Healthcare-associated infections

Grandad: why did you say that the worst place to be if you get sick is a hospital?

Carla Pruzzo

DISTAV, Department of Earth, Environment and Life Sciences, University of Genoa, Genoa, Italy. Retired

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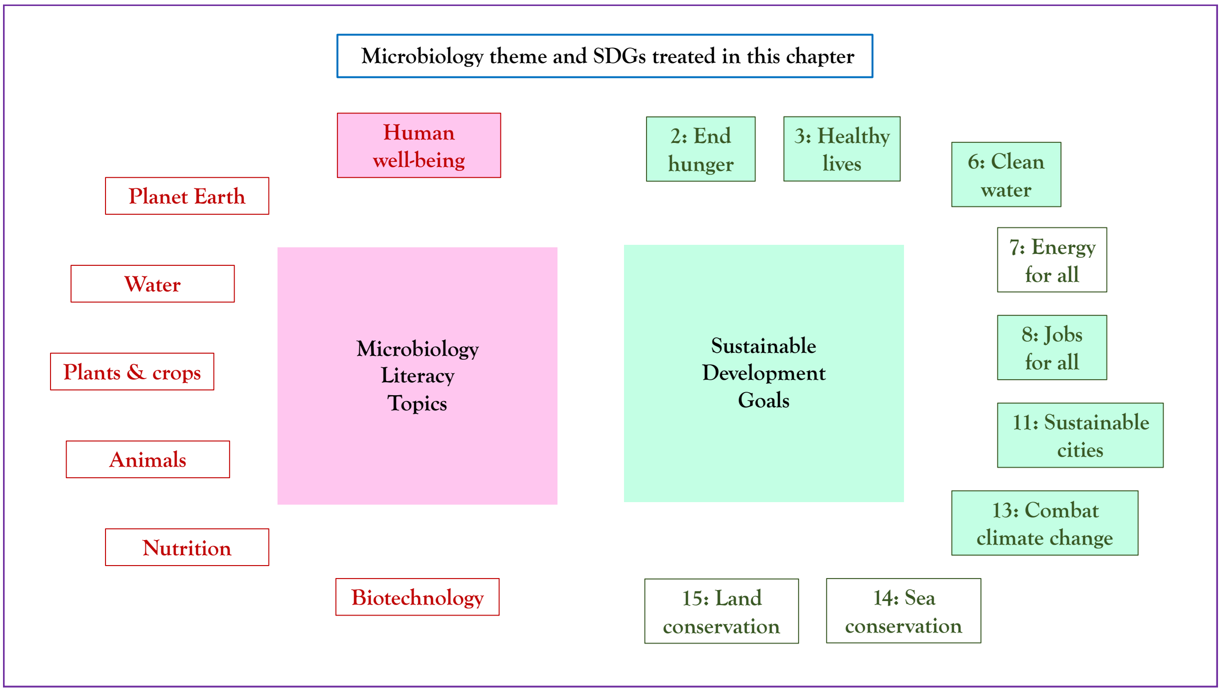
Storyline

Healthcare-associated infections (**HAIs**) are infections acquired by patients during their stay in a hospital or another healthcare setting. They were originally defined as "nosocomial infections" (from old greek "nosokomeion", meaning "hospital") but since the 1990s, with the expansion of out-of-hospital care, there has been a need to expand the concept to health and social care. An issue of great concern in hospital settings is antibiotic resistance. In recent decades, occurrence of antibiotic-resistant pathogens has emerged as one of the greatest threats to public health. Patients are often prescribed antibiotics, and such extensive use of these medicines creates an environment conducive for the emergence, persistence and spread of resistant pathogens. Highly resistant microorganisms such as multi-resistant Gram-negative bacteria are the cause of high incidence rates of HAIs worldwide. To combat this emergency, constantly updated programs for the management of antimicrobials in clinical settings and continuous training of health professionals and citizens on the prudent use of antimicrobials are necessary, among other things.

The Microbiology and Societal Context

The microbiology: microorganisms responsible for HAIs; endogenous and exogenous sources of infection; routes of transmission; risk factors; main types of HAIs; One Health. *Peripheral issues for completeness of the storyline:* some historical notes, the pioneers. *Sustainability issues:* prevention of HAIs; hospitals as hotspots of evolution of resistant bugs; hospitals as hot spots of environmental pollution.



Healthcare-associated infections: the pioneers

(*see also the MicroDiscoverer Heroes Portrait Gallery*)

In 1843, the American physician and writer **Oliver Wendell Holmes** published "The Contagiousness of Puerperal Fever" in the New England Quarterly Journal of Medicine and Surgery. Preceding Pasteur's formulation of the theory of the microbial origin of infectious diseases, his work proposed that the origin of puerperal fever, a deadly infection affecting women during or shortly after childbirth, arose from contact and was carried from one patient to another by the same doctors. He also suggested rules of behavior to prevent the spread of the disease. However, it is not Holmes but the Hungarian **Ignàc Semmelweis** (1818-1865) and the Scot **Joseph Lister** (1827-1912) who are considered the pioneers of the studies on the control of "hospital infections" (https://en.wikipedia.org).

