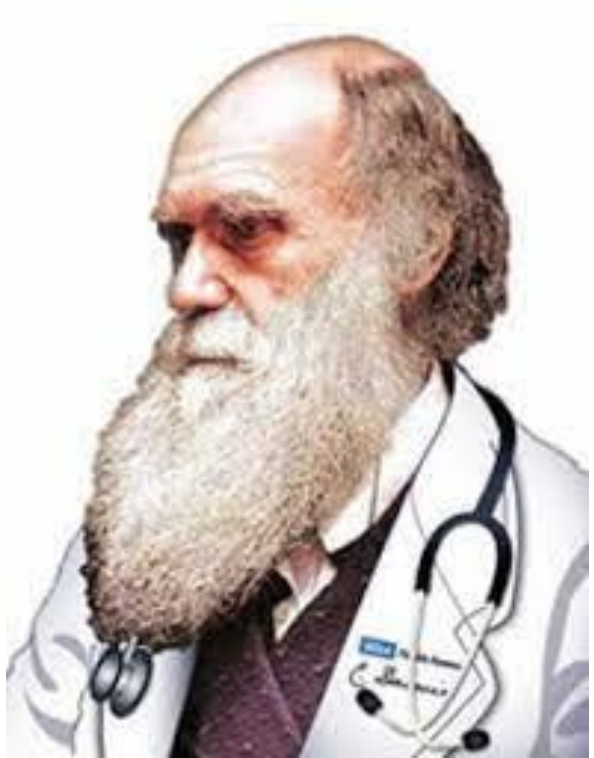
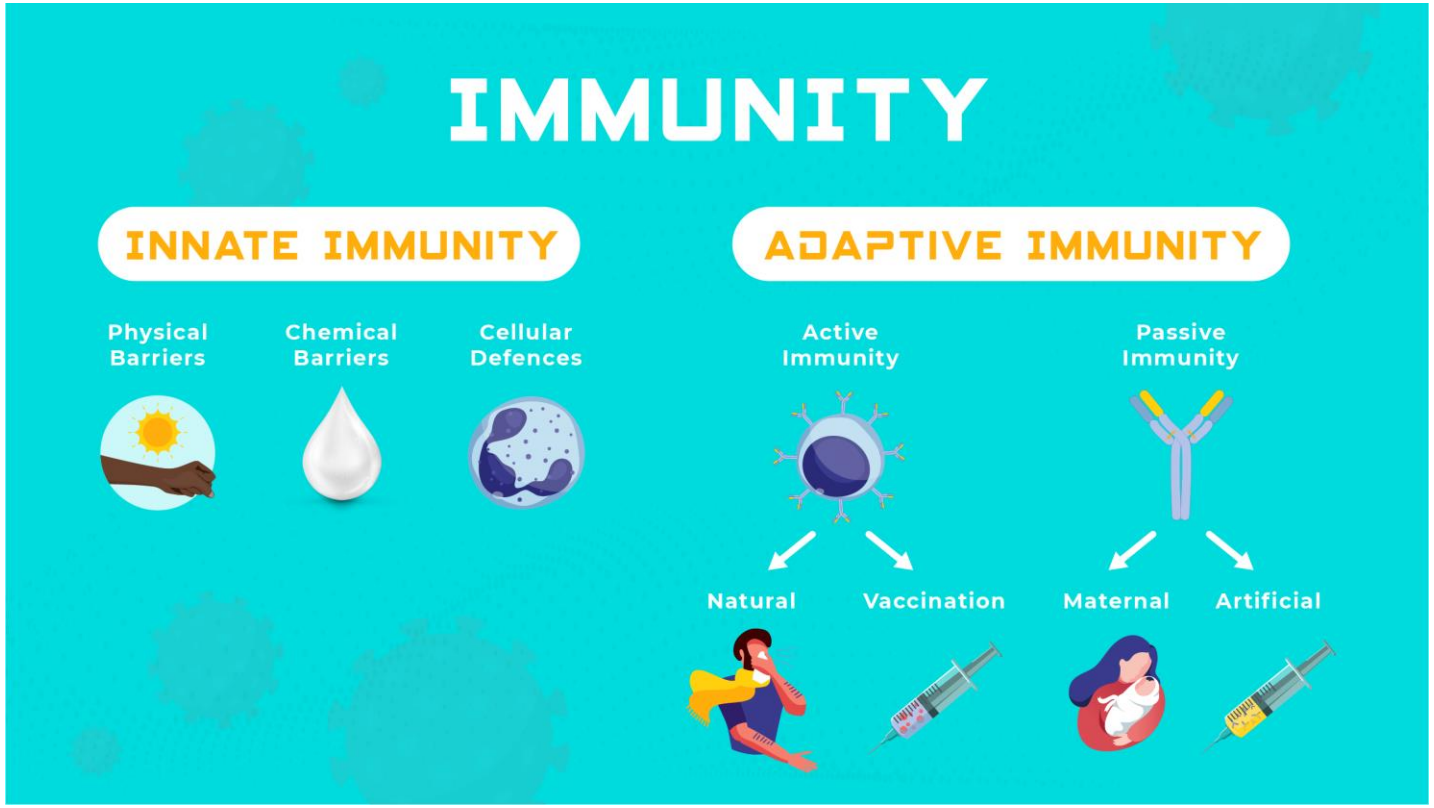
Evolutionary Medicine

