ESN
EUROPEAN SPECIALIST NURSES ORGANISATION

MODULE 1

Microbes

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After reading Module 1,
you will understand the basics of microorganisms. This will include the wide variety of bacteria, viruses, fungi, yeasts and parasites, and their characteristics such as growth, and replication. You will also know more about the diseases caused by microorganisms and their diagnosis, and will be able to communicate these to colleagues and patients.

FLORENCE
NIGHTINGALE

The most important practical lesson that can be given to nurses is to teach them to observe

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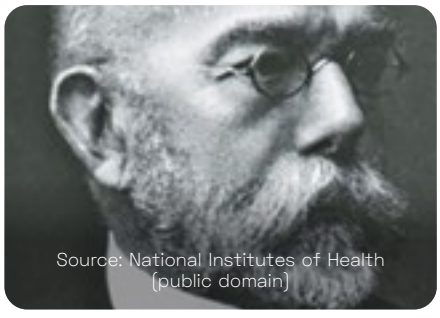
1 The development of microbiology

Microbiology is founded on the discovery of the first single-cell micro-organisms in the 1670s and 1680s by Antonie van Leeuwenhoek (Figure 1), a Dutch businessman.

Source:
Delft Rijksmuseum (public domain)

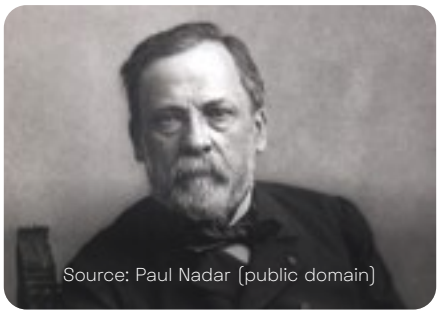
FIGURE 1: ANTONIE VAN LEEUWENHOEK (1632-1723)

Modern understanding of bacteriology began with the German doctor Robert Koch (Figure 2), the French biologist, chemist and microbiologist Louis Pasteur (Figure 3), and the German biologist Ferdinand Cohn (Figure 4). In a presentation to the Berlin Physiological Society in 1882, Koch made the connection between single-celled organisms and the development of certain diseases [1]. Research carried out by Pasteur, in the second half of the 19th century, supported the germ theory of disease, and the development of prophylactic vaccines [2]. Cohn's work was in applied microbiology, including understanding the classification and physiology of bacteria [3].



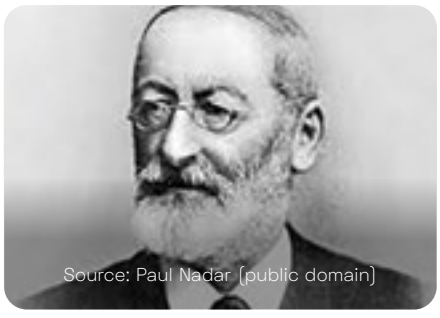
Source: National Institutes of Health (public domain)

FIGURE 2: ROBERT KOCH (1843-1910)



Source: Paul Nadar (public domain)

FIGURE 3: LOUIS PASTEUR (1822-1895)



Source: Paul Nadar (public domain)

FIGURE 4: FERDINAND COHN (1828-1898)

Through their work, and the work of others, it became increasingly clear that infectious diseases were mostly caused by bacteria and viruses, and that bacterial infections and viral infections needed to be treated differently – for example, antibiotics do not work for viral infections. For nurses such knowledge is essential for the prevention and treatment of bacterial and viral infections, and for the control of the development of antibiotic resistance, the adaptation of microbes to medication.

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2 An introduction to microbes

2.1 "Meet your Microbes"

Nurses are familiar with the body systems and vital organs in our bodies, but their training may overlook the normal human microbiota [4]. This is the population of microorganisms that naturally live on our skin, and in our respiratory, digestive and reproductive systems, and are part of our healthy daily life. When you eat a cheese sandwich, you can digest it not only because of the digestive enzymes, but also thanks to the almost 1.5 kilos of intestinal bacteria. When you defecate, half of this is bacteria. When you wash, a few million microbes get rinsed away, but soon get replaced.

The right balance of microorganisms of all forms and shapes, more than one hundred thousand billion or 14,000 times the number of people on earth, play a key role. Everyone has their unique set of microbes, and the majority of these protect us and help us to stay healthy. This is known as the microbiota.

For more information, go to the NIH Human Microbiome Project website **(QR code 1)**.

These microbes do not normally cause disease in healthy people. However, in people with a weakened immune system, or a disrupted gut microbiota, some of the microbes (opportunistic pathogens) can cause disease.

Some microbes are always pathogenic, and the immune system acts to keep these under control. When these are no longer controlled by the immune system, they cause an infection. Symptoms vary per infection, but generally include:

- Redness
- Swelling
- Fever
- Pain

SCAN ME
(QR code 1)

Infections can range from a minor illness to systemic and life-threatening disease. Typical pathogens include: Salmonella typhi, Mycobacterium tuberculosis, Clostridioides tetani, Influenza viruses, Poliomyelitis viruses, Aspergillus niger and many others.

Infectious microorganisms can spread through water, food, insect bites, shaking hands, sneezing and coughing, blood, wounds or sexual contact. People can also be carriers of potentially harmful bacteria, without becoming ill themselves. They may spread these through their stools, urine, blood and saliva.

3 Bacteria

Bacteria are real survivors. They were here before humanity appeared on the earth and will remain when we have gone. Certain bacteria can survive in extreme conditions, for example in sulphuric acid, boiling or freezing water, and under extremely high pressure. For example, Deinococcus radiodurans withstands extreme cold, drought and acid, and even lives in the walls of nuclear reactors.

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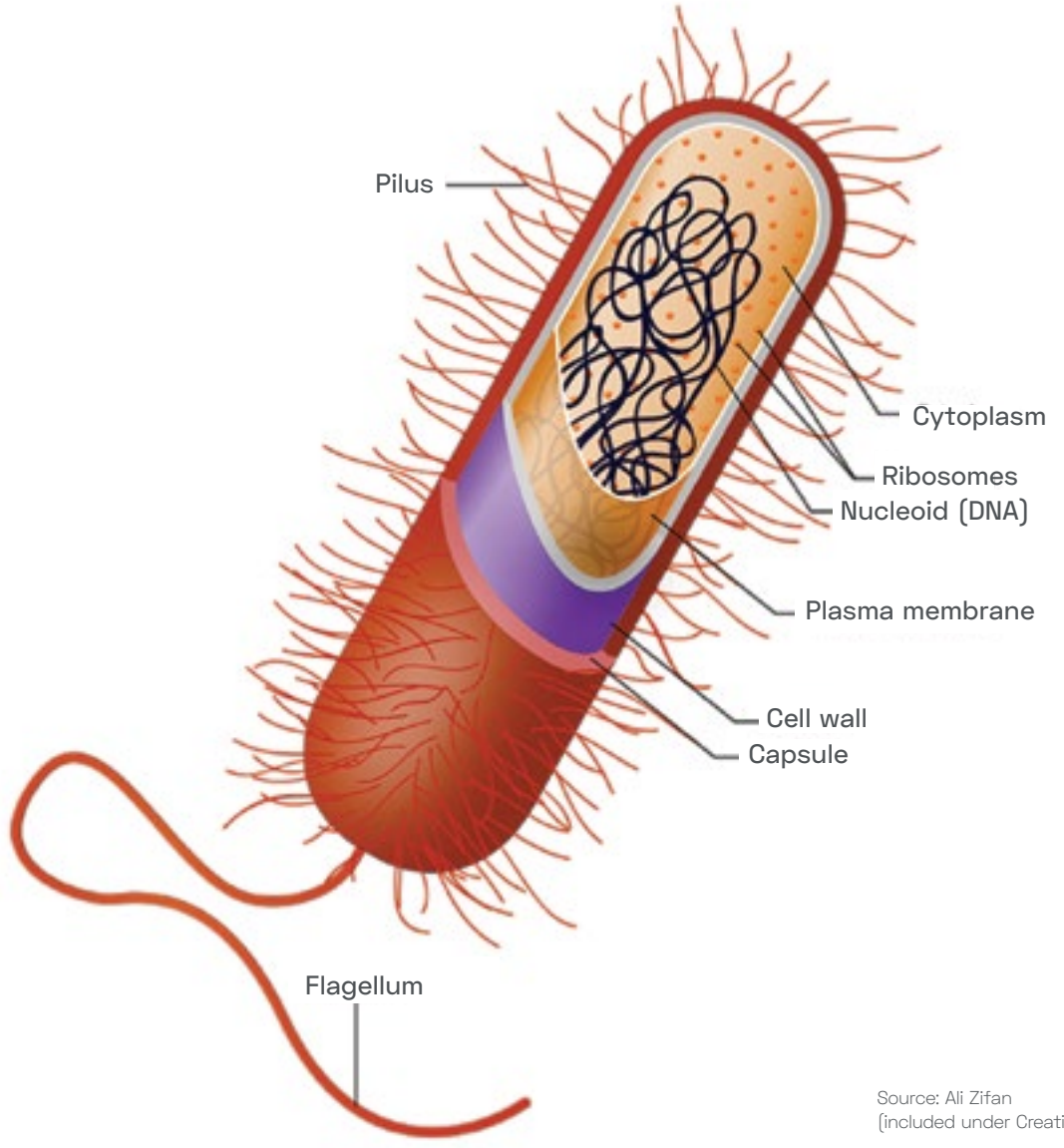
3.1 Structure

Bacteria are single cells, typically around 0.5-4-5 µm (Figure 5). Bacteria are simpler than mammalian (including human) cells (Figure 6), and do not have mitochondria, endoplasmic reticulum, or nuclear membranes. The bacterium is typically made up of cytoplasm and DNA surrounded by a cell membrane.

FIGURE 5: STRUCTURE AND CONTENTS OF AN EXAMPLE OF A GRAM-POSITIVE BACTERIAL CELL



Source: Ali Zifan
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Bacteria have a peptidoglycan (protein and sugar) cell wall around the membrane, and some also have an additional slime layer or cell envelope. Bacteria may also have protrusions, known as flagella and pili. The cell membrane is used as a target by researchers developing antimicrobial medications, looking to exploit weak spots and neutralise defence mechanisms.

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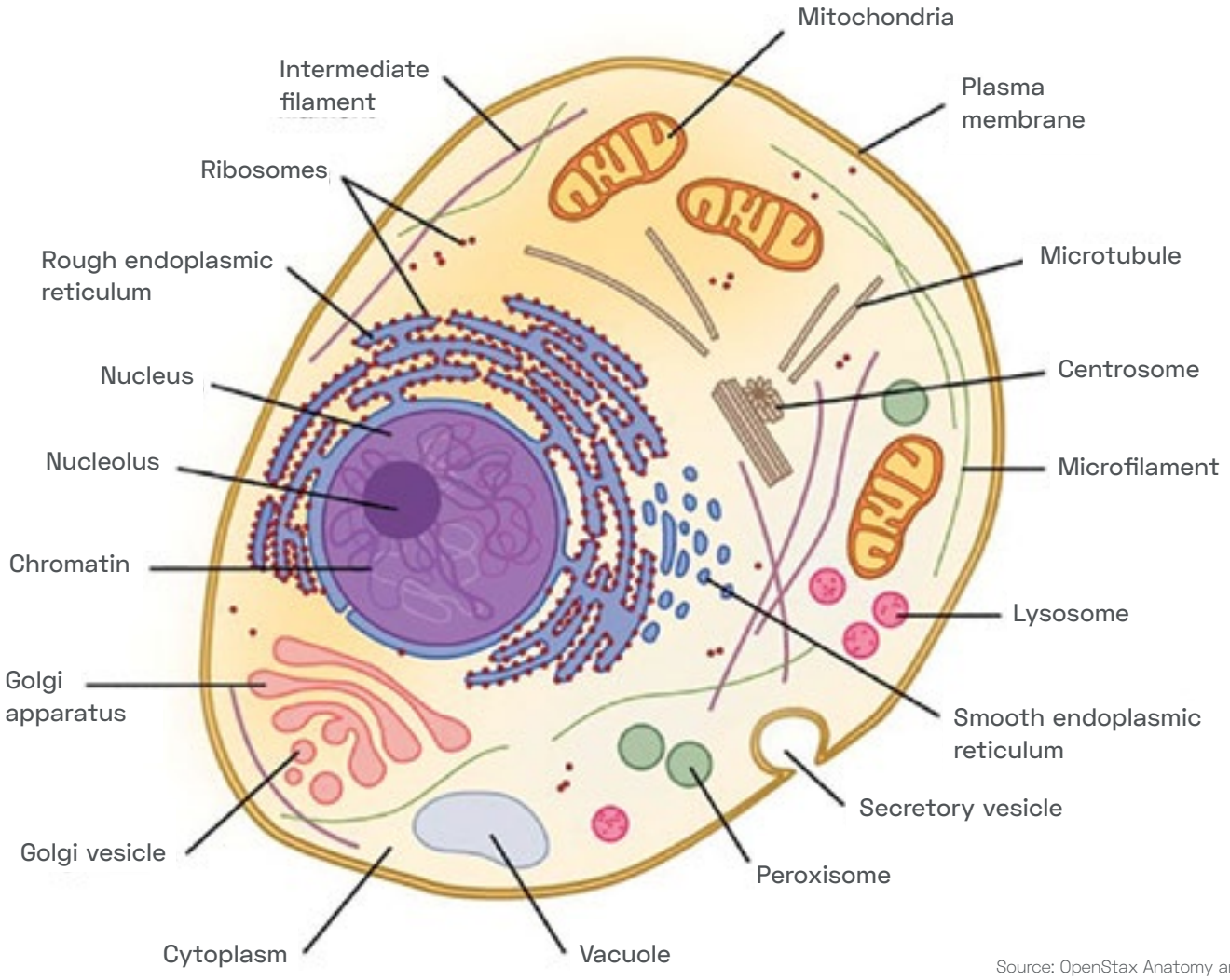
FIGURE 6: STRUCTURE AND CONTENTS OF A TYPICAL MAMMALIAN CELL



Source: OpenStax Anatomy and Physiology (included under Creative Commons licence)

3.1.1 Shape and form

The shape of bacteria is used for systematic classification, and to show relationships. The forms that the bacteria create as they multiply can also be used to identify them (Figure 7).

- **Cocci (sphere)**
  - > Streptococci form chains
  - > Staphylococci form grape-like clusters
- **Bacilli (rods)**
  - > Some bacilli, for example Bacillus species, form spores
  - > The plague-causing bacterium Yersinia pestis forms a slime layer

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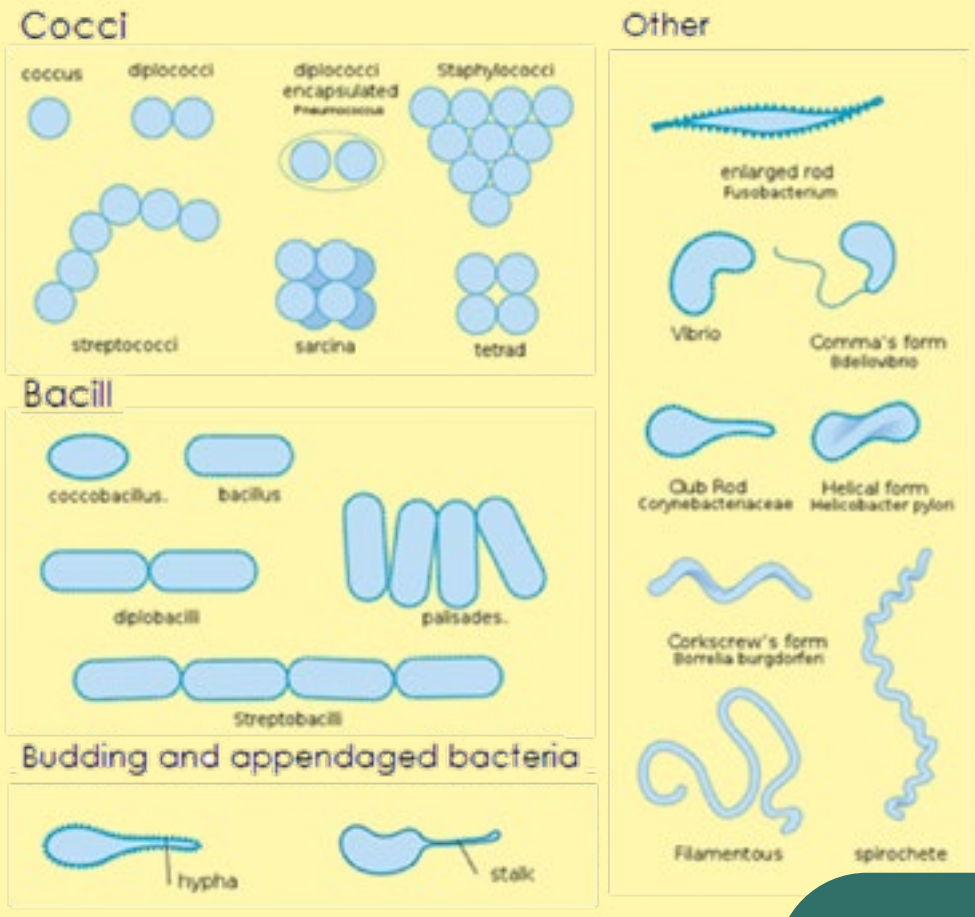
- **Vibrio (commas or curved rods)**
  - > Vibrio bacteria are motile, and move around using flagella
- **Spirillum (spiral-shaped rods)**
  - > Some spirillum have flagella

FIGURE 7: SHAPES AND TYPES OF BACTERIA



Source: Mariana Ruiz [LadyofHats] (public domain)

Actinobacteria, once thought to be fungi, are rod-shaped bacteria that create fungal-like forms. Actinobacteria are the source of many drugs, including antibiotics.

