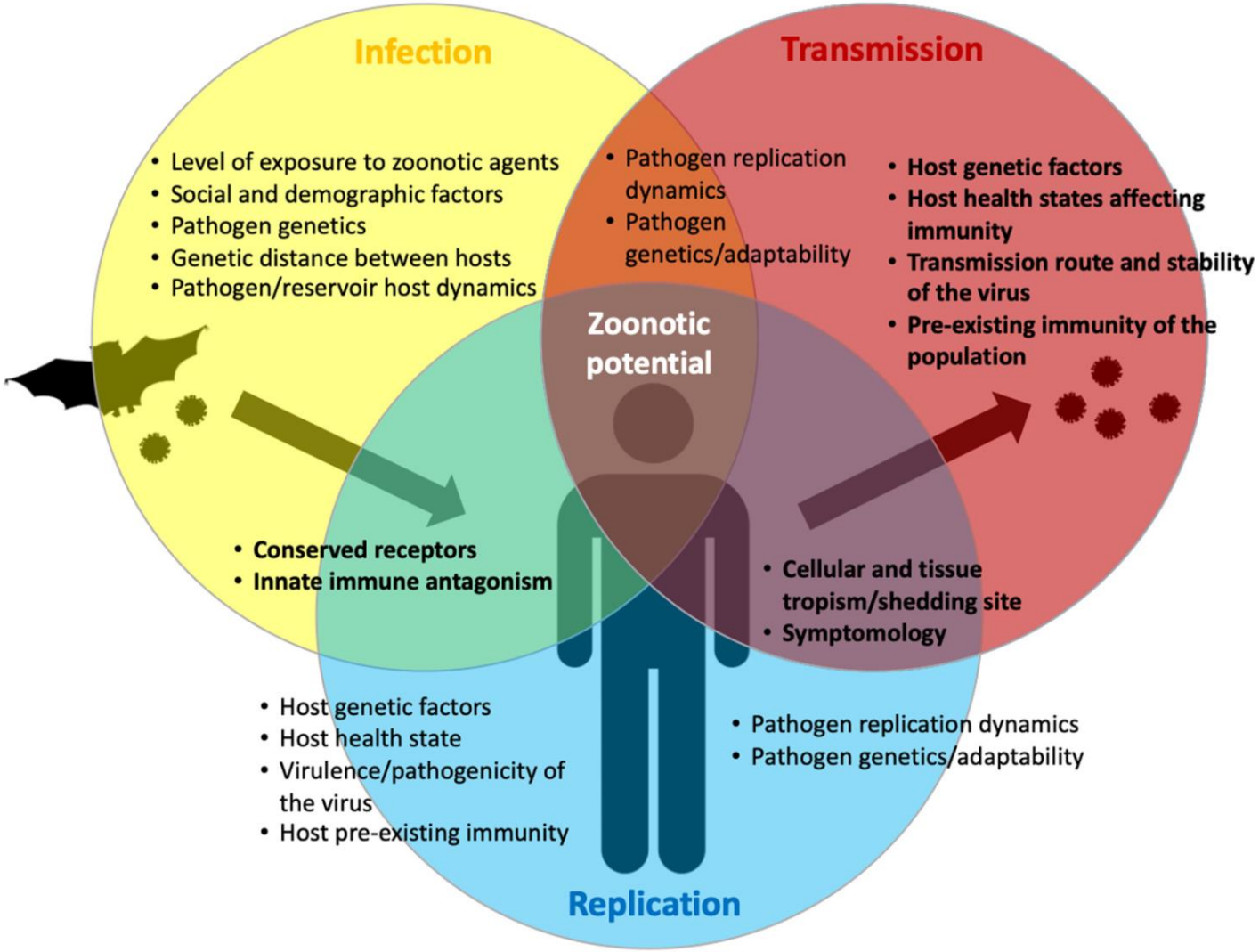


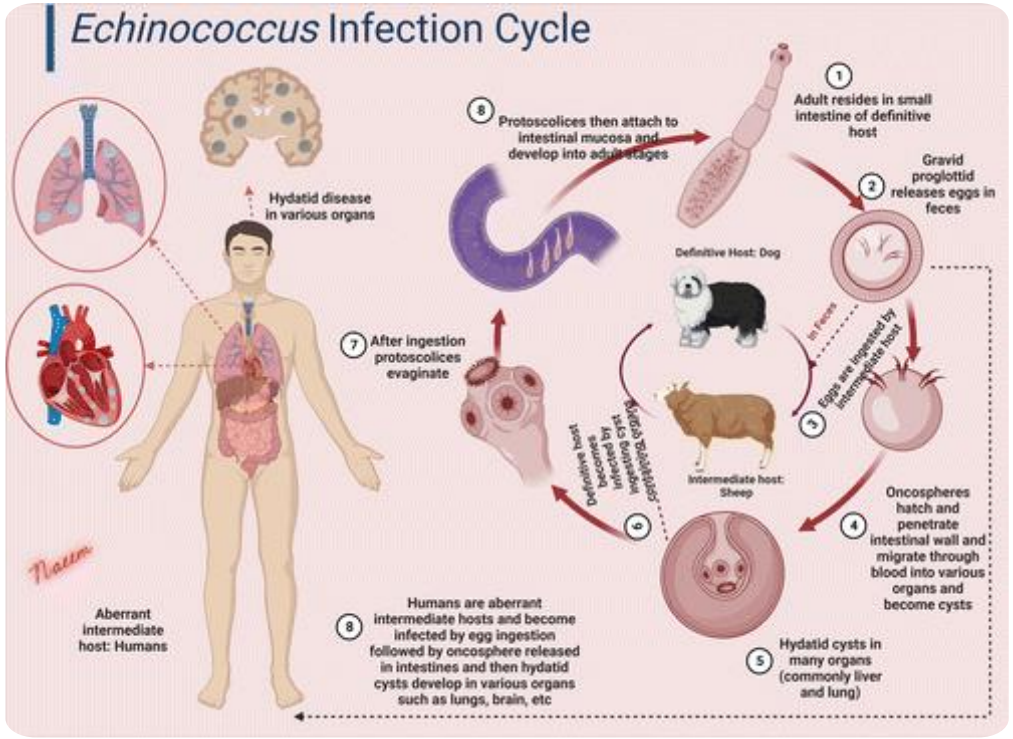
- Most infections originate and are sustained by close interpersonal contact and/or by contact with animals. Many viruses that infect humans have their origin in domesticated animals. For example, the influenza virus originated in pigs and poultry, and it is possible that the human measles virus evolved from the closely related morbillivirus that causes the cattle disease rinderpest (see Sharp 2002)—the close similarity between measles virus and the morbillivirus that causes canine distemper suggests a later jump in the opposite direction, from humans to dogs (see Uhl et al. 2011). It is generally accepted that HIV is derived from the lentivirus simian immunodeficiency virus (SIV); this is a slow-QAUASI- M growing subtype of retrovirus that infects Old World primates.
- There are many previous incidences of the transmission of such viruses between species, but the critical event for the origin of human HIV was likely to have been transmission from (depending on the strain of HIV) chimpanzees or sooty mangabeys to humans, most likely as result of blood contact during hunting and butchering of these species for bush-meat. We may never know the precise location or time of the transmission, but research suggests that the origins were south central Cameroon and possibly Guinea Bissau during the 1940s or 1950s. What determines the transmission of an infectious disease from animals to humans? Why is it a relatively rare event? The answer seems to be that a successful shift in host from animal to human involves several distinct events. Consider the influenza A virus H5N1, a strain of avian influenza which has only infected a few humans who have been in particularly close contact with infected poultry, but about which there is much concern for the potential for human-to-human transmission. Studies of the influenza pandemics of 1918, 1957, and 1968 give some clues.