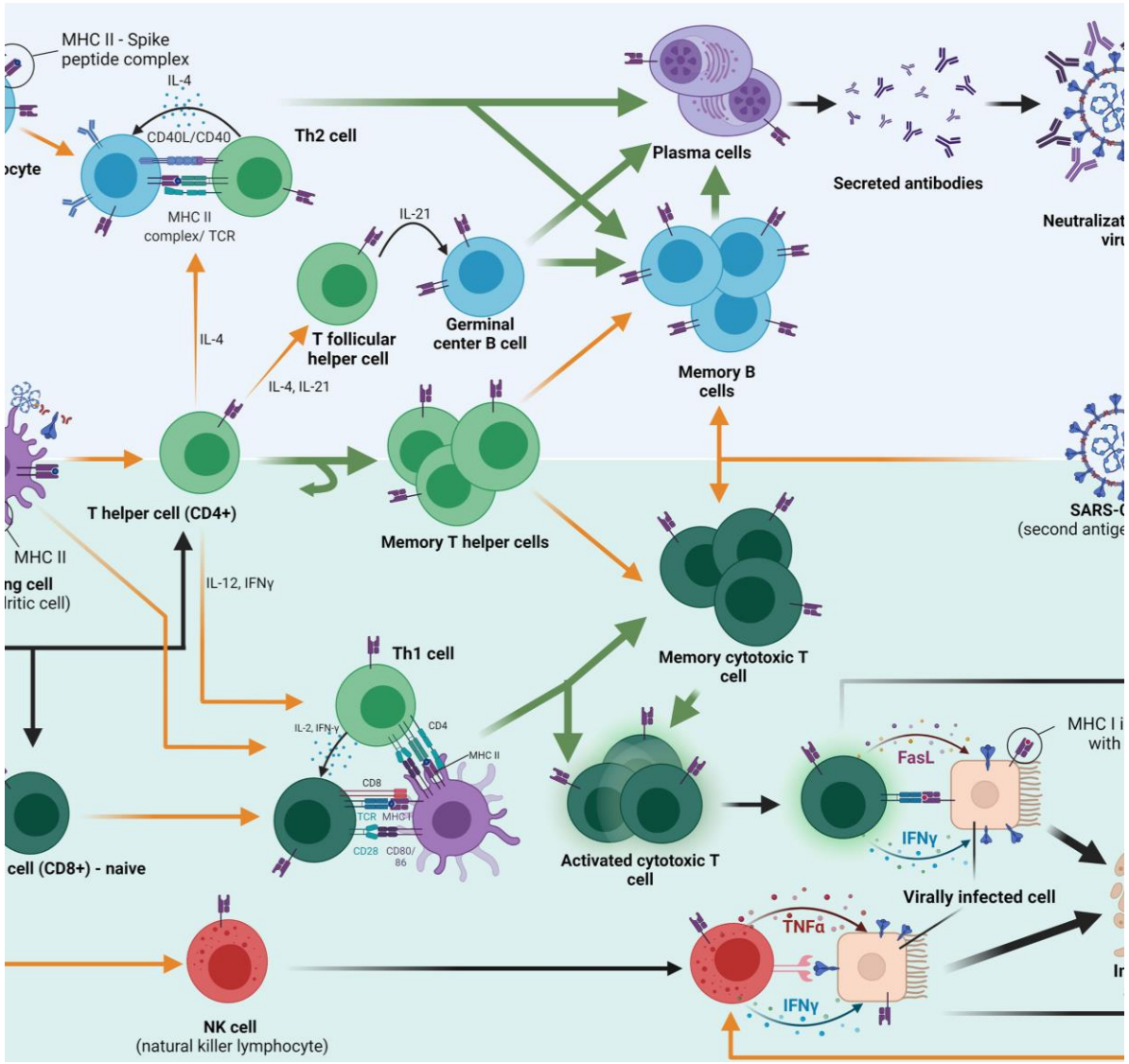
Miriam Nývltová Fišáková

Department of Physiology

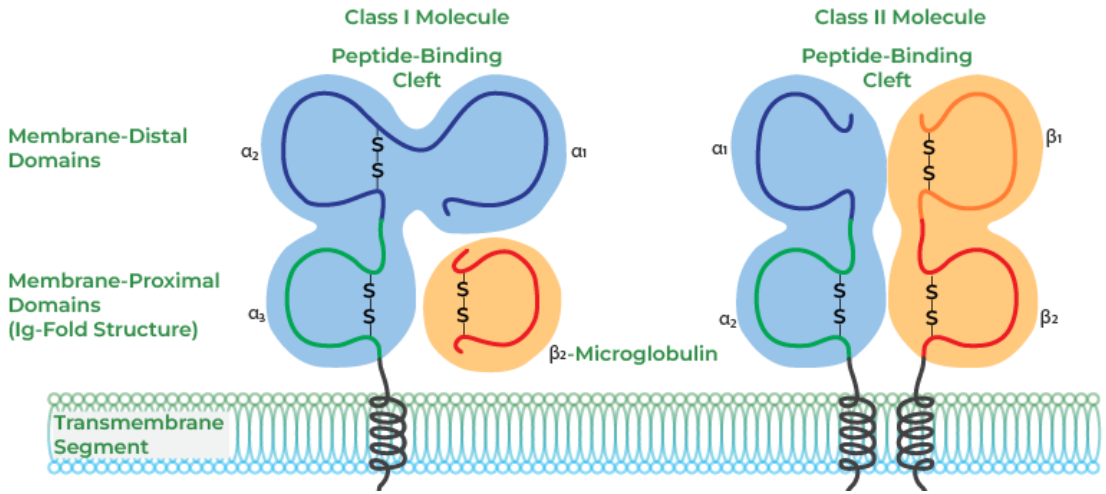


Adaptive Immunity



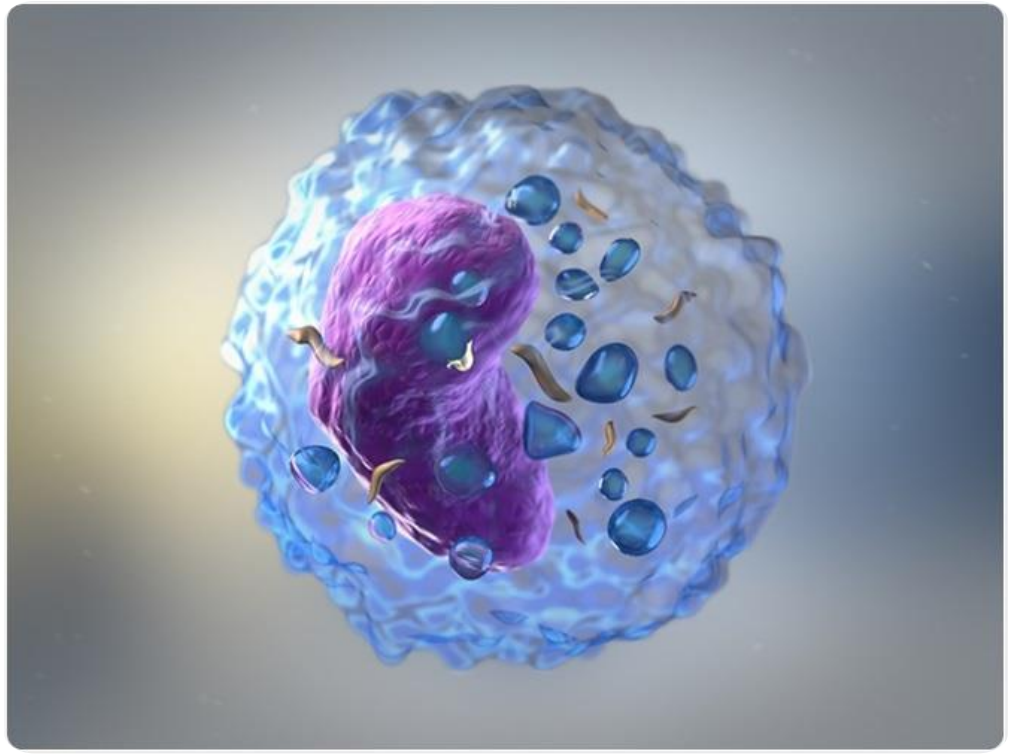


- The adaptive immune system is the key weapon in the vertebrate war against microbial infection. The adaptive immune system differs from the innate immune system in two general ways. First, it is able to respond to any antigen that is perceived by the individual as non-self rather than to a non-specific pattern signaling the presence of a pathogen. Second, although the initial response of the adaptive immune system to a new challenge is relatively weak, it has a “memory” that ensures that subsequent encounters with the same antigen cause faster and stronger responses than did the first challenge. It is this second feature that gives the adaptive immune system its name. The adaptive immune system provides vertebrates with a powerful defense against microbial infection and immune surveillance against aberrant clones of its own cells, but its exquisite specificity has two clinically relevant consequences: susceptibility to autoimmune and atopic disease, and rejection of transplanted tissue. The adaptive immune system has evolved as a highly complex and multilayered mechanism. Briefly, however, it comprises two arms: cell-mediated immunity and humoral immunity. As its name implies, cell-mediated immunity involves direct counter-attack by the effector cells of the immune system, mostly T (for “thymus”) cells and natural killer cells. Cell-mediated immunity has its major role in defense against intracellular pathogens such as viruses and in immune surveillance against host tumor cells. Humoral or antibody-mediated immunity involves the action of circulating immunoglobulins, made by B (for “bone marrow”) cells, which bind to their target antigens on pathogens and inactivate them directly or mark them for destruction by other components of the immune system. Humoral immunity generally functions against extracellular pathogens such as bacteria.

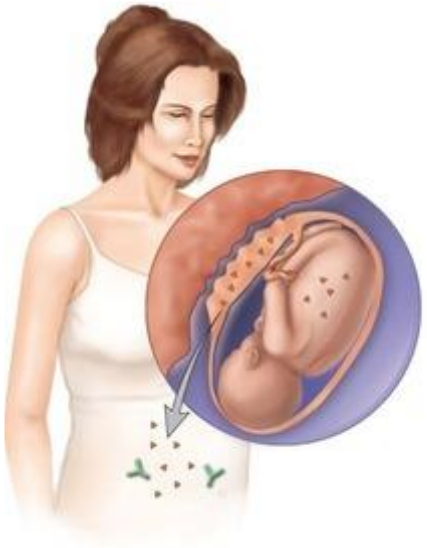


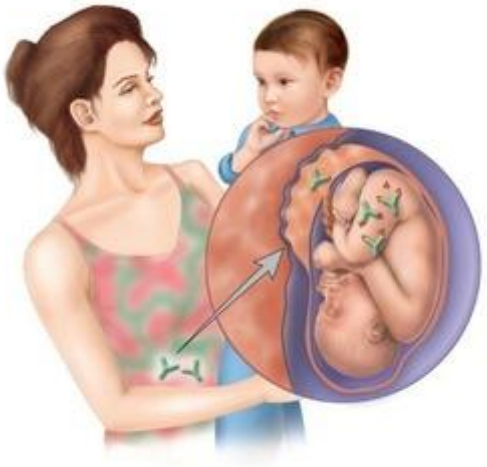
- As well as acting as effector cells, some subtypes of T cell also initiate and promote (T helper or Th cells) and regulate (Treg cells) immune reactions. The ability to discriminate between self and non- self is critical to the function of the adaptive immune system, and defects in this process of *immunological tolerance* underlie autoimmune diseases (see Romagnani 2006). The fundamental basis of recognition of self or non- self macromolecules by the adaptive immune system is the display of fragments of those molecules on the cell surface bound to proteins of the *major histocompatibility complex* (MHC). There are two classes of MHC molecule: nearly all cells of the body express class I molecules, which display fragments of the normal proteins of the cell, allowing the immune system to detect whether the cell's protein synthetic machinery has been subverted by viral infection or tumorigenesis. Conversely, class II molecules are only expressed by specialized antigen- presenting cells, which phagocytose and degrade micro- organisms and display protein fragments from foreign antigens. Recognition by a Th cell of a displayed peptide as non- self triggers an immune response: in general, recognition of non- self in the context of MHC class I causes a cell- mediated response that kills the subverted cell, whereas recognition in the context of MHC class II causes both a cell- mediated and an antibody- mediated response.

- The multi- subunit MHC molecules are coded for by genes on chromosome 6, each of which is extraordinarily diverse (up to several hundred alleles), much of which is expressed at the peptide- binding site of the molecule. This combination of allelic variation and subunit pairing means that the resulting MHC complexes are capable of binding a huge variety of different peptides. Such genetic diversity is best explained by balancing selection, driven by the different ability of particular MHC alleles to protect against particular pathogens. Even in a small population there will be many different combinations of MHC alleles that protect against the multiple pathogens in the environment and thwart the evolution of new pathogen epitopes

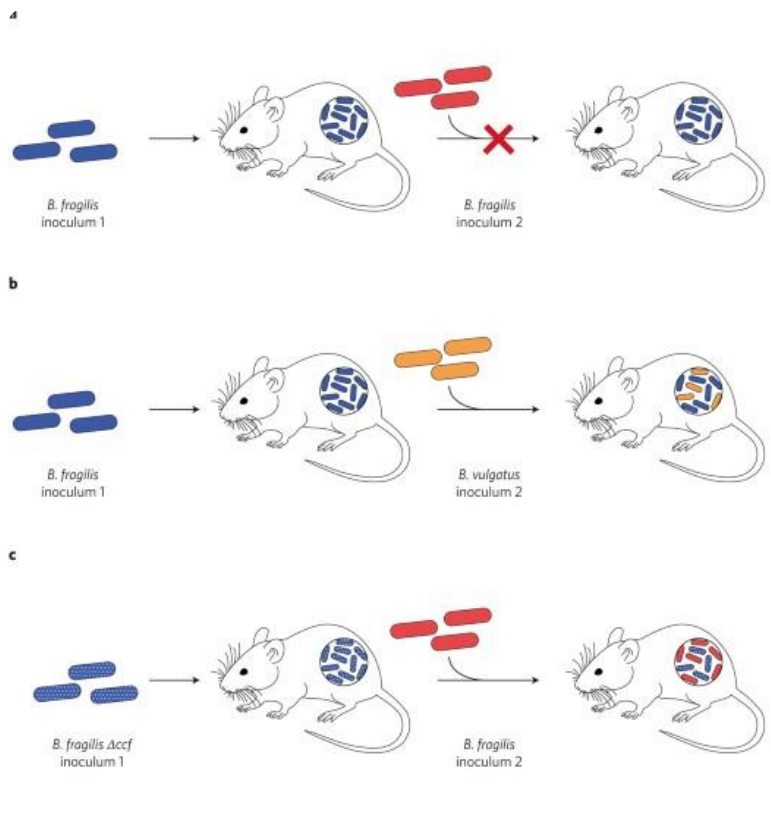


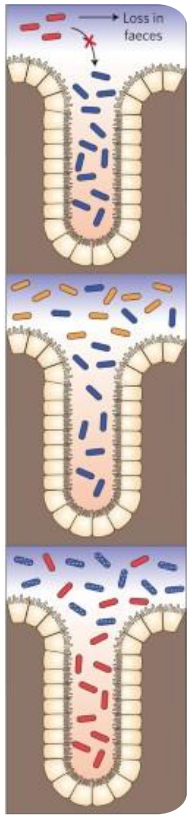
- In humans, the MHC system is also known as the *human leukocyte antigen* (HLA) system. The HLA system is the predominant determinant of tissue compatibility after transplantation, and the wide diversity of HLA alleles makes tissue rejection likely unless careful matching is performed. Another situation where tolerance between HLA- incompatible individuals is critical is at the maternal– fetal interface. The fetal trophoblast cells that contact maternal tissues during pregnancy do not express classical MHC class I or II molecules on their surface, and instead express a set of minor HLA genes with restricted allelic diversity and immunosuppressive properties towards maternal cells. Two facets of the adaptive immune system use selective processes at a cellular level to ensure immunological self- tolerance and strong antibody affinity. First, recognition of self antigens is critical for immunological tolerance and the avoidance of autoimmune disease. The “education” of the immune system to distinguish self from non- self is a selective process that takes place in the thymus during early life. Immature T cells, each of which carries a T- cell receptor on its surface that binds to just one of the estimated 10 million different types of epitope recognized by the human immune system, are normally programmed to undergo apoptosis and die shortly after they are formed. In the thymus, they are exposed to the full range of self antigens, and those that fail to react are “rescued” from the apoptotic process and released into the blood. This “fail- safe” mechanism of negative selection ensures that the organism develops with a set of T cells that only respond to foreign antigens. The second process is the clonal expansion of B cells. During their development, each B cell is programmed to produce a single one from the wide range of possible immunoglobulins, and this is displayed on its surface as part of the B- cell receptor. Once released into the circulation, if it encounters that epitope it is stimulated to proliferate, leading to the production of millions of identical B cells that secrete immunoglobulins with the correct specificity. In the course of this clonal expansion, further fine- tuning of immunoglobulin specificity occurs by a process of somatic hypermutation, which promotes erroneous DNA repair and increases the mutation rate in the variable region of the immunoglobulin gene by about a million- fold. The resulting variations in immunoglobulin amino acid sequence are random, but only those cells with the highest affinity for antigen are selected to survive and proliferate. The end results of this Darwinian process of variation and selection, which can be seen as a form of somatic evolution, are two- fold: plasma cells that secrete large amounts of immunoglobulin of high specificity, and the development of memory B cells containing the relevant DNA sequence that persist for years in lymph nodes and are activated rapidly on new exposure to the antigen. It is the existence of this immunological memory that forms the basis of vaccination





