Fever
(is it good or bad for you?)

The school nurse said I had a high temperature last Tuesday, and I was feeling hot and cold for the rest of the week. Why do we get a fever when sick? - Chelsea, aged 15

When we're sick, we often need to reach for a tissue, and can feel awful.
In addition, sometimes our body starts to heat up, and we get a fever. Image by C. Moro (2021).

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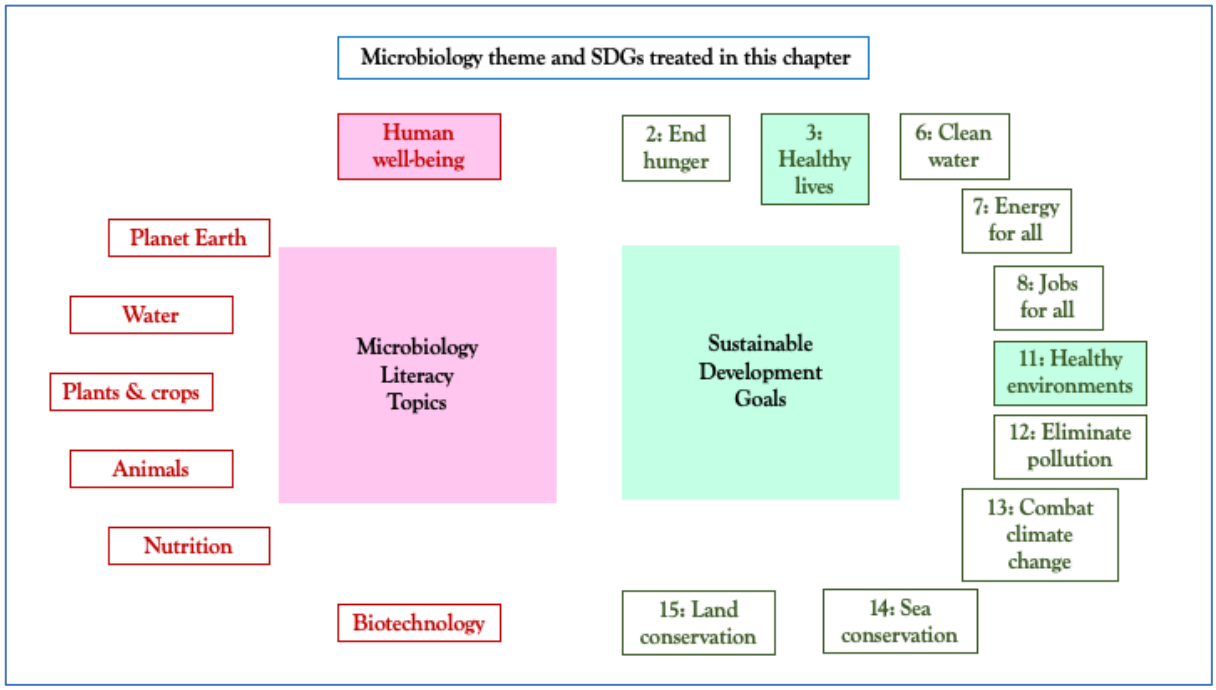
Fever

Storyline

Fever occurs when our body temperature rises above normal levels. It is a clinical feature that typically appears during the course of infectious diseases. However, whilst fever is often viewed as the main point of concern, the underlying processes occurring within our body can be beneficial. Fever acts as a protective mechanism that assists to enhance immune cell function and promote antimicrobial activities.

The Microbiology and Societal Context

The microbiology: human well-being; enhancing immune system response; immunological process; normal response to infection. *Sustainability issues*: healthy lives; promote well-being; child health (Figure 1).