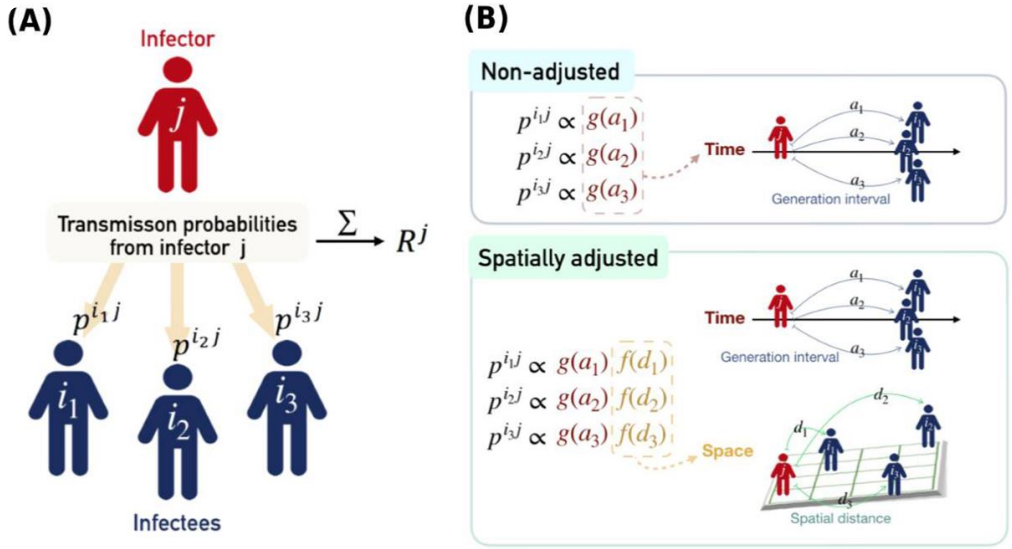
- Influenza viruses are endemic in bird populations, both in the wild and in domesticated species, and in some other animals such as pigs, and they are highly mutable. Each pandemic is thought to represent the emergence of mutated forms that have escaped the immunity of previous influenza infections in humans and successfully made the transition from reproducing in an animal host to reproducing in a human host. The so-called Spanish flu virus, which produced the 1918 pandemic in which 50 million people died worldwide, may have been due to the transfer of a complete avian virus into humans, although others have proposed an intermediate mammalian vector (see Taubenberger et al. 2012). In contrast, the more common influenza A virus shows relatively linear evolution. The antigenic properties of the influenza virus change from year to year as a result of mutation (antigenic drift), necessitating the production of new vaccines and annual vaccination of susceptible members of the population. But on top of this there have been several large shifts in antigenicity in the past century, such as the “Asian flu” in 1957 and “Hong Kong flu” in 1968, arising from reassortment of genes between two viral strains co-â•‰infecting an individual. Close proximity between humans and animal hosts offers the potential for initial direct inoculation (e.g., through a cut). In the case of H5N1, the first transmission to humans was reported in 1997 and this is the stage at which H5N1 currently exists: infection from the animal host can occur, but human-o-human transmission remains unconfirmed. The critical next step will be if the H5N1 virus exchanges genomic material with a flu virus that has the potential to be transmitted between humans because it can bind to surface receptors on cells in the human respiratory tract. If this happens a pandemic could result, because there may be little resistance in the human population in any country. Given that viruses replicate with very short generation times, the chances of individual mutations are high. The cumulative effect of those mutations in inducing a virulent pathogen depends on whether the human defense mechanisms are adequate or whether technology in the form of isolation, vaccination, or medication can reduce the spread of the organism and contain the epidemic.