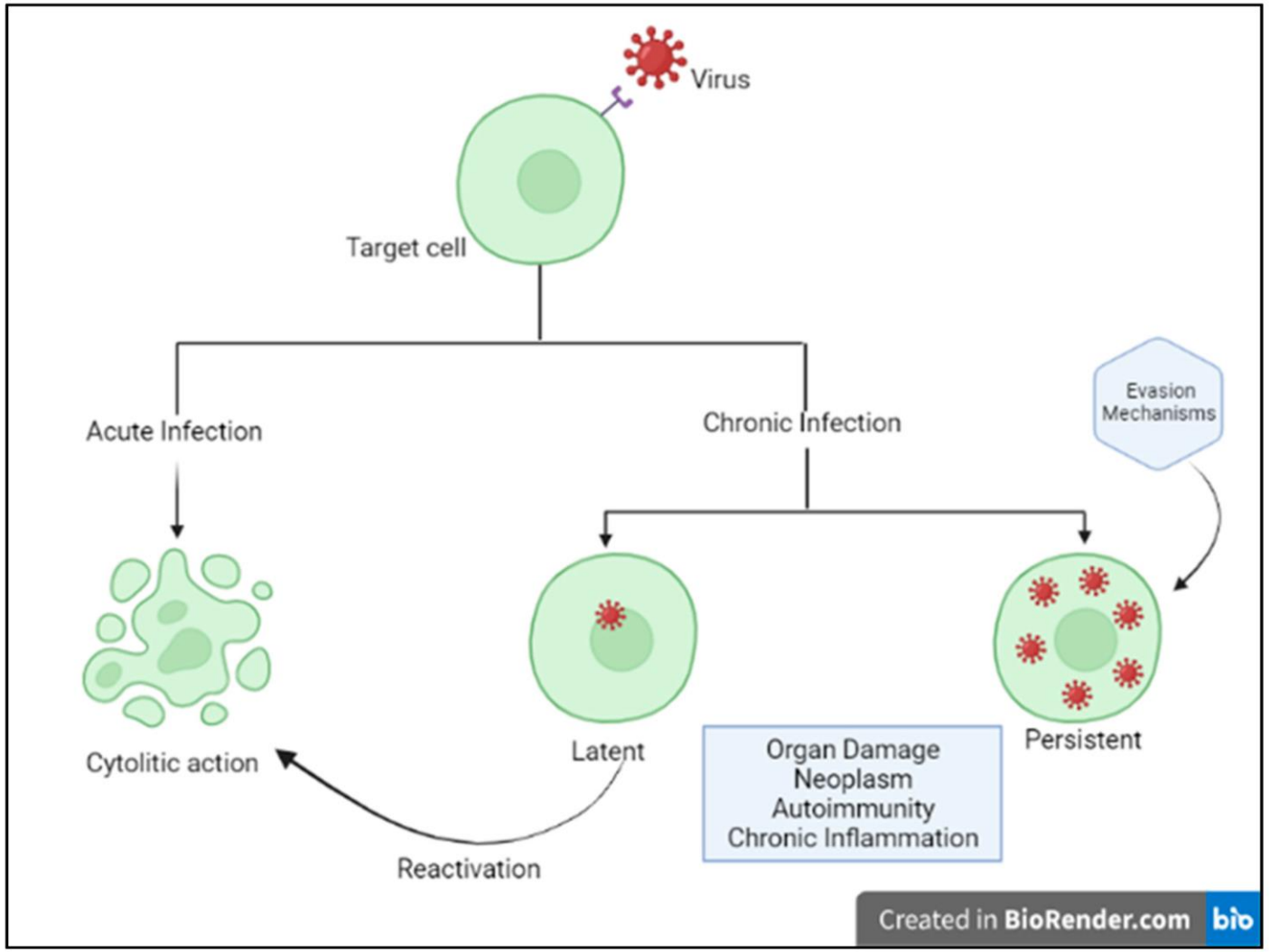
- The adaptive immune system has evolved in the presence of the associated commensal microflora which, because of its extent and diversity, must represent a major antigenic challenge to the host. How is it that the adaptive immune system does not respond to this challenge, and how does it filter out signals of pathogen intrusion from the noise of the millions of commensally derived antigens? To do so, the commensal antigenic burden must either be minimized or tolerated. The first is achieved by limiting exposure of host tissue to commensals using the barrier defenses, while the second involves development of tolerance to the commensal microflora so that the host immune system sees it as “self” rather than “nonself” (see Lee and Mazmanian 2010). Development of this tolerance occurs early in life, facilitated by the immature immune system of the neonate which is oriented towards immunoregulation— discovering “self” and establishing tolerance towards it— rather than to mounting effective immune and inflammatory responses. This early life deficit in protective immunity underlines the importance for neonatal health of the passive immunity transferred in breast milk. The importance of early exposure to the gut microflora for development of the adaptive immune system is shown by the impaired phenotype of animals reared under sterile (“germ- free”) conditions. Such animals show deficiencies in the development of their intestinal mucosal barrier and immune system tissues, both in the gut and systemically. They also have defects in immunoregulation, as indicated by the properties of their Th and Treg cell populations, and are more susceptible to pathogen infection.

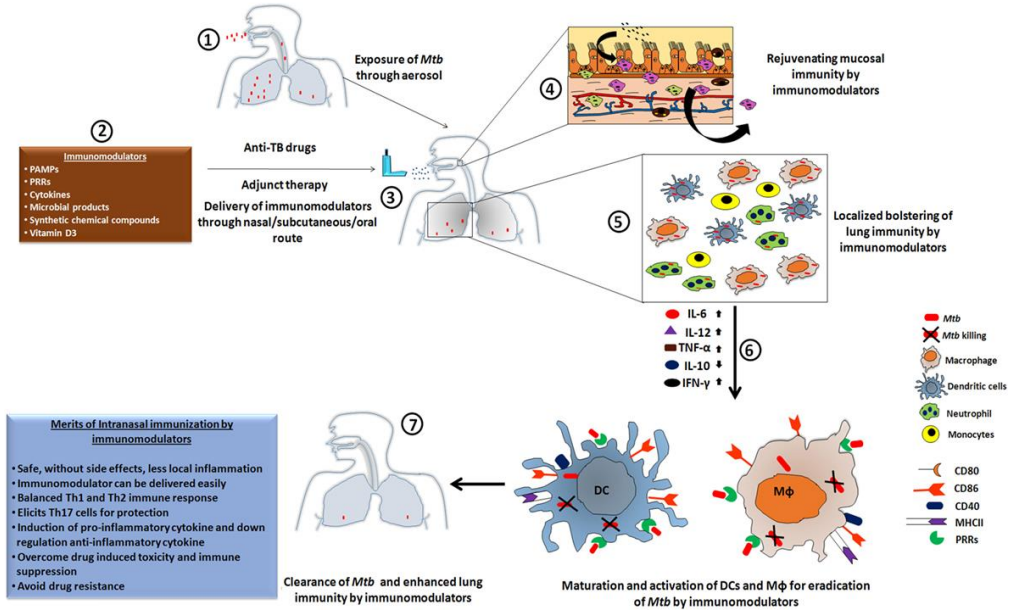




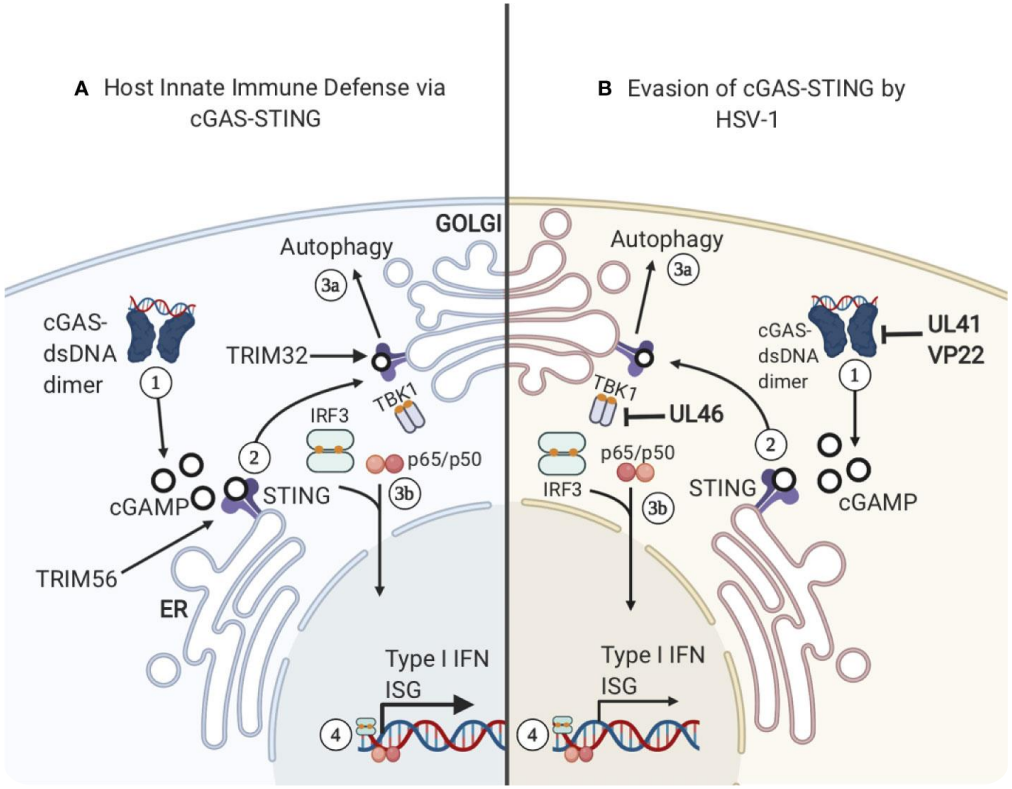
- Experimentally, replacement of the mikroflóra with a single species of gut micro- organism, *Bacteroides fragilis*, can ameliorate these immunoregulatory defects. This effect can be mimicked by a single secretory product (polysaccharide A or PSA) from the bacterium, suggesting that factors secreted from the gut microflora can direct the maturation of the host immune system (see Ivanov and Honda 2012).