Semmelweis, an obstetrician at the General Hospital in Vienna, was concerned by the very high number of deaths of women in childbirth due to puerperal fever. He was convinced that this depended on the fact that, in the ward, doctors and students first performed autopsies on deceased women and immediately afterwards - without washing their hands - visited the pregnant women. It is worth mentioning that the statement “A gentleman does not need to wash his hands” was widespread among health workers in those days. Clashing with most of his colleagues, the young doctor ordered all the doctors in the autopsy room to wash their hands with a solution of calcium chloride, thus reducing the mortality of mothers by 90%.

Lister, active at the Glasgow hospital, was frustrated by the enormous problem of lethal postoperative complications. Aware of Pasteur's work and the microbial theory of infection, he developed a spray system based on carbolic acid to disinfect instruments, the skin of patients and that of surgeons. Lister published the results of his studies in the prestigious journal “The Lancet” (March,1867). In the title of the article: “Antiseptic Principle of the Practice of Surgery” the term "antisepsis" (see Glossary) appeared for the first time.

Both Semmelweis and Lister were victims of the hostility of colleagues. Semmelweis could not bear these hostilities, went into depression and ended up being hospitalized in an asylum where he died. Lister's discovery was also not well received, the practice of antisepsis appeared only as a waste of time. But he had the authority to enforce strict antisepsis regulations, at least in the structures he headed and, in the end, Lister had the satisfaction of seeing his merits recognized and became the most famous surgeon in the United Kingdom.

In this context, one cannot fail to mention another major figure who dedicated her life to assisting the sick in hospitals, relieving their suffering and reducing the mortality rate in such structures: **Florence Nightingale**. She was born on the 12th May, 1820, into a rich, upper-class British family. Her father William Edward Nightingale named her Florence after the city she was born in: Florence, in Italy. Against her family’s wishes she took up nursing. She learned basic nursing skills in Germany where she received training at The Institution of Protestant Deaconesses, at Kaiserswerth-am-Rhein. In 1860 she opened a nursing school in London at St. Thomas's Hospital, thereby initiating the modern science of nursing of which she is rightly considered the founder. Her activity was aimed at improving living conditions in hospitals and to this end she identified five environmental factors: fresh air, pure water, efficient drainage, cleanliness or hygiene and light or direct sunlight. Her sentence "It may seem strange to state as a first requirement in a hospital that it must not harm the sick" illustrates her thought well.

Florence Nightingale in a hospital ward (by Joseph-Austin Benwell, c. 1856).

Healthcare-associated infections: the Microbiology

1. ***What are healthcare-associated infections?*** HAIs are defined as infections due to bacteria, fungi, viruses or other less common pathogens, contracted in any healthcare setting (hospitals, surgery clinics, dialysis centers, long-term care, home care, residential facilities territorial). In other words, at the time of entry into the facility or before the provision of assistance, the infections were neither clinically manifest, nor developing. Diseases that occur after discharge from the hospital within a period of time that varies from situation to situation (14 days as a general rule) are also considered HAIs.

With regards to their frequency, the World Health Organization (WHO) estimated that, globally, HAIs are the most frequent adverse outcomes during care delivery and no countries were able to completely eliminate this problem. Based on large studies from the USA and Europe, HAI incidence ranged from 130 to 203 episodes per 1000 patient-days, and pooled cumulative incidence was about 170 episodes per 1000 patient-days in adult high-risk patients in industrialized countries.

While some of these infections can be easily treated, others can be more serious, increasing patient length of stay and hospital costs, and causing significant distress to affected patients. All hospitalized patients are susceptible to contracting an HAI, although some patients are at greater risk than others: young children, the elderly and immunocompromised individuals (see Glossary) are the most susceptible.

2. ***Microorganisms responsible for HAIs.*** Any pathogen is able, on occasion, to cause HAIs**.** Microbes responsible for HAIs include bacteria, viruses, and fungi, but bacteria are the most common. Depending on the pathogenicity properties of the involved microorganism and the patient health status, different types of infections of different severity may occur.

    a. Bacteria are the most common pathogens responsible for HAIs. Some even belong to natural microbiota of the patient but cause an infection when his/her immune system is depressed. Gram-positive (*e.g.*, coagulase-negative staphylococci, *Staphylococcus aureus*, *Streptococcus* and *Enterococcus* species, *Clostridium difficile*) and Gram-negative (*e.g.*, *Klebsiella pneumoniae* and *Klebsiella oxytoca*, *Escherichia coli*, *Proteus mirabilis*, *Enterobacter* species, *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and *Burkholderia cepacia*) organisms are involved. Multidrug-resistant bacteria are commonly seen in HAIs (see below) and are associated with significant mortality (see Glossary).

b. Fungal pathogens cause HAIs in immunocompromised (see Glossary) individuals and those with indwelling devices, such as central lines or urinary catheters. The most common fungi are *Candida* species, such as *Candida albicans*, *Candida parapsilosis*, *Candida glabrata*.

c. Infections by viral pathogens make up 1-5% of all HAIs. Healthcare-acquired hepatitis B and C and human deficiency virus (HIV) have been implicated in unsafe needle practices. Globally 5.4% of all HIV infections are healthcare-associated and frequently occur in developing countries. Other reported viral pathogens include rhinovirus, cytomegalovirus, herpes simplex virus, rotavirus, and influenza. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) responsible for Coronavirus disease 2019 (COVID-19) must be included in this list since the COVID-19 outbreak in December 2019. Public healthcare facilities are hotspots of rapid spread of COVID-19 disease if appropriate transmission prevention protocols are not implemented and adhered to diligently. Both person-to-person and contaminated environmental surfaces-to-person spread have been reported in hospital settings.