Pathogen Virulence and Transmission

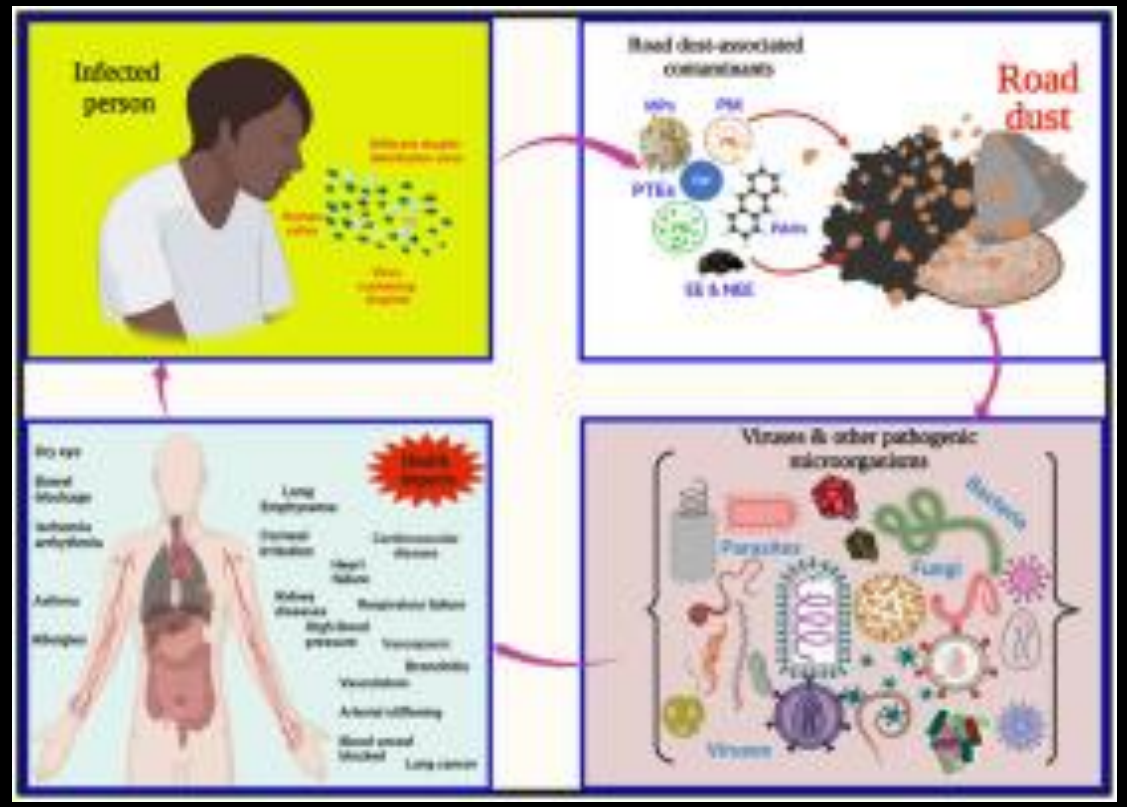




- The evolutionary aim of a parasite, like that of all other species, is to maximize its reproductive success. The parasite does this by shaping aspects of its life cycle to optimize survival and replication in its host and transmission to its next host. Two of the traits that evolution uses to optimize reproductive success are virulence and transmissibility. By definition, a pathogen is a parasite that causes morbidity and mortality in its host. It may do this by secreting a toxin, damaging cellular function, competing for nutrients, or simply by causing mechanical damage. The extent of this damage is termed its *virulence*. Virulence may appear as incidental damage to the host that does not benefit the infecting organism, or as damage that does benefit the infecting organism, such as by increasing resource extraction from the host or enhancing the transmission of the pathogen. For example, the principal morbidity caused by HIV is gradual destruction of the host's immune system, increasing susceptibility to opportunistic infections and malignancy. This type of damage to the host does not benefit the virus by directly enhancing its sexual transmission, although the temporal pattern of the infection, with a long asymptomatic period during which numerous sexual partners can be infected, does promote transmission. Contrast this with cholera, ingested for example via water contaminated with feces containing the cholera bacterium. The organism clings to the wall of the gut and secretes a toxin which triggers the secretion of serous fluid and rapidly produces violent diarrhea. This trait is adaptive for the cholera organism in that it allows greater spread to other hosts; it may also serve to displace commensal gut microbiota, giving the pathogen a competitive advantage in the gut environment.



- For a pathogen to be evolutionarily successful, it must also be transmitted to a new host. Parasite fitness is often expressed as basic reproductive ratio, *R*0, the average number of new host individuals infected during the life cycle of the parasite. *R*0 must be at least 1 if a parasite is to persist within its host population; high values of R0 indicate that the parasite is spreading rapidly. Conversely, if *R*0 is below 1, because of poor transmission or strong host defenses, the infection will die out. A pathogen will evolve to an equilibrium established by the optimal trade- off of virulence against transmission to ensure that it infects the greatest possible number of new hosts. High virulence kills the host quickly, so the pathogen needs to be highly transmissible. Conversely, low virulence allows the host to survive for long enough to infect many other hosts, so the pathogen can afford to be less transmissible. Optimization of this trade- off depends on a number of factors. These include whether transmission is vertical (between mother and offspring) or horizontal (across all members of a species) as well as the method of transmission. Pathogens can be transmitted horizontally by many routes, for example by airborne droplets (exemplified by the common cold virus and influenza), by contaminated water (e.g., cholera and typhoid), by contact with infected body fluids (e.g., HIV, Ebola), by contact with dormant organisms in the environment (e.g., smallpox), by sexual intercourse (e.g., syphilis, HIV) or by an intermediate vector (e.g., malaria).