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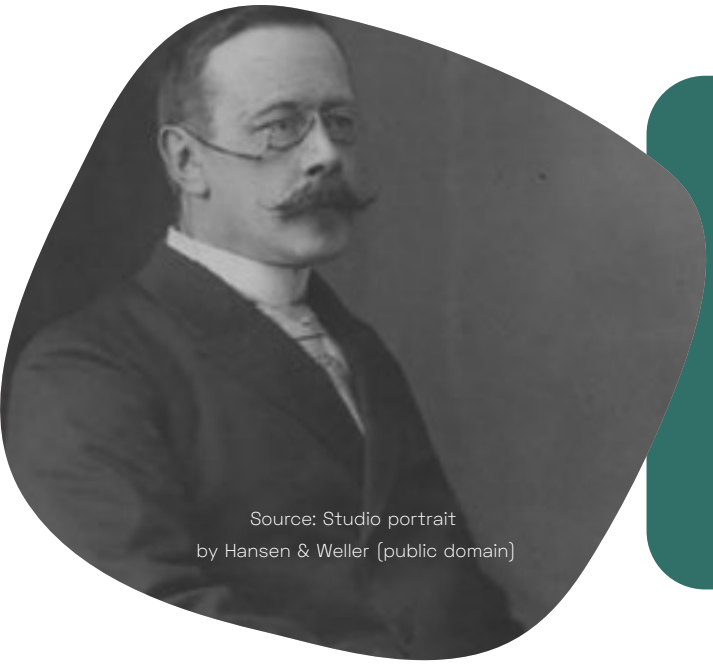
3.1.2 Gram-positive and Gram-negative bacteria

Bacteria are divided into Gram-positive and Gram-negative, and this is all about colours. The Gram method is named after its inventor, the Danish scientist Hans Christian Gram (Figure 8).

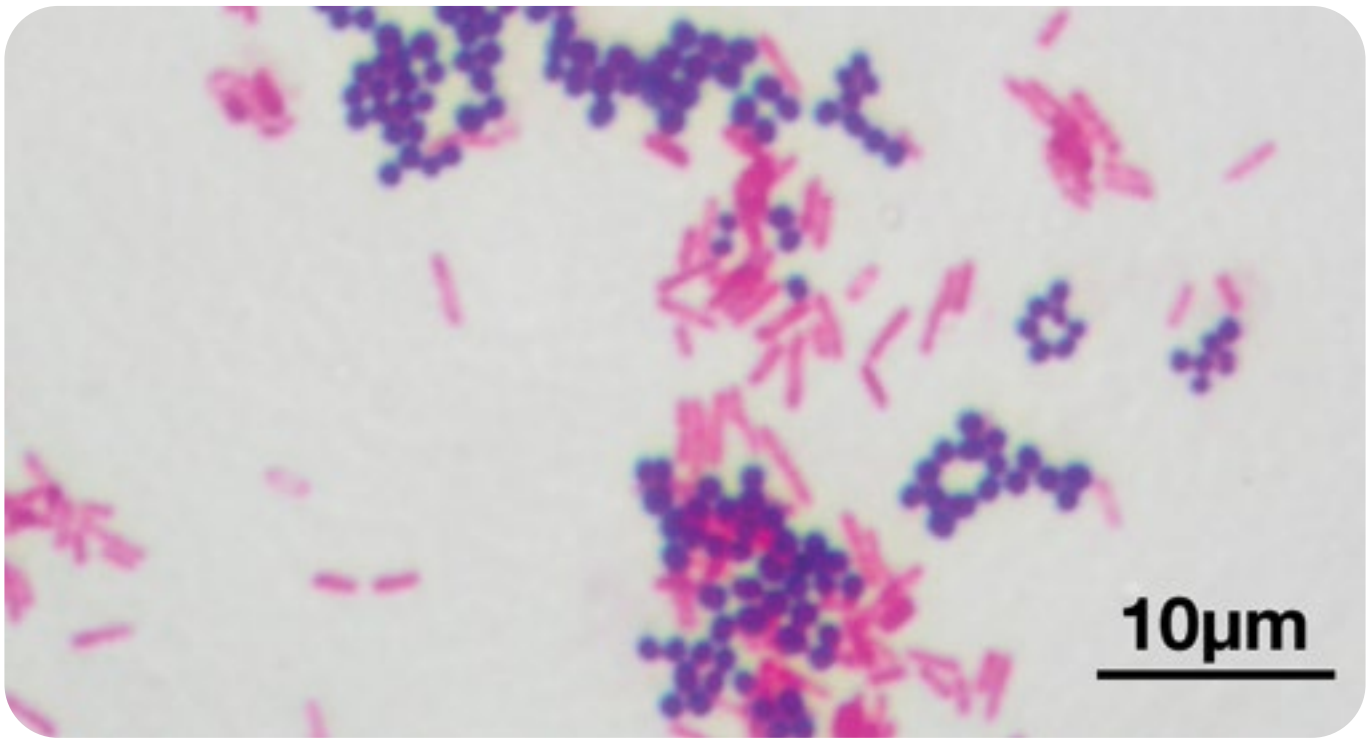


Source: Studio portrait by Hansen & Weller (public domain)

FIGURE 8: HANS CHRISTIAN JOACHIM GRAM (1853-1938)

Gram developed a technique to identify bacteria based on their cell wall. Gram staining is used to show the thickness of the peptidoglycan cell wall in bacteria (Figure 9 and Table 1). Gram-staining is used in the classification and identification of bacteria, and helps to support antibiotic treatment decisions.

FIGURE 9: GRAM STAIN OF GRAM-POSITIVE COCCI AND GRAM-NEGATIVE BACILLI



Note: Gram-positive – Staphylococcus aureus, purple; Gram-negative – Escherichia coli, pink Source: Y tambe (GNU Free Documentation License)

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TABLE 1: GRAM STAINING

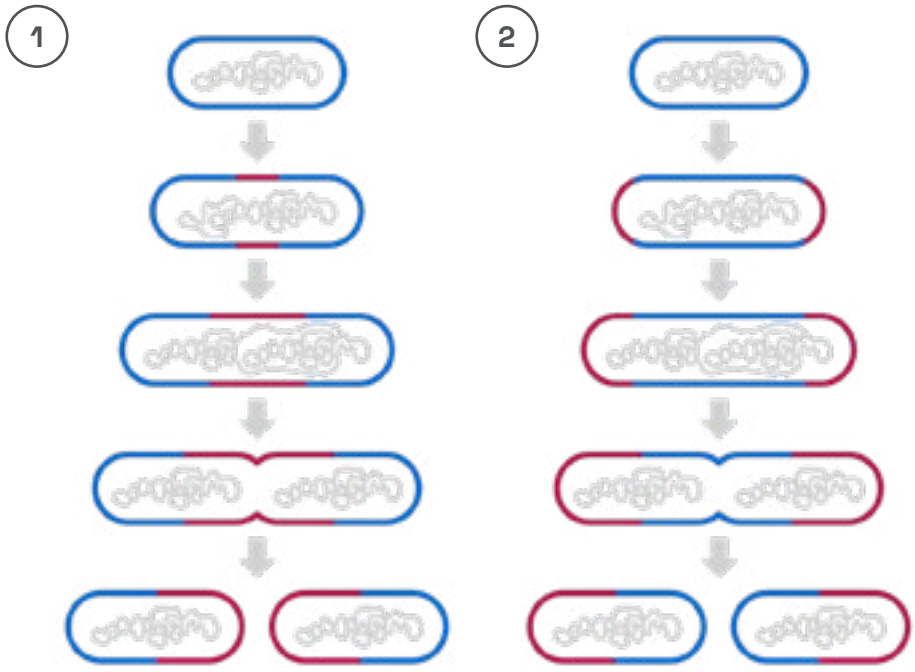
Gram-positive	Gram-negative
Bacteria with a thick wall of peptidoglycan take up both the crystal violet primary stain and the pink fuchsin counterstain in the gram stain, and so are stained blue-purple	In bacteria with a thin wall of peptidoglycan, the crystal violet is washed out, leaving the bacteria stained pink with the counterstain
Most gram-positive bacteria do not have an extra layer outside of the cell wall casing	

Source: Beveridge [5]

3.2 Reproduction

Bacteria reproduce through binary fission. The bacterium divides into two cells (Figure 10), and the cell content of each of the new 'daughter' cells is the same as the original 'mother' cell. Some bacteria, such as Escherichia coli, can divide every 20 minutes in the right conditions.

FIGURE 10: ELONGATION AND BINARY FISSION OF BACILLI



Notes: Blue and red lines indicate old and newly generated bacterial cell wall, respectively. (1) growth at the centre of the bacterial body. e.g. Bacillus subtilis, E. coli, and others. (2) apical growth. e.g. Corynebacterium diphtheriae Source: Y tambe (Creative Commons)

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3.3 Bacteria classification

Bacteria can be classified in a number of different ways to help distinguish between different types and strains [6].

3.3.1 Nutrition

Bacteria can be heterotrophic (which means they cannot produce their own food), or autotrophic, which can produce complex organic compounds, such as carbohydrates, fats, and proteins.

Heterotrophic bacteria

Heterotrophic bacteria need organic nutrients (nutrients derived from living or dead things). Bacteria that get their nutrients from living things are called parasites or pathogens. Bacteria that extract their nutrients from dead material are called saprophytes (sapros = rotten).

Autotrophic bacteria

Autotrophic bacteria can produce their own organic materials. They can be classified according to their energy source, for example photoautotrophic bacteria get their energy from sunlight through photosynthesis, and chemoautotrophic bacteria convert materials from inorganic materials such as sulphur compounds, carbon dioxide and water.

3.3.2 Temperature

Different bacteria grow best at different temperatures, and this can be used for classification.

- **Psychrophilic bacteria or psychrophiles [7]**
  - Temperature range of -20 °C to +12 °C
  - Can spoil refrigerated foods
- **Mesophilic bacteria or mesophiles [8]**
  - Temperature range of +20 °C to +45 °C
  - Includes most bacteria that are human pathogens, which grow at +35 °C to +37 °C
- **Thermophilic bacteria [8]**
  - Temperature range of +41 °C to +122 °C
  - Found in hot springs, peat bogs and compost

3.3.3 pH

The pH measures how acidic or alkaline a substance is, on a scale from 0 to 14. Anything above 7 is alkaline, and anything below 7 is acid. Water has a pH level of 7. Most bacteria grow at a neutral pH of 7, and can tolerate a pH range of 5 to 8. An acidogen is a micro-organism that can form acids from food sources, which then lowers the pH.

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Bacteria can be classified by pH (acidity or alkalinity).

- **Acidophilic bacteria or acidophiles [9]**
  - > Can grow at a low pH (2.0 or below; acid environment)
- **Alkaliphile**
  - > Can grow at a high pH (9-11; alkaline environment) [10]

3.3.4 Oxygen levels

Bacteria are subdivided into four groups according to their sensitivity to oxygen:

- **Aerobe – survives and grows in the presence of oxygen**
  - > Obligate aerobe – requires oxygen
  - > Microaerophile – needs oxygen, but at low levels
- **Anaerobe – does not require oxygen for survival or growth**
  - > Obligate anaerobe – harmed by oxygen
  - > Aerotolerant anaerobe – cannot use oxygen for growth, but tolerates it
  - > Facultative anaerobe – can live with or without oxygen; uses oxygen if present

3.4 Bacterial survival strategies

Bacteria have many different strategies for survival. In unfavourable conditions, some bacteria, for example the Firmicutes, can form endospores. These dormant capsules contain the essential part of the bacterium and are like spores or seeds. Endospores can reproduce after freezing, boiling, drying out, treating with disinfectants or ultraviolet radiation.

Bacteria, such as Azotobacter species, can form cysts, where the entire bacterium encapsulates. These are resistant, but not as resistant as endospores.

3.5 Selected pathogenic bacteria

The body is home to many types of bacteria and most of the time these do not cause any problems. These microbes do not normally cause disease in healthy people. However, in people with a weakened immune system, or a disrupted gut microbiota, opportunistic pathogens can cause disease.

Some microbes are always pathogenic, and the immune system acts to keep these under control. When these are no longer controlled by the immune system, they cause an infection. Certain bacteria can produce harmful toxins, in diseases such as cholera, plague, or tetanus.

3.6 Brief review of some of the most important bacteria in human diseases

The tables in this section give examples of some of the most significant disease-causing bacteria, and some of the diseases that these may cause.

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TABLE 2: AEROBIC GRAM-POSITIVE COCCI

Genus	Species	Diseases include:
Staphylococcus	S. aureus	Skin infections, respiratory infections, food poisoning, bone, joint and wound infections, infective endocarditis, sepsis, medical implant infections
	Coagulase-negative staphylococci (CoNS)	Infective endocarditis, catheter-associated infection
Streptococcus	S. pyogenes	Pharyngitis, scarlet fever, severe soft-tissue infection, rheumatic fever, glomerulonephritis
	S. pneumoniae	Pneumonia, sinusitis, otitis media, meningitis
	Viridans-streptococci	Infective endocarditis
Enterococcus	E. faecalis	Urinary tract infection (UTI), peritonitis, infective endocarditis, wound infection, sepsis

TABLE 3: AEROBIC GRAM-POSITIVE RODS

Genus	Species	Diseases include:
Corynebacterium	C. diphtheriae	Diphtheria
	C. diphtheroides	UTI, sepsis, wound infection
Listeria	L. monocytogenes	Listeriosis (gastro-enteritis; meningitis, infective endocarditis, severe neo-natal burden)
Bacillus	B. anthracis	Anthrax: particularly dangerous disease (PDD) - type A in CDC classification (skin, gastro-intestinal, pneumonia, sepsis)
	B. cereus	Gastro-enteritis

Other important Gram-positive rods include Mycobacteria. M. tuberculosis causes tuberculosis; the pulmonary form is the most frequent. Diseases caused by non-tuberculosis Mycobacteria include pneumonia and wound infections.

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TABLE 4: AEROBIC GRAM-NEGATIVE COCCI AND COCCO-BACILLI

Genus	Species	Diseases include:
Neisseria	N. gonorrhoeae	Gonorrhoea
	N. meningitidis	Meningitis
Haemophilus	H. influenzae	Pneumonia, sinusitis, otitis media, meningitis
Bordetella	B. pertussis	Pertussis

TABLE 5: AEROBIC GRAM-NEGATIVE RODS (FERMENTATIVE) – ENTEROBACTERALES

Genus	Species	Diseases include:
Escherichia	E. coli	UTI, sepsis, wound-, gastro-intestinal-infection
Klebsiella	K. pneumoniae	UTI, hospital-acquired pneumonia (HAP), wound-, gastro-intestinal- infection, sepsis
Enterobacter	E. cloacae	UTI, wound-, gastro-intestinal-infection, sepsis
Serratia	S. marcescens	UTI, wound-, gastro-intestinal-infection, sepsis
Proteus	P. mirabilis	UTI, wound-, gastro-intestinal-infection, sepsis
	P. vulgaris	
	M. morgannii	
	P. rettgeri	
Citrobacter	C. freundii	UTI, wound-, gastro-intestinal-infection, sepsis
Salmonella	S. typhi	Abdominal typhus
	S. enterica spp	Salmonellosis
Shigella	S. dysenteriae	Dysentery
	S. flexneri	Dysentery
	S. boydii	Dysentery
	S. sonnei	Dysentery
Yersinia	Y. pestis	Plague
	Y. enterocolitica	Gastro-enteritis

Another infection from Gram-negative rods, but comma-shaped, is cholera (Vibrio cholerae). This is an example of a particularly pathogenic bacterium.

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TABLE 6: AEROBIC NON-FERMENTATIVE GRAM-NEGATIVE RODS

Genus	Species	Diseases include:
Pseudomonas	P. aeruginosa	Wound infection, HAP, muco-viscidosis, hospital acquired UTI, sepsis
Acinetobacter	A. baumannii	Wound infection, HAP, hospital acquired UTI, sepsis

TABLE 7: ANAEROBIC SPORE-FORMING BACTERIA

Genus	Species	Diseases include:
Clostridioides	C. perfringens	Gas gangrene, necrotizing fasciitis, mixed wound infections
	C. tetani	Tetanus
	C. botulinum	Botulism, PDD caused by botulin exotoxin
	C. difficile	C. difficile-associated diarrhoea – after antibiotic therapy

TABLE 8: ANAEROBIC NON-SPORE-FORMING BACTERIA

Genus	Species	Diseases include:
Bacteroides (Gr (-) rods)	B. fragilis	Gastro-intestinal, peritonitis, mixed wound infection, deep organ abscesses sepsis
Fusobacterium (gr (-) rods)	F. nucleatum	Periodontal disease, wound infection
Peptostreptococcus (Gr (+) cocci)	P. anaerobius	Deep organ abscesses, obstetric and gynaecological sepsis, intraoral infections
Propionibacterium (Gr (+) rods)	P. acnes	Skin infections, acne
Actinomyces (Gr (+) rods)	A. israeli	Actinomycosis: wound infections, deep organ abscess

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TABLE 9: SPIRAL-SHAPED BACTERIA

Genus	Species	Diseases include:
Campylobacter	C. jejuni	Gastro-enteritis
Helicobacter	H. pylori	Gastritis, peptic ulcer, gastric carcinoma

TABLE 10: SPIROCHETES (HELICAL-SHAPED BACTERIA)

Genus	Species	Diseases include:
Treponema	T. pallidum	Syphilis
Borrelia	B. burgdorferi	Lyme disease
Leptospira	L. inerrogans	Leptospirosis

TABLE 11: INTRACELLULAR BACTERIA, INCL. CHLAMYDIA

Genus	Species	Diseases include:
Rickettsia	R. provazeki	Epidemic recurrent typhus
	R. conorii	Marseilles fever
Coxiella	C. burnetii	Q fever
Chlamydophila	C. pneumoniae	Atypical pneumonia
	C. psittaci	Psittacosis
	C. trachomatis	Trachoma, conjunctivitis, urogenital chlamydiosis, lymphogranuloma venereum

Genus Mycoplasma are also intracellular pathogens. M. pneumoniae causes atypical pneumonia, while M. hominis and M. genitalium are the causative agents in uro-genital mycoplasma infections.