3. ***Main types of HAIs.*** The most frequent types of infections include catheter-associated urinary tract infections, central line associated bloodstream infections, surgical site infections and ventilator-associated pneumonia, whose main features are as below.

a. *Catheter associated urinary tract infections (CAUTIs)*. CAUTI is the most common type of HAI globally. A catheter is a medical device consisting of a flexible tube that can vary, depending on its use, in material and length. The tube is introduced into a body cavity (through a process called catheterization) for diagnostic, therapeutic or surgical purposes. The urinary catheter, which is used to drain urine from the bladder, is inserted through the urethra into the bladder. The catheter is then connected to a urine collection bag. Between 15-25% of hospitalized patients receive urinary catheters during their hospital stay. However, catheters aseptically placed inside may serve as a conduit for entry of bacteria. The origin of the infection can be exogenous, i.e. from outside the patient, generally due to the contamination of tools by the hands of the personnel, or, more commonly, endogenous, i.e. originating from the patient's own microbes, and it is the bacteria residing in the colon of the patient that are the usual cause of these infections. The most important risk factor for developing a CAUTI is prolonged use of the urinary catheter. CAUTIs may be caused by both Gram-negative and Gram-positive bacteria, as well as fungi. *Escherichia coli* is the most common pathogen.

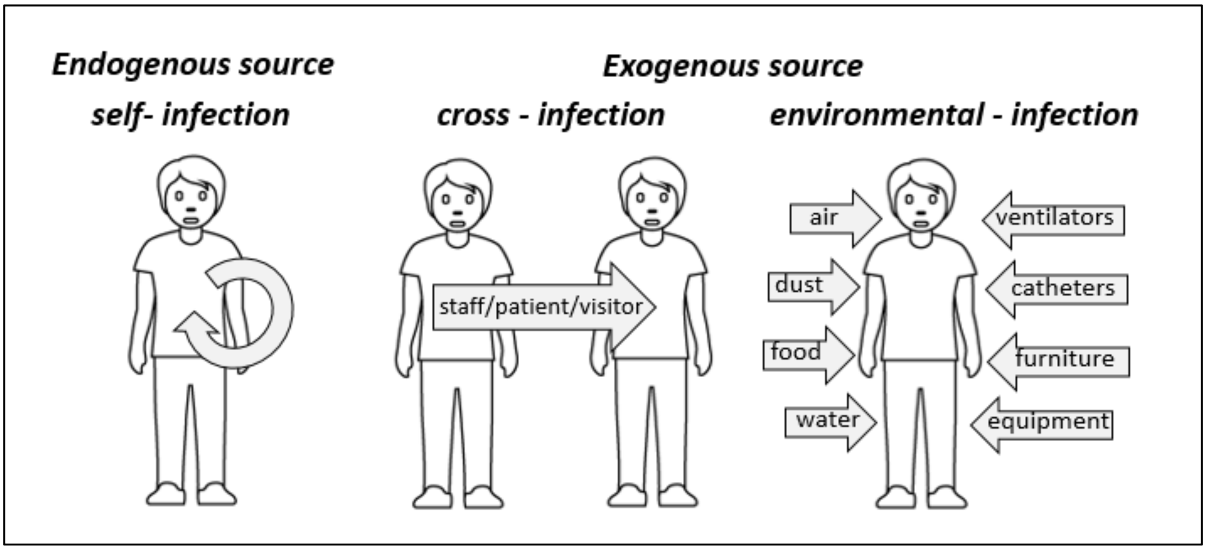
b. *Central line-associated bloodstream infections (CLABSIs)*. CLABSIs result in thousands of deaths each year and billions of dollars in added costs to healthcare systems. A catheter is inserted into a large vein above the heart through a vein in the neck, chest, or arm, to provide fluid and medicines. It is called a central venous line or central line. A CLABSI occurs when microorganisms enter the bloodstream through the central line. The port of entry into the bloodstream is the point where the catheter enters the blood vessel. The origin of the microorganisms, most frequently bacteria, varies: the skin area where the catheter is inserted, the hands of the personnel who position the catheter, contaminated fluid flowing through the central line. Healthcare providers must follow a strict protocol when inserting the line to make sure the line remains sterile and a CLABSI does not occur. Causative pathogens associated with CLABSI include Gram-positive bacteria (*Staphylococci*, *Enterococcus faecalis*), Gram-negative bacteria (*Klebsiella pneumoniae*, *Escherichia coli*, *Enterobacter*, *Pseudomonas aeruginosa*), and fungi (*Candida albicans*).

