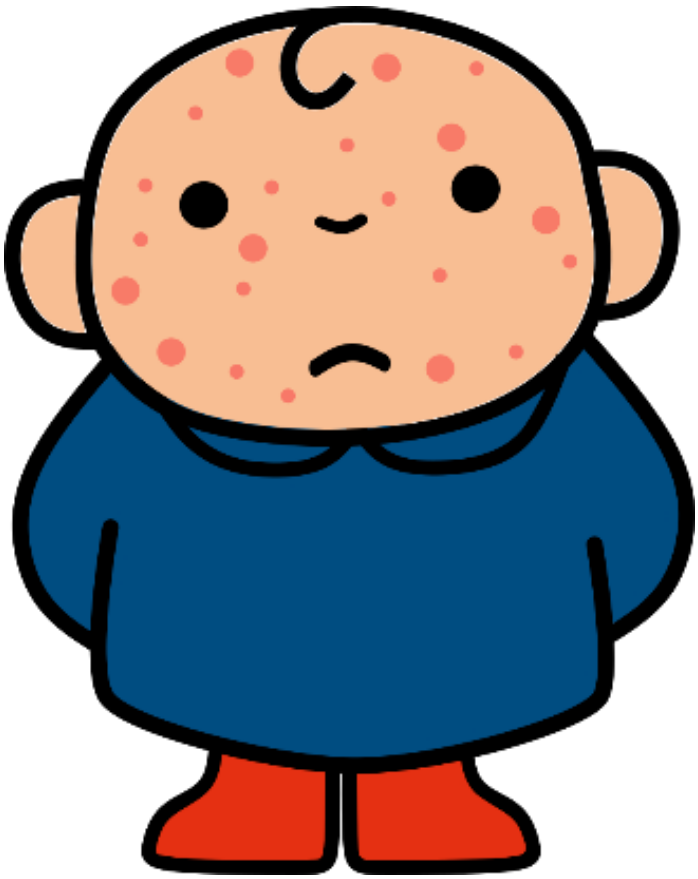
Susceptibility to infections: from cradle to grave

Mom, why did my sister Anny and I get the chickenpox but not you?



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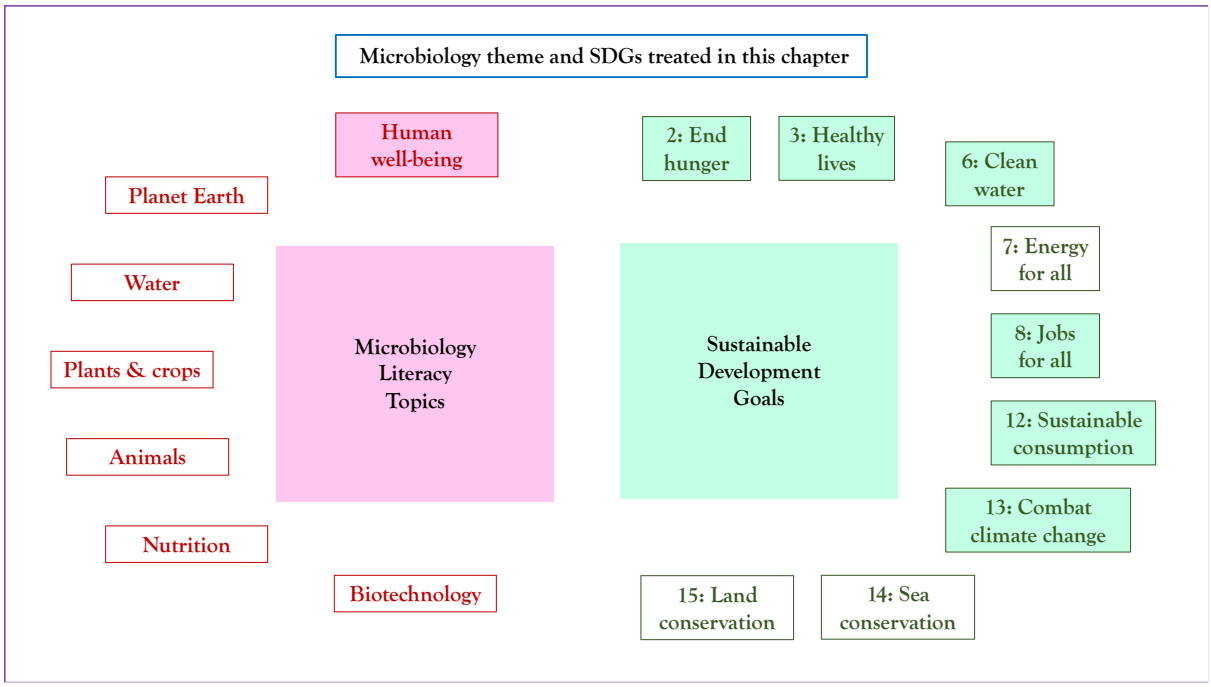
Susceptibility to infections: from cradle to grave