Fever: The Microbiology

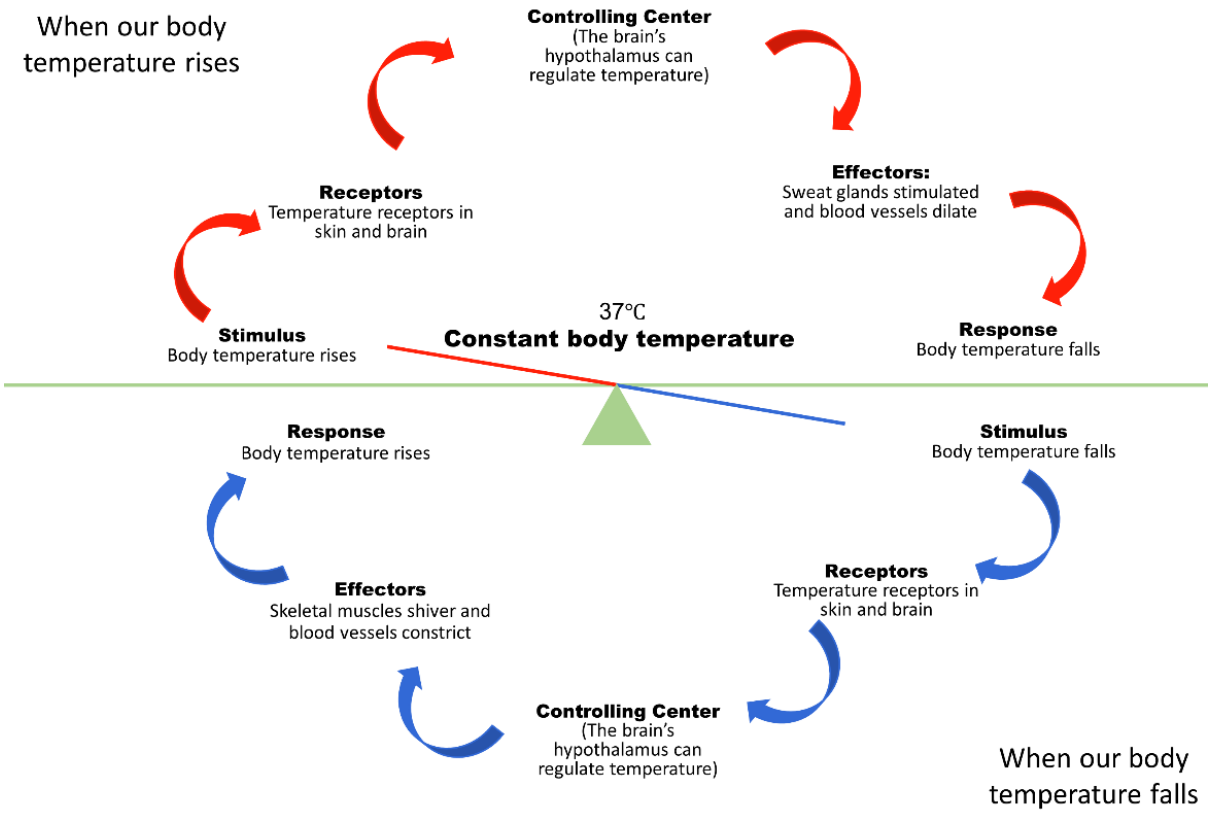
1. ***What happens when we get a fever?*** In 500BC Parmenides stated "Give me the power to produce fever and I'll cure all disease", appearing to comprehend the curative power of the body's natural response to infection. Throughout the era of Hippocrates, the 'fathers of modern medicine' characterised and wrote widely about the benefits of fever, igniting a 'hot topic' in medical interest for centuries. However, it was not until 1917, when fever was formally used as a medical intervention. Austrian physician Julius Wagner-Jauregg proposed a surprising treatment for syphilis, the bacterial infection that had been ravaging Europe for centuries. He would infect patients suffering from syphilis with malaria, the mosquito-borne disease that triggers raging fevers, and would later administer a medication (quinine) to curb the malaria. In 1927, this outlandish method won Wagner-Jauregg the Nobel Prize in medicine. From this point on, fever became seen as the 'miracle cure' until penicillin's rise in the 1940s.

The presentation of fever is common across the animal kingdom, where it has remained a primary and effective response to infections for millions of years. It has been observed in mammals, reptiles, amphibians, fish, and even some invertebrate species. We often worry when our loved ones have a fever. Many parents exhibit "fever phobia" due to misconceptions regarding the risks of fever. This makes it one of the most common complaints for which parents take their children to medical centres, and can result in inappropriate use of medications, and unnecessary parental anxiety and fear when their child presents with even a low-grade fever.