c. *Surgical site infections (SSIs)*. While advances have been made in infection control practices, including improved operating room ventilation, sterilization methods, barriers, surgical technique, and availability of antimicrobial prophylaxis, SSIs remain a substantial cause of disease, prolonged hospitalization, and death (SSIs account for 20% of all HAIs). The pathogens causing SSI arise from endogenous microflora of the patient. Not all wounds have the same degree of risk of infection: the greatest is that of wounds that cross areas rich in bacteria which have insufficient blood supply, and present necrotic phenomena (*i.e.*, irreparable changes in cells that lead to their death). This common type of HAI is mainly caused by *Staphylococcus aureus.*

d. *Ventilator associated pneumonia (VAP)*. VAP is a lung infection that develops in a person who is on a ventilator. A ventilator is a machine that is used to help a patient breathe by giving oxygen through a tube placed in a patient's mouth or nose, or through a hole in the front of the neck. An infection may occur if germs enter through the tube and get into the patient's lungs. VAP is found in 9–27% of patients on a mechanically-assisted ventilator. 86% of nosocomial pneumonia is associated with ventilation. Usual Gram-negative microorganisms involved in VAP are *Pseudomonas aeruginosa*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Acinetobacter species*; *Staphylococcus aureus* is the major Gram-positive microorganism. Respiratory viruses including influenza, respiratory syncytial virus, and others may be responsible for VAP.

4. ***Sources of microbes.*** In healthcare settings, the main sources of infection are other patients and healthcare workers, although the environment also plays an important role as a reservoir of potential pathogens that contributes to their spread. Microbes are common on inanimate surfaces, such as furniture, floors, walls, equipment and in indoor air. Infected patients spread microorganisms through the release of saliva droplets, fluids from infected wounds, urine, blood, other body fluids, but also through clothes and blankets.

The source of microorganisms can be endogenous and exogenous.



Endogenous and exogenous sources of microorganisms responsible for HAIs

a. *Endogenous microbial source – self-infection*. Microorganisms belong to the patient's normal microbiota and are usually non-pathogenic in their normal location and population levels but potentially pathogenic if they move to a different location or multiply to higher population levels that allow them to overwhelm the defenses that normally keep them in check. The endogenous origin of microorganisms is facilitated by the frequency with which chemotherapy treatments and instrumental interventions are carried out in the healthcare facility.

b. *Exogenous microbial source.*

i. *Cross – infection*. Microorganisms derive from another human source (*e.g.*, personnel, other patients and visitors).

ii. *Environmental infection.* Microorganisms derive from the hospital environment (air, surfaces, food, diagnostic or therapeutic instruments, etc.). Patients often come into contact with microorganisms that can survive on the inanimate surfaces and in the environmental matrices (air, water). In some cases, the source also acts as a vehicle; in other cases, vehicles connect the source to the subject who will suffer the infection.

5. ***Hospital environment and microorganisms.*** Studies suggest that hospitals are home to thousands of distinct types of bacteria, with the mix of species varying according to several factors, including most notably the building and space used to provide patient care, the equipment used to support the patient care and, last but not least, people, including patients, medical staff and visitors. The type and state of conservation of building materials and equipment, furnishings, plumbing, heating and air conditioning systems, and in general the hygienic conditions of the premises, strongly influence the presence and type of microorganisms in the hospital environment. This microbial assemblage includes both microorganisms that come from outside and microorganisms released by people within healthcare facilities. Their number and type are influenced by the number of people present in that environment and by their effective state of health; therefore, in addition to harmless environmental microorganisms, microorganisms (pathogenic and non-pathogenic) of human origin are also part of this complex community.

Bacterial diversity varies between different hospital areas: halls, lounges, patient rooms and bathrooms have been shown to exhibit more diverse bacterial compositions than the isolated intensive care unit, where various management practices, including stricter sanitation protocols, favor the survival of microorganisms expressing genes for resistance to common disinfectants and antimicrobial agents (see below). Interestingly, it has been suggested that patients and hospital workers can alter the microbial composition of the hospital in the specific areas they occupy, resulting in unique microenvironments within the larger hospital environment.

Microorganisms can survive for long periods of time in the healthcare environment and can be detected in the air, water and surfaces of medical equipment, floors, walls, tables, etc. Their persistence and growth are influenced by a series of factors such as the degree of humidity, light, temperature, solar radiation, the presence of materials capable of supporting microbial growth, their properties (*e.g.* porosity, organic or inorganic composition, state of conservation, substances that coat the material, products artificially applied to the material) and, in general, their bioreceptivity *i.e.* the aptitude of a material to be colonized by one or more microorganisms.

6. ***Routes of transmission of microorganisms associated with HAIs.*** As with other infections, the pathogens associated with HAIs can be transmitted by direct / indirect contact, by air, by a contaminated vehicle or a combination of these.

a. *Direct contact* occurs between a healthy and an infected person, especially when a person performs patient care activities that require direct personal contact. Direct contact can also occur between two patients.

b. *Indirect contact* via a contaminated vehicle is often a result of unclean hands contaminating an object. The microorganism remains on this surface to be picked up by the next person who touches it and may then develop an infection.

c. *Air transmission via large droplets* (>5 μm) that are emitted from the respiratory tract of an infected person through coughing, sneezing and talking. These droplets travel short distances (up to 2 m) and enter the susceptible host through contact with his/her conjunctivae, nasal mucosa or mouth. Infected droplets may also persist on surfaces for long periods of time (indirect contact).

d. *Air transmission via small droplets* (< 5 μm) that travel long distances. Microorganisms carried in this manner remain suspended in the air for long periods of time and can be dispersed widely by air currents. All the air in a room may be contaminated. Poorly maintained air-conditioning systems can cause respiratory tract infections; Legionnaire's Disease is spread by air-conditioning systems, among other things. Patients with a compromised immune system or lung disease are the most vulnerable.

e. *Transmission through a common contaminated vehicle* (food, infusion liquids, etc.). This type of transmission often involves materials and medical devices for diagnostic and therapeutic interventions (*e.g.*, vascular and urinary catheters, endoscopes, syringes, infusion liquids, pharmacological solutions). Foods can cause HAIs when they come from infected animals or other infected sources, or become contaminated during preparation and improper storage.