How Pathogens Evade Host Defenses



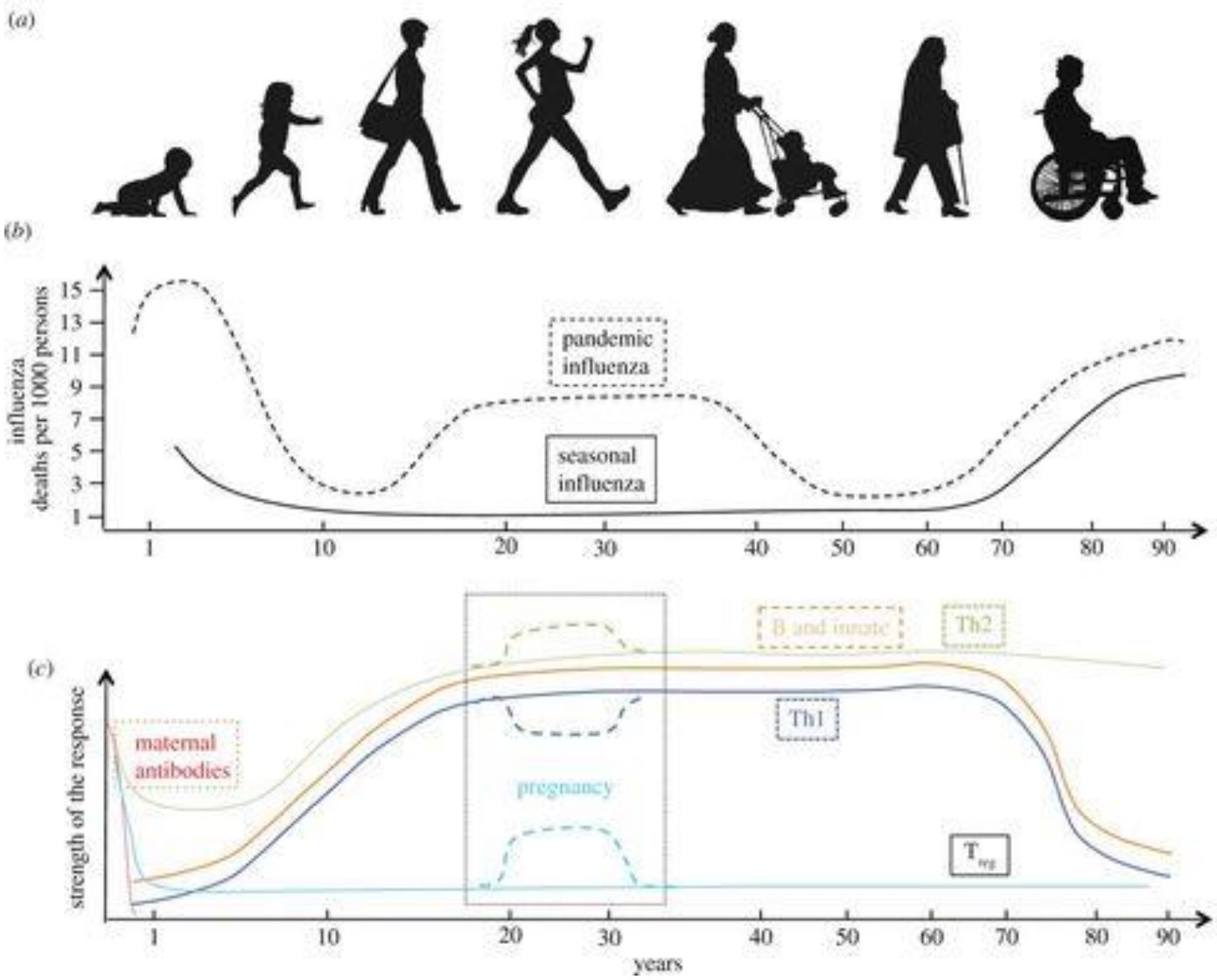


- Pathogens have evolved mechanisms to evade and neutralize the defenses mounted by the innate and adaptive immune systems, buying themselves enough time to survive, proliferate, and be transmitted to the next host. Host barriers against infection can be overcome by the secretion of toxins that inhibit ciliary action or the production of a protective biofilm. Many bacteria shield themselves from the PAMP recognition system by secreting masking molecules on their cell surface; the intracellular pathogen *Mycobacterium tuberculosis* uses lipids both to mask its cell surface PAMPs and to attract benign (to it) macrophages in the lower respiratory tract that engulf it and transport it into lung tissues (see Cambier et al. 2014). The trick of hiding inside host cells is used by many pathogens, from the retroviruses such as HIV that hide within the genome to the malarial parasites such as *Plasmodium* that live within red blood cells. Other pathogens hide from the adaptive immune system by constantly changing their cell surface antigens, so that the host's immune response always lags behind the pathogen's antigenic appearance. One example concerns the contingency loci found in several genera of bacterial pathogens. These loci, usually associated with gene products that interact in some way with the host, contain short sequence repeats that are liable to mis-pair, resulting in frameshift mutations in the resulting cell surface proteins and therefore high phenotypic diversity that enables the pathogen to evade host responses. A somewhat similar process is used by the trypanosomes that cause sleeping sickness to generate the variant surface glycoproteins (VSGs) that act as decoys for the host immune response, although here the variants arise from an archive of pre-existing *VSG* genes rather than from *de novo* mutations. A final example is provided by the extreme diversity in the envelope proteins and drug-target molecules of HIV, originating from mutations promoted by the low fidelity of the virus's reverse transcriptase.



- Some evasion mechanisms directly target the adaptive immune system. Viruses such as herpesvirus,which cause persistent lifelong infections, inhibit the host antigen presentation machinery that would normally alert the immune system to their presence within cells (see Zuo and Rowe 2012). Other pathogens, including trypanosomes, hepatitis C virus, and HIV, can subvert B-cell-mediated immune responses (see Nothelfer et al. 2015). Some pathogens interfere with the cytokine signaling required for an effective immune response; for example, interferon is a cytokine secreted in response to viral infection, and many viruses, including papillomavirus and measles virus, are able to inhibit the production or action of interferon (see Devasthanam 2014).

Over-reaction of Host Defenses Can Cause Morbidity and Mortality



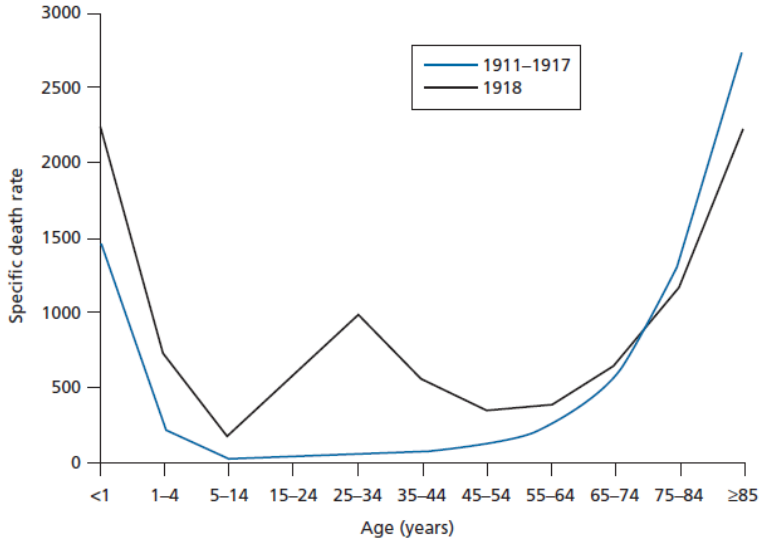
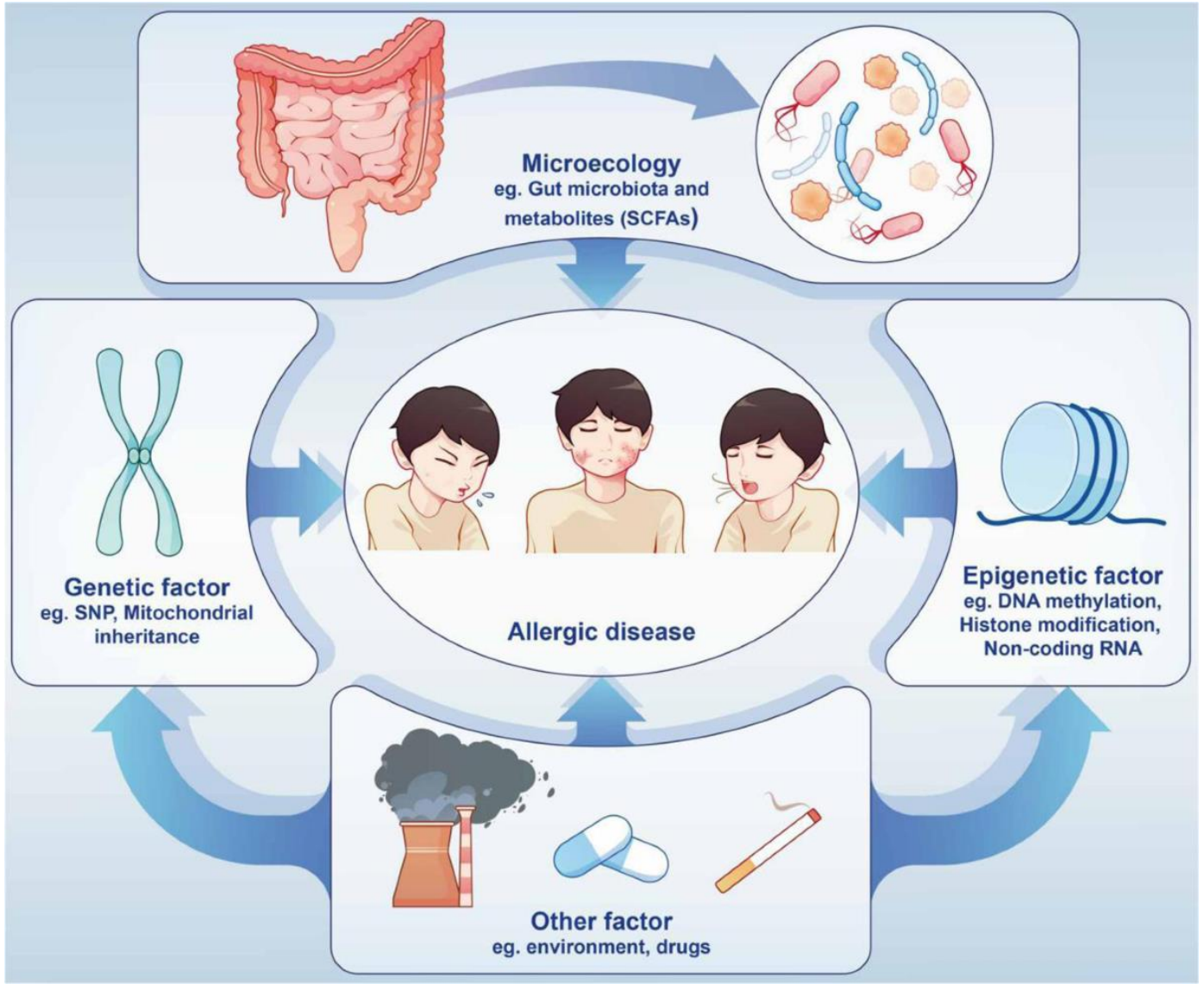


Figure 10.1 Age-specific mortality rates in the influenza epidemics of 1911–17 and the so-called Spanish flu epidemic of 1918. The high virulence of the 1918 virus may have resulted from an aberrant host response. From Taubenberger and Morens (2006), with permission.

- The interplay between host defenses and pathogen biology represents the sum of two evolved trade-offs. The pathogen must balance how much it damages its host by its virulence and evasion mechanisms against the need for the host to be able to transmit the infection, and the host must calibrate its defensive response to the severity of the threat while avoiding collateral damage to its own tissues. Nevertheless, exaggerated host responses can contribute to morbidity and mortality. The case fatality rate in the 1918 Spanish influenza pandemic was particularly high because the virus elicited an aberrant host immune response that caused extensive tissue damage in the lungs, which may explain its unusual pattern of age-specific mortality (see Morens and Fauci 2007).

- Another example of an exaggerated immune response is that to staphylococcal enterotoxins. These secretion products of *Staphylococcus aureus* cause mild gastrointestinal symptoms, but when introduced systemically act as “superantigens,” causing widespread activation of the immune system and massive release of cytokines (a “cytokine storm”). The resulting toxic shock syndrome involves vascular leakage, hypotension, and disseminated intravascular coagulation, leading to multiorgan failure (see Krakauer 2013). Such a dramatic outcome can be envisaged as an unintentional consequence of the evolved virulence of the bacterium, which exists as a human commensal and opportunistic pathogen that has little evolutionary interest in the rapid death of its host. To the patient, host defenses like fever and cough can appear as debilitating over-reactions to relatively mild infections, such as with the common cold virus. In this situation, symptomatic treatment with antipyretics and antitussives makes the patient feel better and is generally unlikely to have effects on the eventual outcome of the infection. Suppressing these evolved defensive responses may not always be a good idea. For example, there is some evidence that suppressing fever in critically ill patients increases mortality (see Schulman et al. 2005).