It is correct that fever can be an important indication of disease and illness. However, in these cases it's the *infection* which is of concern, not the fever itself. In fact, fever is a natural process and an important response of the body to infection (see Topic Framework 'Infections' for a more detailed treatment of this subject).

The aim of this *Topic Framework* on fever is not to discuss whether to suppress a fever or 'let it ride' (and be sure to seek medical advice if fever is a worry), but instead to summarise some of the reasons our body heats up, and the beneficial outcomes of this process. Thus, we focus on the body's response to fever-inducing causes, rather than on clinical interventions that may or may not ensue.

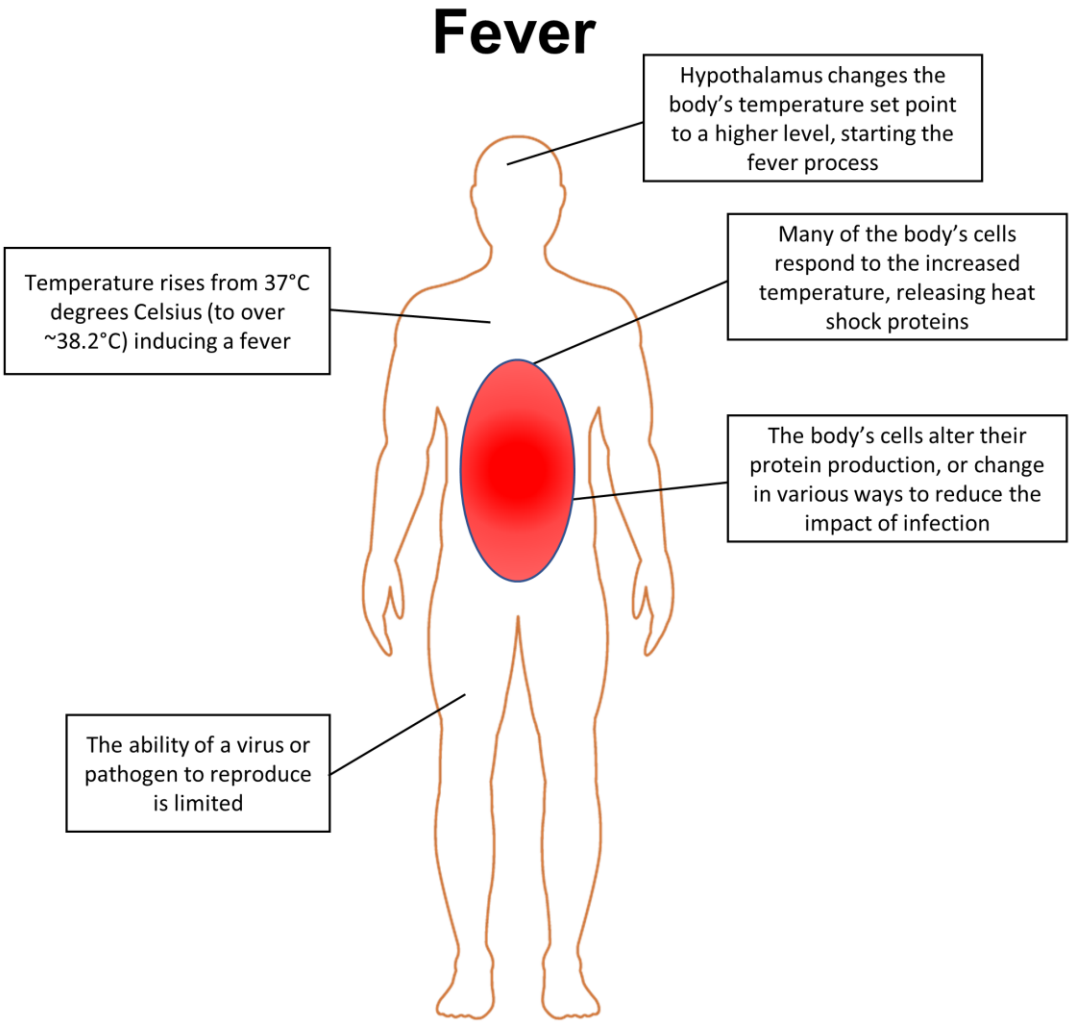
2. ***Temperature regulation.*** Before we can discuss the body heating up, let's look at how normal temperatures are regulated. The human body's internal temperature is tightly maintained at 37 degrees Celsius by a process called thermoregulation. This core temperature is vital to sustain in order to ensure the normal functioning of the body systems. An area in the brain, called the hypothalamus, controls thermoregulation.