7. ***Risk factors.*** The subjects at risk of contracting an HAI are mainly patients and, less frequently, the staff involved in assistance. The factors that make these subjects, but especially patients, at risk of contracting an HAI belong to two main types, intrinsic and extrinsic.

a. *Intrinsic factors* include age, gender, other infections or serious concomitant diseases (*e.g.*, tumors, immunodeficiency, diabetes), trauma, burns. In general, the frequency and severity of HAIs increase as the patient's defense mechanisms against infections become compromised. Immunocompromised hosts (subjects who do not have the ability to respond normally to an infection because of an impaired or weakened immune system) are at high risk of contracting HAIs. Inability to fight infection can be caused by different conditions, including diseases (*e.g.* diabetes, human immunodeficiency virus [HIV] infection), malnutrition, and drugs.

b. *Extrinsic factors* include length of stay in the hospital ward, crowding, use of invasive devices (*e. g.*, bladder catheter, intubation), admission to intensive care, surgical interventions, control and prophylaxis measures implemented by the healthcare facility.

8. ***How to prevent HAIs.*** A crucial point for combating HAIs is the definition and application of good care practices and other measures, according to an integrated program that must be adapted to each care setting. Of all the measures to prevent HAIs, proper hand washing remains the most important measure.

Other precautions to prevent exogenous and endogenous transmission of microorganisms in healthcare settings include (but are not limited to):

Exogenous transmission:

- Compliance with isolation precautions
- Correct use of personal protective equipment (gloves, gowns, masks, etc.)
- Avoid unnecessary use of internal devices and remove them as soon as appropriate
- Avoid unnecessary diagnostic and therapeutic procedures
- Correct use of antibiotics and disinfectants
- Practice proper aseptic and/or sterile techniques when inserting and maintaining devices
- Ensure the cleaning and use of cleaning agents on walls, floor, windows, beds, baths, toilets and other medical devices.
- Regular check of filters and ventilation systems
- The quality of food should meet standard criteria
- Routine disinfection of surfaces, patient equipment and medical devices
- Vaccination of health professionals
- Surveillance of infections and timely identification and control of outbreaks

- Proper waste management

Examples of measures that must be taken to prevent HAIs: hand washing, use of gloves, gowns and masks, room cleaning

Endogenous transmission

- Avoid excessive and improper use of broad-spectrum antibiotics. Appropriate antimicrobial use with the correct agent, dose, and duration is needed to minimize the growth of antibiotic-resistant pathogens
- Use all precautions to prevent the transfer of microorganisms from one part of the body to another (as with urinary tract infections)
- Keep the patient's immune status in shape with an adequate diet
- Avoid, when possible, the use of chemotherapy that can weaken the patient's immune defenses

9. ***Resistant bugs in clinical settings.*** One of the most important scientific breakthroughs in the history of medicine is undoubtedly the discovery of antibiotics. With the discovery of penicillin by Alexander Fleming in 1928 and the dawning of the antibiotic era, the body's own defenses gained a powerful ally. These molecules represented a revolution in the therapy of infectious diseases, saving millions of lives.

Subsequently, however, enthusiasm about them has been mitigated by a phenomenon called antibiotic resistance, the ability of microbes, and especially pathogens, to resist the inhibitory activity of antibiotics which thus compromises antibiotic therapy. This is a problem that surfaced not long after the introduction of penicillin and now threatens the usefulness of these important medicines.

There are two types of antibiotic resistance: intrinsic and acquired. *Intrinsic resistance* is the innate ability of a microbial species to resist the action of an antibiotic as a consequence of cell characteristics. For example, the outer membrane of bacteria like *E. coli* naturally protects the cell against aminoglycoside antibiotics and polymyxins.

A more worrying problem is *acquired resistance* that occurs when microorganisms that are normally susceptible to antibiotics become resistant as a result of either spontaneous mutation in their DNA or acquisition of antibiotic resistance genes from other microbes by *horizontal gene transfer* (see Glossary). These processes occur in the absence of the selective agent, *i.e.* the antibiotic; however, when the antibiotic is present, microorganisms that have become resistant are not inhibited or killed (in contrast to the sensitive ones), and proliferate and become predominant.

Since acquired resistance is found only in some members of a microbial species, it is more difficult to trace than intrinsic resistance, and each new isolate may have acquired resistance to a different spectrum of antibiotics. Many bacteria and fungi have acquired resistance to more than one antibiotic, making microbial resistance to antibiotics one of the most pressing public health problems. It was estimated that in 2019, 4.95 million people died from illnesses in which antimicrobial resistant bacteria played a part. Of those, 1.27 million deaths were the direct result of antibiotic resistance — meaning that drug-resistant infections killed more people than HIV/AIDS (864,000 deaths) or malaria (643,000 deaths). Rates of antibiotic resistance may continue to climb if effective infection prevention and control measures are not adequately implemented, and if antibiotic agents continue to be inappropriately used. The O'Neil Report of 2016 predicts that by 2050, as many as ten million people could die each year as a result of antimicrobial resistance.