Storyline

All humans are exposed to disease-causing micro-organisms throughout their lives. Our immune system plays an essential role in the protection against these pathogens and determines to a large extent our susceptibility to an infectious disease. The immune system develops throughout life, while susceptibility to infection changes and is higher in young children and the elderly. Newborns rely in the first months to a large extent on immunity that is passed on from mother to child during pregnancy, called 'maternal immunity'. Children develop adaptive immunity through frequent exposure to a whole range of infectious agents and by vaccination. As an adult, our overall health, heavily influenced by our lifestyle, affects the susceptibility to infection. Aging leads to gradual deterioration of the immune system, making elderly more susceptible to infectious diseases. Human behaviour affects the exposure to infectious agents and the rise of pandemics. Understanding and monitoring infection susceptibility at various stages of immune development can help prevent and control infectious diseases.

The Microbiology and Societal Context

Microbiology; infection susceptibility in different life stages: routes of infection and modes of transmission; vaccination; immune suppression; innate and adaptive immune system.
Peripheral issues, for completion of the storyline: emerging pathogens, zoonotic diseases, lifestyle
Sustainability issues: nutrition; health; economy and employment; global warming.



Infection Susceptibility: the Microbiology

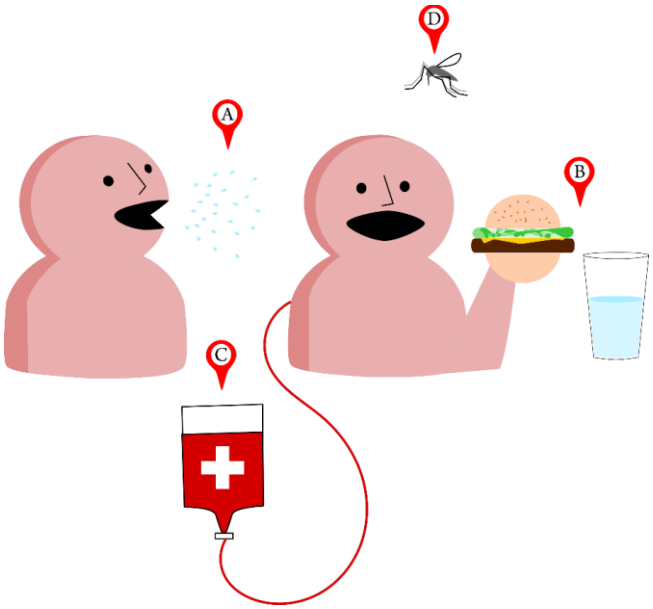
1. ***All humans encounter disease-causing microorganisms throughout their lives.*** While most microorganisms are harmless to humans, some can cause disease. These microorganisms are called **pathogens**. To get an **infection** a person must first come into contact with the pathogen, which can be a virus, bacterium, fungus or a parasite.

The way the pathogen spreads from person to person and enters the body is called the **mode of transmission**. Many airway diseases, such as the Influenza virus but also SARS-CoV-2, the coronavirus causing COVID19, are transmitted through droplets. By coughing or sneezing, microscopic liquid droplets laden with pathogens derived from upper and lower airways are spread into the environment. When another person comes in contact with the droplets, for example by inhalation, they can become infected with the pathogen.

Some **airborne** infections such as measles are spread through even smaller droplets, which are called 'aerosols', that linger in the air long after the infected person has sneezed or coughed. Aerosol-mediated transmission can thus spread rapidly over a long distance from person to person.

Food can also be a source of pathogen spread. While salmonella and cholera infections are perhaps the most well-known **foodborne diseases**, *Campylobacter* infections are the most common. Diseases caused by food borne pathogens are colloquially called **food poisoning**. You can get infected by foodborne pathogens when eating or drinking contaminated food and water. Foodborne disease is thus often found in impoverished areas with poor hygiene and a lack of clean water.

Some pathogens, such as the Human Immunodeficiency Virus (HIV), enter the body through **sexual intercourse** or **blood contact**. These diseases spread less rapidly than airborne or foodborne infections, as contagion occurs only between sexual partners, mother and child, or through contact with contaminated blood.