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4 Viruses

The impact of viral infections can be underestimated, but infections such as influenza can have significant impacts on individuals and society. Nurses need to remain up to date on the treatment and prevention of viral infections.

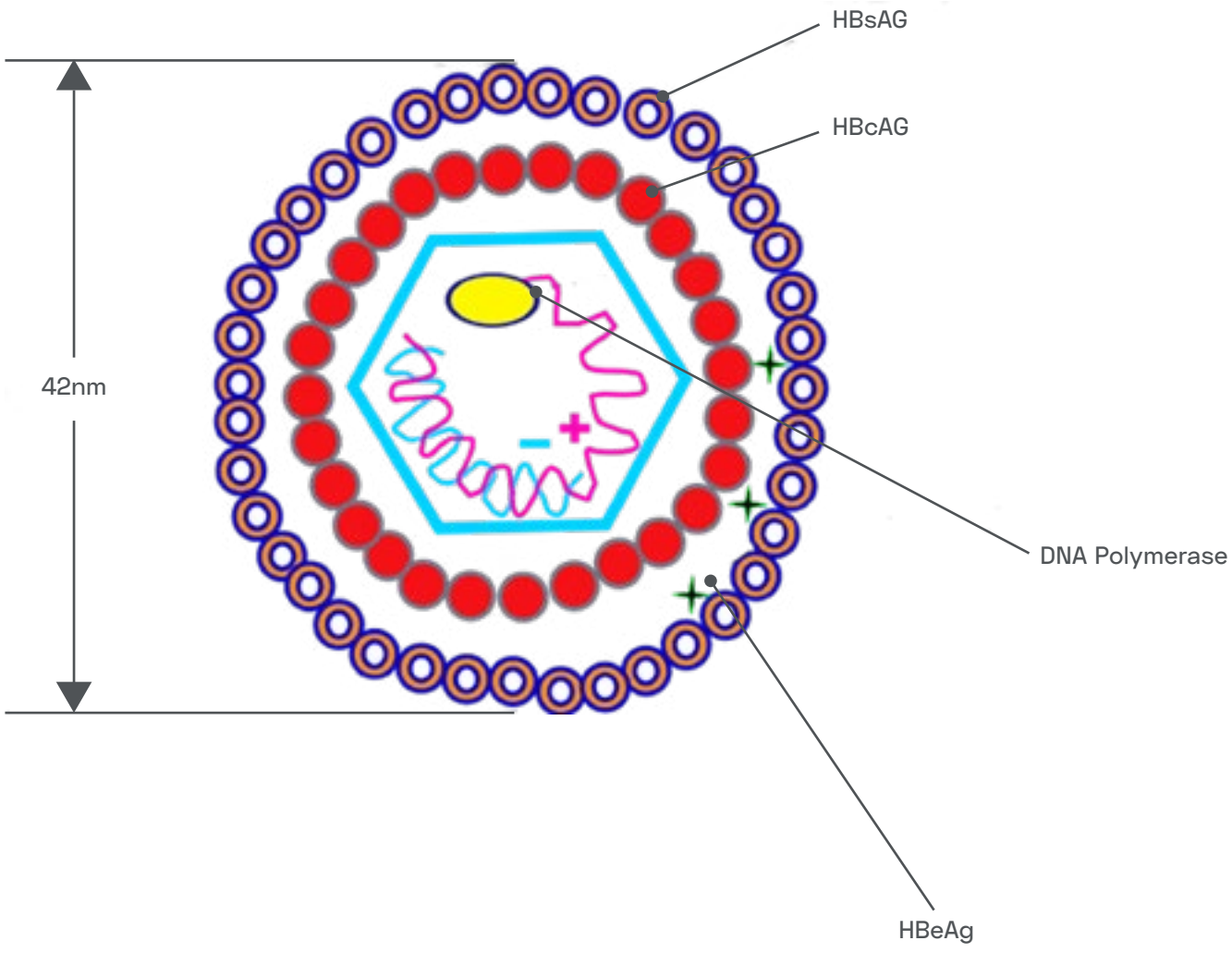
Viruses are infectious agents that do not have their own reproductive mechanism and metabolism, and so are completely dependent on other organisms. Viruses can infect all living organisms, from microbes to humans, and are likely to have existed since the first living cells. Antibiotics do not work on viral infections.

4.1 Structure

Viruses are much smaller (from 20 nm to 400 nm) than bacteria, and have a simpler structure. Some viruses can change from generation to generation, making them difficult to tackle using antiviral agents. Viruses come in a variety of shapes – see Figure 11, Figure 12 and Figure 13 for examples.

FIGURE 11: HEPATITIS B VIRUS

Source: GrahamColm (public domain)



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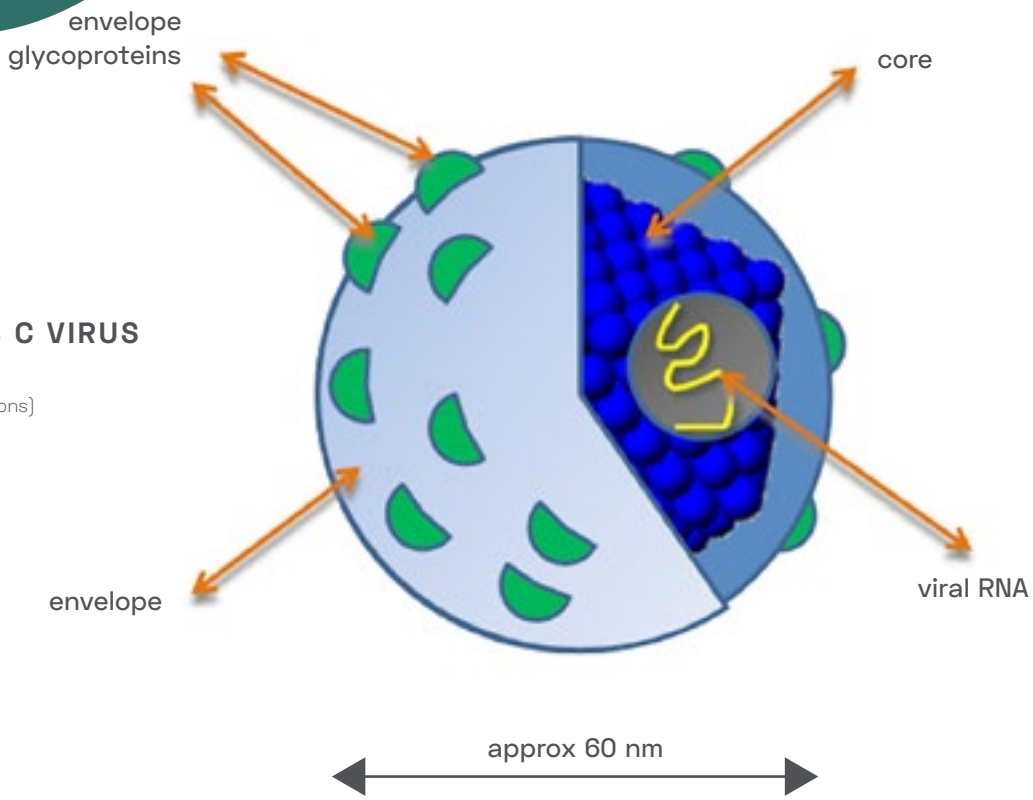

FIGURE 12: HEPATITIS C VIRUS

Source: GrahamColm (Creative Commons)

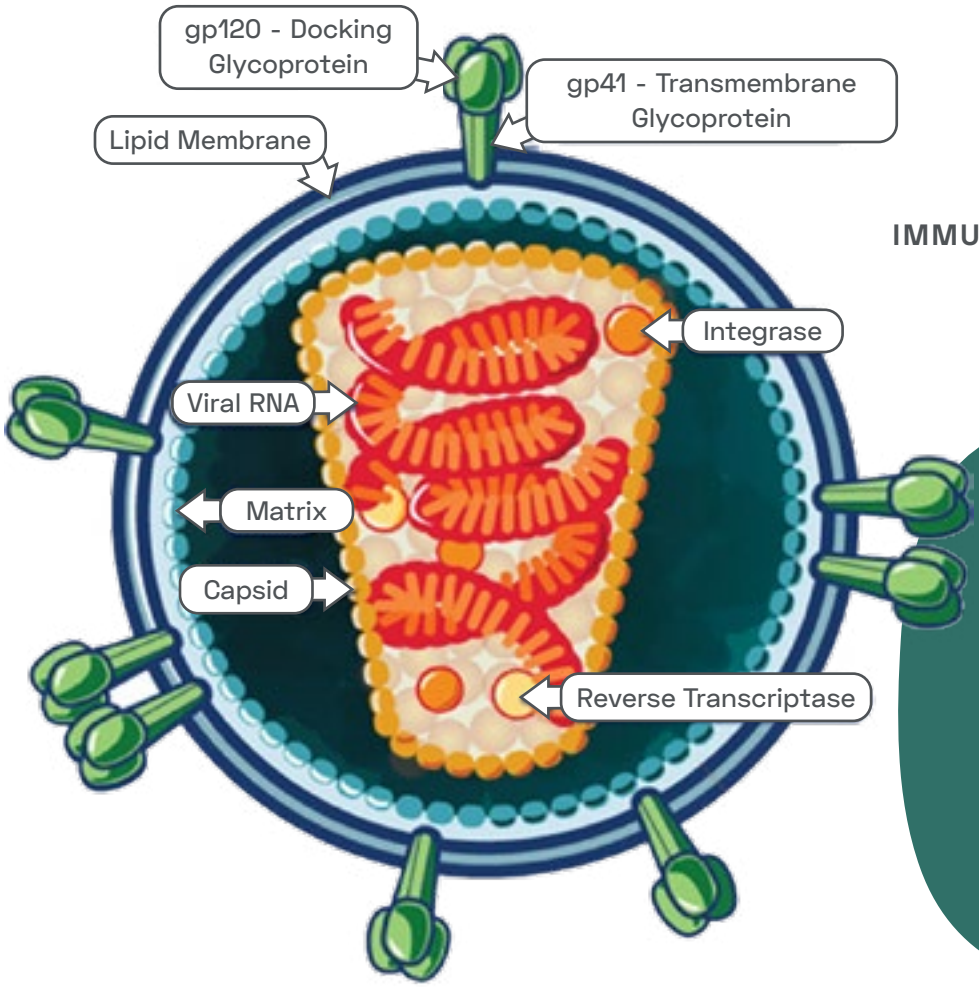

FIGURE 13: HUMAN IMMUNODEFICIENCY VIRUS (HIV)

Source: NIAID (Creative Commons)

Viruses have a viral genome – only DNA (deoxyribonucleic acid) or RNA (ribonucleic acid), contained within a protein capsule/capsid, consisting of capsomers – this structure is called nucleocapsid.

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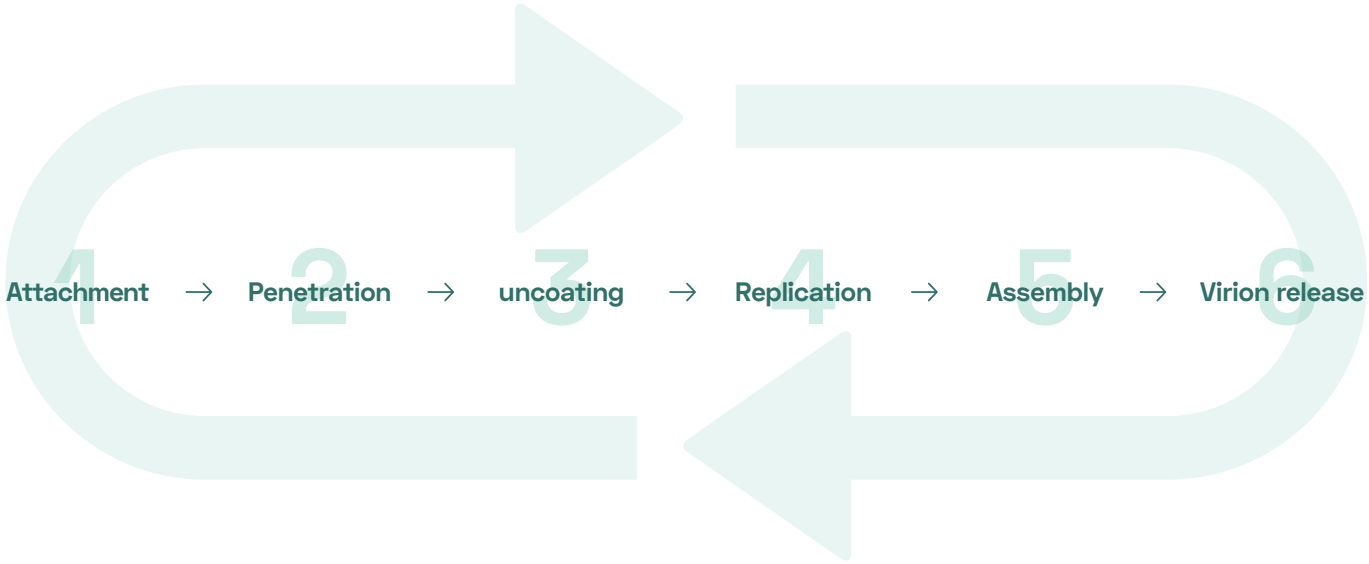
4.2 Reproduction

Viruses use the workings of the host cell to replicate. Virus life cycles differ widely, but there are six basic steps (Figure 14):

FIGURE 14: THE VIRAL REPLICATION CYCLE



A virus connects to a cell by attaching to specific receptors on the cell surface. The protein coat of the virus and antigens on the cell mean that the virus attaches to a specific host cell.

The virus penetrates the cell by injecting its own genetic material or merging with the cell. Some viral enzymes may be introduced into the cell. These, or host enzymes, degrade the virus coating, releasing the genetic material.

Inside the host cell, the genetic material of the virus gives the order to make new viruses. A virus can only multiply if it is in a host cell. The new viruses are then released.

Viral replication can be lytic or lysogenic:

- **Lytic reproduction**
  - > The host cell typically creates new viruses and then dies
- **Lysogenic reproduction**
  - > The virus remains in the host cell
  - > The virus does not cause the death of the host cell, and causes symptoms virus when the immune system is weakened, or as a response to UV radiation or chemicals. An example is process is seen with the herpes virus, which causes cold sores.

In 2016, the International Committee on Taxonomy of Viruses distinguished 4404 species of viruses in 735 genera, 122 families and 8 orders [11].

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4.3 Selected pathogenic viruses

TABLE 12: SELECTED PATHOGENIC VIRUSES

	Structure	Family	Some important members
DNA VIRUSES	Ds, brick or ovoid shaped, (+) envelope	Poxviridae	Smallpoxvirus (variola)
	Ds, icosahedral, (+) envelope	Herpesviridae	Herpes simplex virus 1,2 (HSV-1, HSV-2)
			Varicella-Zoster virus (VZV)
			Epstein-Barr virus (EBV)
			Cytomegalovirus (CMV)
		Hepadnaviridae	Hepatitis B virus (aHBV)
	Ds, spherical, (+) envelope	Adenoviridae	Adenovirus
	Ds, icosahedral, (-) envelope	Papillomaviridae	Human papillomavirus
		Polyomaviridae	JC virus
			BK virus
		Poxviridae	Parvovirus B 19
	Ss, icosahedral, (-) envelope		
RNA VIRUSES	Ds, icosahedral, (-) envelope	Reoviridae	Rotavirus
	Ss, bullet-shaped, (-) envelope	Rhabdoviridae	Rabies virus
	Ss, filamentous, (+) envelope	Filoviridae	Ebola virus
	Ss, icosahedral, (-) envelope	Picornaviridae	Polio-viruses
			ECHO-viruses
			Coxsackie – viruses
			Hepatitis A virus
			Rhino-viruses
			Norovirus
	Ss, icosahedral, (+) envelope	Calciviridae	Rubella virus
		Togaviridae	Influenza viruses
	Ss, spherical, (+) envelope	Orthomyxoviridae	Parainfluenza viruses
		Paramyxoviridae	Respiratory syncytial virus (RSV)
			Measles virus
			Mumps virus
			Human metapneumovirus
			Human coronavirus
		Coronaviridae	SARS-CoV
			MERS-CoV
		Retroviridae	Human immunodeficiency viruses (HIV)
			Dengue virus
		Flaviviridae	West Nile virus
			Zika virus
			Hepatitis C virus

TABLE 13: HUMAN HERPESVIRUSES

Type	Name	Pathophysiology
HHV-1	Herpes simplex virus-1 (HSV-1)	Oral and/or genital herpes (for example cold source) (mainly orofacial)
HHV-2	Herpes simplex virus-2 (HSV-2)	Oral and /or genital (mainly genital)
HHV-3	Varicella zoster virus (VZV)	Chicken-pox and shingles
HHV-4	Epstein-Barr virus (EBV), lymphocryptovirus	Mononucleosis infections, Burkitt's lymphomas, lymphoma of the nerve system, post transplantation lymphoproliferative syndrome, nasopharyngeal carcinoma
HHV-5	Cytomegalovirus (CMV)	Mononucleosis infections, retinitis, hepatitis, pneumonia, pancreatitis, nephritis, myocarditis
HHV-6, -7	Roseolavirus	Roseola
HHV-8	Kaposi's sarcoma associated herpesvirus (KSHV), human herpesvirus 8, rhadinovirus	Kaposi's sarcoma, primary effusion lymphoma, and multicentric Castleman's disease

Source: viruSITE

4.3.1 Rabies

Rabies is a serious condition caused by an infection with the Rabies lyssavirus. It is passed on through a bite or scratch from a rabid animal, such as a dog, fox, bat or cat. Symptoms include headache, fever, weakness, numbness, muscle spasms, seizure and fear of water. Once symptoms appear, rabies is almost always fatal.