Most antibiotic-resistant infections are thought to occur in clinical settings/hospitals that may serve as major hotspots of antibiotic resistance appearance and selection. Indeed, many of the key factors contributing to the development and spread of antimicrobial resistance (immunocompromised patient populations, large numbers of indwelling devices and widespread use of broad-spectrum antibiotics…) are present in these settings.

A drug-resistant organism may be introduced into a healthcare facility with the admission of a patient (infected by such a strain) but also with visitors and personnel. Alternatively, antibiotic resistant cells may emerge among pathogenic or commensal (see Glossary) microorganisms that colonize a patient or among microorganisms present in the hospital inanimate environment. Regardless of origin, as a consequence of the selective pressure exerted by the antibiotic present at high concentrations in the healthcare setting, resistant microorganisms can proliferate and infect patients, often via the contaminated hands of healthcare personnel, contaminated medical or surgical equipment, or the inanimate hospital environment.

Multidrug resistant pathogens, including carbapenem-resistant *Pseudomonas aeruginosa*, vancomycin-resistant enterococci (VRE), methicillin-resistant *Staphylococcus aureus* (MRSA), and extended-spectrum β-lactamases (ESBL)-bearing *Acinetobacter baumannii*, *Escherichia coli*, and *Klebsiella pneumoniae,* are amongst the most problematic due to the paucity of treatment options, increased hospital stay, and high medical costs.

Healthcare personnel can prevent the spread of resistant germs by following recommended hygiene practices (*e.g.*, cleaning their hands, wearing gowns and gloves, and thoroughly cleaning patient care areas and medical equipment).

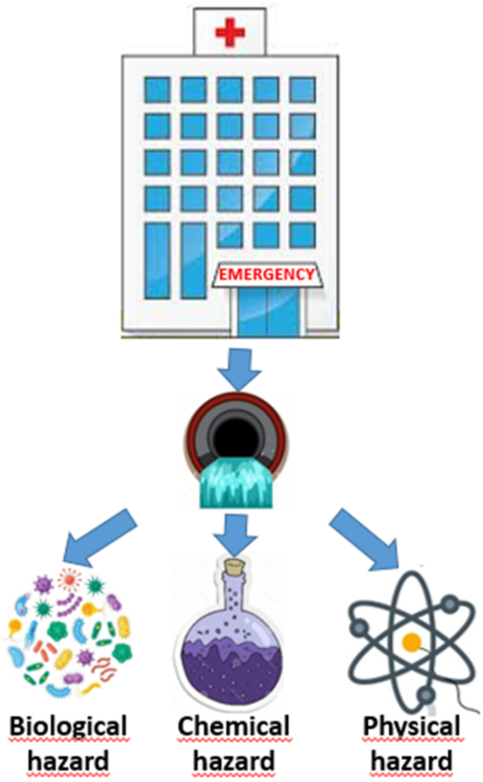
Unfortunately, parallel to the increase in antimicrobial resistance, the rate of development of new antimicrobials is falling and thus alternative strategies are urgently needed to prevent and treat HAIs.

One such strategy is the development of vaccines against pathogens involved in HAIs. However, for most of the pathogens involved in HAIs, vaccines are not currently available, so still need to be developed. It has also to be considered that a great part of HAIs is caused by commensal pathogens present prior to hospitalization (endogenous infections), and that some HAI at-risk patients are also patients who have a weakened immune system and hence may mount only a weak response to vaccines. Until vaccination strategies that overcome these difficulties are available, measures to monitor antimicrobial usage and antimicrobial resistance spread in clinical settings continue to be crucial in the prevention of HAIs and should be strengthened.

Another strategy is the development of therapies based upon predators of antimicrobial resistant pathogens, such as bacterial viruses (phages) and bacterial predators like *Bdellovibrio* (see BeeVee in the MicroDefender Portrait Gallery).

10. ***Environmental pollution and the ONE HEALTH approach.*** Environmental pollution has become a major concern for the future of life on our planet; medical care, especially in hospitals, contributes to this pollution. Hospitals generate a large volume of waste of which approximately 85% is non-dangerous general waste. The remaining 15% consists of hazardous residues of various kinds, such as chemicals, chemotherapeutic drugs, radioactive material and infectious material, which pose chemical, biological and physical risk to public and environmental health. These substances are present in the waste in a wide range of concentrations depending on the size of the hospital, the number of beds and patients, the number and type of wards and services provided, as well as the geographical location and climate.