Modes of transmission. A) Pathogens spread through droplets or aerosols from lungs, throat, and mouth when an infected person coughs or sneezes. B) Contaminated food and polluted water are a source of food borne pathogens. C) Contact with contaminated blood or re-used needles can cause infection of pathogens spread by blood contact or sexual transmission. D) Insects such as mosquitos can harbour and transmit pathogens.

Lastly, some pathogens hitch a ride on other species to find their host. These **vector-borne pathogens** often use insects to take them from person to person. The single-celled *Plasmodium* parasites that cause malaria disease, for example, are found in the saliva of mosquitoes. When the mosquito bites, the parasite is transferred to the human blood leading to severe disease.

2. ***Our immune system has an essential role in the prevention of infection by pathogens.*** Fortunately, our body has an army to keep pathogens at bay: **the immune system**. The immune system is trained to recognize and kill intruding pathogens. The system is composed of two lines of defence (Box 1). The first line is the **innate immune system** that recognizes and eliminates intruders in a non-specific way. If the first response needs assistance a second line of defence is triggered, the **adaptive immune response**.

The cells of the adaptive immune response recognize a pathogen very specifically and start an immune reaction, such as the production of **antibodies**. The frequent infections occurring in the first years of life serve to build the pool of immune **memory cells** that will prevent reinfection or development of disease by commonly encountered pathogens. When someone is infected again, the cells quickly recognize the pathogen and induce a fast immune response leading, for example, to the reactivated production of antibodies. This **immunological memory** can prevent or reduce a second infection by the same pathogen.

Everyone's immune system is different and therefore we respond differently to infection leading to contrasting outcomes of disease. Our **susceptibility to infection** largely depends on the state of our immune system. This is determined by many different factors, including environmental exposure, genetic makeup (Box 2) and age.