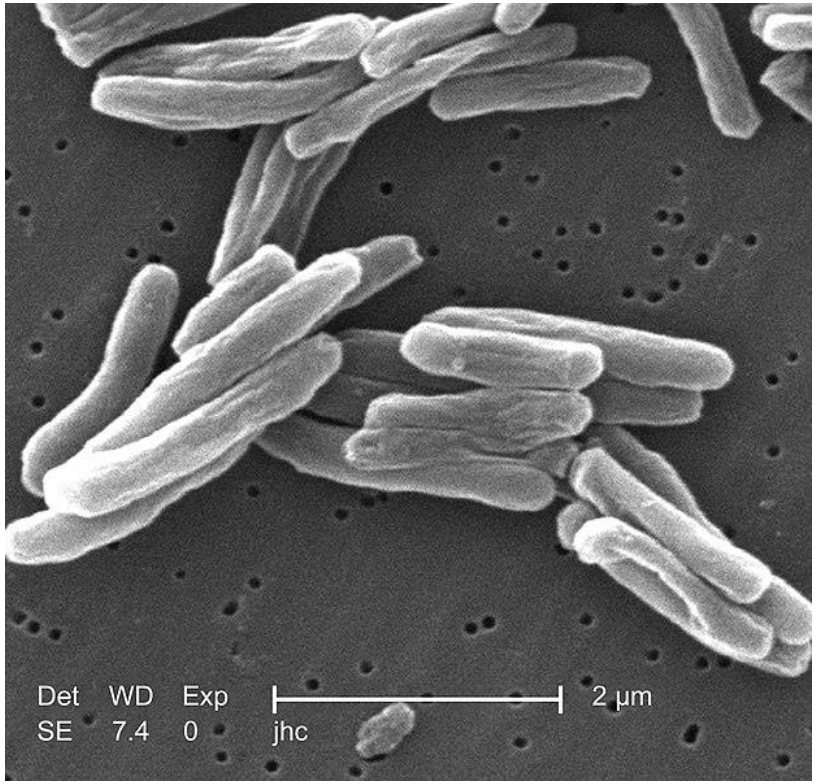


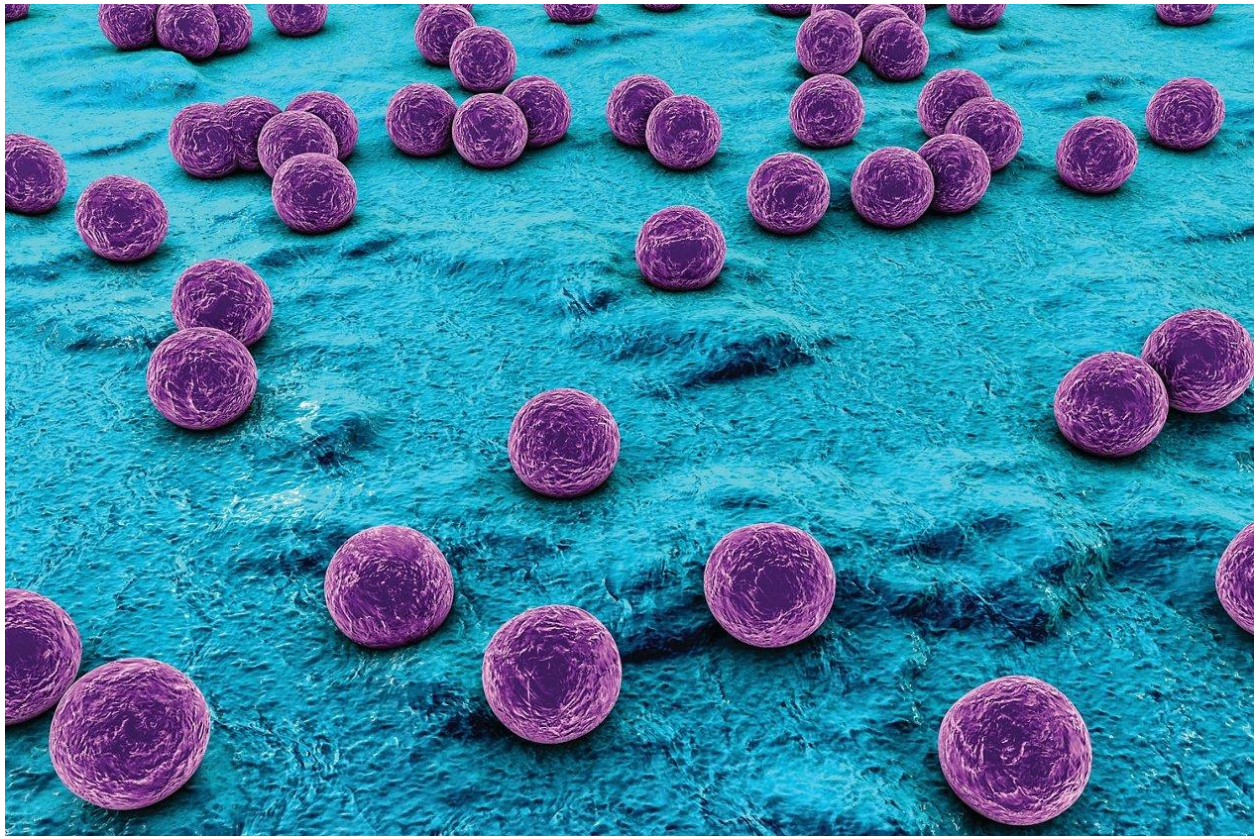
- Exclusively vertical transmission of human pathogens is unknown, although many diseases, such as HIV, can be transmitted both vertically and horizontally. (Some animal parasites, such as *Wolbachia*, an intracellular bacterial symbiont of invertebrates, are normally transmitted only vertically.) The virulence of horizontally transmitted pathogens often depends on the method of transmission. For example, gastrointestinal pathogens such as cholera that are transmitted in contaminated water can afford to be highly virulent, as they do not depend on continued survival of the infected host to achieve high values of *R*0. Conversely, a pathogen that is exclusively transmitted by sexual contact would be expected to have low (or, at least, delayed) virulence, as achieving $R0 > 1$ relies on survival of the host to infect more than one partner. The setpoint of the virulence/ transmission tradeoff of a particular pathogen in a particular host will depend on both pathogen and host factors and the history of the coevolutionary interaction between them. In general, we might predict that the longer the relationship between pathogen and host, the lower the virulence of the pathogen in that host. This is because the host will have had time to evolve resistance or tolerance to the pathogen and the pathogen will have evolved its virulence/ transmission trade- off to a level that allows its maintenance in the host population. Such reduction in virulence can be observed experimentally (see Bérénos et al. 2009) and in the field, where a reduction (although to still high levels) in the virulence of the myxoma virus was observed in the decades after its artificial introduction into Australia to control the rabbit population (see Di Giallonardo and Holmes 2015).

The converse situation is relatively common, however, for organisms that normally infect other hosts but are opportunistic pathogens in humans, where their virulence can be very high. The Ebola virus is a good example. Its natural host is a species of fruit bat, in which it appears to have little or no virulence. However, when transmitted to humans, possibly via consumption of infected bush- meat, it is highly contagious and the resulting hemorrhagic fever has a very high case fatality rate. But this very high virulence limits the ability of the virus to spread to a large number of hosts, and isolation and quarantine, properly applied, are effective in further restricting the pool of potential hosts and containing the outbreak. The virulence/ transmission trade- off can be manipulated artificially, and this is the basis of the live attenuated vaccines developed in the 1950s and still used for immunization against some diseases such as poliomyelitis. The process relies on serial passage of the pathogen in the laboratory in cell or tissue culture under "ideal" conditions where transmission is assured (high *R*0) and the host (the cell culture) cannot evolve resistance or tolerance because each passage is into naiive tissue previously unexposed to the pathogen. The result is that the pathogen evolves towards high virulence in its new host but decreased virulence in its natural (human) host, and this "attenuated" strain is used for vaccination.

