Microbiology

Unit 6 · Lesson 1 · How microbes cause disease

The notes for Lesson 1 of Unit 6: chapters 6.1 to 6.2 of the unit book, with their figures, worked examples, exam traps and quizzes, in one file. The full unit book, with every chapter, the exam question bank and the glossary, is linked at the end.

Lesson 1 of 3 | 2 chapters | Chapters 6.1 to 6.2

About these notes

These are the notes for **Lesson 1 · How microbes cause disease** of the University free n easy video lessons on Microbiology Unit 6, Medical, Environmental and Industrial Microbiology. They are chapters 6.1 to 6.2 of the unit book, unchanged, so a page here is the same page in the full book.

6.1 Microbial pathogenicity; nosocomial and opportunistic infections

Most microbes never harm us. A pathogen is one that can cause disease, and pathogenicity is that ability. To cause disease a microbe must enter the body, stick, multiply, dodge the immune system and damage tissue, and then leave to reach the next host. Each step needs a molecule, called a virulence factor. Hospitals add a special twist: sick patients with tubes and wounds, plus heavy antibiotic use, let even weak microbes cause disease. Those are nosocomial and opportunistic infections, and they are why hospital hygiene is a science.

You need: bacterial cell structure, capsule and the Gram-negative outer membrane (Unit 2, Bacterial cell wall: Gram-positive and Gram-negative); antimicrobial resistance (Unit 5, Antimicrobial resistance).

Pathogenicity and virulence

Pathogenicity is a yes-or-no quality: can this species cause disease? **Virulence** is a degree: how much disease does this strain cause? Two strains of *Escherichia coli* are the same species, yet one lives quietly in your colon and another (an enterohaemorrhagic strain) causes bloody diarrhoea. They differ in virulence.

Virulence is measured in animals or cell culture with two numbers. The **ID50** (infectious dose 50) is the number of microbes that infects half of the test hosts. The **LD50** (lethal dose 50) is the dose that kills half of them. A smaller ID50 or LD50 means a more virulent microbe. *Shigella* can infect with very few cells, which is why it spreads so easily through contaminated food.

A **primary (true) pathogen** causes disease in a healthy person. An **opportunistic pathogen** causes disease only when defences are weakened. The same microbe can be both: *Staphylococcus aureus* lives harmlessly in the nose of many people but causes wound and bloodstream infections in surgical patients.

The steps of infection and their virulence factors

1. **Entry.** Through a portal: the respiratory tract (tuberculosis), the gut (typhoid, cholera), the skin through a cut or an insect bite (malaria), or the genital tract.
2. **Adhesion.** Pili (fimbriae) and surface proteins called **adhesins** bind host receptors, so the microbe is not washed away by urine, mucus or gut movement. Uropathogenic *E. coli* use P-fimbriae to hold on in the urinary tract.
3. **Invasion and spread.** Some bacteria make the host cell swallow them (*Salmonella*, *Shigella*). Enzymes such as hyaluronidase and collagenase loosen tissue; coagulase and streptokinase build or dissolve fibrin clots.
4. **Evasion of defences.** A **capsule** stops phagocytes from gripping the cell (*Streptococcus pneumoniae*). IgA protease cuts the antibody of mucous surfaces. Antigenic variation changes surface proteins faster than antibodies can follow. Siderophores steal iron, which the host keeps locked away.
5. **Damage.** Mostly by toxins, compared below, and partly by the host's own inflammation.
6. **Exit and transmission.** Coughing, faeces, blood, or a vector such as a mosquito carries the microbe to the next host.



Virulence = how much damage a strain causes; measured as ID50 or LD50 (smaller = more virulent).

Opportunist: steps 2 to 5 succeed only when skin, flora or immunity is damaged (catheter, burn, surgery, HIV, cancer drugs, long antibiotic use).

Figure 6.1.1 The six steps a pathogen must complete, with the virulence factors that serve each step. Notice that damage (orange box) is only one step; blocking any earlier step, for example adhesion, also prevents disease.

Exotoxins and endotoxins

FEATURE	EXOTOXIN	ENDOTOXIN
Chemistry	Protein	Lipid A part of lipopolysaccharide (LPS)
Source	Secreted by living cells; Gram-positive and some Gram-negative bacteria	Outer membrane of Gram-negative bacteria; released mainly when cells lyse
Heat	Mostly destroyed by heat	Stable to boiling
Potency and action	Very potent, specific target (nerve, gut, heart)	Less potent; general fever, low blood pressure, septic shock
Toxoid vaccine	Possible (tetanus, diphtheria)	Not possible

Many exotoxins are **A-B toxins**: the B part binds the host cell and the A part enters and acts as an enzyme. Diphtheria toxin stops protein synthesis; cholera toxin keeps the gut cell pumping out salt and water, which causes watery diarrhoea.

Nosocomial and opportunistic infections

A **nosocomial** infection, now usually called a **healthcare-associated infection (HAI)**, is one the patient did not have or was not incubating at admission; by convention it appears 48 hours or more after admission. The four commonest are urinary tract infection linked to a catheter (CAUTI), bloodstream infection linked to a central line (CLABSI), ventilator-associated pneumonia (VAP) and surgical site infection (SSI).