Nurses need to remain vigilant for cases of rabies when people with bites or scratches attend healthcare services. They need to ask where the bite happened, and if they have travelled from areas where rabies is endemic.

5 Other microbes

5.1 Clinically important fungi

Fungi are more complex than bacteria and viruses, and have a rigid cell wall. As with bacteria, many fungi naturally live on the body as part of the microbiota.

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5.1.1 Different types of fungi

There are two kinds of clinically important fungi.

- Yeasts, which exist as unicellular form and replicate asexually
- Moulds, multicellular filamentous organisms which replicate sexually or asexually. They consist of filaments called hyphae and form budding forms, called spores.

Most fungi exist in one of these forms, however some clinically important fungi can exist in both forms – they are called dimorphic fungi.

FUNGAL FACT

We have around 150 species of fungi on our feet: About 80 species on our heels, about 60 on our nails and about 40 between our toes. The first response might be, 'get rid of it' but bear in mind, when in right balance, these protect us against harmful microbes

5.2 Fungal infections

When things get out of balance, fungi can cause superficial and invasive infections. These range from mild to life-threatening.

5.2.1 Superficial fungal infections

Fungi, most commonly Trichophyton and Microsporum, can cause skin and nail infections.

TABLE 14: FORMS OF TINEA (RINGWORM)

Name	Area of infection
Tinea pedis (athlete's foot)	Feet
Tinea unguium (onychomycosis)	Fingernails, toenails, and the nail bed
Tinea corporis (ringworm)	Arms, legs, and trunk
Tinea cruris (jock itch)	Groin area
Tinea manuum (ringworm of the hands)	Hands and palm
Tinea capitis (ringworm of the scalp)	Scalp and hair
Tinea faciei (ringworm of the face)	Face
Tinea barbae (beard ringworm)	Facial hair
Tinea Gladiatorum or tinea corporis gladiatorum (RINGWORM IN WRESTLERS)	Head, neck and arms

Source: Ely [12]

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TABLE 15: SUPERFICIAL FUNGAL INFECTIONS

Infection type	Pityriasis versicolor	Dermathophytoses	Onychomycosis	Mycotic keratitis	Lymphocutaneous sporotrichosis
Cause	Malassezia furfur	Microsporum spp. Trichophyton spp. Epidermophyton floccosum	Candida spp Aspergillus spp. Trichosporon spp. Geotrichum spp.	Fusarium spp. Aspergillus spp. Candida spp.	Sporothrix schenckii

Source: Kidd [13]

5.2.2 Invasive fungal infections

Fungal infections of the vagina and other mucous membranes are relatively harmless, but a fungus can also penetrate deeper into the body, infecting the bloodstream, lungs, brain, kidneys or liver. These invasive fungal infections are rare and usually occur in people who are seriously ill, have a reduced immunity for example following a solid organ transplant or cancer chemotherapy, or have been treated with antibiotics [14].

Symptoms of invasive fungal infections

Symptoms depend on where the infection is located, for example, a fungal infection in the lungs can lead to coughing and shortness of breath. The symptoms are not specific to a fungal infection and can also be caused by another disease [14].

Most common invasive fungal infections

Aspergillus species

Aspergillosis is most commonly caused by Aspergillus fumigatus, Aspergillus niger and Aspergillus flavus. While people may inhale thousands of Aspergillus spores daily, these are generally dealt with by the immune system. Aspergillus is ubiquitous. In the hospital environment it is in the air, showerheads, potted plants, and water-storage tanks. Levels increase during building work.

Aspergillus infections can cause a 'fungus ball'. This may be asymptomatic, or cause cough, fever, chest pain, coughing up blood and problems with breathing. The infection can also spread through the blood. A serious infection leads to fever, chills, shock, delirium, seizures, blood clots and organ failure, and can be fatal, especially in patients with compromised immune systems.

Candida species

The infection is called candidiasis. Apart from the most common C. albicans, infection can be due to other species as C. guiliermondi, C. tropicalis, C. krizei, C. glabrata, C. parapsillosis, C. dubliniensis, C. auris. Some of them are more resistant to antifungal agents, and especially C. auris.

Systemic candidiasis or candidaemia is not the same as Candida syndrome, also known as Candida hypersensitivity syndrome. Candida syndrome symptoms are claimed to include abdominal pain, fatigue and depression. However, no epidemiological or therapeutic studies have shown evidence for the existence of this syndrome. [15].

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Cryptococci

The infection is called cryptococcosis. Cryptococcus neoformans, the main pathogens, are spherical yeasts surrounded by a polysaccharide capsule. Infection is frequent in persons living with HIV due to an impaired cell immunity. Initially, the infection develops in the lungs and is followed by a meningitis.

The opportunistic fungus Pneumocystis jirovecii (previously known as Pneumocystis carinii) causes pneumonia in immunosuppressed patients, including those with AIDS resulting from HIV infection.

Histoplasma

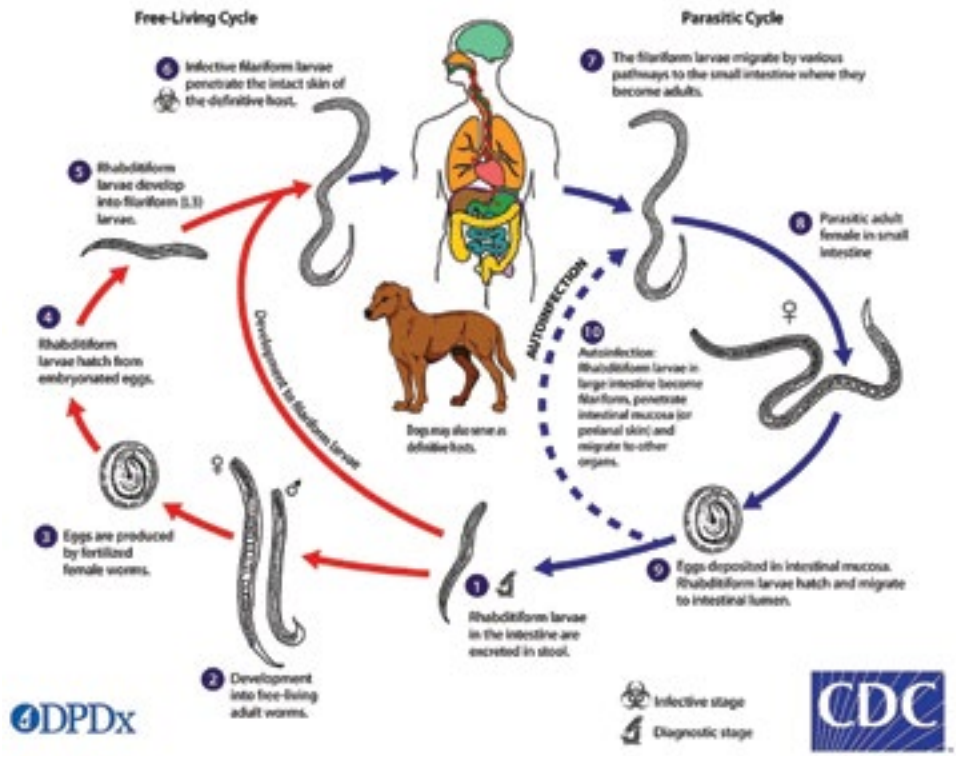
Histoplasmosis, caused by Histoplasma capsulatum, includes pneumonia and skin and bone lesions.

5.3 Parasites

A parasite is an organism that lives within or on another organism (host). The parasite uses the host's resources to maintain itself and support its life cycle. Parasites vary widely. Around 70% are not visible to the human eye, such as the malarial parasite, but some worm parasites can reach over 30 meters in length. Different parasites have different effects.

Endoparasites live inside the host. They include heartworms, tapeworms, roundworms and flatworms – see Figure 15 for an example. **An intercellular parasite** lives inside the host's cells, and includes bacteria and viruses. Endoparasites rely on a third organism, known as the vector, or carrier. The vector transmits the endoparasite to the host. The mosquito is a vector for many parasites, including Plasmodium, a protozoan that causes malaria.

FIGURE 15: STRONGYLOIDES STERCORALIS (ROUNDWORM) LIFE CYCLE



Source: CDC (public domain)

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Epiparasites feed on other parasites in a relationship known as hyper-parasitism. A flea lives on a dog, but the flea may have a protozoan in its digestive tract. The protozoan is the hyper-parasite.

There are three main types of parasites.

- Protozoa: Examples include Plasmodium, a single-celled organism. Protozoa can only multiply within the host.
- Helminths: These are worm parasites, and examples include roundworm, pinworm, trichina spiralis, tapeworm, and fluke.
- Ectoparasites: These live on, rather than in their hosts, and examples include lice and fleas.

5.3.1 Babesiosis

Babesiosis, also called tick fever or piroplasmosis, is an infection caused by the Babesia parasite (Theileria microti). Babesiosis is transmitted by the Dermacentor reticulatus tick. It can also be passed on through a blood transfusion. Many people have no symptoms. If symptoms occur, these are flu-like and develop between a week and a few months. Babesia lives in red blood cells and can destroy them, leading to haemolytic anaemia, which may be life-threatening.

5.3.2 Malaria

Global travel now means that diseases previously described as tropical, such as malaria, are now present in Europe. These cases are either transmitted by local Anopheles mosquitoes infected by a returning traveller (introduced malaria) or by an infected mosquito transported by aircraft from a malaria-endemic country (airport malaria). Introduced mosquitoes are also more likely to survive longer because of climate change. For an example of European mosquito distribution, see Figure 16.

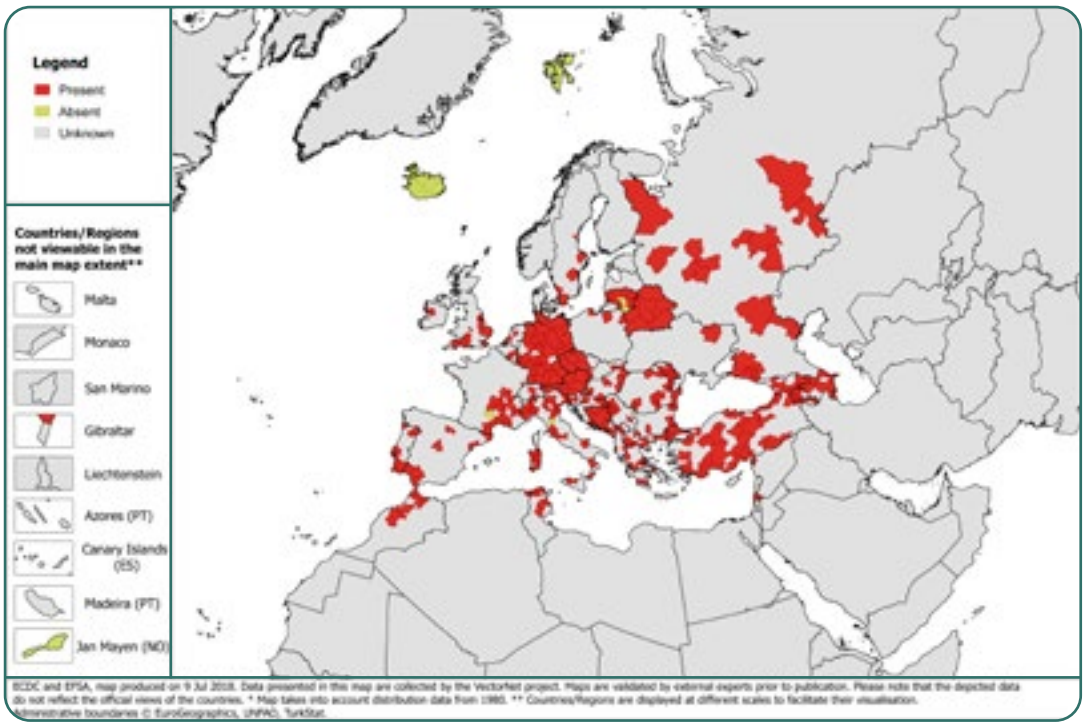

FIGURE 16: ANOPHELES MACULIPENNIS S.L. COMPLEX - CURRENT KNOWN DISTRIBUTION, JULY 2018

Source: European Centre for Disease Prevention and Control

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Nurses need to remain vigilant for cases of malaria when people with fevers attend healthcare services, and ask if people have travelled from areas where malaria is endemic. Nurses also need to remain aware that, because of climate change, cases of malaria can be picked up locally and not just from outside of Europe.

The Eurosurveillance website provides information on communicable disease surveillance, prevention and control **(QR code 2)**.

For more infection about parasitic diseases, go to the CDC website **(QR code 3)**.

SCAN ME
(QR code 2)

5.4 Creutzfeldt-Jakob disease

Prions and proteinaceous infectious particles are cellular proteins that are wrongly folded. Prion diseases are rare, affecting around 1-1.5:1,000,000 people each year. Creutzfeldt-Jakob disease (CJD) is the most common human prion disease, and most cases arise sporadically in middle or old age (sCJD; 80-95% of prion diseases), or are genetic (familial), occurring in younger people (fCJD; 10-15% of prion diseases).

Bovine spongiform encephalopathy (BSE) or 'mad cow disease' is a neurodegenerative disease seen in cattle, where they have weight loss, signs of pain, problems walking, and odd behaviour such as aggression and anxiety. It was first seen in the UK in the 1980s, and is transmitted when the animals eat food made from infected animals, such as feed made from sheep with the prion infection scrapie. BSE peaked around 1992-1993, and was controlled by the early 2000s.

Variant CJD (vCJD), which was first seen in the United Kingdom in 1994-1995, makes up less than 1% of all cases of prion disease. It is the only prion disease that is transmitted from animals to humans, and is linked with eating meat from cows with BSE. Cases of vCJD have declined since 2000, and there have been no new cases since 2012. Symptoms begin with dementia and dysesthesia (an unpleasant feeling when touched), with involuntary movements developing a few months later. People live for an average of 14 months after developing vCJD.

There is no cure for CJD and other human prion diseases, and symptoms should be treated to make patients more comfortable, for example anti-anxiety drugs, antidepressants and anticonvulsants.

Prion diseases, including CJD, can be passed on through contaminated human growth hormone, dura mater and corneal grafts, neurosurgical instruments or blood products. Prions cannot be destroyed by usual methods of disinfection and sterilization, such as formalin, alcohol, heat and radiation.

Where possible, autoclave instruments at 134 °C for 1 hour. All disposable instruments, materials, and wastes that come in contact with high infectivity tissues (brain, spinal cord, and eyes) and low infectivity tissues (cerebrospinal fluid, kidneys, liver, lungs, lymph nodes, spleen, and placenta) of suspected or confirmed patients should be incinerated [16-18].

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(QR code 3)

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5.5 Emerging microbial infections

Because of the increasing ease of global transport, added to migration and climate change, diseases previously only seen in tropical countries are spreading worldwide.

5.5.1 West Nile virus fever

West Nile virus (WNV), a member of the Flavivirus family, is transmitted by mosquitoes. Most people infected do not develop symptoms; for example, fever and other symptoms such as headache, vomiting, or a rash are only seen in around 20% of patients. Further, only 1 in 150 persons infected develops a serious CNS illness such as an encephalitis or meningitis. There is no vaccine or specific antiviral treatment for West Nile virus infection. In severe cases, patients need to be hospitalized to receive supportive treatment, such as intravenous fluids, analgesia, and skilled nursing care.

5.5.2 Zika virus infection

Zika virus (ZIKV) is a member of the Flavivirus family, and is transmitted primarily through the bite of an infected Aedes species mosquito, such as Aedes albopictus (see Figure 17). Nonhuman and human primates are the main reservoirs of the virus. Other transmission routes include perinatal, in utero, and sexual, as well as transfusion and transplantation.

FIGURE 17: DISTRIBUTION OF THE AEDES ALBOPICTUS MOSQUITO AS OF JUNE 2018

Source: European Centre for Disease Prevention and Control

Most cases are asymptomatic, but some patients develop fever, rash, arthralgia, and conjunctivitis. Other symptoms are myalgia and headache. These symptoms are usually mild and last for several days to a week. Some patients may develop a Guillain-Barré syndrome (an immune attack to the nerves, causing muscle weakness). However, during pregnancy, Zika virus infection is a cause of microcephaly and other severe foetal brain defects. There is no vaccine or specific antiviral treatment for Zika virus infection.

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5.5.3 Dengue

Dengue virus, a member of the Flavivirus family, is transmitted by the mosquito Aedes aegypti (see Figure 18). Most cases are asymptomatic (40% - 80%). Other patients present with a fever, headache, vomiting, muscle and joint pains. In severe forms, around 5% progress to bleeding, with haemorrhagic fever and shock. The fatality rate of severe dengue has reduced with proper medical care and is now below 1%. There are no specific antiviral drugs available, and treatment involves hydration (including intravenous fluids if required), fever reducers and painkillers such as paracetamol. NSAIDs (non-steroidal anti-inflammatory drugs), such as ibuprofen and aspirin should be avoided [19].