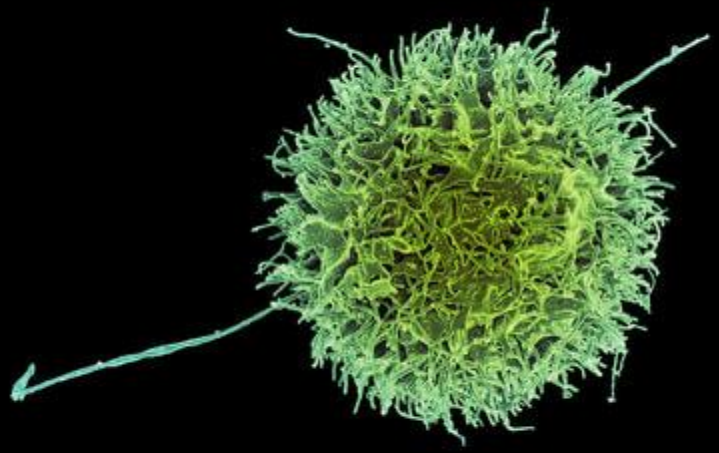
https://www.youtube.com/watch?v=I_xh-bkiv_c&ab_channel=AndresTrevino

Whether or not we succumb to an infection is often not simply a question of whether we have come into contact with the pathogen, but rather the size of the infectious load to which we are exposed. Simple procedures such as hand- washing greatly reduce the risk of cross-infection in hospitals by reducing the infectious load; the major advance in patient survival after surgery afforded by Lister's invention in 1869 of the crude but effective carbolic acid spray was due to the reduction of the infectious load rather than achieving complete sterility, a principle that stills holds true in operating theatres today. The estimated infective dose for pathogens—that is, the number of organisms required to infect a host—varies widely (Leggett et al. 2012), ranging from just one cyst for the gut parasite *Entamoeba histolytica*, ten or fewer organisms for Ebola virus and *Mycobacterium tuberculosis* (the causative bacterium of tuberculosis), and up to 104–106 organisms for *Staphylococcus aureus* (a cause of skin infections) and other common bacterial pathogens. Generally, the greater the virulence of the pathogen, the lower the infective dose, as would be predicted from the virulence/transmission trade-off.





Host Defenses



Humans have evolved in the presence of a large repertoire of associated micro-organisms. Some of these are pathogens or potential pathogens, but the human "meta-organism" (i.e., the body plus its microbiome) also contains a large number of mutualistic or commensal species, which normally vastly outnumber the pathogens. From this perspective, our evolved antimicrobial strategies should be seen not only as defenses against pathogens but also as mechanisms to ensure peaceful coexistence with our commensals. Reciprocally, not only do commensals themselves provide protection against pathogens, but exposure to commensals in early life appears to be a prerequisite for maturation of the adaptive immune system (see Belkaid and Hand 2014).

Innate Immunity

BioCode
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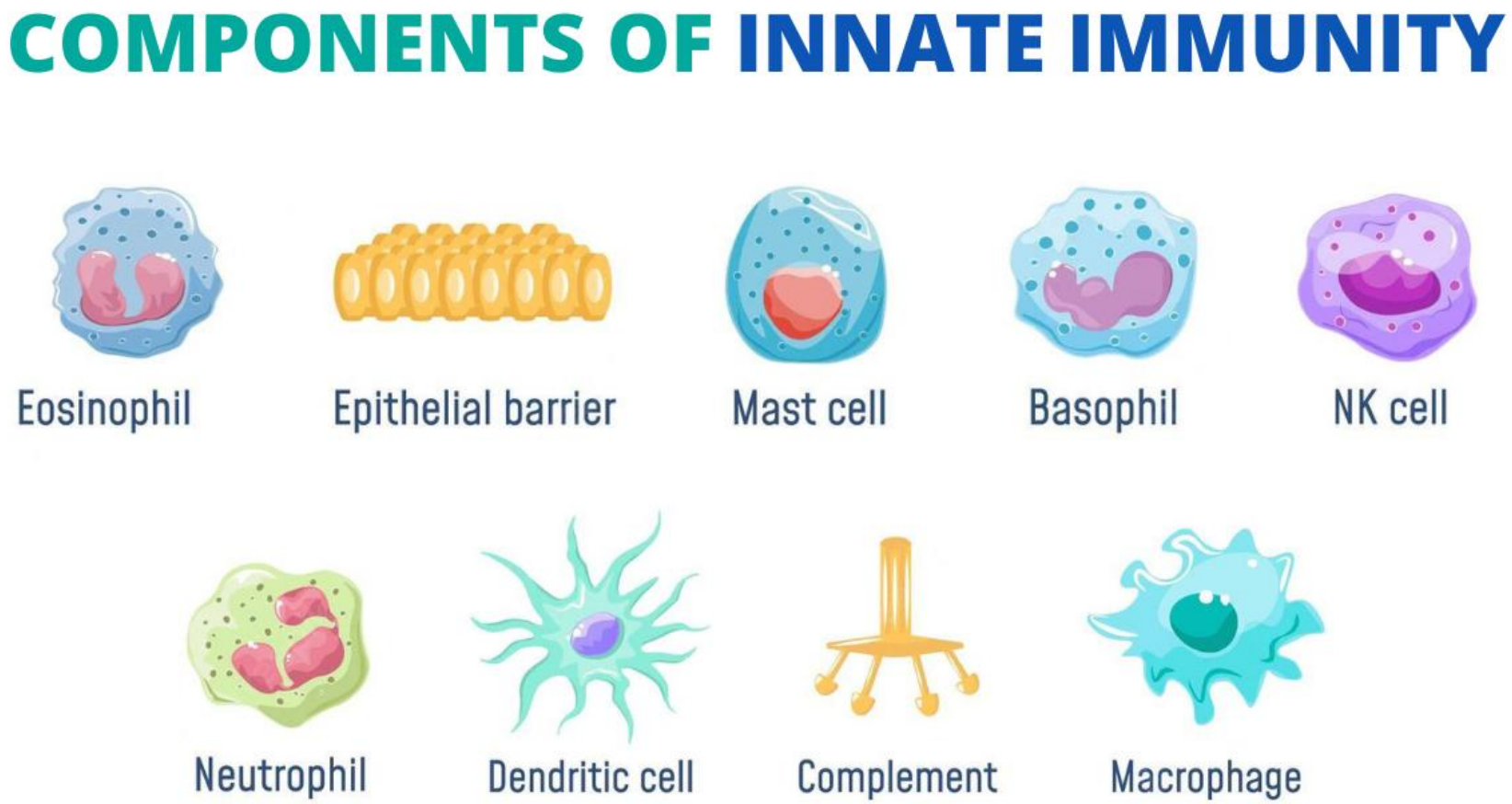
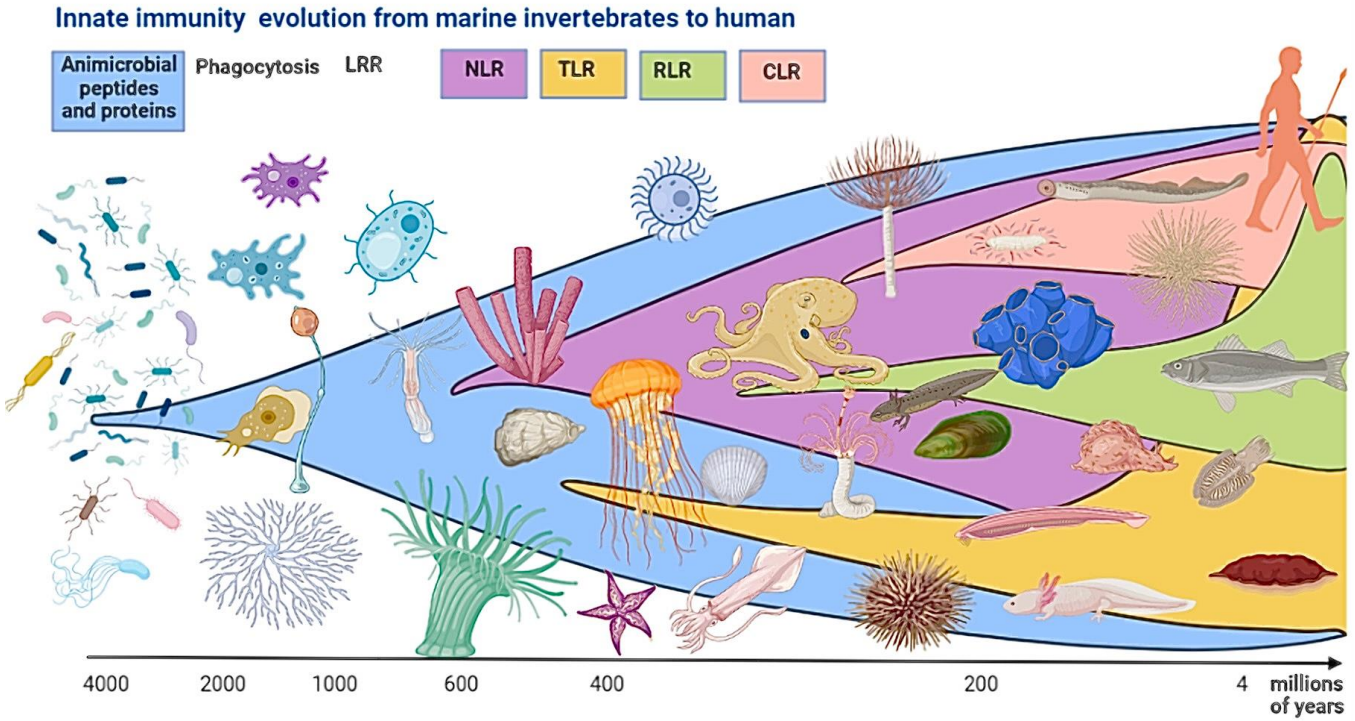
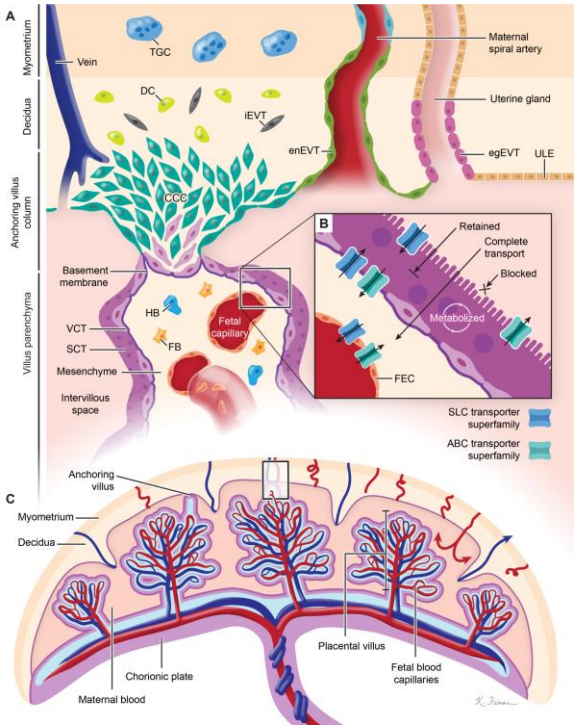