Autoimmune and Allergic Disorders

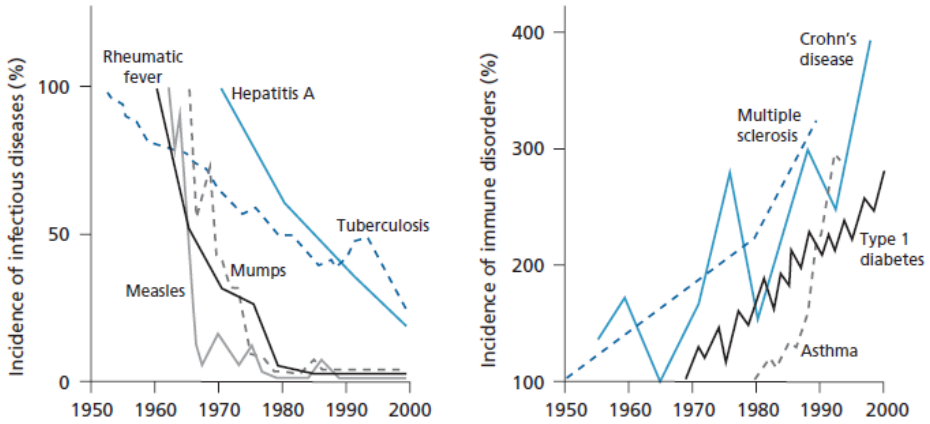
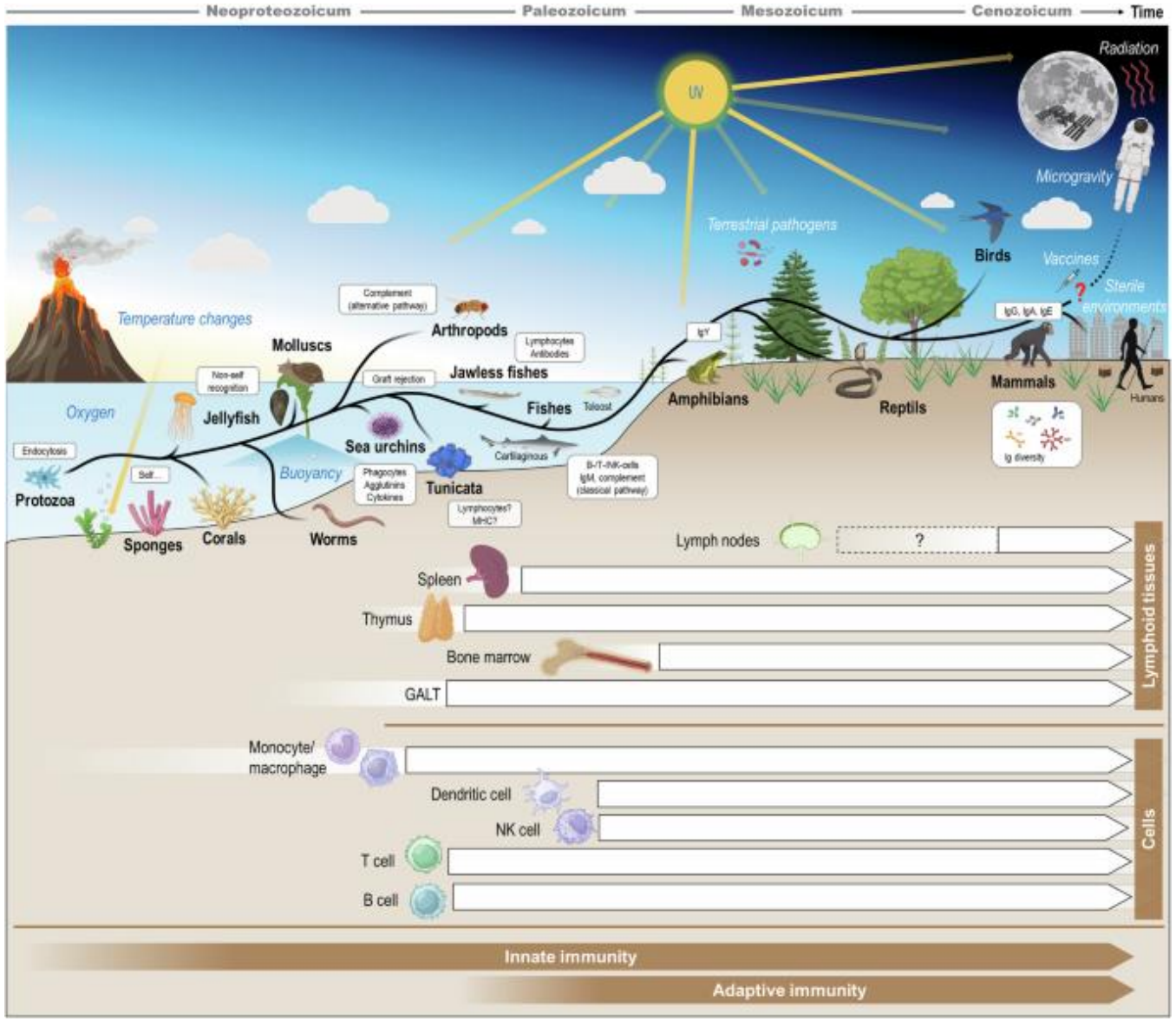


Figure 10.2 As the incidence of infectious disease has fallen in high-income countries, the incidence of immune-related disorders has increased. From Bach (2002), with permission.

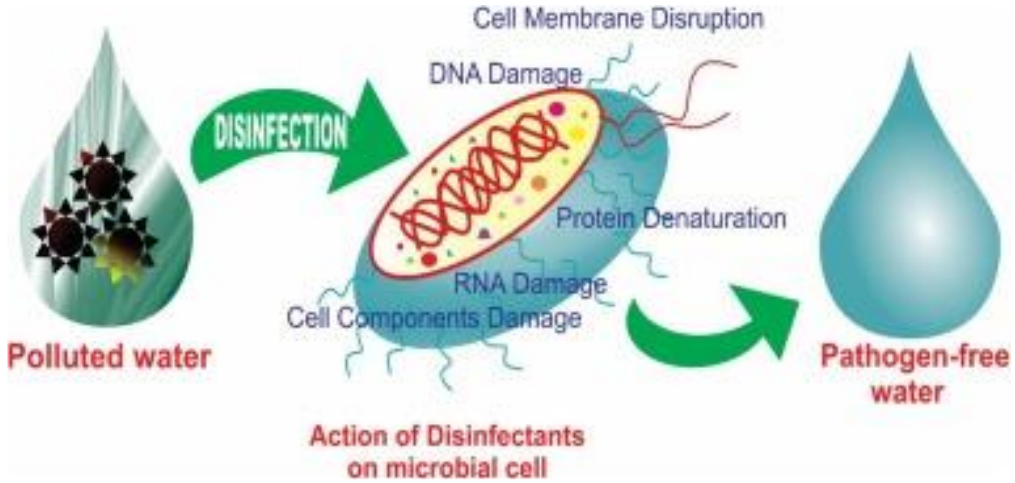
- The autoimmune, inflammatory, and allergic disorders have their proximal cause in the dysregulation of the immune system. Diseases in which the immune system attacks the body's own cells, as if mistaking them for non-self pathogens, are termed autoimmune diseases. Examples include type 1 diabetes and multiple sclerosis. Other conditions such as Crohn's disease and ulcerative colitis result from inappropriate activation of the inflammatory response. Allergies such as allergic rhinitis ("hay fever") are caused by hypersensitivity of the immune system to environmental antigens that are inappropriately perceived as harmful. In this book we have seen repeatedly that environmental change producing evolutionary novelty can pose a threat to human health. We can contrast the fall in morbidity from infectious diseases seen in high-income countries over the past 100 years or so with the dramatic increase in the prevalence of autoimmune, inflammatory, and allergic disorders. What could explain this apparent negative association? There are both genetic and environmental determinants of susceptibility to disorders caused by immune dysregulation. The genetic determinants are often associated with particular alleles of the HLA system. For example, HLA-DR2 is associated with systemic lupus erythematosus (more common in females) and ankylosing spondylitis is associated with HLA-B27 (more common in males). Ankylosing spondylitis develops gradually during adolescence and young adulthood, causing chronic inflammation and structural changes in joints, especially the spine. The rapid change in the prevalence of immune-related disorders makes any genetic explanation unlikely. For example, not all HLA-B27 males develop ankylosing spondylitis, so there must be some other environmental trigger. There is evidence to suggest that the trigger in some cases is a response to *Klebsiella* commensals which inhabit the gut, perhaps itself triggered by an acute infection, since there are cross-reacting epitopes between *Klebsiella* and human cell-surface antigens (Husby et al. 1989).

There are other subtleties in the environmental associations of immunoregulatory disorders that may provide clues to the underlying mechanisms. For example, there is a lower prevalence of asthma and atopic disorders in children in rural compared with urban communities. Inflammatory bowel disease is common in highly sanitized, industrialized areas of the world, but uncommon in rural areas where living quarters are crowded and unhygienic. Breastfeeding in infants has a protective effect in reducing the later risk of asthma, and it is known that breast- and formula-fed infants are exposed to different types of bacterial flora. We described how the vertebrate adaptive immune system has coevolved with both commensal and potentially pathogenic micro-organisms, and that appropriate exposure to microbes early in life is essential for establishing immunoregulatory pathways. For instance, germ-free mice experience abnormal development of their immune system, which can be corrected by re-introduction of intestinal commensal bacteria. A unifying mechanism to explain all these observations, termed the *hygiene hypothesis*, proposes that lack of early exposure to the full range of microbes leads to inappropriate activation of immune responses which are then manifest as allergic or autoimmune disease. In other words, such deficient exposure has changed the set-point of the trade-off between efficient pathogen defense and susceptibility to autoimmunity (see Bergstrom and Antia 2006). Although early versions of the hygiene hypothesis tended to emphasize common childhood infections as the contributing exposures, many such infections have only become prevalent in recent human history because of the crowding caused by the post-Neolithic move to large settlements. A more nuanced version of the hypothesis proposes that the contributing organisms are the “old friends” of commensals and parasites that were present during the evolution of the human adaptive immune system (see Rook 2012). Other candidate organisms are helminth worms. Intestinal infestation with helminths was nearly universal in human evolutionary history, but is now rare in high-income countries. Areas with high infestations of helminths have low levels of autoimmune disease, although as ever there is a trade-off—because of parasite-associated immunosuppression, vaccine response rates in these areas are lower than in unaffected areas (see LaBeaud et al. 2009). Although infestation with helminths can cause IgE-mediated responses, the organisms are difficult to clear and the host tends to develop tolerance rather than mounting a futile and self-damaging immune reaction. Experimental studies show that helminth infestation is protective against a number of immune-mediated diseases. Observational studies in patients with one autoimmune disease, multiple sclerosis, suggest that disease progression is inversely correlated with parasite load, such that antihelminthic therapy leads to worsening of the autoimmune disorder (see Correale and Farez 2011). Clinical trials involving deliberate helminth infestation of patients who have inflammatory bowel disease (the pig whipworm, *Trichuris suis*, was used since it is not pathogenic in humans) have indicated a reduction in disease activity in patients with ulcerative colitis and Crohn’s disease (see Heylen et al. 2014). If such trials are successful and a clear link is established between parasite-driven immunoregulation and immune disorders, then new possibilities for treatment will become available. Conversely, efforts to clear helminth infections from low-income countries may need to take account of a possible rise in the level of allergies and inflammation (see Wammes et al. 2014).