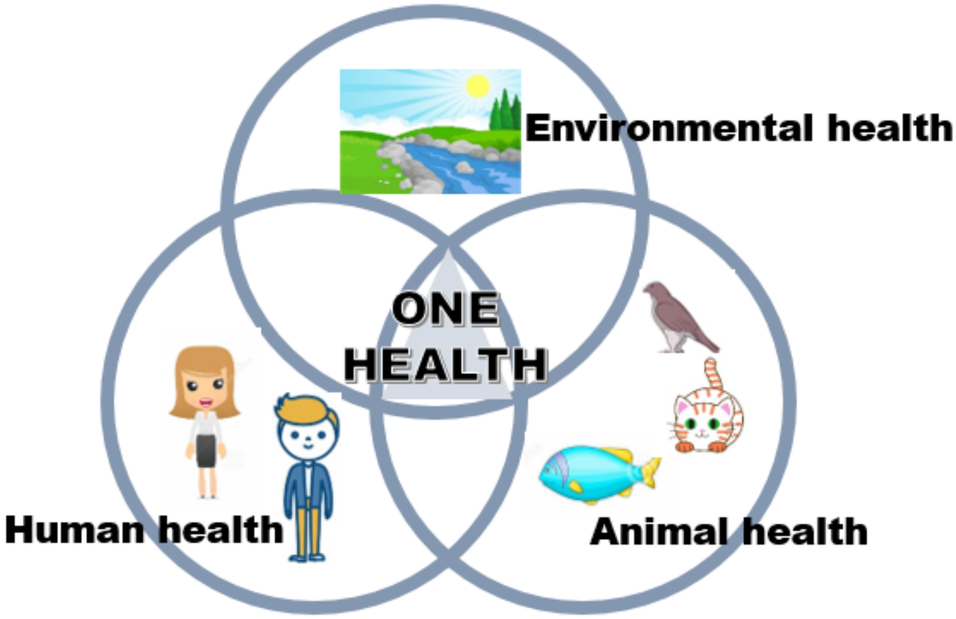
In some countries, hazardous substances produced in hospitals have a regulatory status that defines how to handle and treat hospital effluent. Additionally, hospital effluent is pre-treated before discharge into the municipal sewer system. Other countries, on the other hand, consider hospital wastewater as domestic and therefore discharge it directly into the sewage system without any pre-treatment and control. The major problems that have recently emerged concern substances and microorganisms that do not have a regulatory status, such as residues of antibiotics and specific pathogens that can remain active for prolonged periods in purification plants. The large variety of pathogenic microorganisms (bacteria, protozoa, helminths and viruses) present in wastewater are mainly derived from the feces of infected humans and secondly by bodily fluid discharge, usually in small quantities. Because even the most advanced technologies cannot completely eliminate them, pathogenic and resistant microorganisms, resistance genes and drug residues can contaminate soils and waterways, potentially altering indigenous ecosystems important consequences on key cycles/mechanisms/processes thus compromising fundamental ecological processes.



Hospital wastewater represents risks for public and environmental health

In the external environment, antibiotic resistance can move between clinical and environmental isolates through horizontal gene transfer. At the same time, the progressive accumulation of antimicrobial substances can exert a continuous selective pressure favoring an increase in the level of resistant organisms and the formation of an environmental reservoir of resistance genes and resistant pathogens. From the environment, such genes and such pathogens can reach animals and humans in an interconnection that is properly expressed by the **One Health** approach.

This approach is based on the belief that we cannot truly understand and protect the health of humans, animals and the environment by addressing each of these elements individually. The One Health approach states that humans live in the environment and their health is closely linked to it and animal health (One Health Commission, 2019). The health of any of these ecosystems may affect the health of the others, including human health. It means that if a threat occurs in the environment or in animals, it can have profound consequences for humans. On this basis, due to the flow of bacteria and genes among animals, people, and their environment, it is easy to understand that all factors improving the presence of resistance determinants in the environment or in animal pathogens could affect human health.



One Health is at the intersection of human health, animal health, and environmental health

Relevance for Sustainable Development Goals and Grand Challenges

The issue of HAI impacts many of the SDGs, both directly and indirectly, including

- **Goal 2. End hunger.** Insufficient or inadequate nutrition can reduce the efficiency of the immune response and consequently increase the susceptibility to infections. This is also true for hospitalized patients; thus, ending all forms of malnutrition is an important tool to combat HAIs.
- **Goal 3. Healthy lives.** Hospitals play an essential role in human welfare through the health services they provide. Due to the presence in clinical contexts of frail people and subjects with compromised or weakened immune systems, strategies must always be applied to prevent and control the presence and spread of pathogenic microbes in the environment. Clinical settings use a great amount of antimicrobials that may persist in the environment providing ideal conditions for the selection of resistant bacteria. Thus, programs to monitor antimicrobial usage and the

presence and spread of antimicrobial resistant microorganisms are crucial. Appropriate training of clinical staff support the adopted measures