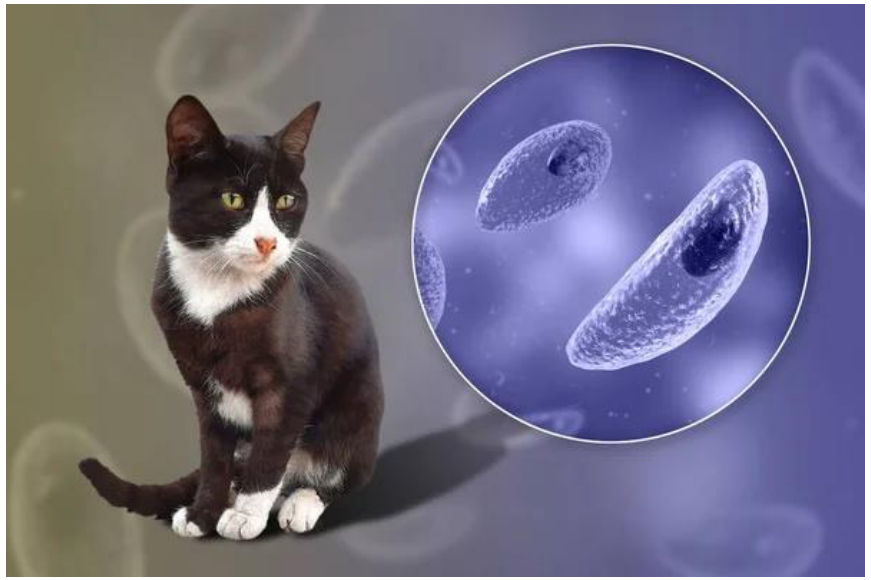
All multicellular animals possess an innate immune system; this protects them from infection by maintaining defensive barriers against penetration by micro-organisms and by mounting chemical and cellular defenses against any microbes that do reach the interior of the organism. Innate immunity is non-specific and, unlike the adaptive immune system, does not lead to any lasting protective immunity (or “memory”). The innate immune system is phylogenetically ancient, and many of its features are conserved across both vertebrates and invertebrates. The physical barriers that resist invasion by micro-organisms include the skin as well as the epithelial mucosa lining the alimentary tract and parts of the respiratory and reproductive tracts. These barriers are equipped with sensory receptors that are deployed at strategic points, where they have greater sensitivity. Sensitivity is greatest on the most frequently exposed parts of our skin such as the fingers and face; mechanoreceptors can detect very small inhaled particles in the nose or larynx and, on the skin, can detect small wounds. Tight junctions between epithelial cells provide good protection against the passage of micro-organisms; the waterproofing of the skin limits passage of water-borne organisms, and the mucus-secreting glands and ciliary action of the mucous membranes help to expel ingested or inhaled organisms. Some attackers have evolved highly effective ways of penetrating these barriers, such as the proboscis of the mosquito, and other parasites such as the malaria protozoan use this as a way of gaining access to a host’s body.