Neoproteozoicum
Paleozoicum
Mesozoicum
Cenozoicum
Time
Radiation
UV
Microgravity
Terrestrial pathogens
Birds
Vaccines
Sterile environments
IgG, IgA, IgE
IgY
Temperature changes
Molluscs
Arthropods
Complement (alternative pathway)
Lymphocytes Antibodies
Jawless fishes
Graft rejection
Fishes
Teleost
Amphibians
Reptils
Mammals
Humans
Ig diversity
Oxygen
Non-self recognition
Jellyfish
Sea urchins
Cartilaginous
B-/T-/NK-cells IgM, complement (classical pathway)
Endocytosis
Self...
Buoyancy
Phagocytes Agglutinins Cytokines
Tunicata
Lymphocytes? MHC?
Protozoa
Sponges
Corals
Worms
Lymph nodes
?
Spleen
Thymus
Bone marrow
GALT
Lymphoid tissues
Monocyte/ macrophage
Dendritic cell
NK cell
T cell
B cell
Cells
Innate immunity
Adaptive immunity

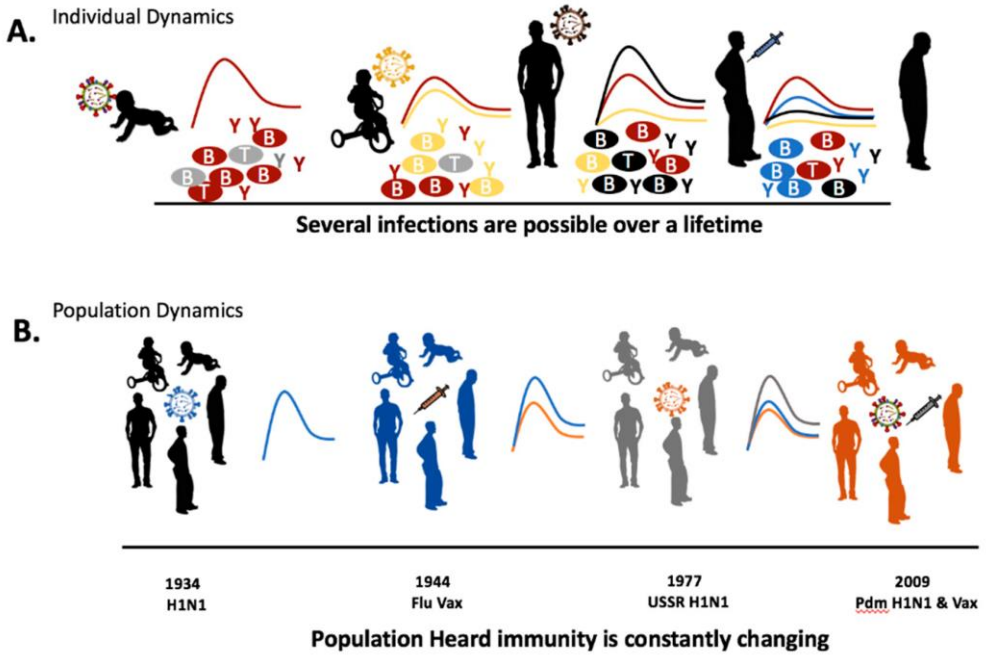
Public Health Measures

PHSM Knowledge Hub: Evidence and tools for assessing the impact of Public Health and Social Measures during health emergencies.

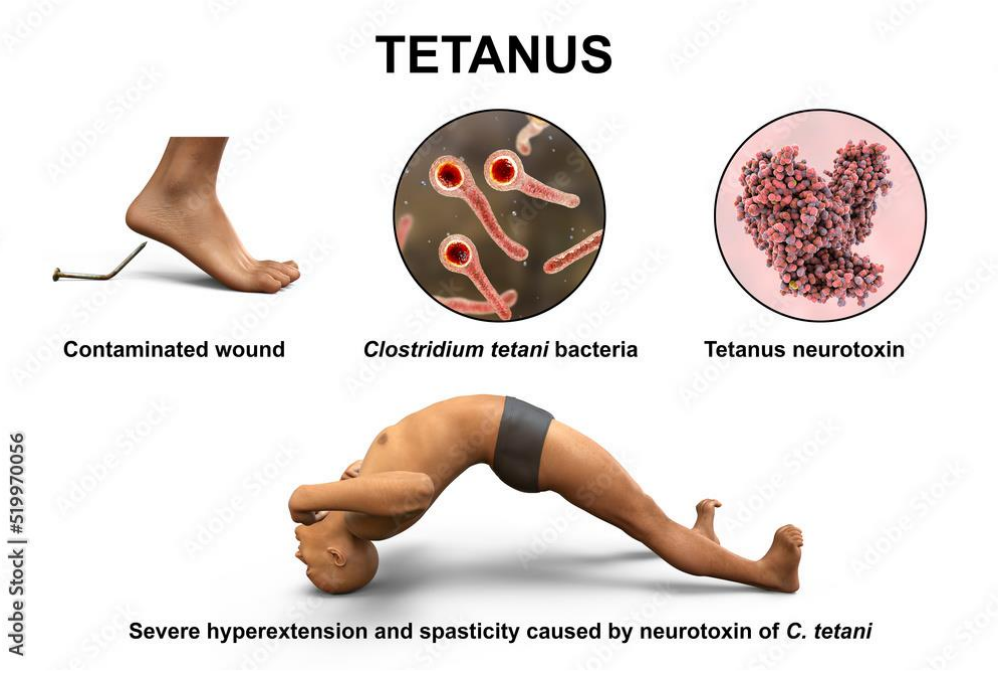


- In addition to our immune systems, the evolved extended human phenotype now includes technological defenses against microbial infection. The three arms of these defenses are public health innovations, vaccination, and antibiotics. Improved nutrition and sanitation underpin much of the fall in morbidity and mortality from infectious disease over the past 150 years. The interaction between poor nutrition and infection is particularly important in low- and middle-income countries, and especially in children. An early effect of malnutrition is the suppression of immune function. For example, in a population of subsistence farmers in The Gambia with highly seasonal food availability, people born in the “hungry season” showed ten-fold higher infection-related mortality as young adults and decreased life expectancy, suggesting that immune function may be compromised by events early in life. In this population, thymus development was sensitive to early life nutrition, with smaller thymuses observed in those born in the hungry season. Furthermore, size at birth was positively correlated with antibody responses to vaccination (see Moore et al. 2006). Such observations may represent the results of trade-offs in which the body prioritizes resource use and favors immediate survival over investment in long-term defense mechanisms. The importance of uncontaminated water supplies and efficient removal of sewage in limiting the oro-fecal transmission of disease have been known since Dr. John Snow removed the handle of a public pump in London in 1854 to curb an outbreak of cholera. Because waterborne diseases such as cholera and typhoid are easily transmitted to multiple new hosts, and retain their virulence because transmission is not dependent on continued host viability, improvement of sanitation is one of the most effective measures to combat infectious disease.

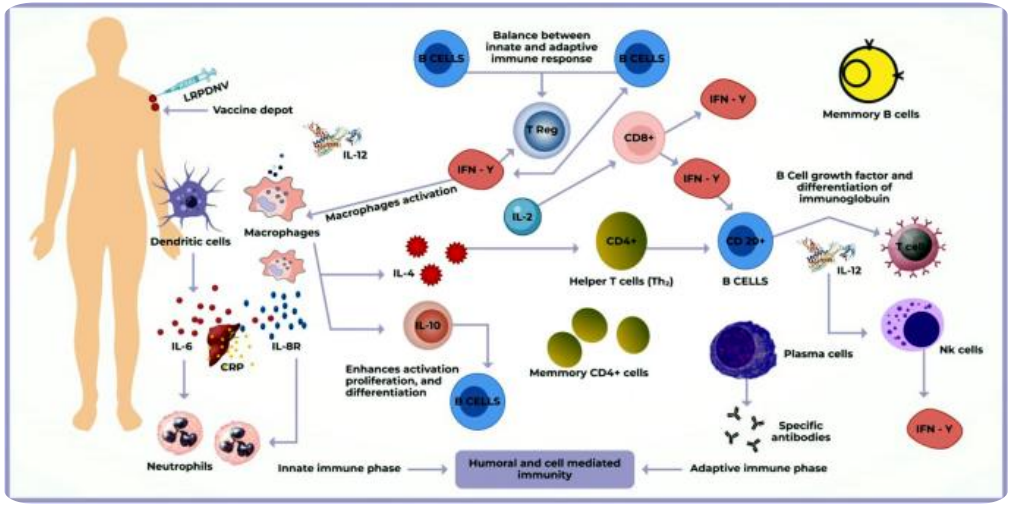
Vaccination



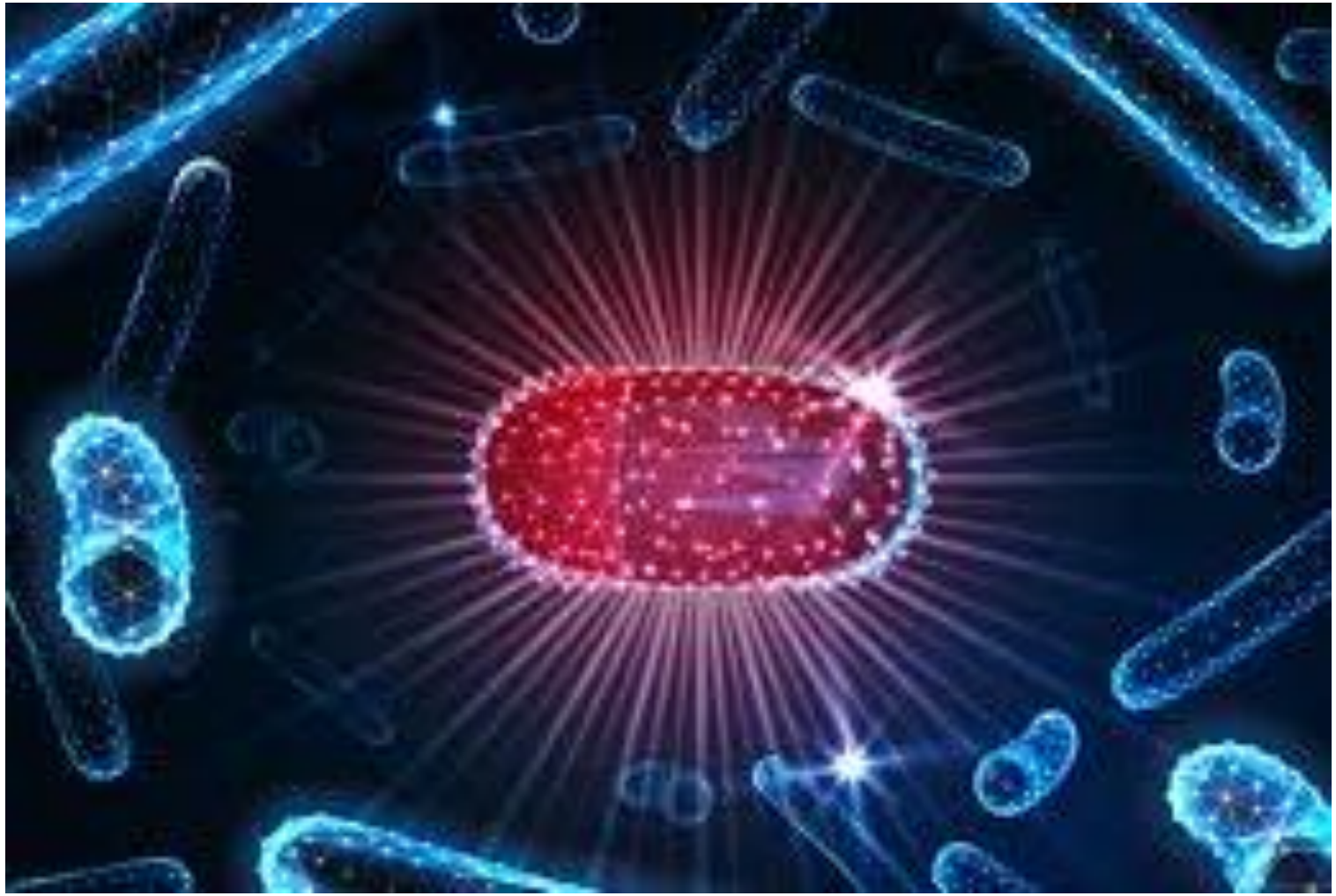
- Vaccination takes advantage of the ability of the adaptive immune system to retain a memory of previous antigen challenges, so that future exposure to the antigen results in prompt and vigorous protective responses (immunization). Vaccination has eradicated one human disease (smallpox), is close to eradicating another (poliomyelitis), and in high-income countries controls several acute childhood infections, such as rubella and measles. It is a characteristic of these diseases that natural infection with these agents, if not fatal, generally provides lifelong protection against a second infection since the causative viruses show little or no antigenic drift (mutation of the sites to which protective antibodies bind) in the wild; vaccine-induced immunity against these pathogens similarly results in lifelong protection. However, recent reports of a vaccine-resistant strain of poliovirus should be a reminder that antigenic stability should not be taken for granted see (Drexler et al. 2014). In contrast, pathogens that are able to evolve their antigenic properties in the wild can cause repeated infections. Influenza virus shows both antigenic drift and antigenic shift (where virus subtypes combine to produce a new strain), which means that the immune response to one strain is ineffective against a new strain. For such diseases, public health strategies require continual surveillance of circulating viruses and the regular administration of new vaccines formulated against their predicted antigen profile.