Why hospitals? The patients are already weak; tubes and wounds bypass skin and mucosa; staff hands and instruments carry microbes from bed to bed; and heavy antibiotic use selects resistant strains. The infection is **endogenous** when it comes from the patient's own flora and **exogenous** when it comes from outside. The resistant hospital group is remembered as **ESKAPE**: *Enterococcus faecium*, *Staphylococcus aureus* (including MRSA), *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacter* species. Hand hygiene is the single most effective control; Ignaz Semmelweis showed this in a Vienna maternity ward in the 1840s.

Opportunistic infections follow a fall in defence. In advanced HIV infection the classic ones are *Pneumocystis jirovecii* pneumonia, cryptococcal meningitis (*Cryptococcus neoformans*, a capsulated yeast seen with India ink) and oral and oesophageal candidiasis. Aspergillosis (*Aspergillus fumigatus*) affects patients on cancer treatment. In 2021 India saw many cases of mucormycosis ("black fungus") in COVID-19 patients with uncontrolled diabetes or heavy steroid use, a clear lesson in how host state decides disease.

WORKED EXAMPLE

Question (6 marks). The infection control team of a Chennai hospital ICU records, in one month, 5,000 patient-days, 3,600 urinary catheter-days and 9 catheter-associated urinary tract infections (CAUTI). Calculate the CAUTI rate and the catheter utilisation ratio. A second ICU had 6 CAUTIs in 1,500 catheter-days. Which ICU performed better, and why must you not simply compare 9 with 6?

1. A device-associated rate counts infections per 1,000 device-days: rate = (number of infections ÷ device-days) × 1,000.
2. ICU 1: (9 ÷ 3,600) × 1,000 = 2.5 CAUTIs per 1,000 catheter-days.
3. Catheter utilisation ratio = catheter-days ÷ patient-days = 3,600 ÷ 5,000 = 0.72. So catheters were in place on 72% of patient-days.
4. ICU 2: (6 ÷ 1,500) × 1,000 = 4.0 CAUTIs per 1,000 catheter-days.
5. ICU 1 performed better (2.5 is lower than 4.0) even though it had more infections. Raw counts ignore exposure: ICU 1 had more than twice the catheter-days, so more chances for infection.

Answer: 2.5 per 1,000 catheter-days; utilisation 0.72; ICU 1 is better. Its next target is the high utilisation ratio, by removing catheters that are no longer needed.

EXAM TRAPS

- Pathogenicity is the ability (species level); virulence is the degree (strain level). Do not use them as synonyms in a definition question.
- Endotoxin is lipid A of LPS, not the whole cell wall, and only Gram-negative bacteria have it. Exotoxins are not only from Gram-positives: cholera toxin is from a Gram-negative.
- A lower LD50 means a more dangerous microbe. Students often reverse this.
- An infection present on admission is not nosocomial, even if it is diagnosed in the hospital.
- Favourite question: "Differentiate exotoxin and endotoxin" (five points in a table) and "What are nosocomial infections? Give sources and control measures."

CHECK YOURSELF

– REMEMBER **Define ID50 and LD50.** 2 marks

ID50 is the number of microbes that infects 50% of test hosts; LD50 is the number that kills 50%. Both measure virulence.

– REMEMBER **Expand ESKAPE.** 2 marks

Enterococcus faecium, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *Enterobacter* species.

– UNDERSTAND **Why does a capsule make a bacterium more virulent?** 3 marks

The slippery polysaccharide capsule stops phagocytes from binding and engulfing the cell and hides surface antigens from complement, so the bacterium survives and multiplies in tissue.

– UNDERSTAND **Why can a toxoid vaccine be made for tetanus but not for endotoxin shock?** 3 marks

Tetanus toxin is a protein; formaldehyde treatment removes its toxicity but keeps its antigenic shape, so antibodies form. Endotoxin is lipid A, a poor antigen with no such inactivated form.

– APPLY **A ward had 4 CLABSIs in 2,000 central-line days. Find the rate.** 2 marks

(4 ÷ 2,000) × 1,000 = 2.0 CLABSIs per 1,000 central-line days.

– APPLY **Classify each infection as endogenous or exogenous: (a) *E. coli* UTI from the patient's own gut flora after catheterisation; (b) MRSA spread from a nurse's hands.** 2 marks

(a) Endogenous; (b) exogenous.

– ANALYZE **A strain loses its pili but keeps all its toxin genes. Predict its virulence in the urinary tract and explain.** 4 marks

Virulence falls sharply. Without pili it cannot adhere, so urine flow washes it out before it multiplies or makes enough toxin. Toxin genes are useless if an earlier step fails.

BEYOND THE SYLLABUS

This is not for the exam. Modern pathogenicity research uses "molecular Koch's postulates": a gene is a virulence gene if knocking it out lowers virulence and putting it back restores it. Drug developers now target virulence factors (anti-adhesion and anti-toxin molecules) instead of killing the microbe, hoping to slow resistance. Hospitals track HAIs with surveillance software and genome sequencing of isolates to find outbreak chains. Search "anti-virulence therapy", "HAI surveillance India ICMR" and "One Health".