Body temperature regulated by homeostatic processes 'thermoregulation'. Image by C. Phelps (2021).

The hypothalamus receives sensory information from receptors in the body (predominately in the skin) that communicate if the temperature is too hot or too cold. If the hypothalamus detects the body is too hot, it will produce signals to activate the sweat glands to produce sweat, which will reduce the body temperature. Blood vessels will also dilate (expand), which will allow blood to move closer to the skin's surface, in turn releasing heat and cooling you off. In contrast, if the body is too cold, skeletal muscles will be activated to start shivering and blood vessels will constrict to generate heat and increase the temperature We call this *homeostasis*.

3. ***Inducing fever.*** Fever is a process where the normal body temperature is elevated above homeostatic conditions. Immune cells that are fighting an infection can induce a fever by triggering a biochemical cascade that instructs your hypothalamus to increase its baseline temperature. Your body then gets to work to meet its new "set point" using the mechanisms it would to generate heat when cold. Until it reaches this new temperature, you'll feel comparatively cool, which is why you might experience chills.



The body's response to a fever-induced increased temperature. Image by C. Moro (2021).

The induced fever is detected by a number of cells in the body. In this way, fever acts somewhat as a signalling process, letting the body know there is an infection. Some cells, when the high temperature environment is detected, release a family of molecules called heat shock proteins (HSP). These heat shock proteins stimulate a number of changes in the nearby environment. As a result, this process inhibits the spread and damage that the infection pathogen can perform. Therefore, fever can be an important response of the body to infection.

4. Protective actions. The development of fever during infection from pathogens can be described as an evolutionary advantage. When our temperature heats up, our body responds. Some of the outcomes of this response provide a range of benefits in order to fight and clear the infection. This includes the fact that fever:

- Induces the release of heat shock proteins, which help our cells prepare for, survive, and reduce inflammation during stressful events, such as infections.
- Activates immune cells, and alters them so that they can better reach infection sites.
- Protects cells against attack from harmful molecules coating the surface of some bacteria.
- Reduces organ damage from infections.
- Makes it harder for microbes to reproduce, create toxins, or do damage.
- In some animal models, increased body temperature enhances the resistance to diseases such as herpes, polio, coxsackie B, rabies, pneumonia, gastroenteritis and others.
- Reduces the shedding and spread of some viruses.
- Reduces the amount of viral levels in diseases such as influenza.
- Speeds up healing of skin sores and reduces skin itchiness in diseases such as chicken pox.
- Remains a primary response to infection, which has been conserved for millions of years, and exhibited across many species.

5. A heated environment. High body temperatures may also create an environment that is less hospitable to some disease-causing microbes. An observation of this occurring was when patients infected with the common cold breathed in humidified air heated to 43 degrees Celsius. This resulted in reports of symptomatic improvements, and a reduction in the disease's severity. One microbe that causes the common cold, rhinovirus, grows best at around 35 degrees Celsius, the same temperature as the inside of the nose (the region it typically infects). As such, it makes sense that heated conditions might help to inhibit the reproduction and spread of these types of infections (Figure 3).

Nonetheless, in most cases although it's often thought that that higher temperatures would directly harm pathogens, many microbes are able to adjust to the heat quite rapidly and effectively. This means that the heated environment is likely to be more for our body's benefit, rather than a direct attack on the infection, making fever's main effect the rapid induction of a whole-body immune response and stimulating the release of beneficial messenger signals, such as heat shock proteins.

6. Fever phobia. Many myths surround fever, such that it can cause brain injury or damage. To date, in otherwise healthy people, there is little evidence that the usual levels of fever seen in illness can be harmful. The body has mechanisms in place to prevent its core temperature from naturally reaching levels higher than around 41 degrees Celsius. It is true that high temperatures can cause damage, but it is at severe levels, such as those that can be reached when a child is left in a closed car during hot weather.