- Where a pathogen is pathogenic by way of a toxin, immunization against the toxin (which is likely to be less variable) may address the pathogenic process while leaving the host immune system to eradicate the actual infection. This is the basis of protection against tetanus. There are also several examples of existing human and veterinary vaccines where evolution of the targeted organism in the host has been demonstrated in response to the selection pressure of the vaccine, and in the case of one veterinary disease (Marek's disease, a virus- induced neoplasm in poultry) this has led to large- scale failure of the vaccine. How might a pathogen respond to a vaccine? First, it might evolve by selection against the epitopes recognized by the vaccine. Such epitope shifting, potentially leading to loss of effectiveness of the vaccine, has been observed for several human viral and bacterial vaccines including those for hepatitis B, pertussis, and pneumococcal disease. For example, a resurgence of whooping cough infections in high- income countries has been linked to strains of *Bordetella pertussis* that have evolved to no longer express pertactin, a virulence factor that is an antigen included in modern acellular vaccines (see Lam et al. 2014). Secondly, the pathogen might evolve to change its virulence, a situation that particularly applies to so-called "imperfect" vaccines that are not sterilizing (i.e., preventing all infection) but are rather partially effective in preventing transmission or reduce the severity of any infection that does occur. Recall from the discussion of virulence that a pathogen will evolve to a particular level of the virulence/ transmission trade- off that optimizes its reproductive success. If vaccination acts to increase the survival of an infected host, giving it more time to transmit the pathogen to the next host, then the set point of the trade- off will move towards increased pathogen virulence (Gandon et al. 2003; Mackinnon et al. 2008). Although vaccinated hosts will not be affected, unprotected hosts who do not benefit from the survival advantage conferred by vaccination will experience more severe disease. At a population level, pathogen evolution of this kind may negate the benefit of a vaccination program by increasing the cost of managing the disease in unprotected individuals. The failure of the Marek's disease vaccine in chickens was caused by vaccine driven increases in viral virulence.

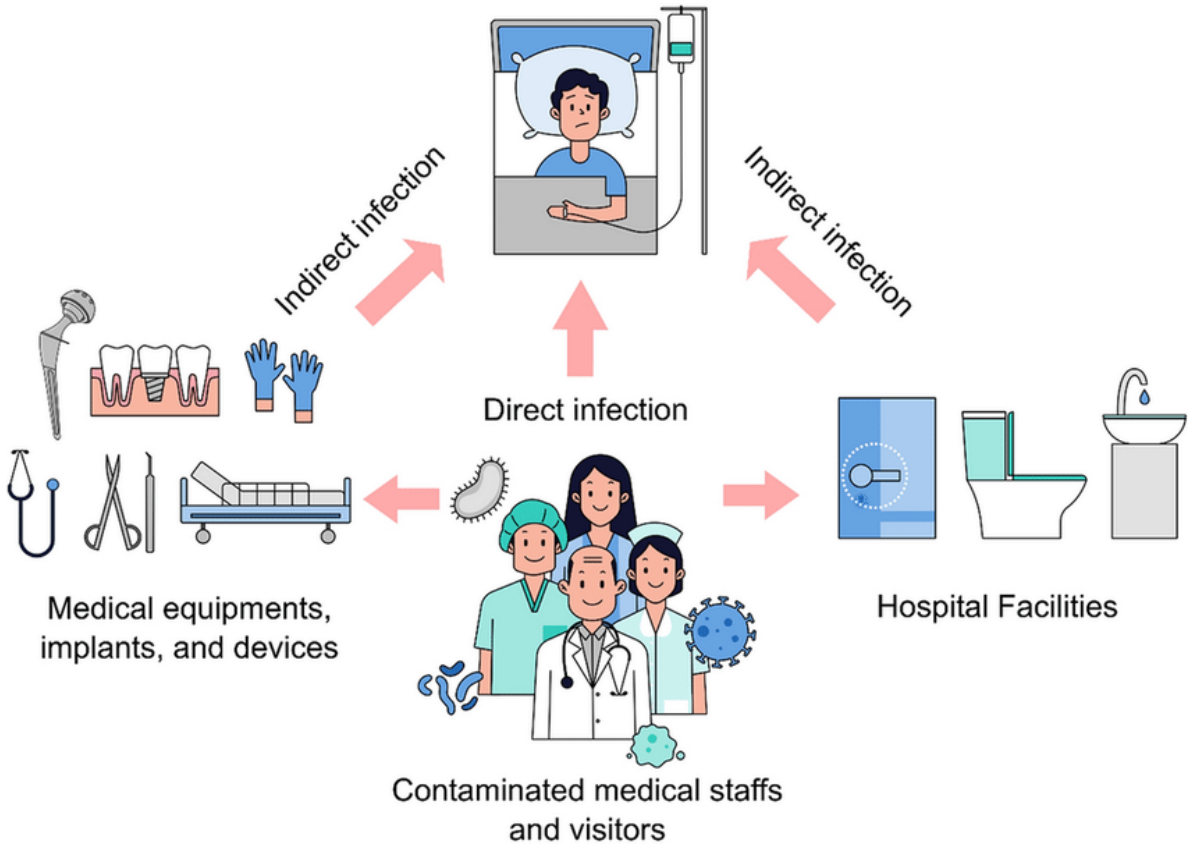


- For some infections, vaccination of an entire population is not necessarily essential to prevent outbreaks of disease. As long as a sufficiently high proportion of the population is vaccinated, any outbreak will be contained because it is likely that the potential hosts exposed to the pathogen will already be immune and unable to develop and transmit the disease. The vaccination coverage necessary to produce this “herd immunity” (or, more elegantly, “social immunity”) varies from disease to disease depending on transmissibility; it is estimated to be 90– 95% for a highly transmissible disease such as measles. One advantage of herd immunity is that members of the population who cannot be vaccinated, for example frail or immunocompromised individuals, also benefit from vaccination programs. On the other hand, “freeloaders” who take advantage of the protection conferred by community vaccination without exposing themselves to the (very small) risk involved in receiving vaccines will also benefit. This, together with misplaced antivaccine attitudes, has led to vaccination coverage in some areas of high- income countries declining below that necessary for herd immunity, allowing outbreaks of previously controlled childhood diseases (see Fine et al. 2011). Current vaccine development is aimed at diseases where host immunity fails to control the pathogen and initial infection becomes chronic; such diseases include HIV and malaria. For these pathogens, the important issue is the agility of their epitope composition that presents an ever- shifting target for the host immune system and for the vaccine developer. The genetic diversity of HIV is a function of its highly error- prone reverse transcriptase (see Smyth et al. 2012). The malaria parasite uses antigenic variation and polymorphism, as well as active immune evasion strategies, to slow and misdirect the immune response of the host; these properties are likely to have coevolved with the human immune system (see Pierce and Miller 2009). The failure, despite decades of effort, to develop vaccines against these diseases suggests that knowledge of the coevolutionary relationships of the human immune system might provide us with new therapeutic approaches.

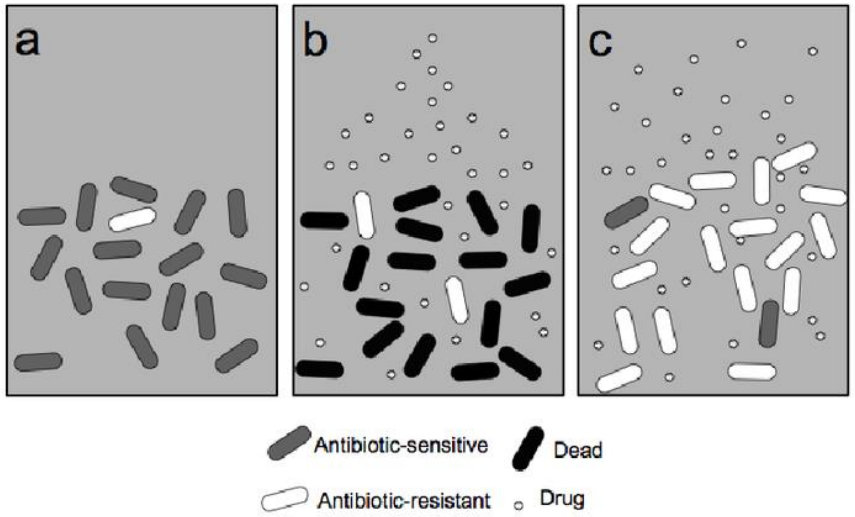


Antibiotics

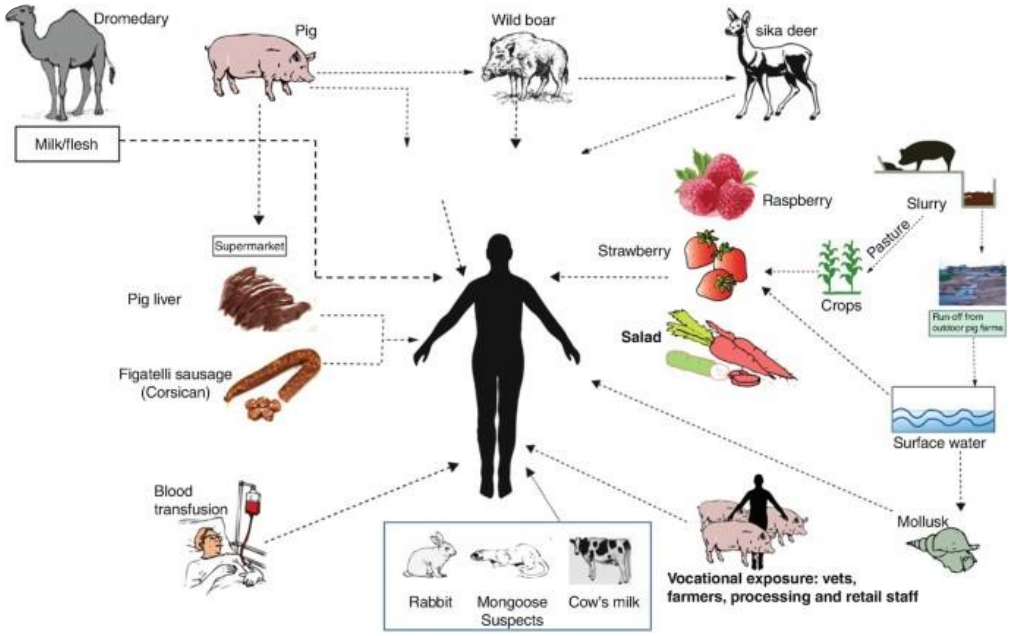
- Antimicrobial chemotherapy kills or inhibits the growth of micro-organisms, and is used to prevent or treat infection. In this section we particularly discuss antibiotics, which are substances used against bacteria; antivirals and antifungals are also mentioned briefly. There is a wide variety of mechanisms of action of antibiotics. Molecular targets include the bacterial cell wall (e.g., pencillin and its derivatives), DNA replication (quinolones), RNA synthesis (rifamycins), protein synthesis (macrolides and aminoglycosides), and metabolism (sulfonamides). A characteristic of these targets is that the affected pathway does not exist or is only weakly affected in eukaryotes, ensuring that the toxic effect is confined to the prokaryotic organism. Most antibiotics are derivatives of naturally occurring compounds that have evolved in micro-organisms as defenses against other micro-organisms; the classic example is the production of penicillin by the mold *Penicillium*. The evolution of these defensive chemicals places selective pressure on the targeted micro-organism; consequently, all microbial defense mechanisms, and their countermeasures, will have been tested by millions of years of coevolution. This implies that resistance mechanisms against most if not all naturally derived antibiotic classes will already have evolved. Samples of bacteria from a cave thought to have been isolated for over 4 million years were found to be resistant to multiple classes of modern antibiotics (see Bhullar et al. 2012). The mechanism underlying resistance generally involves denying the antibiotic access to its target site. For example, this could be by the acquisition of degradative enzymes such as beta-lactamases or of efflux pumps that remove the antibiotic from the bacterial cell. Alternatively, the sensitivity of the target site to the antibiotic may be decreased, for example by point mutations in the active sites of the DNA-replicating enzymes inhibited by the quinolone antibiotics such as ciprofloxacin. A particular feature of antibiotic resistance, with implications for the therapeutic use of these compounds, is the ease with which pathogens can acquire the trait. Resistance can evolve by *de novo* mutations as a result of the selective pressure of exposure to the antibiotic, because the large population size and short generation time of bacteria mean that resistance-conferring mutations will frequently occur and spread even within the human host. Additionally, resistance can be acquired by horizontal gene transfer, not only from members of the same bacterial species but also from phylogenetically distant prokaryotes. Together, these processes mean that clinically relevant levels of resistence usually appear within 2–4 years of the introduction of a new class of antibiotic (see Hawkey 2008). However, the innovation pipeline for new antibiotics is narrow, with fewer new drugs being approved each year