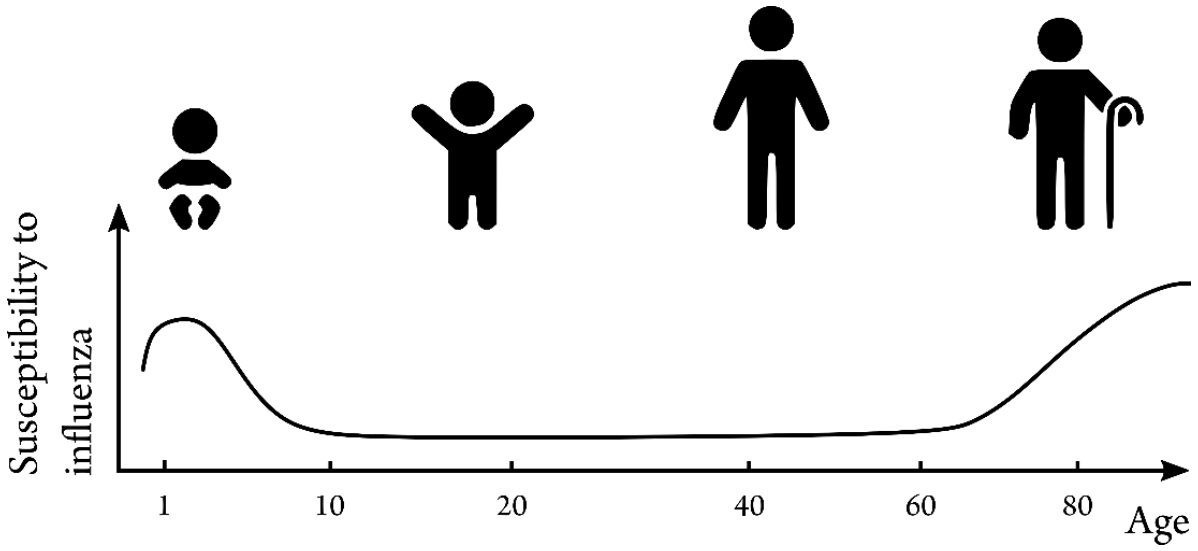


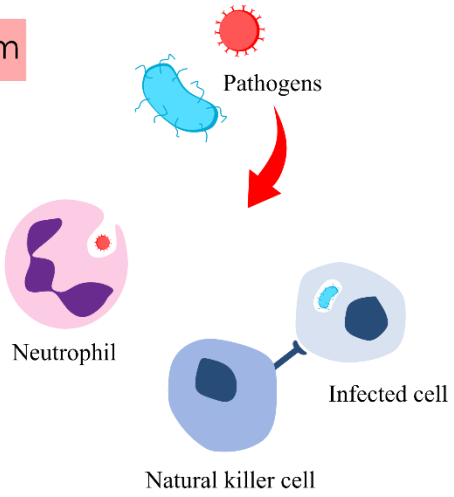
Figure 2: Infection susceptibility changes with age. Development of the immune system during life leads to changes in susceptibility to infectious diseases such as influenza. However, the dynamics of susceptibility holds true for many infectious diseases. Neonates and infants are especially susceptible due to an underdeveloped adaptive immunity. Through exposure to micro-organisms and vaccinations, the immunological memory develops and susceptibility to infections decreases. Elderly too have a heightened susceptibility to infection due to aging of the immune system. Image based on Simon *et al.* (2015).

Box 1: The Immune System

A defense against pathogens

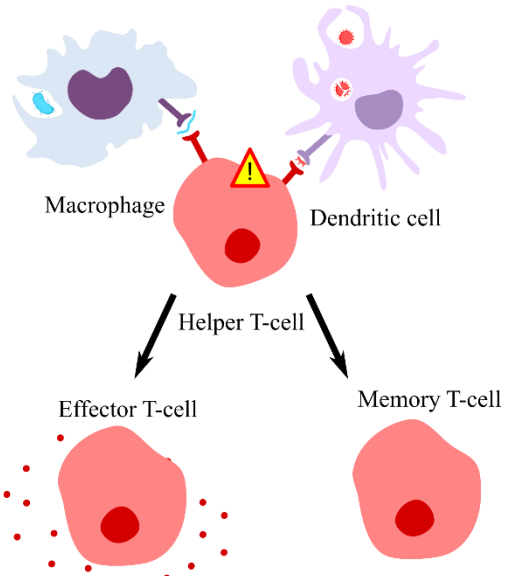
When pathogens invade the body, the **innate immune system** serves as the first line of defense. This is a non-specific response to all invading pathogens.

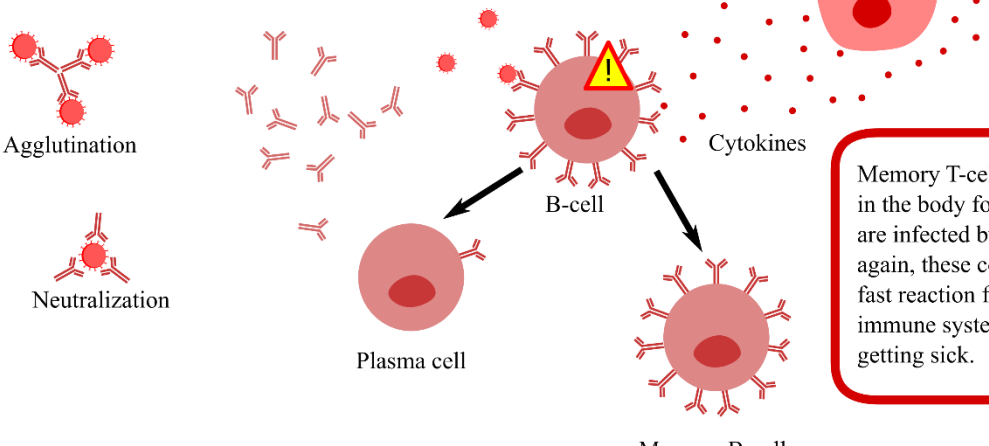
Immune cells and infected cells detect the presence of a pathogen and produce molecules called **chemokines** to alert the immune system of infection. This is called the **inflammatory response.** This attracts the cellular components of the innate immune system: phagocytes and natural killer cells. **Phagocytes** (**neutrophils**, **macrophages** and **dendritic cells**), engulf and break down pathogens, while **natural killer cells** detect and kill infected cells.



The **adaptive immune system** generates a response specific to the invading pathogen. The adaptive immune system consists of a cellular and a humoral response.

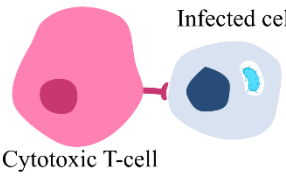
Macrophages and dendritic cells present particles of the pathogen, called **antigens**, to **helper T-cells**. Helper T-cells are then activated and multiply. Some daughter cells become **memory T-cells**. Others become **effector T-cells**. Effector T-cells release **cytokines**, small signalling molecules, that alarm other components of the immune system such as B-cells and cytotoxic T-cells.