Even small increases in body temperature can be beneficial, and have been associated with improved survival and disease clearance for some infections in various species. This is a good thing, as the body has to work particularly hard to generate this heat. For every 1°C of temperature increase there is around a 6 - 12% increased metabolic requirement. On average, for some people this might equivalent to around 20 minutes of jumping jacks, or jogging.

For parents attending to a child with fever, the risk remains that in the rush to treat the fever, there may be less emphasis placed on other more important considerations. For example, if the child looks very sick, this can sometimes indicate more about the seriousness of the cause than the thermometer's temperature reading. As such, there is often no need to 'treat' fever, although its presence is something to be wary of, and keep a close eye on the infected person and consult a medical professional if there are any concerns.

Nonetheless, if treatments are used, some clinical trials have shown that fever suppressor drugs don't necessarily worsen symptoms or alter the overall recovery rates. This is why there's no definitive rule on whether to suppress a fever or leave it to ride its natural course. Doctors will usually decide the preferred interventions on a case-by-case basis. Considerations may include the overall fever's duration and intensity, as well as the individual immune status of the patient, their age, and comfort levels, before opting for a choice of treatments. If the fever is left to ride its course, plenty of bed rest and ample fluids to prevent dehydration will go a long way to help the body fight the infection and recover.

Overall, fever itself remains a normal response to infection and assists the immunological process in many ways. Fever works to help us get better – it's one of the good guys! In the words of the English Physician, Thomas Sydenham (1624-1689), "Fever is nature's engine which she brings into the field to remove her enemy".

Relevance for Sustainable Development Goals and Grand Challenges

The considerations of fever relate to SDG 3 and SDG 11, as it can help ensure healthy lives and promote well-being (The United Nations 2030 agenda for sustainable development: Sustainable Goal 3). *Microbial aspects in italics*:

- **Goal 3. Ensure healthy lives and promote well-being for all at all ages** (*improve health, reduce preventable disease and premature death*). The main consideration for patients presenting with fever is to ensure any underlying infection or disease is tested for and treated, which can assist affected patients to recover as soon as possible. As well as this, promoting education and improving health literacy surrounding fever can also enhance the overall well-being for humans.
- **Goal 11. Make cities and human settlements inclusive, safe, resilient and sustainable** (*healthy environment*)**.** Assisting those with fevers and infections to recover sooner can help maintain healthy environments and rapid recoveries for communities around those who are ill (Figure 1).

Potential Implications for Decisions

1. ***Individual***

   a. Do personal fears or a general "fever phobia" sometimes create unnecessary worry, anxiety and concern for parents with a child who has an infection?

   b. If an infection does not lead to a fever, do we sometimes anecdotally consider this "less dangerous" and focus less on the treatment options?

c. Could parents focus too much on the thermometer reading itself, rather than the overall health and status of the child when a fever is present?

d. Does having a fever lead to more people using medications unnecessarily in an attempt to suppress it?

2. ***Community policies***

a. Local health costs associated with an increased rate of hospital and doctor visits due to the fear of having a fever.

b. Health costs associated with people seeking extra, sometimes unnecessary medications to suppress fevers.

3. ***National policies relating to fever presentations***

a. Education regarding the fact that fever is a natural response to infection, in an attempt to reduce the anxiety and fear when someone is caring for another with a fever.

b. Education to encourage plenty of fluids and bed rest when someone is sick, and to seek medical attention when concerned.

c. Education to reduce expectation-demand for antibiotics to treat conditions involving fever where they are deemed to be clinically inappropriate.

Pupil Participation

1. ***Class discussion of the issues associated with developing a fever and what it could indicate.***

a. Does having a fever indicate the severity of any infection?

b. Can you be very sick and not have a fever?

c. Do you find that you become worried when you get a fever?

2. ***Pupil stakeholder awareness***

a. Antibiotic resistance is a major clinical problem that renders many otherwise life-saving drugs ineffective and whose spread is promoted by the unnecessary use of antibiotics. Therefore, antibiotics should only be used to treat infections causing fever when clinically indicated and we should not demand them as a default therapy.

b. Fever often induces anxiety in us, but in reality it is helping us to fight off disease, so we should not be worried about it *per se*. It is how ill we feel that should determine our level of anxiety, and what we should do.