- **Goal 6. Ensure availability of water for all.** Availability of clean water will ensure adequate personal hygiene, proper hand washing, which is the most important measure to prevent HAIs, adequate cleaning procedures of surfaces of medical equipment, floors, walls, tables, etc. It is also important that every water use is examined and evaluated for its risk of harboring and transmitting pathogens. For example, drains from hospital sinks and toilets can pose a risk for harboring antibiotic-resistant pathogens that can spread to patients.
- **Goal 8. Promote sustained, inclusive, and sustainable economic growth.** Economic growth enables improvement of hygienic conditions, clinic care facilities, and public health measures, leads to the improved control of infectious diseases including HAIs. Job opportunities are linked to the development/improvement of the network of microbiological quality control services. Technical innovations are essential for improving infectious diseases diagnostics and anti-infective treatments.
- **Goal 11. Healthy environment.** Hospitals are also responsible for generating large volumes of wastewater. Hospital wastewater is complex and contains a large amount of emerging, organic and biological contaminants (antibiotic-resistant bacteria, antibiotic-resistant genes, persistent viruses). Poor management of hospital waste contributes to environment pollution, directly affecting many ecosystems and species. Hospital waste must be properly managed and disposed of to protect the environment, general public and workers, especially healthcare and sanitation workers who are at risk of exposure to biomedical waste as an occupational hazard.
- **Goal 13. Climate change.** The effects of climate change on human health are innumerable and become increasingly severe as the pace of climate change accelerates. Some existing health threats will increase and new health threats will emerge. There are strong indications that climate change may lead, among others, to an increase in respiratory and cardiovascular diseases, injuries and premature deaths related to extreme weather events, changes in the prevalence and geographical distribution of food and waterborne diseases and other infectious diseases. Of course, all of this increases the risk of hospitalizations. The result of increased hospitalizations, particularly for those with serious illnesses requiring intensive care, will be more days with invasive devices and, as a likely result, higher risk of HAIs, which are often antibiotic resistant. Therefore, in order to control HAIs and associated human health risks, we should also strengthen the control of environmental and climatic factors.

Potential Implications for Decisions

1. *Individual*

a. Wash often your hands when in the hospital

b. Remind your loved ones and visitors to clean their hands

c. Talk to your doctor to learn what you should do to reduce the risk of getting a HAI

d. Help prevent antibiotic resistance by only using antibiotics when prescribed by a doctor and always following his/her advice

e. Remember that antibiotics don't work against viruses like the ones that cause the common cold

f. Protect yourselves and those around by getting vaccinated. Without vaccines, we are at risk of serious illness and disability from diseases.

2. Community policies

a. Good education to promote knowledge of which diseases can be contracted in hospital, which are the factors that increase the risk of contracting them, and which microorganisms are involved

b. Good education to promote knowledge of good practices that must be implemented by both clinical staff and citizens

c. Good education for a better use of antibiotics

3. National policies

a. Strengthening of actions for routine monitoring of quality healthcare service and ensuring the hospital team meets the high standards required for patient care

b. Assigning adequate resources to healthcare services

c. Continuous monitoring of HAIs

d. Continuous monitoring of antibiotic resistance in bacteria and fungi and antimicrobial usage

e. Funding research programs to study new measures, other than antibiotics, for prevention and treatment of HAIs

f. Improvement of long-term, national and international actions to enhance the knowledge on climate change and its impacts on pathogen biology, ecology and transmission to humans

g. National vaccination program

Pupil participation

1. Class discussion of the issues associated with HAIs.

2. Pupil stakeholder awareness

a. What do you think are the most important measures to take when visiting a friend or relative in hospital?

b. Can you think of anything that could be done to reduce the transmission of pathogens in a clinical setting?

c. Why do you think it is important to take the antibiotic only under the supervision of your doctor?

3. Exercises

a. Show to pupils images of bacteria and viruses of different shapes and sizes, both pathogenic and non-pathogenic to humans.

b. Show pupils images of nutrient agar plates showing microbial colonies forming after children have placed their hand on the surface before and after washing. Several videos are available on the Internet on this topic.

The Evidence Base, Further Reading and Teaching Aids

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Glossary

Antisepsis: it is a procedure that destroys or inhibits the multiplication of microorganisms present on living tissues (skin and mucous membranes)**.** The organic and inorganic substances used for this purpose are called antiseptics. They are distinguished from disinfectants, which destroy microorganisms found on non-living objects.
Commensal: are those type of microbes that reside on surface of the body or mucosa without harming human health. The microbes living in harmony with humans mostly consist of bacteria which are present in our body and contribute to human health in several ways: protecting from various pathogenic bacteria, synthesizing various useful factors, boosting the host immune system to prevent various diseases (*e.g.*, inflammatory bowel disease, celiac disease, rheumatic disease, allergies, and some neurological diseases), shaping innate and adaptive postnatal immunity conditions.
Horizontal Gene Transfer: it is a process by which genetic material is exchanged between two organisms without a familial relationship existing between the two. Horizontal gene transfer is different from vertical gene transfer where an organism takes its genetic material from its parents. In prokaryotes there are three mechanisms through which horizontal gene transfer can occur: transformation (a cell takes up genetic material present in the environment that derives from other cells or viruses), transduction (the genetic material is transferred from one bacterium to another via a bacteriophage infection), conjugation (a cell, called recipient, receives genetic material from another, called donor, through physical contact between the two cells).
Immunocompromised: having a weakened immune system. People who are immunocompromised have a reduced ability to fight infections and other diseases. This may be caused by certain diseases or conditions, such as AIDS, cancer, diabetes, malnutrition, and certain genetic disorders. It may also be caused by certain medicines or treatments, such as anticancer drugs, radiation therapy, and stem cell or organ transplant. Also called immunosuppressed.
Mortality: it refers to the number of deaths in a certain group of people in a certain period of time. Mortality may be reported for people who have a certain disease, live in one area of the country, or who are of a certain gender or age (https://www.cancer.gov/publications/dictionaries/cancer-terms/def/mortality).