Memory T-cells and B-cells are stored in the body for a long time. When you are infected by the same pathogen again, these cells make sure there is a fast reaction from the adaptive immune system, preventing you from getting sick.

B-cells are decorated with **antibodies**. When they encounter a pathogen, and the antibody matches specifically with that pathogen, B-cells are activated and multiply. Daughter cells become either **memory B-cells** or **plasma cells**. Plasma cells then produce large amounts of antibodies specific to the invading pathogen. Antibodies help to fight the infection by **agglutination**; binding pathogens together, making them easier targets for phagocytes. Antibodies can also **neutralize** a pathogen: shielding the parts it needs to enter a cell, preventing it from infecting cells.



Cytotoxic T-cells are the last cellular component of the innate immune system. They recognise and kill infected cells.

3. ***Babies rely to a large extent on maternal immunity.*** Newborns (neonate)s are dependent on **maternal immunity**. During pregnancy, antibodies that have been produced by the cells of the adaptive immune system are passed from mother to child through the placenta. When the baby is born, these **maternal antibodies** still circulate in their bloodstream. This is important, because neonates are not producing their own specific antibodies and the innate immune system is still developing, meaning that they are dependent on their mother's antibodies for protection against pathogens.

Over time maternal antibodies are degraded and so the level of maternal antibodies rapidly decreases as the infant gets older. Right after birth, the baby's immune system is in part supplemented with antibodies through breast milk. Breast feeding can help protect the baby from pathogens in early stages.

About 3 to 6 months after birth, the infant starts to produce its own antibodies. As the infant grows older, antibody levels derived from the mother decrease, while it is still developing its own immune system. This leaves a gap of several months during which the infants have an increased vulnerability to infection.

4. ***Children develop a strong immune system through exposure to infectious agents.*** Through interaction with others and contact with the outdoors, children are exposed to a large range of microbes and pathogens. As a child's immune system is still developing, they are more susceptible to disease than adolescents and adults. Children therefore often have upper airway infections.

Due to improved hygiene and vaccination (see point 5), cases of serious disease during childhood and **child mortality** have strongly decreased over the years. Exposure to pathogens is important for the establishment of immunological memory (Box 1), so that the immunological response to pathogens in a child can protect a person throughout adulthood. A great example of this is **chickenpox**. This disease, caused by the varicella-zoster virus, is common among infants and young children. It spreads quickly in kindergartens and schools, and most people are infected by the virus sometime during their childhood. After the initial infection, children are immunized against the virus. Because the adaptive immune system has developed antibodies against the virus, a second infection can be prevented by a targeted response from the adaptive immune system. The adaptive immune system ensures that you only suffer from the chickenpox once.

5. ***Children develop adaptive immunity to infectious diseases through vaccinations.*** In the same way exposure to chickenpox prevents a second infection, **vaccination** can induce a response from the adaptive immune system to a pathogen.

A **vaccine** contains either a weakened form of the pathogen or characteristic pathogen-specific molecules, **antigens,** that can be recognised by the immune system. Vaccinations are a form of **induced immunity**. After vaccination, the adaptive immune system produces immunological memory against the pathogen. When you are exposed to the pathogen later in life, it is quickly recognized by vaccine-induced antibodies, and the immune system is alerted to fight the infection.

Vaccines strongly reduce infection susceptibility by inducing immunity without exposure to the harmful pathogen, and thereby protect us against infectious diseases. For this reason, many countries have state monitored vaccination programmes to protect their people from dangerous infectious diseases.

6. ***Your lifestyle as an adult affects susceptibility to infection.*** Throughout adulthood, we are continuously exposed to new pathogens. It is important to keep the immune system in good condition in order to protect ourselves against these pathogens.

Our overall health, heavily influenced by our lifestyle, determines the reactivity and effectivity of the immune system. Factors such as diet, stress, exercise, smoking and the use of drugs, alcohol and medication have been shown to impact the immune system. These lifestyle choices thus affect infection susceptibility.

Obesity is known to reduce lifespan by promoting the age-related decline of immunity (see point 7). A calorie-restricted diet on the other hand, can improve the longevity of the immune system. Furthermore, **chronic stress** can be damaging to the immune system, even impairing the response to vaccination.

Regular, moderate intensity exercise can reduce susceptibility to infection by strengthening the immune system through improved distribution of the immune system components. However, extreme and sporadic forms of exercise, as well as lack of exercise, negatively impact the immune system.