3. ***Exercises***

a. What kinds of illnesses should you immediately call an ambulance for or present to a hospital?

b. When ill, what kinds of events or feelings would prompt you to meet with a general practitioner (doctor) for a consultation?

c. Looking at the SDGs, how can we help others seek medical attention, education and training around the processes that occur during fever, in order to reduce the anxiety and concern?

d. Quiz: Fever. https://ed.ted.com/lessons/why-do-you-get-a-fever-when-you-re-sick-christian-moro#review

The Evidence Base, Further Reading and Teaching Aids

- Video: Why do you get a fever when you're sick (Ted-Ed). https://youtu.be/jRvxnpfCDSo
- Video: What are the benefits of fever. https://youtu.be/BxgEoLmOACo

Glossary

Antimicrobial activity: the process of killing or inhibiting the disease-causing microbes.
Bacteria: Single-celled organisms that exist in many environments; many live in harmony with humans but some can be disease-causing.
Bacterial infection: Occurs when bacteria enter the body and begin to multiply, causing a reaction in the body that could be harmful without treatment.
Biochemical cascade: A series of chemical reactions that occur within a biological cell when initiated by a stimulus to produce a response (also known as signalling pathway).
Clinical trials: Research investigations to test new treatments to prevent, treat or manage various diseases or medical conditions.
Dehydration: Our bodies consist of around 60% water, and need it to function normally. Loss of water occurs when the body loses more water than what is being taken in and is called dehydration. If not corrected by an increase in water intake, it can be dangerous.
Disease: A condition that impairs the normal functioning of all or part of an organism, commonly characterised by signs or symptoms.
Feedback systems: Response to control and regulate processes, where the output influences the stimulus.
Fever: Fever is a rise in body temperature above the normal temperature, usually caused by infection.
Illness: An unhealthy condition of the body or mind.
Immune cells: Cells of the immune system that help the body to fight infections and other diseases.
Inflammation: Immune system response that causes a localised reaction, producing redness, heat, swelling and pain as a result of infection, irritation or injury.
Heat shock proteins (HSP): Specific proteins made when cells are exposed to temperatures above their normal growth rate that act to regulate survival of other cells (also known as stress proteins).
Homeostasis: The state of a steady internal, physical, and chemical environment for an organism to survive.
Hypothalamus: Small region in the brain that controls many body functions, including the release of hormones, temperature regulation and maintaining homeostasis.
Immune status: Determined by the immune system of an organism and its capacity to defend itself against infections and pathogens.
Immune system: Network in the body that protects from harmful substances that invade the body, such as viruses, bacteria, and foreign bodies.
Infect: To spread a disease-causing substance to someone or something.
Infection: The invasion and multiplication of microorganisms (bacteria, viruses, fungi, parasites) in the body that are not normally present, resulting in a reaction.
Infectious diseases: Infectious diseases are caused by the spread of microorganisms from one person to another.
Interventions: The act of interfering with the intent of modifying the outcome, in order to treat or cure a condition.

Low-grade fever: A mild elevation of the normal body temperature.
Malaria: A mosquito-borne infectious disease that affects humans and animals, causing symptoms of fever, headaches, vomiting, tiredness.
Medications: A substance used to treat an illness or disease.
Metabolic requirement: The amount of energy the body requires to keep the body functioning at rest (also known as basal metabolic rate).
Microbes: A microscopic, single-celled organism, including bacteria, viruses, fungi, parasites (also known as microorganism).
Pathogen: Disease-causing microorganisms.
Receptors: Proteins, usually found on the surface of cells, that receive chemical signals and induce a variety of different processes (e.g. cell growth, cell binding).
Resistance: The ability to withstand a destructive agent or condition.
Thermometer: An instrument for measuring temperature.
Thermoregulation: The ability of an organism to maintain its core body temperature, even when the environment is different.
Toxins: A substance that is synthesised by a plant species, an animal, or by micro-organisms, that is harmful to another organism.
Viruses: Infectious agent that can only replicate within a host organism.