- Hospital-associated (nosocomial) infection with resistant bacteria is a particular threat. This arises because of the high rates of antibiotic use within the hospital setting, generating strong selective pressure favoring resistant strains and clearing sensitive ones, making colonization of patients and staff by resistant strains more likely. In addition, the high turnover of patients in a hospital imposes selective pressure for a resistant strain to transmit rapidly so as to remain endemic within the hospital. In 2013, the US Centers for Disease Control and Prevention reported that each year in the USA at least 2 million people acquire serious infections with antibiotic-resistant bacteria, and at least 23,000 people die each year as a direct result (Centers for Disease Control and Prevention 2013). The financial impact of resistence may be as high as US$20 billion in excess direct healthcare costs, with additional costs to society for lost productivity of as much as US$35 billion a year. Antibiotic resistance clearly presents a considerable problem, and there is a fear that bacterial strains with multiple resistance to all known antibiotics could arise, with disastrous consequences. However, we must remember that major progress in reducing deaths from infectious disease occurred in the pre-antibiotic era as a result of advances in vaccination, nutrition, and sanitation, and so the application of more traditional methods must not be overlooked. Antibiotic resistance is another consequence of human manipulation of the environment. Overuse through unnecessary prescribing is a major cause, but antibiotics are also added to animal feedstuffs to promote growth. Measures to prevent over- use include reduction of the use of antibiotics in animal feed, as well as education of prescribers and patients to promote “antibiotic stewardship,” using protocols that ensure antibiotics are used only when necessary and that the right antibiotics are prescribed and administered in the right way. There has been interest in evolutionary- based treatment protocols to reduce the development of antibiotic resistance in hospitals. These include antibiotic cycling (where use of different classes of antibiotics is alternated across the whole hospital on a regular schedule) and antibiotic mixing (where individual patients receive one of several antibiotic classes used simultaneously in the hospital). The rationale behind these approaches is that if strains resistant to one antibiotic evolve, they will be susceptible to the new agent (in the case of cycling) or will not spread to nearby patients (in the case of mixing). Although there have been many theoretical studies of such protocols (see Bergstrom et al. 2004), it is only recently that trials have begun to test their efficacy (van Duijn and Bonten 2014)



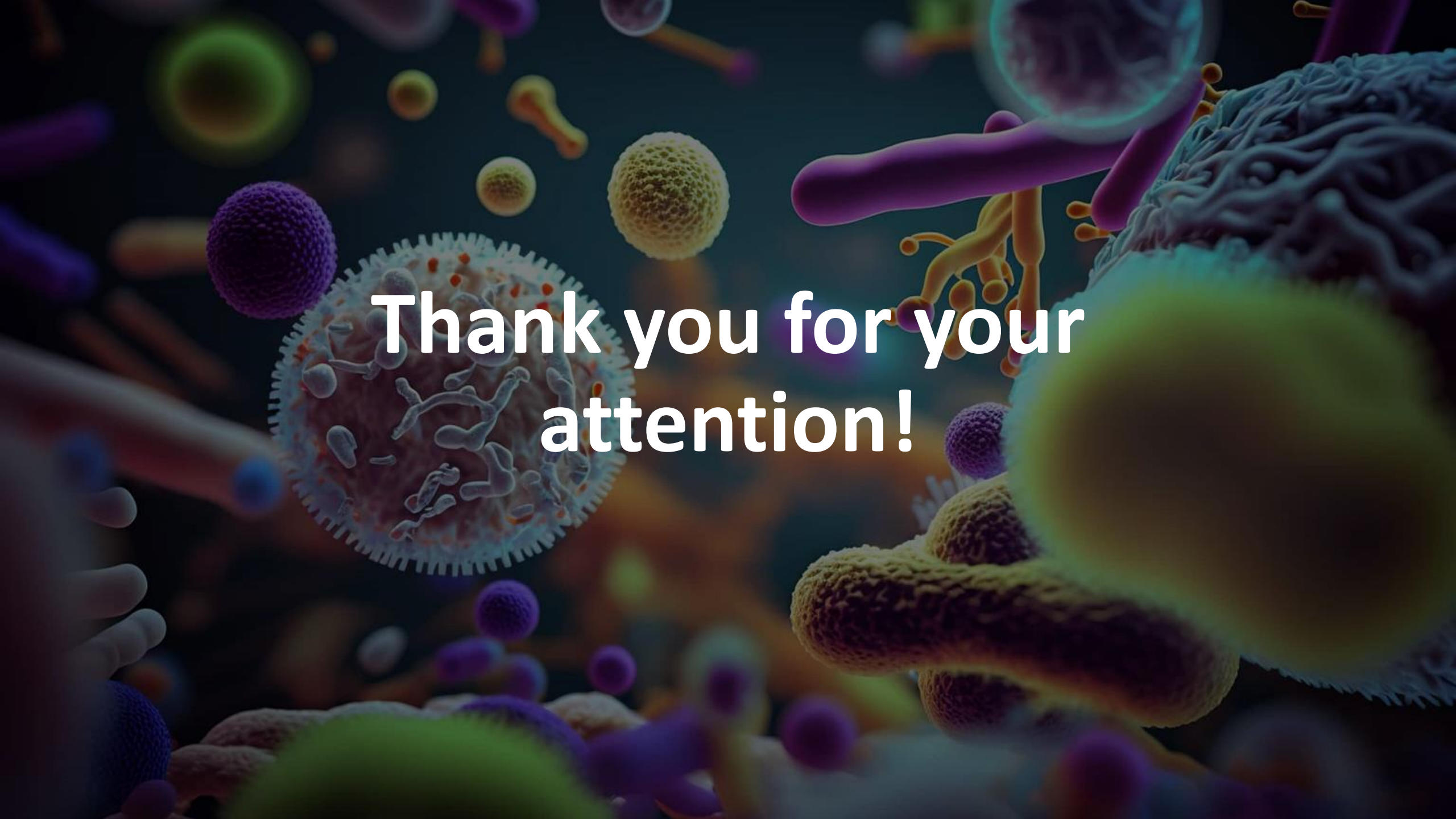
- Another potential approach is to adjust antibiotic administration schedules to ensure a better balance between curing the infection and preventing the evolution of resistance (see Kouyos et al. 2014). Traditionally, aggressive therapy with high dosages for long durations has been used to achieve maximum bacterial kill. However, clinical cure can be achieved by use of moderate dosages and durations if the treatment buys time for the patient's immune response to kill the pathogen or develop tolerance to it (see RÍberg et al. 2009). In this situation, lower dosages of antibiotics could prevent the evolution of resistance, first by allowing the survival of susceptible strains to compete with resistant strains, and second by reducing the emergence of resistance in "bystander" non- pathogenic commensals and subsequent horizontal gene transfer into the pathogen. Targeting secreted bacterial "public goods. Antivirals and antifungals also act against the survival or replication of the infecting microorganism, but the range of molecular targets of these agents is potentially limited by the characteristics of the pathogen. Viruses often use part of the host's biochemistry for their replication, ruling out targeting those pathways. Consequently, antivirals target other virus- specific features, as exemplified by the reverse transcriptase inhibitors used to inhibit replication of retroviruses such as HIV (e.g., nevirapine). Another approach is to inhibit the release of viruses from infected cells; the HIV protease inhibitors (such as ritonavir) and the influenza virus neuraminidase inhibitors (such as zanamivir) work in this way. Development of resistance to antiviral drugs is the result of the high mutability of viruses in the face of the selection pressures caused by the antiviral treatment. An extreme example is HIV, in which the high mutation rate conferred by an error- prone replicative mechanism leads to rapid evolution of resistance to antiretrovirals, even in individual patients. Consequently, antiretroviral therapy in patients with HIV infection is based on combination therapy to delay development of resistance, along with (in high-income countries at least) monitoring of viral load and resistance testing to guide treatment changes.



- By analogy with the situation of “imperfect” vaccines, evolutionary theory predicts that intensive treatment of HIV infection in a population will increase its virulence. Transmission will be favored by rapid progression to high viral load, and this higher virulence that might lead to death of the host before transmission can be offset by treatment. Conversely, in an untreated population virulence should decrease, because lower viral load and the consequent greater host longevity favor transmission. This prediction appears to be confirmed by reports of opposing trends in HIV virulence in Europe (see Pantazis et al. 2014) and Africa (Payne et al. 2014). Fungi, like their hosts, are eukaryotes, meaning that molecular targets unique to the prokaryote domain are not available. Most antifungals target the fungal cell membrane, which differs in lipid composition from animal cell membranes; examples include amphotericin, which disrupts membrane structure, and ketoconazole, which prevents membrane lipid synthesis.

Key Points

- Many causes of extrinsic mortality are biotic, including competition for nutrient supplies with other organisms of the same or different species, predation, and infection by micro-organisms.
- Humans have evolved with their pathogens, parasites, and commensals. This process of coevolution has shaped aspects of human physiology as well as the biology of the microbiota.
- The role of the human gut microbiome in human physiology is increasingly understood; it contributes to defense against pathogens, metabolic health, and regulation of the immune system.
- The adaptive immune system of vertebrates is a key component of protection against microbial infection. Its specificity is a consequence of Darwinian processes of variation and selection.
- Trade- offs between virulence and transmissibility influence the ways in which microbial infections progress in individuals and populations. The balance between these attributes of the pathogen can evolve and change rapidly under some circumstances, with important consequences for therapeutic strategies.
- Human technology in the form of public health measures, vaccination, and antibiotics has greatly reduced the threat from infectious disease in high- income countries. Infection is still a major cause of morbidity and mortality in low- income countries.
- The concerning development of antimicrobial resistance in pathogens can be understood in terms of an evolutionary arms race. This understanding can provide insights into how to reduce this risk by adjusting treatment regimens.


Thank you for your attention!