Lastly, many forms of drugs and medication suppress the immune system, either as side effects or purposely as part of the treatment (Box 2). Such immunosuppressive drugs make users more susceptible to many types of infections.

The lifestyle choices we make as an adult can thus have a great impact on our susceptibility to infection and ultimately on our health and lifespan.

Box 2: Immunodeficiency
What if your immune system does not work properly?

Sometimes, the immune system is weakened or suppressed. This increases the susceptibility to infection. So-called **immunodeficiency** can be hereditary, acquired or induced.

Hereditary immunodeficiency is caused by mutations in the patient's genes. A common example is **Cystic Fibrosis** (CF). CF patients are highly susceptible to pneumonia because thick mucus in the lungs prevents protection by the immune system. Very rarely, the adaptive immune system is completely inactivated due to genetic mutations. Children with so-called **Severe Combined Immunodeficiency** (SCID) are extremely vulnerable to infection and must therefore live in hermetically sealed chambers. SCID is thus also called **bubble baby disease**.

Some pathogens, such as the **Human Immunodeficiency Virus** (HIV), cause acquired immunodeficiency. HIV destroys a patients T-cells, thereby disabling a key player in the adaptive immune response. Patients are left susceptible to general infections as the disease progresses to **Acquired Immunodeficiency Syndrome** (AIDS).

Lastly, it can be favourable to induce immunodeficiency. For example, when someone receives an organ transplant, the immune system might recognise it as foreign and attack it, which could result in rejection of the organ. In this case, **immunosuppressive drugs** that weaken the immune system are often used.

7. ***The elderly are more susceptible to disease.*** As we get older, many bodily functions begin to deteriorate. Ageing also applies to our innate and adaptive immune system. In a process called **immune senescence**, the immune system becomes ineffective at its central tasks. Infection susceptibility increases, as pathogens can no longer be kept at bay. Once infected, mortality rates in elderly are much higher compared to younger adults, as the immune system cannot gain control over the pathogens anymore.

On top of that, the immune system becomes worse at detecting the difference between self and intruder, leading to an increased number of **autoimmune diseases** among the elderly. The decline of the immune system is especially clear when looking at influenza infections.

Approximately 90% of deaths caused by influenza are in people aged 65 or above. While the influenza virus is relatively harmless to most healthy adults, the aged immune system of elderly people makes them more susceptible to the infection and less likely to survive once infected.

8. ***Novel exposure to emerging diseases can lead to worldwide pandemics.*** A large-scale outbreak of an infectious disease, such as a **pandemic**, occurs when a large part of the population is susceptible to the infection. For common diseases, most people have gained immunity throughout their life, and only a small group of people is susceptible at any given time, preventing an outbreak of disease. However, when a new pathogen is introduced, nearly everyone is susceptible, and a large outbreak can easily occur, witness Covid-19. These new **emerging diseases** are increasingly common.

Emerging diseases can result from known pathogens that have **mutated** and changed over time. This is the case with the common flu; due to rapid changes to the flu virus, it circumvents recognition by the immune system. This process leads to yearly flu outbreaks. On the other hand, human practice also increases the number of emerging diseases. Due to population growth, pollution, and agricultural pursuit, many **ecological habitats** have become much smaller in the past years. This means humans live much closer to wild animals than before and contact between them is more likely. This has led to the rise of **zoonotic diseases**, like Covid-19, infectious diseases that are passed from animals to humans.

Climate change also contributes to outbreaks of emerging diseases. As the temperatures change, pathogen-carrying vectors, such as mosquitoes or ticks, can now tolerate living in new geographical areas and bring pathogens along with them. This brings pathogens into new areas, where the people are mostly still susceptible.

Lastly, diseases can spread between people much faster than before due to higher population densities and increased travel movements that has come with globalisation. All these factors together mean that new diseases are emerging and spreading faster than ever before, with the potential of becoming pandemics.