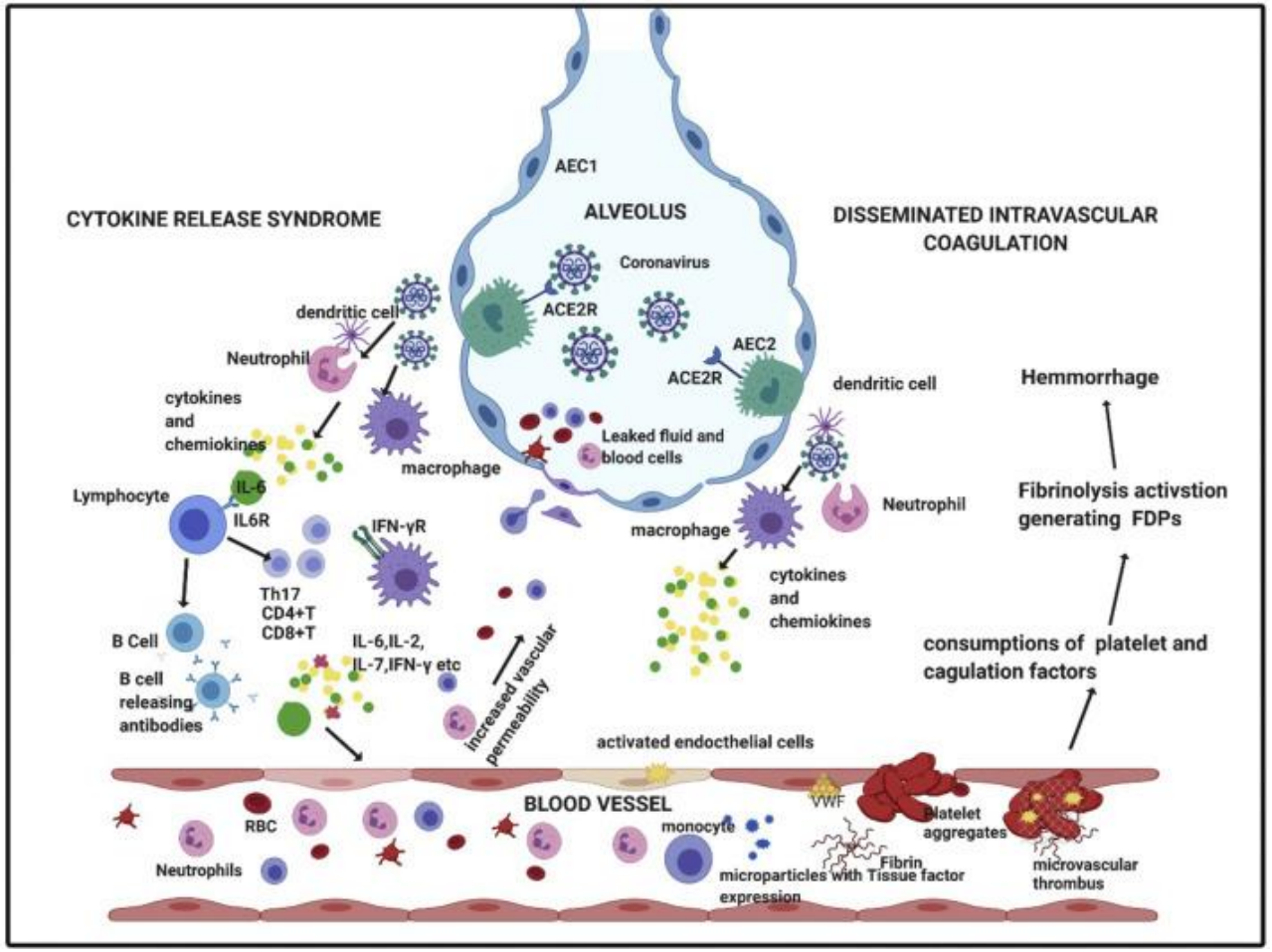
Other barriers within the body have different degrees of penetrability and defensive strategies (see Doran et al. 2013). The human placenta, for example, is somewhat “leaky,” prioritizing exchange and transport functions over defense, and so some micro-organisms such as the syphilis spirochete (*Treponema pallidum*), rubella virus, *Toxoplasma gondii, Listeria bacteroides*, and cytomegalovirus can pass from mother to fetus. At the other extreme the barrier between the blood and the brain is very tight apart from at the cribriform plate, which conducts the olfactory nerves from the nose—this provides a route for infection leading to meningitis. *Amoebic meningitis*, a very rare disease, can arise when contaminated water found in natural hot springs enters the nose. The epithelial mucosae, such as those lining the respiratory tract and gut, are among the sites most exposed to the microbiota, yet they must allow the passage of oxygen and nutrients. Epithelial cells and their associated inflammatory and phagocytic cells, such as macrophages and neutrophils, secrete mucus, IgA, and other antimicrobial substances such as those of the complement system to provide physical and chemical barriers to the penetration of micro-organisms. The triggering of these defenses to invading organisms involves recognition of chemical structures, called pathogen-associated molecular patterns (PAMPs), that are common to micro-organisms but not found in more complex animals. In other words, this form of discrimination between self and non-self takes the form of a generalized ability to distinguish between multicellular and single-celled organisms. PAMPs include microbial proteins such as flagellin, cell wall molecules such as mannose and lipopolysaccharides, as well as unmethylated DNA (most eukaryotic DNA is methylated). The family of pattern recognition receptors that sense PAMPs can trigger phagocytic and inflammatory responses in mucosal tissue, leading to engulfment and destruction of invading micro-organisms (see Albiger et al. 2007).