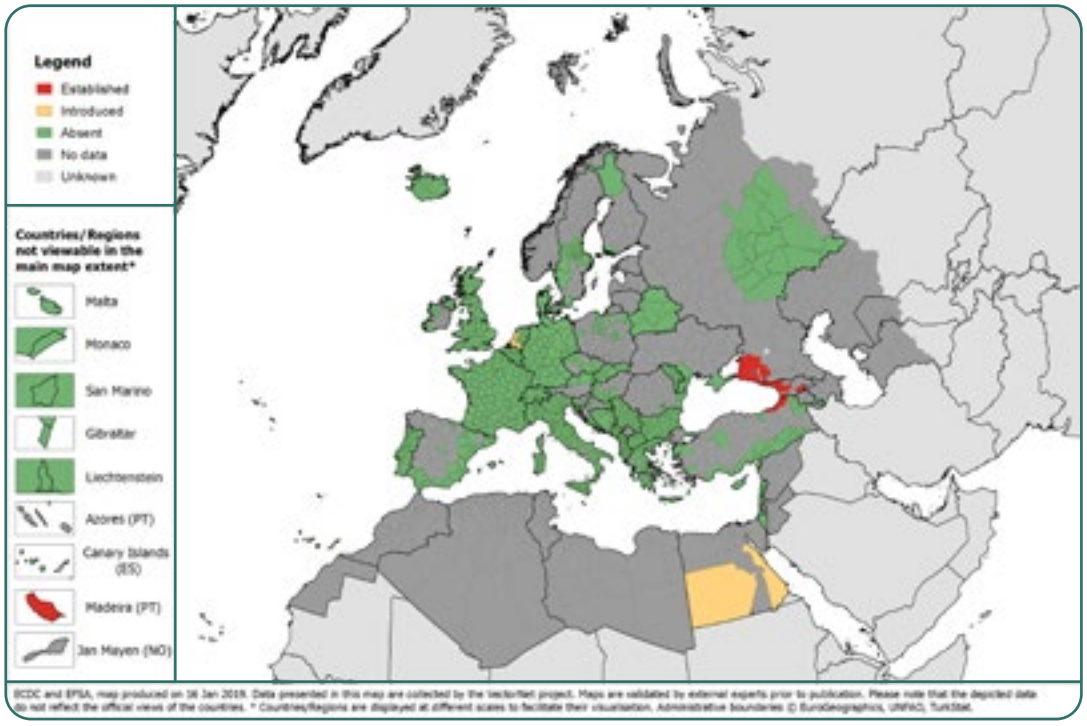

FIGURE 18: DISTRIBUTION OF THE AEDES AEGYPTI MOSQUITO AS OF JANUARY 2019

Source: European Centre for Disease Prevention and Control

The incidence of dengue fever is growing, and around half of the world's population is at risk [19].

5.5.4 Ebola virus haemorrhagic fever

Ebola virus belongs to the Filoviridae family. It is responsible for haemorrhagic fever with an average fatality rate of 50, ranging from 25% to 90%. Ebola viruses have caused outbreaks in the past, mostly in sub-Saharan Africa. People are initially infected with Ebola virus through contact with an infected animal (fruit bat, ape or monkey). The virus then spreads from person to person through direct contact (broken skin or mucous membranes in the eyes, nose, or mouth): via blood or body fluids (urine, saliva, sweat, faeces, vomit, breast milk, and semen) of an infected person or who has died from Ebola virus disease (EVD). The infection is also spread by needles and syringes contaminated with the body fluids, and even from the semen of male patients following recovery from EVD. The disease typically develops after an incubation period of 2 to 21 days, and with symptoms such as fever, severe headache, muscle pain, diarrhoea, vomiting, abdominal pain, and haemorrhages. Recovery from EVD depends on good supportive clinical care and the patient's immune response. All activities should be performed at the 4th level of biological security and in full biological personal protective equipment. There is not a specific treatment, but supportive care includes rehydration with oral and intravenous fluids, and treatment of specific symptoms. A vaccine has now been approved, and the first-ever multi-drug randomized control trial began during the 2018/2019 Ebola outbreak in the Democratic Republic of Congo [20].

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5.5.5 Lyme disease

Lyme disease or Lyme borreliosis is an infection caused by the Borrelia bacterium. The bacteria is spread by Ixodes ticks (Table 16). It is the most common tick-borne infection in temperate parts of Europe, North America and Asia, and its reach around the world is increasing [21].

TABLE 16: TICKS AND BACTERIA LINKED WITH LYME DISEASE

Region	Tick	Bacterium
Europe	Ixodes ricinus	Borrelia afzelii Borrelia garinii Borrelia burgdorferi Borrelia bavariensis Borrelia spielmanii
North America	Ixodes scapularis	Borrelia burgdorferi

Source: ECDC [21]

The numbers of ticks in Europe are growing, driven by climate change, increasing numbers of deer, and changes in land management [22]. See Figure 19 for European distribution of Ixodes ricinus and Figure 20 for an image of the tick.

FIGURE 19: IXODES RICINUS - CURRENT KNOWN DISTRIBUTION: JULY 2019

Source: ECDC [23]

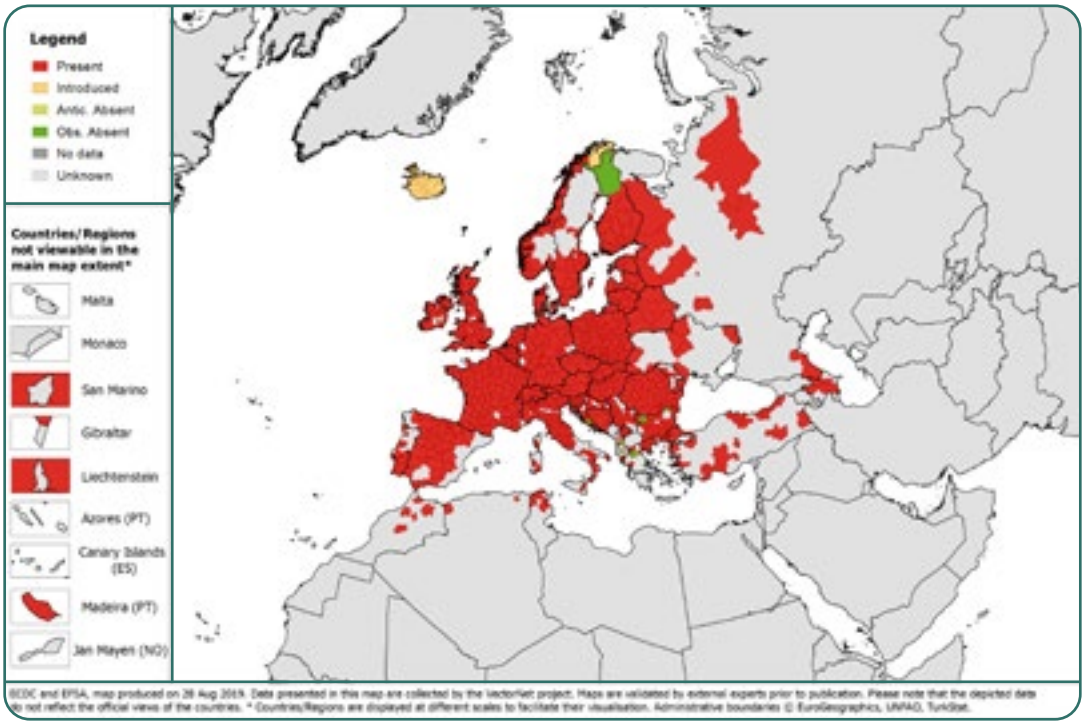

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FIGURE 20: IXODES RICINUS

Source WWalas (Creative Commons)

In 1883, German doctor Alfred Buchwald described a skin rash, now known as acrodermatitis chronica atrophicans, the third stage of Lyme disease. The neurological complications of Lyme disease were first described in the 1920s and 1930s.
Lyme disease has three stages: [24-26].

Stage 1: Primary or localised infection, with flu-like symptoms 1-30 days after the bite, and a characteristic expanding rash (erythema migrans; bull's eye rash) at the site of the tick bite, usually within 7-14 days after the tick is removed. Other symptoms can include tiredness, muscle and joint pain, fever, chills and neck stiffness.

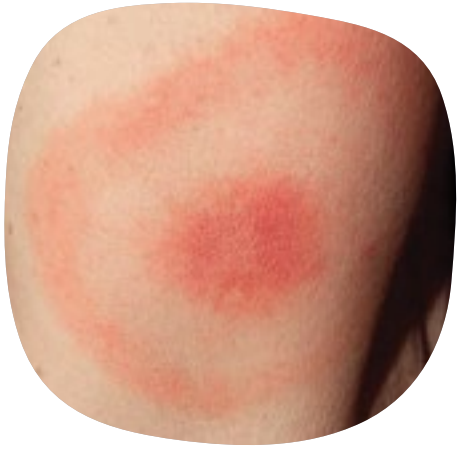
Stage 2: Early disseminated disease, weeks to months after the bite as the bacteria spread through the body

- Fever and malaise, blurred vision, eye pain
- Nervous system disorders (neuroborreliosis): Symptoms include painful inflammation of the nerves of the spine (Bannwarth syndrome), facial paralysis (Bell's palsy), meningitis, and encephalopathy, including confusion, memory loss, and issues with concentration, mood and sleep
- Lyme arthritis: Symptoms include swelling and pain in one or a few joints. This most commonly affects the knees, but also includes the ankle, shoulder, elbow, or wrist

Stage 3: Chronic neuroborreliosis can set in months or years after infection, and includes central and peripheral nervous system symptoms (chronic neuroborreliosis). There is no consensus among experts on the prevalence of chronic neuroborreliosis.

FIGURE 21: ERYTHEMA MIGRANS

Source: Centers for Disease Control and Prevention (public domain)

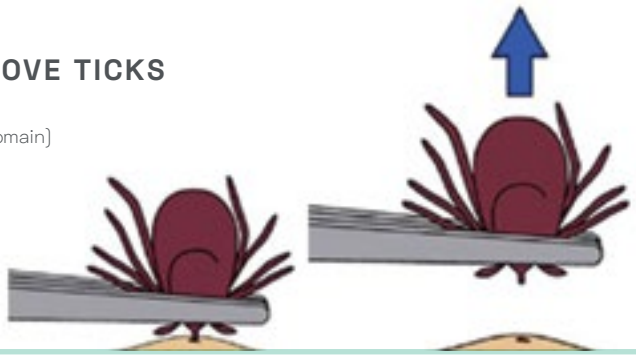


Treatment

Ticks should be removed as quickly as possible (Figure 22). Grip the tick as close to the skin surface as possible, pull upwards with steady even pressure, and then clean the skin and hands with soap and water or alcohol. Dispose of the tick by putting it in alcohol, sealing it in a bag, wrapping it in tape, or flushing it down the toilet [27].

FIGURE 22: HOW TO REMOVE TICKS

Source: CDC (public domain)



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High-risk patients, who have been bitten in an area where disease is highly endemic, and where the tick has been attached for 36 hours or more, may benefit from a preventive single dose of an antibiotic such as doxycycline.

Treatment depends on the disease stage and clinical manifestation. See Table 17 for guidance but also refer to local and national guidelines for further details.

TABLE 17: CLINICAL PRESENTATION AND THERAPY FOR THE STAGES OF LYME DISEASE

Disease stage	Clinical manifestations	Treatment route	Duration
Early localized	Erythema migrans	Oral	7-14 days
Early disseminated	Multiple erythema migrans	Oral	14 days
	Isolated cranial nerve palsy	Oral	14-21 days
	Meningoradiculoneuritis	Oral	14-28 days
	Meningitis	Intravenous or oral	14-21 days
	Carditis – ambulatory	Oral	14-21 days
	Carditis – hospitalized	Intravenous followed by oral	14-21 days
	Borrelial lymphocytoma	Oral	14 days
Late	Arthritis	Oral	days
	Recurrent arthritis after oral therapy	Oral or intravenous	28 days or 14-28 days
	Encephalitis	Intravenous	14-28 days
	Acrodermatitis chronica atrophicans	Oral	21-28 days

Source: Meyerhoff [24]

Patients with chronic disease may benefit from long-term antibiotic treatment.

5.5.6 Coronavirus 2019-nCoV

In December 2019 and January 2020 there was a cluster of cases of pneumonia in China caused by a novel coronavirus, 2019-nCoV. The first cases were reported in Wuhan City, Hubei province, China on 31

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Source European Commission

What is the outbreak about?

From what ECDC (European Centre for Disease Prevention and Control), national and international agencies currently know, the outbreak is caused by a novel coronavirus. There are still many unknowns regarding to the virulence and pathogenicity of the virus, the severity of affected patients, its transmission patterns, reservoir and source of infection. Epidemiological analyses available to date are also limited which leads to many uncertainties on the characteristics and the dynamic of the outbreak.

What are coronaviruses?

Coronaviruses were identified in the mid-60s and are known to infect humans and a variety of animals (including birds and mammals). This family of viruses are known to cause illness in humans ranging from the common cold to more severe or even fatal diseases such as Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS).

There is currently limited information about the epidemiological and clinical characteristics of the infection caused by COVID-19. Although the data available to ECDC is currently very scarce (see e.g. open source platform nextstrain.org which visualises phylogenetic analysis and relation between the nCoV and SARS and other beta-coronaviruses). This novel coronavirus seems genetically closely related to the 2003 SARS virus and appears to have similar epidemiological characteristics.

What are the symptoms and treatment options?

Even if severe and fatal infections have been observed, human infections with common coronaviruses are mostly mild and asymptomatic, resembling those of a common cold (cough, fever, runny nose, etc.). These viruses are able to cause lower respiratory tract infections and pneumonia in humans.

Are vaccines and treatments available?

There are currently no vaccines against coronaviruses. There is not specific treatment for this disease so the clinical approach is symptomatic-based on the patient's clinical condition. Moreover, supportive care (e.g. supportive therapy and monitoring – oxygen therapy, fluid management, empiric antimicrobials) for infected persons can be highly effective.

Since there is no specific treatment for this disease, the clinical approach is based on the symptoms of the clinical condition of the patient.

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WHO ON
#COVICD

December 2019, with links to a wholesale fish and live animal market selling different animal species. By 30 January 2020, there were cases in 18 countries outside of China, with confirmed human-to-human transmission.

Coronaviruses were first identified in the 1960s, and cause infections in humans and animals. Two coronaviruses have crossed over from animals to humans: SARS-CoV (2002) and MERS-CoV (2012). These were both likely to have originated in bats, and spread to Himalayan palm civets, Chinese ferret badgers and raccoon dogs sold for food. The origin of the coronavirus 2019-nCoV is not yet clear. Symptoms of the coronavirus 2019-nCoV include fever, cough, muscle pain and tiredness [28,29]. The WHO website (**QR code 4**) has up to date information.

SCAN ME
(QR code 4)

NOTE FROM THE EDITOR:

During the preparation of this guide, the CORONA-19 virus infection became a pandemic. Because of changing advice, we are not able to include all available information but refer you to aspects of Infection Prevention Control in Module 5. In the second edition we will provide more information, with implications for clinical practice.

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MODULE 2

Medication

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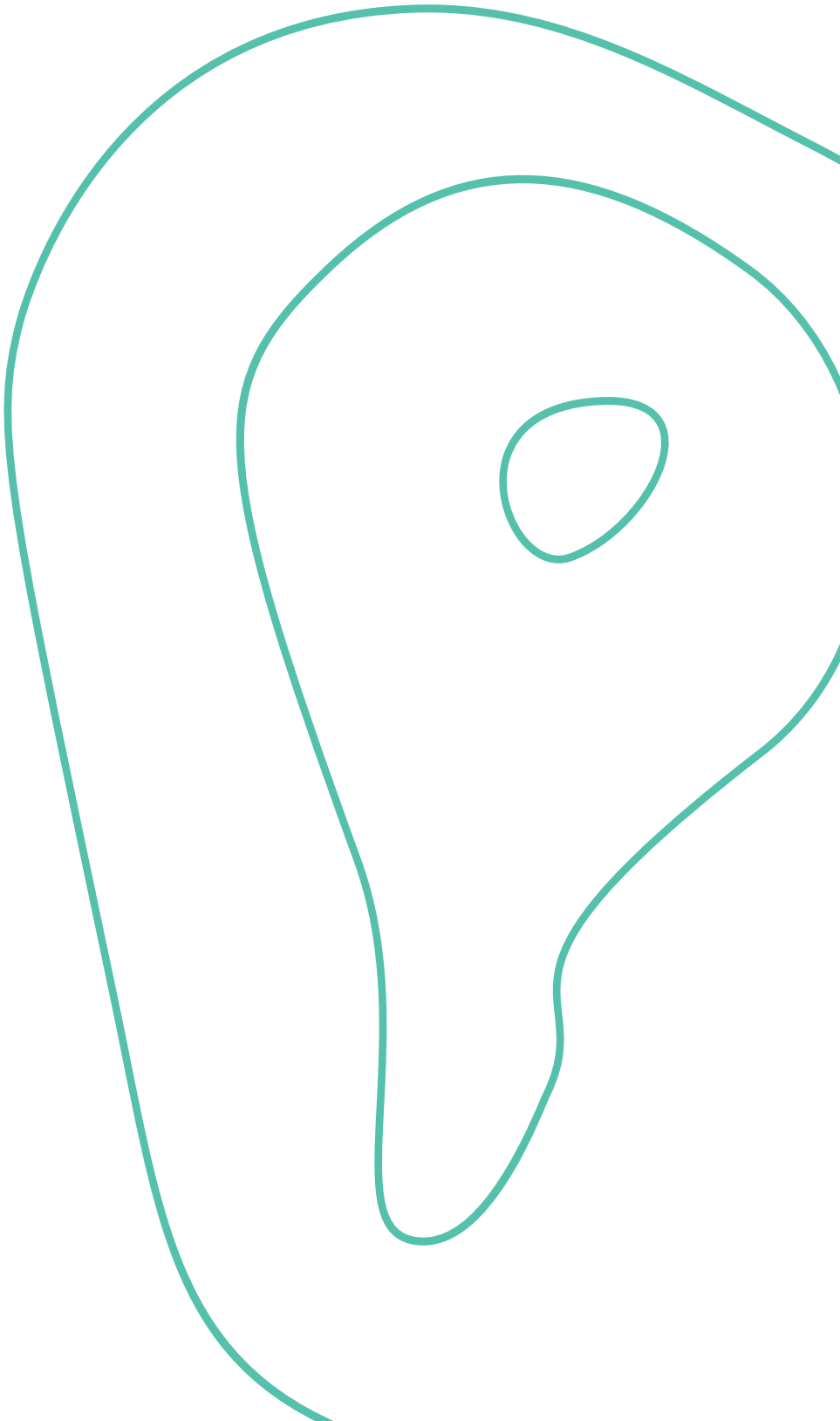
After reading Module 2,
you will understand the essentials of how vaccines, antibiotics and other antimicrobials work. You will know more about how vaccines are used to prevent infectious disease caused by bacteria and viruses, and that there are vaccines in development against fungi and parasites. You will be able to educate patients about antibiotics, including that they are not effective against viruses. You will be better at communicating and discussing the responsibilities of nurses, nurse specialists and physicians.