Relevance for Sustainable Development Goals and Grand Challenges

The microbial dimension of infection susceptibility relates to several SDGs (microbial aspects in italics), including

- **Goal 2: End hunger, achieve food security and improved nutrition and promote sustainable agriculture** (*end hunger and malnutrition, increase agricultural productivity*). Malnutrition can lead to a weakened immune response and increased susceptibility to infection.
- **Goal 3: Ensure healthy lives and promote well-being for all at all ages** (*improve health, reduce preventable disease and premature deaths*). Vaccination and breast feeding is important for the development of the immune system. Stress and exercise have a significant effect on the immune system and therefore affect susceptibility to infection. Knowledge on the prevention of infection will support the protection against infectious diseases.
- **Goal 6: Ensure availability and sustainable management of water and sanitation for all** (*assure safe drinking water, improve water quality, reduce pollution, protect water-related ecosystems, improve water and sanitation management*). Purified water will prevent the spread of food borne diseases such as cholera and other gastrointestinal infections.
- **Goal 8: Promote sustained, inclusive, and sustainable economic growth, full and productive employment and decent work for all** (*promote economic growth, productivity and*

innovation, enterprise and employment creation). Economic growth enables improvement of hygienic conditions, clinic care facilities, and public health measures, leading to the improved control of infectious diseases.

- **Goal 9: Industry, Innovation, Infrastructure** (*development of biotechnology and medical equipment*). Technical innovations are essential to continuously improve vaccination, infectious diseases diagnostics and anti-infective treatments.
- **Goal 12: Ensure sustainable consumption and production patterns** (*achieve sustainable production and use/consumption practices, reduce waste production/pollutant release into the environment, attain zero waste lifecycles, inform people about sustainable development practices*). Improvement of environmental and hygienic conditions will improve the health status and reduce the vulnerability for infectious diseases.
- **Goal 13: Climate change** *(energy transition, reducing CO2 concentrations)*
  There is a strong indication that air pollution is associated with (chronic) lung diseases including lung infections. This can be prevented by the reduction of greenhouse gas emissions. Global warming can lead to the emergence of infections, such as vector borne infections in Europe.

Potential implications for Decisions

1. ***Individual***
   a. Parental decisions about breast feeding, vaccination of children and teaching of personal hygiene influence the development of the child's immune system.
   b. Lifestyle choices such as diet, stress, and exercise, influence the functioning of the immune system and susceptibility to infectious diseases.
   c. Travelling across the world can lead to exposure to new pathogens.

2. ***Community policies***
   a. Assuring clean water and unpolluted air,
   b. Sufficient sport facilities and space for recreation,
   c. Good education to promote a healthy lifestyle.

3. ***National policies related to infection susceptibility***
   a. National vaccination programme,
   b. Health care systems,
   c. Good education, to establish a circular economy.

Pupil participation

1. ***Class discussion of the issues associated with infection susceptibility***

2. ***Pupil stakeholder awareness***
   a. Infection susceptibility has a great impact during your life. What do you think are the most important measures to take to strengthen your defence against pathogens?
   b. What changes can we make, in line with the sustainable development goals, to prevent the outbreak of an emerging disease?

3. ***Exercises***

a. What lifestyle choices can you think of that will reduce susceptibility for infection?

b. Do you think people who are more susceptible to disease, for example due to immunodeficiency, should pay more for health insurance?

c. What measures can a government take to improve protection against infectious diseases in the national population?

The evidence base, further reading and teaching aids

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Glossary

Acquired Immunodeficiency Syndrome (AIDS)
Disease caused by human immunodeficiency virus (HIV). Due to destruction of T-cells, patients are highly susceptible to infection and often die prematurely from infectious disease.

Adaptive immune response
The specific immune response to invading pathogens by B-cells, T-cells. This includes the development of immunological memory.

Agglutination
Antibody mediated clumping together of pathogens.

Airborne pathogens
Pathogens spread through microscopic droplets. Droplets act as volatile substance and linger in air after coughing or sneezing.

Antibodies
Molecules expressed by all B-cells, and in secretory form by plasma cells. Aimed specifically for recognition of a pathogen binding site (see **antigen**).

Antigen
Molecule or fragment, e.g. on pathogen surface, that is recognised by an antibody or T-cell receptor.

Autoimmune diseases
Disease caused by an adaptive immune response to normal bodily components.

B-cells
Cells of the adaptive immune system responsible for the production of antibodies. After encountering a compatible antigen, B-cells differentiate into **memory B-cells** and **plasma cells**, which start mass production of extracellular antibodies.

Blood contact
Direct contact between blood of two people, e.g. during birth, non-sterile blood transfusion or the re-use of injection needles.

Bubble baby disease
See **severe combined immunodeficiency syndrome.**

Chemokines
A family of proteins, secreted upon detection of a pathogen. Chemokines attract and activate various components of the immune system.

Chickenpox
Contagious disease caused by the varicella-zoster virus, resulting in skin rash and blisters.

Child mortality
Death of children under the age of 5, commonly expressed as child mortality rate, the average child mortality per 1000 live births.