Treponema pallidum

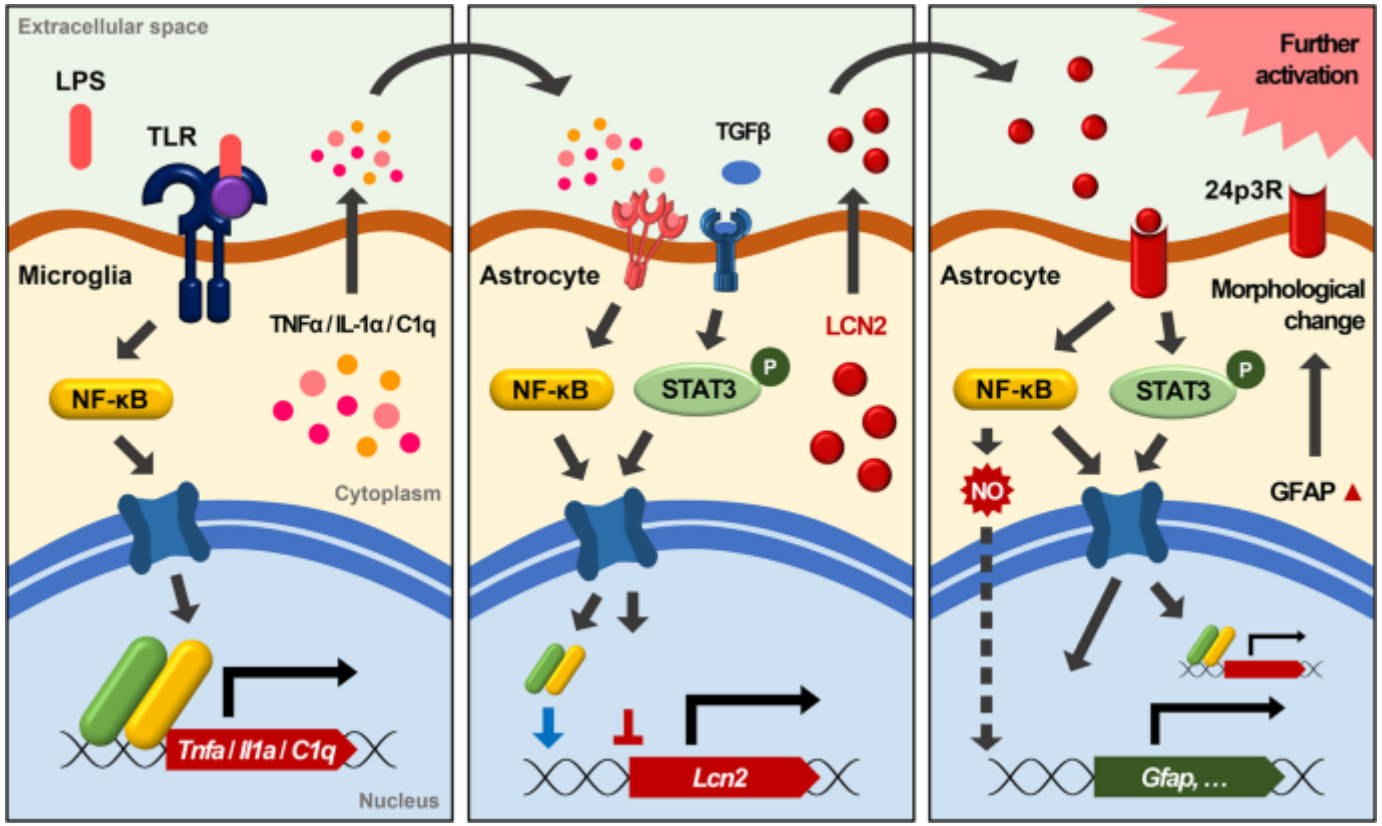




The release of cytokines such as interleukin-6 from cells of the innate immune system (e.g., macrophages) in response to PAMPs causes fever, one of the most characteristic responses to infection. In mammals, fever is mediated centrally by hypothalamic mechanisms that drive thermogenesis and promote peripheral vasoconstriction to reduce heat loss. In turn, this induced hyperthermia drives further activation of both the innate and adaptive immune systems (see Evans et al. 2015). This may occur by secretion of heat-shock proteins into the circulation. Heat-shock proteins are a diverse group of proteins with multiple intracellular functions, so named because they are induced in a cell when it is exposed to elevated temperatures (see Srivastava 2002). These proteins control the transcription of a range of genes, such as those involved in glucocorticoid secretion, as well as expression of cytokine and chemokine genes. Thus a febrile response may be part of an evolved defense mechanism that uses the resulting expression of heat-shock proteins to stimulate the immune system. Although microbial replication may be less efficient in a hyperthermic host, some pathogens such as the malaria parasite produce their own heat shock proteins that probably serve to protect the organism during episodes of fever (see Przyborski et al. 2015).



Competition for the essential nutrient iron illustrates another form of interaction between host and invader. Microbial growth in host tissues is limited by the availability of free iron, and infection induces secretion by the host of iron-binding proteins such as transferrin, which act to sequester iron intracellularly and make it unavailable for bacterial metabolism. For their part, bacteria secrete siderophores, which are small peptides that bind iron and transport it into their cells. In turn, the host processes that detect PAMPs stimulate the secretion of a small protein called lipocalin 2, which binds the bacterial siderophores with very high affinity and deprives the pathogens of iron. In experimental animals the absence of this defense mechanism can result in sepsis and death. Infection-associated anemia is a common clinical finding, particularly with chronic infection, leading to the question of whether iron supplementation in such situations is deleterious or beneficial. For example, iron deficiency appears to be protective against severe malaria in children (see Gwamaka et al. 2012), and untargeted iron supplementation of children in an area with a high risk of malaria has been shown to increase hospitalization and mortality (see Sazawal et al. 2006). Nevertheless, current WHO recommendations favor iron supplementation of children in areas endemic for malaria, in conjunction with measures to prevent, diagnose, and treat the disease. Protection against pathogens can also result from direct action of the commensal microflora. The mechanisms involved include colonization resistance, which is the exclusion of pathogens by the commensals in competition for nutrients, and niche manipulation, for example by altering the local pH, as well as secretion of antimicrobial peptides and production of metabolites such as short chain fatty acids that can alter the virulence profile of invading pathogens. In this way, the innate immune system of the host has evolved barrier and defensive functions to control the growth of commensal organisms but can also co-opt these organisms to control invasive pathogens.



TO BE CONTINUED...