HIPPOCRATES

The greatest medicine of all is teaching people how not to need it



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7 An introduction to antimicrobial medication

From the days of Florence Nightingale, distributing medication has been a key responsibility for nurses. As medications have become more complex, nurses' roles have grown to include more than just distribution (Figure 23).

FIGURE 23: NURSES' ROLES IN ANTIMICROBIAL MEDICATION

For work in infection, it is crucial that nurses have a working knowledge of microbiology, and understand the mechanisms of action of medications used in its prevention and treatment.

This module will use antimicrobials as a word to cover the drugs used against bacterial, viral, fungal, parasitic and other infections, and antibiotics to describe the drugs specifically used against bacterial infections.

7.1 Developing medications

There are many different medications available for a huge variety of diseases, from high blood pressure to depression, and from cancer to infection. In the 1960s, there were only a few hundred medications available in Europe; today there are thousands. Some of these medications are for common diseases, others for very rare conditions.

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Drugs are assessed in clinical trials, and then approved for use in patients after careful evaluation by the European Medicine Agency (EMA), a coalition of national institutes that look at the efficacy and safety of medication. The EMA is supported by working groups that involve patients and health professionals, including specialist nurses.

7.2 Naming medications

Medications have three different names:

- **Chemical name:**
  - The scientific name that describes the molecule and its structure; for example, **N-methyl-3-phenyl-3-[4-(trifluoromethyl) phenoxy]propane-1-amine**
- **Generic name:**
  - The International Non-proprietary Name (INN) for the drug; for example, **fluoxetine**
  - This remains the same, even if the drug is made by different manufacturers. This makes communication more precise, and helps to avoid prescribing errors.
  - Generic names may have a suffix that shows they belong to a certain class, for example -cidin for naturally occurring antibiotics or -cillin for derivatives of penicillin.
  - Where two medicines are combined into a single dose, their generic names may be joined by a hyphen or slash, for example suspensions combining trimethoprim and sulfamethoxazole may be described as trimethoprim-sulfamethoxazole or co-trimoxazole.
- **Trade name:**
  - The name given by the pharmaceutical company; for example, **Prozac.**
  - Many drugs have multiple trade names, reflecting marketing in different countries, manufacture by different companies, or both.

8 Antibiotics and how they work

8.1 Antibiotic essentials

The European Centre for Disease Prevention and Control definition is: [1]

Antibiotics, also known as antimicrobial drugs, are medicines that can kill or inhibit the growth of bacteria to cure infections in people, animals and sometimes plants. Antibiotics are medicines for bacterial infections (such as pneumococcal pneumonia or staphylococcal bloodstream infections); antimicrobial drugs that are effective against viruses are usually called antiviral drugs (such as those for influenza, HIV and herpes).

This section covers both bactericidal antibiotics (kill bacteria directly), and bacteriostatic antibiotics (stop bacteria from growing).

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For example:

- **Bactericidal:** The antibiotic polymyxin B **damages the plasma membrane of bacteria,** upsetting the balance of salts on both sides of the plasma membrane. Polymyxin B also lets other important molecules, like DNA and RNA, leak out, so the bacterium is destroyed.

- **Bacteriostatic:** Tetracycline antibiotics stop bacteria from growing by **preventing them from making proteins.** When bacteria run out of the proteins they need, they can no longer replicate. Other bacteriostatic antibiotics interfere with DNA replication or other metabolic processes in the bacteria.

A limited number of antibiotics also possess antiprotozoal activity such as malaria.

8.2 The evolution of antibiotics

Source: Imperial War Museums (public domain)

FIGURE 24: PROFESSOR ALEXANDER FLEMING IN HIS LABORATORY AT ST MARY'S, PADDINGTON, LONDON (1943)

Alexander Fleming (Figure 24) is credited with the discovery of the first antibiotic. In 1928, he saw that a fungus (Penicillium chrysogenum), that had accidentally ended up in a bacterial culture, inhibited the growth of Staphylococcus aureus. That was the start of penicillin, leading to the subsequent development of many antibiotics, but was also the start of the race against antimicrobial resistance [2].

The discovery of penicillin, however, built on a number of different breakthroughs, from the invention of the microscope by van Leeuwenhoek, to Rudolf Virchow's cell theory, Claude Bernard's understanding of the importance of balance within the organism, and Louis Pasteur and Robert Koch's development of germ theory, showing that microorganisms cause diseases and infections.

Following Fleming's discovery, Paul Ehrlich and Sahachiro Hata developed Salvarsan (arsphenamine, also called compound 606) at the beginning of the 20th century. This was the first effective treatment for syphilis, and began the era of effective antimicrobials [3].

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8.3 How antibiotics work

Different antibiotics work against different bacteria. Their main ways of attack are by targeting the bacterial cell wall, or the cell's protein or nucleic acid synthesis.

The reason that antibiotics do not work against viruses and virus infections is quite simple: the targets for antibiotics are missing in viruses. **Viruses do not have a cell wall or machinery for protein synthesis:** they multiply via human cells. **So, flu and the cold cannot be treated with antibiotics.**

8.3.1 Antibiotics that target the cell wall

Bacteria, except Mycoplasma, have a cell wall. The building blocks for the bacterial cell wall and the machinery in the bacterial cell to make the cell wall – cell wall synthesis – are targets for antibiotics. This allows them to kill bacteria without affecting human cells. For example, beta-lactams target and affect the structure of the bacterial cell wall.

8.3.2 Antibiotics that target protein synthesis

Aminoglycosides, macrolides, lincosamides, streptogramins, tetracyclines, and chloramphenicol inhibit protein synthesis so that bacteria can no longer make the proteins or enzymes they need to survive.

8.3.3 Antibiotics that target bacterial DNA/nucleic acid synthesis

Quinolones , co-trimoxazole and rifampicin target bacterial DNA and affect how the bacteria multiply.

IMPORTANT: All antibiotics have side effects, and it's important to know what these might be.

Quinolones, such as moxifloxacin, ciprofloxacin and levofloxacin can have severe side effects. Because of this, the EMA advises that quinolones should not be used as first line antibacterial medication. See more on the European Medicines Agency website **(QR code 5)**.

SCAN ME
(QR code 5)

8.3.4 Antibiotics that target the surface outer membrane of Gram-negative bacteria

Polymyxins, for example colistin, act as surface inhibitors and disrupt the outer membrane of Gram-negative bacteria.

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8.4 Routes of administration

- **Oral**
  - > Most common, especially for short term treatment of less severe systemic infections
  - > Advantages: Simple, can be administered at home
  - > Disadvantages: Can irritate the stomach
- **Topical**
  - > For local infections, for example skin, eye, ear, surgical site infections
  - > Advantages: Simple, can be administered at home; provides high and sustained concentration of antibiotic at the site of infection; reduces systemic absorption and decreases toxicity; reduces the overall dose required
  - > Disadvantages: Some systemic absorption may occur; accurate dosing is difficult; local hypersensitivity reactions or contact dermatitis may occur; antimicrobial resistance can occur rapidly with topical antibiotics
- **Intravenous**
  - > For deep-seated systemic infections
  - > May be continuous or in separate infusions
  - > Advantages: Allows use of antibiotics that may not be available orally
  - > Disadvantages: Can usually only be administered in hospital; requires IV access
- **Intramuscular**
  - > For short-term courses of antibiotics when oral administration is not possible
- **Special routes**
  - > Intravesical administration of gentamicin in chronic urinary tract infections (UTIs)
  - > Inhaled administration of tobramycin, colistin or aztreonam in pulmonary infections
  - > Intrathecal administration of colistin, vancomycin or amikacin in meningitis
  - > Gentamicin, tobramycin or cefuroxime in bone cement in osteomyelitis

ANTIBIOTIC SWITCHING IN THE NETHERLANDS

For some antibiotics the tissue concentrations obtained by intravenous and oral administration are the same. This allows patients to switch as their clinical situation improves, so that they can continue their treatment at home.

In the Netherlands each hospital has an antibiotic stewardship group. This team monitors the use of intravenous antibiotics daily in order to see when patients can be taken off the antibiotics or switched to an oral dose (see also section 31).

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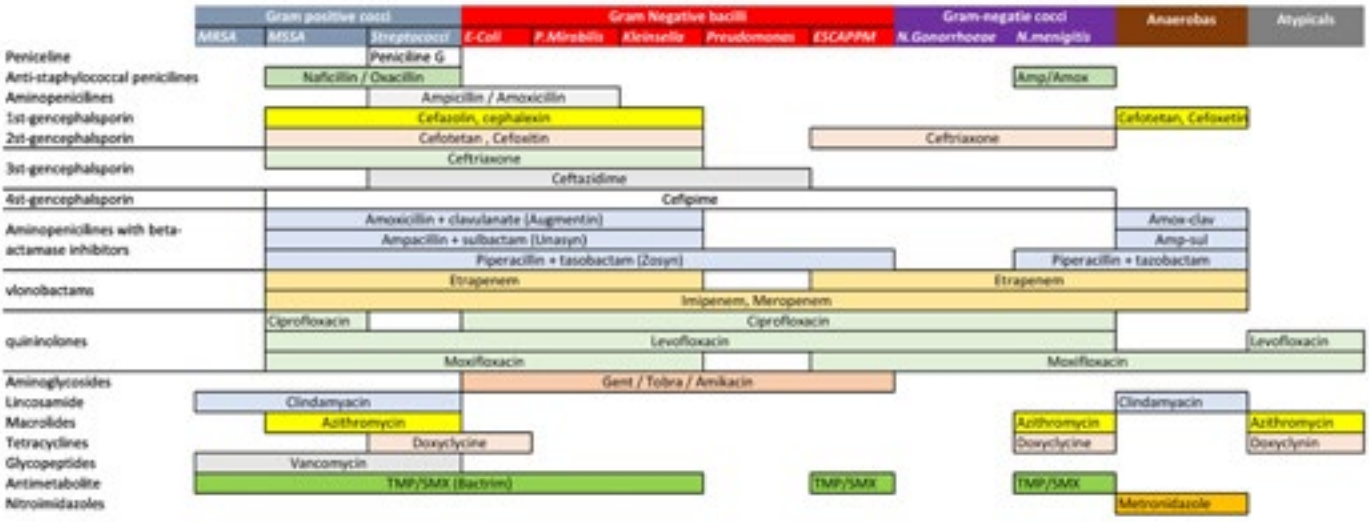
8.5 Broad- and narrow-spectrum antibiotics

8.5.1 Broad-spectrum, what makes it such and when to use it

A broad-spectrum antibiotic acts on a wide variety of bacteria, including Gram-positive and Gram-negative infections (Figure 25).

FIGURE 25: ANTIBIOGRAM



See www.github.com/aetherist/antiogram for detailes. For educational purposes only. TMP/sMX = Trimethoprim-sulfomethamethroxazole, MRSA = Methicillin-resistant Staphylococcus aureus. MSSA = Methicillin-Sensitive Staphylococcus aureus. ESCAPPM = Enterobacter spp., Serratia supp. Citrobacter freundii, Aeromonas spp., Proteus spp., Providencia spp and Morganella morganii

Broad-spectrum antibiotics are used:

- When the causative organism is unknown, but delays in treatment would lead to worsening infection or spread of bacteria to other parts of the body
  - > For example, in meningitis, where the patient can become fatally ill within hours if treatment is not initiated.
- For drug-resistant bacteria that do not respond to narrow-spectrum antibiotics.
- In the case of superinfections, where there are multiple types of bacteria causing the infection
- For prophylaxis in order to prevent bacterial infections occurring
  - > For example, this can occur before surgery, to prevent infection during the operation, or for patients with immunosuppression who are at high-risk for dangerous bacterial infections.

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8.5.2 Narrow-spectrum, what makes it such and when to use it

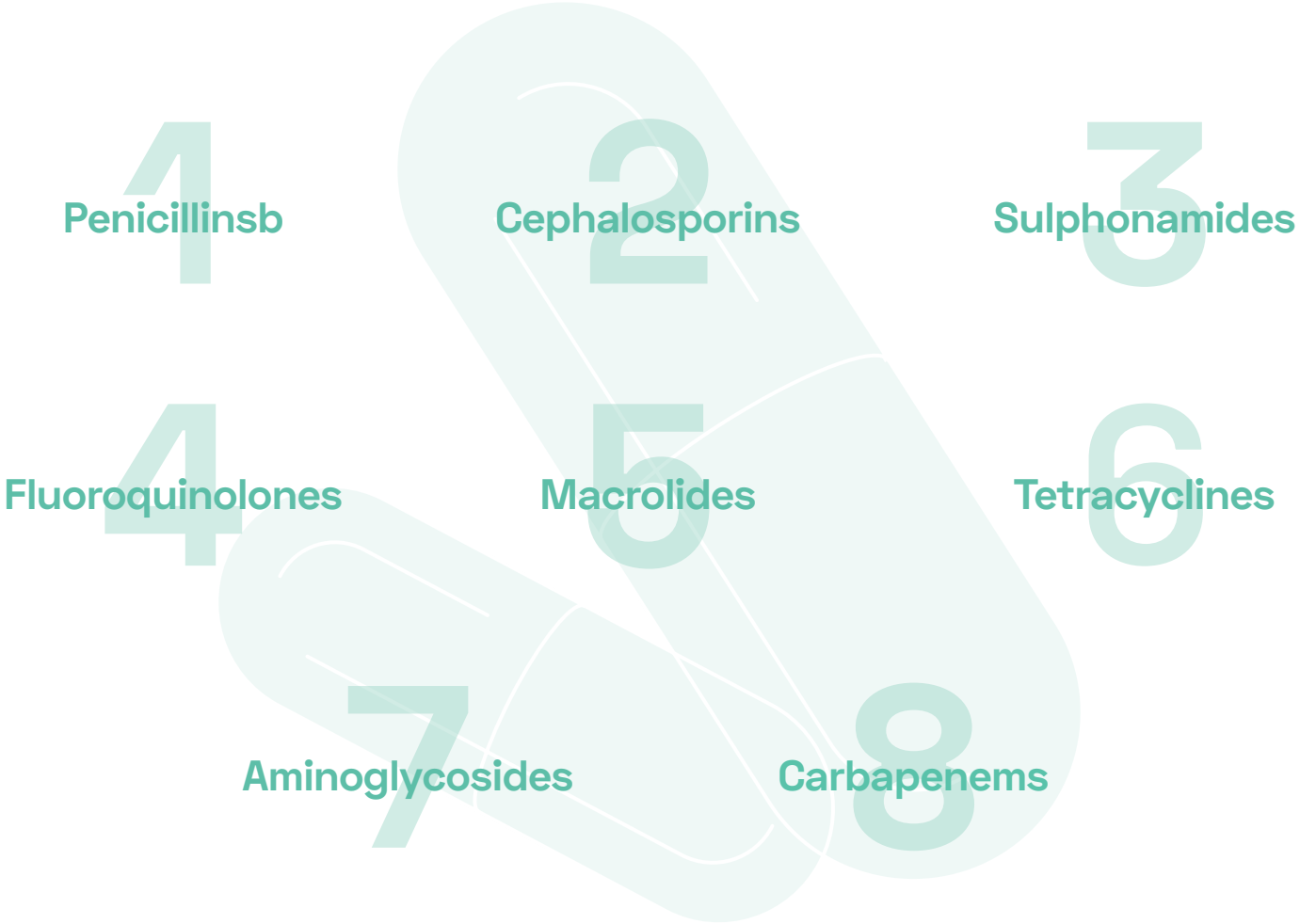
Narrow-spectrum antibiotics are only effective against those bacterial species that are unwanted (i.e. causing disease). This reduces the impact on beneficial bacteria.

Before patients can be treated with a narrow-spectrum antibiotic, it's essential to know which bacterium is causing the illness. Patients may be treated with antibiotics on a trial and error process until results come back. It's expected that in the future new technologies can be used for a quicker determination and to select medication.