Chronic stress
Chronic stress is the physical and emotional response to long-term emotional stress, for example due to sleep deprivation or overworking.

Climate change
The recent change in climate conditions, including extreme drought and rainfall, and a global temperature rise.

Cystic Fibrosis (CF)
Genetic disease causing excessive viscosity of mucus in the lungs, leaving patients vulnerable to pneumonia.

Cytokines
Group of proteins produced by activate effector T-cells to affect the behaviour of other components of the immune system.

Dendritic cell
Phagocyte, engulfs and kills pathogens through phagocytosis. Presents antigen from killed pathogen to activate helper T-cells.

Ecological habitat
The ecological space inhabited by a species. The environment within which a certain species is able to thrive.

Emerging diseases
Infectious diseases that have recently spread

or have the potential to spread among novel, largely susceptible populations.

Food poisoning
Illness caused by ingestion of food contaminated with pathogens.

Foodborne pathogens
Pathogens spread through food or drink, which enter the body through the digestive tract.

Human Immunodeficiency Virus (HIV)
Retroviral infection that destroys T-cells, and therefore strongly weakens the adaptive immune response. Leads to **acquired immunodeficiency syndrome**.

Immune senescence
The gradual decline of the competence of the immune system through the natural aging process.

Immune system
The cells and tissues involved in the bodily defence against pathogens.

Immunodeficiency
Condition wherein parts of the immune system are weakened or suppressed, thereby rendering the immune response ineffective.

Immunological memory
The collection of memory B-, and T-cells that facilitate a faster and more effective immune response upon a second encounter with a pathogen.

Immunosuppressive drugs
Drug that temporarily weakens the immune response. Used mainly to treat **autoimmune disease** and to prevent rejection after an organ transplant.

Induced immunity
The development of immunological memory without exposure to the pathogen in question, e.g. through vaccination.

Infection
The invasion of the body by a pathogen, usually resulting in disease.

Innate immune system
A defence mechanisms against pathogens, active from the start of infection and non-specific.

Macrophage
Phagocyte, part of innate immune system. Can kill extracellular pathogens through phagocytosis and presents antigen to helper T-cell.

Maternal antibodies
Antibodies passed from mother to child through breast milk.

Maternal immunity
Immunological protection of an infant through supplement of maternal antibodies in breast milk.

Memory cells
General term for cells of the adaptive immune system that form the immunological memory.

Mode of transmission
The manner in which a pathogen is spread from one person to the next, often defined by the medium in through which the pathogen is transmitted.

Mutation
An alteration in the genetic code of an organism. This can lead to changes in the appearance of this organism. Mutations can occur randomly and can be induced by exposure to UV light or toxins.

Natural killer cell
Cells of the innate immune system. Recognise MHC-I complex to detect and kill infected or cancerous cells.

Neutralization
The binding of antibodies to important sites of a pathogen, rendering them unable to grow and/or enter cells.

Neutrophil
Most abundant phagocyte, arrives quickly at site of infection and kills extracellular pathogens by phagocytosis.

Obesity
Obesity or overweight is the excessive accumulation of fat, usually due to diet choices and lack of exercise.

Pandemic
A global outbreak of an infectious disease.

Pathogen
Microorganism causing infectious disease.

Phagocyte
White blood cell, part of the innate

immune system. Engulfs and degrades invading pathogens.

Plasma cells
Effector B-cells, see B-cells.

Severe Combined Immunodeficiency Syndrome (SCID)
Hereditary condition where B-cells and T-cells cannot recognise pathogens specifically, effectively neutralizing the adaptive immune response.

Sexual transmission
Mode of pathogen transmission through sexual contact.

Susceptibility to infection
The likelihood or liability of becoming infected by a certain pathogen.

T-cells
Cells of the adaptive immune system responsible for cell mediated immunity. **Helper T-cells** produce **effector T-cells** and **memory T-cells** upon activation. **Cytotoxic T-cells** kill cells infected by pathogens.

Vaccination
The act of activating the adaptive immune system to induce immunological memory against a pathogen by injection or ingestion of either killed or non-pathogenic forms of a pathogen.

Vaccine
A killed or non-pathogenic form of a pathogen, or its characteristic molecules, used during vaccination to induce immunological memory.

Vector borne pathogens
Pathogens spread by living organisms termed vectors. Vectors are commonly insects such as mosquitos or ticks.

Zoonotic disease
Infectious diseases that are transmitted from animals to humans, such as the avian flu.