9 Overview of eight groups of antibiotics

There are dozens of different types of antibiotics, grouped into different classes. The following section includes eight of the most common classes (Figure 26), what they are generally used for and some of the potential side effects.

FIGURE 26: CLASSES OF ANTIBIOTICS



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This section does not cover all of the antibiotics in each class, and prescribing will depend on antibiotic and disease guidelines.

While many of these antibiotics are similar in structure and usage, there are differences that can affect how effective they are for each individual. Side effects will also vary depending on the individual taking them and their dosage levels.

People with non-severe infections are treated initially with commonly used antibiotics, alone or in combination, ideally following microbiological investigation. For severe infections, antibiotics are given based on observation and then tailored following microbiological investigation.

Antibiotics should be given in combinations that are not known to cause cross-resistance. If all of these fail, patients are treated with an antibiotic of last resort. These are used only in these situations to reduce the chance of resistance developing.

9.1 Penicillins

Penicillins, such as amoxicillin, ampicillin, nafcillin, piperacillin and penicillin G, can treat a wide variety of bacterial infections. Because they act specifically on the cell wall of bacteria, they have a wide therapeutic window, and can be administered during pregnancy and to newborn babies.

Penicillin is the most widely prescribed of all antibiotics, usually as amoxicillin. It is usually the first choice for patients with infections such as pneumonia, tonsillitis and dental abscesses. Other common bacterial infections treated with penicillins include strep throat and UTIs. The most common side effects are gastrointestinal, including nausea, vomiting, bloating and diarrhoea, and black hairy tongue.

Benzylpenicillin has a narrow spectrum of activity, mainly against Gram-positive bacteria. It must be given by injection (IM or IV). It is effective against pneumococcal, streptococcal, meningococcal and leptospiral infections.

Flucloxacillin is effective in infections caused by penicillinase-producing penicillin resistant Staphylococci, only used in infections with these bacteria (hospital acquired staphylococcal infections). It can be given orally, but in severe infections it should be given by injection.

Ampicillin and amoxicillin are broad-spectrum antibiotics and active against non-beta-lactamase-producing Gram-positive bacteria. They diffuse into Gram-negative bacteria and are also active against strains of E. coli, Haemophilus influenza and Salmonella. For oral administration, amoxicillin is the drug of choice. Penicillins are inactivated by penicillinase-producing bacteria. Many bacterial beta-lactamases are inhibited by clavulanic acid. A mixture of this inhibitor with amoxicillin results being active in penicillinase-producing bacteria. Co-amoxiclav is indicated in respiratory and urinary infections.

Hypersensitivity is the most important side-effect, including rashes and rarely anaphylactic reactions that are fatal in about 10% of cases.

9.2 Cephalosporins

Cephalosporins were first discovered and isolated in 1945. There are five generations of cephalosporins. The first generation of these antibiotics is usually used for infections that are easier to treat. The latter generations are for more serious bacterial infections.

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Cephalosporins are often used for strep throat, meningitis, pneumonia, UTIs and ear infections. The cephalosporins that are primarily prescribed include cephalexin, cefaclor and ceftriaxone (as an injection). Cefazolin, cefuroxime and cefoxitin are not used as often and normally prescribed for individuals with cystic fibrosis or those undergoing dialysis. The fifth-generation cephalosporin, ceftaroline, is used for antibiotic-resistant infections such as MRSA.

Side effects are similar to those experienced with penicillin. These include nausea, diarrhoea, rash and thrush. If someone is allergic to penicillin it is likely they will be allergic to cephalosporins, since they are similar in molecular structure. Depending on how severe the allergy is, some individuals may be able to still take third, fourth or fifth generation cephalosporins.

9.3 Sulphonamides

Sulphonamides (also known as sulphonamides or sulfa/sulpha drugs) were initially developed as early as 1906 but not used for antimicrobial purposes until the 1930s. These are technically antimicrobials rather than antibiotics, and examples include sulfisoxazole and sulfamethoxazole. Sulphonamides are used for general bacterial infections such as bronchitis and UTIs.

There are a variety of potential side effects associated with sulphonamides, including itching and rash. Older adults can be particularly sensitive to sulphonamides and are usually advised to avoid these medications. Pregnant women are also advised to avoid these antibiotics as they can be excreted in breast milk.

There are dozens of medications that have the potential to interact with sulphonamides, making it extremely important for patients to discuss these with their prescribing healthcare worker.

Sulphonamides are rarely used for bacterial infections because of the development of more effective and less toxic antibiotics. Also, many organisms have developed resistance to sulphonamides.

9.4 Fluoroquinolones

Fluoroquinolones are divided based on pharmacology and their antimicrobial spectrum. The older group of fluoroquinolone antibiotics includes ofloxacin, norfloxacin and ciprofloxacin. The newer group includes moxifloxacin, levofloxacin, delafloxacin and gemifloxacin. Fluoroquinolones work by destroying the ability of the bacteria to replicate.

Quinolones, such as moxifloxacin, ciprofloxacin and levofloxacin can have severe side effects. Because of this, the European Medicines Agency (EMA) advises that quinolones should not be used as first line antibacterial medication. See more on the EMA website (QR code 5).

It is generally recommended to use these antibiotics only after other courses of treatment have failed. There may be some cases, however, such as when treating severe bacterial pneumonia and abdominal infections, that the potential benefits outweigh the risks.

Ciprofloxacin is effective against both Gram-positive and Gram-negative bacteria, including E. coli, Pseudomonas aeruginosa, Salmonella and Campylobacter. Ciprofloxacin is well absorbed orally and intravenously. Side effects are infrequent, and include nausea, vomiting, rashes, dizziness, headache and tendon damage.

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9.5 Macrolides

These antibiotics were discovered during the 1950s. Specific drugs in this class include roxithromycin, clarithromycin, azithromycin and erythromycin. These antibiotics are often used for specific types of pneumonia, chlamydia and urethritis.

Macrolides are usually given orally, but erythromycin and clarithromycin can be given by IV. They have a narrow spectrum mainly against Gram-positive bacteria, similar as benzylpenicillin. They can be given to penicillin sensitive patients with infections caused by streptococci, staphylococci, pneumococci, and clostridia. They do not penetrate the central nervous system and are therefore ineffective in meningitis. Macrolides are also effective against Mycoplasma pneumonia and Legionnaires' disease. Erythromycin is metabolized by the liver, therefore dosage reduction in renal failure is not necessary, unless severe renal failure.

Macrolides are sometimes prescribed to prevent a bacterial infection. If a person has had their spleen removed or suffers from sickle cell disease, then they may need to use one of these antibiotics on a regular basis to prevent an infection.

Minor side effects can include nausea, diarrhoea and ringing in the ears. Macrolides are often a good alternative for individuals that are allergic to penicillin or cephalosporins. However, potential complications regarding these antibiotics include some drug interaction concerns that could lead to serious heart complications.

9.6 Tetracyclines

Tetracyclines were discovered in 1945 and first prescribed in 1948. In 1953, the drug was patented but was not commercially used until 1978. Tetracyclines are usually given orally but may be given by injection. Absorption in the gut is reduced by calcium ions (milk), magnesium irons (antacids), food and iron preparations.

Tetracyclines are broad spectrum antibiotics, but because of increasing resistance their use is limited. They are the drug of choice to treat infections caused by intracellular organisms because they penetrate macrophages, e.g. Chlamydia, Rickettsia (Q fever) and Borrelia burgdorferi (Lyme disease). They have also been used for acne and in combination with other medication for stomach ulcers caused by Helicobacter pylori.

Because tetracyclines bind to calcium in growing bones and teeth, and can cause discoloration of the teeth in the young, they should be avoided in children up to 8 years, and in pregnant and lactating women. Tetracyclines are active against MRSA pathogens and Vancomycin-resistant enterococci.

While many of these antibiotics have similar side effects to those in other classes, tetracyclines may also inhibit appetite. The most common side effects may include nausea, diarrhoea, swollen tongue, troubling swallowing and soreness or swelling in the genital area. A rare but potential serious side effect is possible blindness due to intracranial hypertension.

9.7 Aminoglycosides

In 1943, streptomycin (the first aminoglycoside) was discovered. These antibiotics, unlike most others, are usually administered intramuscularly or intravenously in a clinical setting.

Aminoglycosides are bactericidal and active against Gram-negative bacteria and some Gram-positive bacteria. They kill bacteria directly and are often used for conditions that are difficult to treat. A few types of aminoglycosides can be taken as ear drops, eye drops or orally.

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They have a narrow therapeutic index and potentially toxic. They are excreted by the kidney, renal impairment results in accumulation and greater toxic side effects. One of the most important side effects is the damage to the VIII cranial nerve (ototoxicity), as well as kidney damage. Aminoglycosides may impair neuromuscular transmission and are contraindicated in patients with myasthenia gravis. Resistance to aminoglycosides arises from production of enzymes that inactivate the drug. Other mechanisms are alteration of the envelope to prevent drug access.

Gentamicin is the most important aminoglycoside, and its main use being in the empirical treatment of life-threatening Gram-negative infections (Pseudomonas aeruginosa) in hospitals. Amikacin is less affected by aminoglycoside-inactivating enzymes and is used in infections that are resistant to gentamicin.

9.8 Carbapenems

These antibiotics were introduced in the 1980s. They are a class of antibiotics also known as beta lactams. They work by inhibiting synthesis of the bacterial cell wall. Carbapenems are often used for serious urinary infections, abdominal infections, blood infections and pneumonia.

The carbapenems doripenem, ertapenem, imipenem and meropenem are usually administered intravenously or injected into a muscle. These drugs are often prescribed for infections that are not easily treated with other antibiotics.

Meropenem is a carbapenem (structure similar to penicillin) but highly resistant to most ß-lactamases. It has a wide spectrum and is bactericidal against most Gram-negative and Gram-positive pathogenic bacteria. It is given by injection.

Carbapenems are similar to penicillin. General side effects include nausea, diarrhoea and headache.

9.9 Others

Trimethoprim is an inhibitor of dihydrofolate reductase. It is selectively toxic for the bacterial enzyme. It is widely used in UTIs and in combination with sulfamethoxazole (co-trimoxazole) may produce a synergetic action and increase activity against certain bacteria. It has an important use in the treatment of Pneumocystis jirovecii pneumonia. It is well absorbed orally.

Metronidazole is active against most anaerobic bacteria including Bacteroides species. It is a first choice in certain protozoal infections, i.e. Entamoeba histolytica, Giardia lamblia, Trichomonas vaginalis. It is well absorbed orally and can be given by IV. It is often used as prophylaxis in gut surgery. Side effects include gastrointestinal disturbance. Tinidazole has similar action to metronidazole but has longer duration of action.

Vancomycin is a bactericidal antibiotic that is not absorbed orally. It acts by inhibiting peptidoglycan formation and is active against most Gram-positive bacteria. IV delivery is important for treatment of septicaemia or endocarditis caused by MRSA. It Is given orally for antibiotic associated pseudomembranous colitis (superinfection of the bowel by Clostridioides difficile). Rarely, vancomycin can cause renal failure or hearing loss.

Nitrofurantoin concentrates in the urinary tract and is used in UTIs. The blood levels remain low and it seems to trigger little resistance. It is used long-term to prevent UTIs.

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10 Adverse issues with antibiotics

There are three areas of adverse issues of antibiotics; side effects, interactions and antibiotic resistance.

10.1 Antibiotic side effects

Side effects are classified as very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000, <1/1,000); very rare (<1/10,000). The most **common side effects of antibiotics**, affecting around one in 10 people, are gastrointestinal. There are generally mild and include: vomiting, nausea, diarrhoea, bloating, indigestion, abdominal pain and loss of appetite. These usually subside once the course of treatment is finished. It is therefore important to report all side effects to the prescriber. It is essential to talk to the prescriber about any **additional side effects**, as these can be more serious (see Table 18).

TABLE 18: POTENTIAL SIDE EFFECTS OF ANTIBIOTICS

Group and target	Examples	Mechanism of action	Side effects
Sulphonamides Folic acid inhibitor	Sulfasalazine, sulfadiazine	Bacteriostatic	Nausea, vomiting, headaches, hypersensitivity, bone marrow depression, hepatitis
Trimethoprim Folic acid inhibitor	Trimethoprim	Bacteriostatic	Nausea, vomiting, skin rashes, megaloblastic anaemia (folate deficiency)
Penicillins ß-lactam	Penicillin, benzylpenicillin, amoxicillin, flucloxacillin	Bactericidal	Hypersensitivity (1-10%), nausea, vomiting, encephalopathy (rare)
Cephalosporins ß-lactams	Cefuroxime, cephalexin, cefotaxime	Bactericidal	Hypersensitivity, nephrotoxicity, diarrhoea, skin rashes, headache
Monobactam ß-lactams	Aztreonam	Bactericidal	Skin rashes, occasional abnormal liver function
Carbapenems ß-lactams	Imipenem	Bactericidal	Hypersensitivity, nausea, vomiting, encephalopathy, neurotoxicity at high doses

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Aminoglycosides Protein synthesis inhibitor	Gentamycin, streptomycin, neomycin	Bactericidal	Sensorineural deafness (can also affect the foetus in a pregnant woman), balance
Glycopeptides Cell wall synthesis inhibitor	Vancomycin, teicoplanin	Bactericidal	Nephrotoxicity, rashes, blood disorders, nausea
Macrolides Protein translocation inhibitor	Erythromycin, clarithromycin	Bactericidal/ bacteriostatic	Gastrointestinal effects, hypersensitivity, skin rashes
Lincosamides Protein synthesis inhibitor	Clindamycin	Bactericidal/ bacteriostatic	Nausea, vomiting, rashes, jaundice, neutropoenia, bone marrow suppression
Fusidic acid Protein synthesis inhibitor	Fusidic acid	Bactericidal/ bacteriostatic	Gastrointestinal effects, skin eruptions, jaundice
Quinolones DNA transcription inhibitor	Ciprofloxacin, levofloxacin, ofloxacin	Bactericidal	Gastrointestinal effects, skin rashes, dizziness, headaches. Not to be used with theophylline
Metronidazole DNA synthesis inhibitor, breaks down DNA	Metronidazole, tinidazole	Bactericidal	Nausea, vomiting, metallic taste, intolerance to alcohol, rashes
Nitrofurantoin DNA disruptor	Nitrofurantoin	Bactericidal	Peripheral neuropathy, gastrointestinal effects, lung fibrosis (long term use)
Tetracyclines Protein synthesis inhibitor	Doxycycline, minocycline, oxytetracycline	Bacteriostatic	Nausea, vomiting, diarrhoea, discolouration of teeth in children, intracranial hypertension, photosensitivity
Chloramphenicol Protein synthesis inhibitor	Chloramphenicol	Bacteriostatic	Highly toxic – bone marrow toxicity, neuritis, headache, rashes, grey baby syndrome

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Around 1 in 15 people will have an allergic reaction to antibiotics, most commonly to penicillin and cephalosporins. Symptoms include skin rash and itches, as well as coughing, wheezing, and tightness of the throat, which can cause breathing difficulties. The antibiotic should then be stopped, and allergic reactions reported instantly. The reaction may need antihistamines as an urgent intervention.

In rare cases, an antibiotic can cause a severe and potentially life-threatening allergic reaction known as anaphylaxis. **Initial symptoms of anaphylaxis** are often the same as a mild allergic reaction. They include: feeling lightheaded or faint, breathing difficulties such as fast, shallow breathing or wheezing, fast heartbeat, clammy skin, confusion and anxiety, and collapsing or losing consciousness. There may be other allergy symptoms, including an itchy, raised rash (hives), feeling or being sick, swelling (angioedema), or stomach pain.

Anaphylaxis is a medical emergency and can be life-threatening. Inside a hospital, follow the hospital procedures; outside of a hospital, dial 112 immediately and ask for an ambulance if think someone is going into anaphylactic shock.

Tetracyclines can make **skin sensitive to sunlight** and artificial sources of light, such as sun lamps and sunbeds. Avoid prolonged exposure to bright light while taking these medicines.

In very rare cases, fluoroquinolone antibiotics can cause disabling, long-lasting or permanent **side effects affecting the joints, muscles and nervous system.** Stop taking fluoroquinolone treatment straight away and tell a doctor if the following occur: tendon, muscle or joint pain, usually in the knee, elbow or shoulder, tingling, numbness or pins and needles.

10.1.1 Reporting side effects

In the European Union, reporting side effects of medication is important, and is very straightforward. The EMA is committed to maintaining a strong working relationship with this group and specialist nurses play a key role. There are national routes for reporting side effects, for example the Netherlands Pharmacovigilance Centre (Lareb).

The Pharmacovigilance Risk Assessment Committee (PRAC) is responsible for assessing all aspects of risk management of human medicines, including detection, assessment, minimisation and communication of the risk of adverse reactions, while taking the therapeutic effect of the medicine into account; design and evaluation of post-authorisation safety studies; and pharmacovigilance audit.

10.2 Interactions between antibiotics and other medicines

Antibiotics may interact with unrelated nonantibiotic drugs, and the result may be the enhanced or decreased activity of the antibiotic or other drug.

1. delay emergence of resistant organisms
2. treat mixed or undiagnosed infections; or
3. enhance the rate of bactericidal action.

Whether a combination of antibiotics will be synergic, additive, indifferent, or antagonistic frequently is not predictable. In vitro tests are required to determine synergic combinations. Interactions and the mechanisms of these interactions involving antimicrobial agents in humans are reviewed in this communication.

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10.3 Antibiotic resistance

Some bacteria are naturally insensitive to certain antibiotics, known as intrinsic resistance. Acquired resistance is as a result of selection following mutation and acquisition of genetic material from other bacteria. Bacteria divide very rapidly. With each division there is potential for the introduction of a spontaneous mutation. Many mutations are harmful, and the bacteria do not survive. However, some mutations improve the chance of survival.

Bacteria can, by chance, have mutations that make them antibiotic-resistant. When there is no antibiotic present, this does not improve their chance of survival, and they may die out. If there is an antibiotic present, the mutation **does** increase the chance of survival. While the antibiotic will kill the antibiotic-sensitive bacteria, the antibiotic-resistant bacteria will survive – this is known as selection. The more often an antibiotic is used, the more chance there is that resistant bacteria will be seen.

There are different kinds of AMR. Some bacteria produce enzymes, including beta-lactamases, that break down antibiotics. Others change the makeup of the cell wall, meaning that the antibiotic no longer works.

10.3.1 The spread of resistance

People can spread resistant bacteria to each other through person to person transmission, by touching (directly), or by handling an object that someone else has touched (indirectly). This includes people who are ill, or who are otherwise healthy but are carriers of a resistant strain of bacteria. People can be colonised by resistant bacteria and not get ill, but they can still pass on the resistant strain. The resistant bacteria become a serious problem when the infection becomes invasive, and an infection develops. This infection is not treatable by the antibiotic to which it has developed a resistance. As a result of the combination of selection pressure and transfer of bacteria between people, resistance can spread through an entire population.

Resistance can also spread from bacteria to bacteria, when sensitive bacteria acquire the resistance mechanisms of resistant bacteria by exchanging small, ring-shaped DNA molecules known as plasmids. When antibiotics are present in the environment, these resistant bacteria will spread further at the expense of the sensitive bacteria. This mechanism is starting to play an increasingly important role in the spread of resistance. This form of resistance can spread rapidly on a large scale; all the more reason to limit the emergence of resistant organisms so that infections will remain treatable with relatively cheap, effective and safe means.

10.3.2 Multidrug-resistant organisms

Sir Alexander Fleming said, «It is not difficult to make microbes resistant to penicillin» and Dr Margaret Chan former Director-General of the World Health Organisation once said «A post-antibiotic era means, in effect, an end to modern medicine as we know it. Things as common as strep throat or a child's scratched knee could once again kill» [4].

The development of multi-drug resistant organisms (MDROs) pose a threat to healthcare. For example, there have been reports of pan-resistant (totally resistant) carbapenem-resistant Enterobacterales initially originating from countries such as India [5]. Unless nurses and other healthcare professionals are vigilant and judicious in the use of antibiotics to treat life-threatening infections, the warning of a post-antibiotic era where even simple infections cannot be treated, and where operations such as joint replacements can no longer be carried out, could become a reality.

Organisms do not respect boundaries between community, primary and secondary care. Patients are discharged from hospital to community with MDROs and then from the community back to hospital.

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10.3.3 Extended-spectrum beta-lactamase (ESBL) producing Enterobacteriaceae

Extended-spectrum beta-lactamase (ESBL) producing Enterobacteriaceae have become important in terms of resistance in Gram-negative bacteria worldwide. ESBL-Enterobacteriaceae bacteraemias carry an increased risk both for mortality and delay in effective treatment. ESBL producers are resistant to all beta-lactam antibiotics except carbapenems and usually resistant to other important antimicrobials such as fluoroquinolones, aminoglycosides and co-trimoxazole [6]. The ESBLs break down penicillins and cephalosporins making them ineffective. ESBL-producers are resistant to all beta-lactam antibiotics. Examples include Escherichia coli and Klebsiella species.

10.3.4 Carbapenem-resistant Gram-negative bacteria

Carbapenems are effective against gram-negative bacteria, but resistant organisms produce carbapenemases that make carbapenems ineffective [7].

Carbapenem-resistant Enterobacteriaceae (CRE), Acinetobacter baumannii (CRAB), and Pseudomonas aeruginosa (CRPA) are becoming a major challenge for treatment. To make matters worse, countries in the EU are reporting pan-resistant strains, which cannot be treated by any antibiotics [8-12]. Patients who become positive for CRE remain persistent carriers for up to 1 year [13,14]. These factors create a major challenge for controlling the spread and treating the patient with a clinical infection.

10.3.5 Resistant strains of Staphylococcus aureus

The first cases of Methicillin-resistant Staphylococcus aureus (MRSA) were reported in the late 1960s. The rates of MRSA continued to increase worldwide causing major outbreaks. The incidence of mortality and morbidity increased significantly in the early 2000s both in the US and the UK [15]. According to data from the ECDC, the levels of MRSA are falling [16].

MRSA is transmitted through direct contact with patients who are either colonised or infected, or through equipment and their environment. MRSA is found in the skin, axilla and perineum [17], with the main reservoir in the nose. It is a major problem in hospitals, long-term care facilities and nursing homes, mainly spread through direct skin contact. In addition, MRSA also occurs in various animal species and can be therefore transmitted from animal to human. Patients admitted from hospitals in other countries, or who are routinely in contact with animals, should be checked for MRSA carrier status. Carriers however are less likely to pass on MRSA than people with an active infection.

Management of MRSA infection requires good hand hygiene and good wound care. MRSA cannot be treated with methicillin and other beta-lactam antibiotics. In empiric therapy for staphylococci if possibility of MRSA is low, a penicillinase-resistant penicillin such as flucloxacillin should be used as first treatment choice (or cephalosporins of first/second generation). But MRSA cases should be treated with linezolid, vancomycin or daptomycin according to the site of infection and the antimicrobial susceptibility.

For infections where toxins play an important role, such as toxic shock syndrome (TSS), clindamycin should be added to block toxin production at an early stage.

Nasal S. aureus can be eliminated by short treatments with antimicrobial nasal ointment (Mupirocin 2% 3 times for 5 days). This can be used preoperatively, and to prevent infections in dialysis patients.

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Prophylaxis before surgery, such as mupirocin or fusidic acid in combination with a disinfectant soap (chlorhexidine), may be useful for patients with skin infections, such as furunculosis. However, relapses occur relatively often following treatment.

Vancomycin-resistant Staphylococcus aureus (VRSA) is resistant to the antibiotic of last resort, vancomycin, which is used against MRSA, methicillin-resistant Staphylococcus epidermidis (MRSE) and methicillin-resistant Clostridioides difficile. All cases of MRSA or VRSA need to be reported to the relevant national public health or AMR institute, which will follow up with European institutes.

10.3.6 The fight against resistance

The antimicrobial resistance (AMR) crisis facing hospitals globally is driven by the ESKAPE pathogens (Gram-negatives Klebsiella pneumoniae, Enterobacter cloacae, Acinetobacter baumannii and Pseudomonas aeruginosa, and Gram-positives Enterococcus faecium, and Staphylococcus aureus). These are responsible for the majority of infections in hospital patients that are difficult to manage with antimicrobial therapy.

Resistant forms of these bacteria:

1. Cause frequent and serious illness
2. Have a form of acquired resistance that makes it impossible to treat the patient with the usual antibiotics.
3. Are able to spread if no additional measures are taken, such as isolating a patient.

The ESKAPE pathogens do not include bacteria such as Staphylococcus epidermidis. Even though there is extensive resistance, S epidermis is present on everyone's skin and mucous membranes, and almost never leads to disease in healthy people. Infections only occurs in specific circumstances, such as patients who have a catheter or implant that allows the bacteria to enter the body. Preventing the spread of this bacterium is difficult and would not be a cost-effective approach. That is why in this case we opt for preventive measures aimed at preventing contamination during, for example, the insertion of catheters.

11 Antibiotics in veterinary use and effect on humans

For almost seven decades, antibiotics have been routinely fed to food animals such as pigs; almost as long as people have taken antibiotics. And for just about as long, it has been clear that those antibiotics have been fostering drug-resistant bacteria that can be transmitted from animals to make humans sick.

11.1 Veterinary antibiotics

Giving antibiotics to animals as growth promoters has had a great impact in the environment. Antibiotic-resistant bacteria are in the water, in animals and in food, leading to a global spread of bacteria that are not sensitive to antibiotics. This can only be addressed with the co-operation of governments worldwide. This has led to the World Health Organisation's introduction of the One Health approach.

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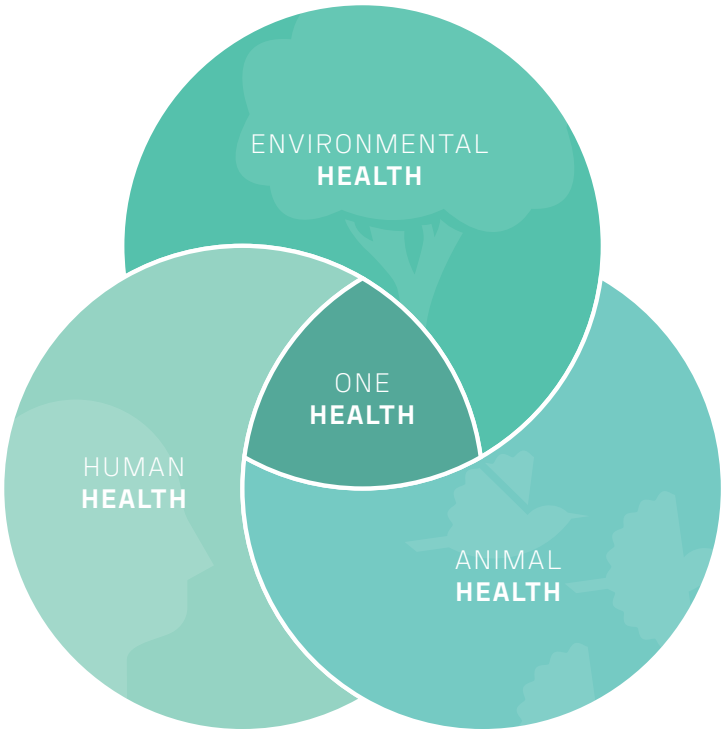
HUMAN HEALTH THREATS RELATED TO VETERINARY USE OF ANTIBIOTICS.

The first outbreaks of drug-resistant foodborne illness were spotted as early as the mid-1950s, when an epidemic of resistant Salmonella swept through south-eastern England. That was the first of waves of outbreaks that occurred over decades, some small and some very large and widespread. One of the largest foodborne outbreaks in US history, which made 634 people in 29 states and Puerto Rico sick in 2013-14, was tracked back to chickens that had been given antibiotics in their feed. Europe has now banned the use of antibiotics as growth promoters.

11.2 One Health

Whereas in the past, health was addressed in silos, with the environment, humans and animals each in their own domain, the n One-Health concept brings a wider approach (Figure 27).

FIGURE 27: ONE HEALTH



11.2.1 What is 'One Health'?

'One Health' is an approach to designing and implementing programmes, policies, legislation and research in which multiple sectors communicate and work together to achieve better public health outcomes. The One Health approach includes food safety, the control of zoonoses (diseases that can spread between animals and humans, such as flu, rabies and Rift Valley Fever), and combatting antibiotic resistance (when bacteria change after being exposed to antibiotics and become more difficult to treat).

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12 Other antimicrobials and how they work

12.1 Antivirals

Viral diseases are treated using antivirals, which reduce the ability of viruses to multiply. These work by:

- Blocking the virus from entering the cell
- Stopping the virus from releasing its contents into the cell
- Preventing the cell from building new viruses
- Inhibiting the release of the new viruses.

Viruses are constantly mutating and changing, and this can make them resistant to antiviral medication. As with antibiotics, if antiviral medications do not completely clear the viral infection, a resistant form of the virus can take over [18].

Vaccines are used to prevent infections, by triggering immunity against a specific virus (see 18: Vaccines and how they work).

12.2 Antifungals

Antifungal medicines are used to treat fungal infections, which most commonly affect skin, hair and nails, but can also affect the lung or brain. Antifungal medicines are often available 'over the counter' pharmacist. Antifungal medicines kill fungal cells by affecting a substance in the cell walls, causing the contents of the fungal cells to leak out and the cells to die, or by preventing fungal cells growing and reproducing. Antifungal medicines are available as:

- topical antifungals – a cream, gel, ointment or sprayed directly to skin, scalp or nails
- oral antifungals – a capsule, tablet or liquid medicine that is swallowed
- intravenous antifungals – an injection into an arm, usually given in hospital
- intravaginal antifungal pessaries – small, soft tablets inserted into the vagina

Infections commonly treated with antifungals include ringworm, athlete's foot, fungal nail infections, vaginal thrush and some kinds of severe dandruff.

Less commonly, there are also more serious fungal infections that develop deep inside the body tissues, such as aspergillosis, which affects the lungs, and fungal meningitis, which affects the brain. These may need to be treated in hospital. People who have a weakened immune system, through illness or because they are taking drugs to suppress their immune systems, are more at risk of getting one of these more serious fungal infections. Often treatment must start before results are known because fungal infections are very dangerous, and time is crucial. In cases of resistance, another antifungal agent can be added, or treatment can be combined with an agent that makes the immune system stronger (immunotherapy).

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One of the last resorts is surgery, where the infection is removed. Antifungals may be prescribed as a precaution for example, in people with acute leukaemia who receive chemotherapy, or in persons living with HIV who have a weakened immune.

Resistance to antifungals occurs naturally, but is also driven by inappropriate use of antifungals, and by use of antifungals in agriculture. Antibiotics may also add to antifungal resistance. There are increasing numbers of Candida infections resistant to fluconazole, and resistance to echinocandins is emerging. Patients infected with Candida resistant to both fluconazole and an echinocandin have few treatment options [19].

12.3 Anti-parasitics

Symptoms of parasitic infections vary widely. Antiparasitic medications target the parasites and destroy them or inhibit their growth. They are given orally, intravenously or topically.

13 Prescribing responsibility of the nurse specialist and physician

The role of nurses in prescribing varies across Europe. In some European countries, nurses have a very marginal role related to medication, for example they may not even be allowed to vaccinate in clinical practice. In other countries, they are able to prescribe, often after an academic education program and certification, for example nurse practitioners, nurse specialists or clinical nurse specialists.

13.1 Authorization to prescribe

As in any other area of practice, nurses need to act within their competence and scope of practice where prescribing is concerned. Not all nurses are able to prescribe.

- **Formal prescribing:**

  within national legislative structure and the boundaries of the nurse's competence. Prescribing may be general or from a range of medications within a particular specialisation. Prescribing can be an independent competence, or under supervision or consultation with another professional such as a general practitioner or family doctor, or a hospital specialist.`

- **Informal prescribing:**

  nurses with specialist knowledge and experience may provide prescribing advice for other colleagues, medical specialists or physicians in training. This provides support for prescribers and helps to improve patient safety.

13.2 Other responsibilities for nurses

Nurses spend a lot of time with patients and have a responsibility in observing patients for medication responses and side effects, especially with antibiotics.

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They are responsible for:

- The correct and timely administration of antibiotics
- Observing patients' condition and reporting changes to the physician
- Taking patients' specimens for investigation and informing physicians about the results
- Understand the significance of infection control measures in hospitals
- Understand the value of vaccination.

Nurses also have a responsibility to educate patients:

- What antibiotics are and why they are taking them
- What side effects can be expected
- What antimicrobial resistance is, and how it can affect them

Nurses are in the best place to be supporters and advisors to patients, and they play a really important and significant role in influencing society and improving antibiotic use. Nurses can also play a role as advisors to medication committees, pharmaceutical companies and EMA.

14 Medicine and market

14.1 Shortage

Medication shortages can affect patients, nurses, pharmacists, and physicians. The main three causes are: shortage of ingredients; problems in manufacturing; and market dynamics.

The causes behind these include:

1. Companies stopping manufacturing because use of a particular drug is declining
   > Medications are developed for certain treatment and often prescribed based on guidelines, but when the insights on a disease changes or a guideline, then the manufacturer may stop production.
2. Competition forcing the price of a drug down, meaning manufacturers drop out
   > This occurs when a product has become so cheap that companies decide to stop producing. When there is a change in the market, it often takes a longer time to start up processing.
3. Shortage of raw materials to make medication.
4. Companies not being able to keep up with demand
5. Pharmacists choosing not to stock cheaper drugs because profit margin is too narrow.

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6. Manufacturing issues
    > Over the past years, some manufactures have been able to build a monopoly position and in some cases a factory had a major incident leading to stop all activities

7. Political sanctions
    > This is most common in politically sensitive regions where there is a ban on delivering products, trade bans or unresolved trade relations and this can lead to shortage.

8. Theft and corruption

In most European countries, patients, nurses and other healthcare professionals can report medication shortages to their national authorities **(QR code 6)**

Medication shortages can be very worrying for patients, and can put their health at risk. Nurses and pharmacists are often on the frontline when shortages occur. Their responsibility is to communicate with the patients and help them to remain on course with their treatments.

At times of shortage, patients may try to buy medications online. However, much of this is falsified. Falsified medicines do not meet the efficacy, safety and quality standards required under EU law. Falsified medicines appear to be genuine, but may be contaminated, may contain incorrect ingredients, or may contain the correct ingredients at an incorrect dose. It is of vital importance that nurses are aware of this.

SCAN ME
(QR code 6)

MORE INFORMATION ON MEDICATION SHORTAGE

Position statement on Medication Shortage European Association of Hospital Pharmacists (EAHP)
European Medicine Agency (EMA) 'Availability on Medicines'

An example on falsified medication was on a medication related to rheumatism. The products not available any more in regular market, it was for sale on the internet. The source was a Mediterranean country, but the product was made in Asia. The fact it was a counterfeit medication was discovered month later after serious relapse of patients with very problematic consequences.

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