6.2 Common infections: tuberculosis, typhoid and malaria

Tuberculosis, typhoid and malaria are three of the biggest infectious diseases of India, and each is caused by a different kind of microbe: an acid-fast bacterium, a Gram-negative gut bacterium and a protozoan carried by a mosquito. Learning them side by side teaches the pattern every infection follows: agent, route, what happens in the body, how the lab confirms it, how it is treated and how it is prevented. Examiners ask exactly these headings.

You need: acid-fast staining (Unit 1, Special stains: acid-fast, endospore, capsule, flagella); protozoa (Unit 2, Protozoa and helminths); the steps of infection (Chapter 6.1).

HEADING	TUBERCULOSIS	TYPHOID (ENTERIC FEVER)	MALARIA
Agent	*Mycobacterium tuberculosis*, acid-fast rod	*Salmonella enterica* serovar Typhi, Gram-negative motile rod	*Plasmodium falciparum*, *P. vivax*, *P. malariae*, *P. ovale* (and *P. knowlesi*)
Spread	Airborne droplet nuclei from coughing patients	Faecal-oral: contaminated water and food	Bite of an infected female *Anopheles* mosquito
Main site	Lungs; any organ	Gut lymphoid tissue, then blood, liver, spleen, gall bladder	Liver, then red blood cells

HEADING	TUBERCULOSIS	TYPHOID (ENTERIC FEVER)	MALARIA
Key lab test	Sputum smear (Ziehl–Neelsen), NAAT (CBNAAT, Truenat), culture	Blood culture (first week); Widal test	Thick and thin blood smear; rapid antigen test
Treatment	Isoniazid, rifampicin, pyrazinamide, ethambutol for 6 months	Ceftriaxone or azithromycin (guided by sensitivity)	ACT for falciparum; chloroquine plus primaquine for vivax
Prevention	BCG at birth, case finding, treating contacts	Safe water, sanitation, typhoid conjugate vaccine	Bed nets, spraying, larval control, vaccines in Africa

Tuberculosis

M. tuberculosis has a waxy wall rich in **mycolic acids**. That wall resists drying and many drugs, keeps the Gram stain from working (so the acid-fast stain is used), and slows growth: the cell divides only about once in 15 to 20 hours, so culture on Löwenstein–Jensen medium takes weeks.

Inhaled bacilli are swallowed by lung macrophages but survive inside them. The immune system walls them off in a **granuloma (tubercle)**: a ball of macrophages and lymphocytes with a cheese-like (caseous) centre. In most people the infection stays **latent**: no symptoms, not infectious. When immunity falls (HIV, diabetes, malnutrition, old age) it becomes **active**: cough for more than two weeks, fever, night sweats, weight loss, blood in sputum.

India has the largest number of TB patients of any country, and the National TB Elimination Programme (NTEP) gives free diagnosis and drugs. Diagnosis uses sputum microscopy and molecular tests: CBNAAT (GeneXpert) and the Indian-made Truenat detect TB DNA and rifampicin resistance in about two hours. Drug-sensitive TB is treated for six months: two months of isoniazid (H), rifampicin (R), pyrazinamide (Z) and ethambutol (E), then four months of H, R and E, written 2HRZE/4HRE. Several drugs are used together so that no single-drug-resistant mutant survives. **MDR-TB** is resistant to at least isoniazid and rifampicin. The BCG vaccine (live attenuated *M. bovis*) protects young children against severe forms such as TB meningitis but protects adults poorly.

Typhoid

S. Typhi is swallowed in water or food contaminated by human faeces; humans are its only host. It crosses the small-intestine lining through M cells over the **Peyer's patches**, survives inside macrophages and spreads through lymph to the blood, liver, spleen and gall bladder. The fever rises step by step over the first week; the pulse may stay slow for the temperature; ulcers of Peyer's patches can bleed or perforate in the third week. Some people carry the bacteria in the

gall bladder for years and shed them in faeces: these **chronic carriers** keep the disease going. *S.* Paratyphi A, B and C cause a milder paratyphoid fever; together they are called enteric fever.

The test depends on the week of illness: blood culture is best in the first week; antibodies (Widal) rise from the second; stool and urine cultures turn positive later. The **Widal test** detects antibodies against the O (somatic) and H (flagellar) antigens. In India many healthy people already have some antibody, so a single low titre means little; a fourfold rise between two samples is meaningful. Resistance to older drugs and to fluoroquinolones is now common, so ceftriaxone or azithromycin is used. A typhoid conjugate vaccine based on the Vi capsular antigen is made in India.

Malaria

The parasite alternates between two hosts. In the **human** it multiplies asexually by schizogony; in the **mosquito** it reproduces sexually. Each burst of red cells releases merozoites and parasite waste, which causes the fever spike. The cycle in red cells takes about 48 hours for *P. vivax*, *P. ovale* and *P. falciparum* (tertian fever) and 72 hours for *P. malariae* (quartan fever).

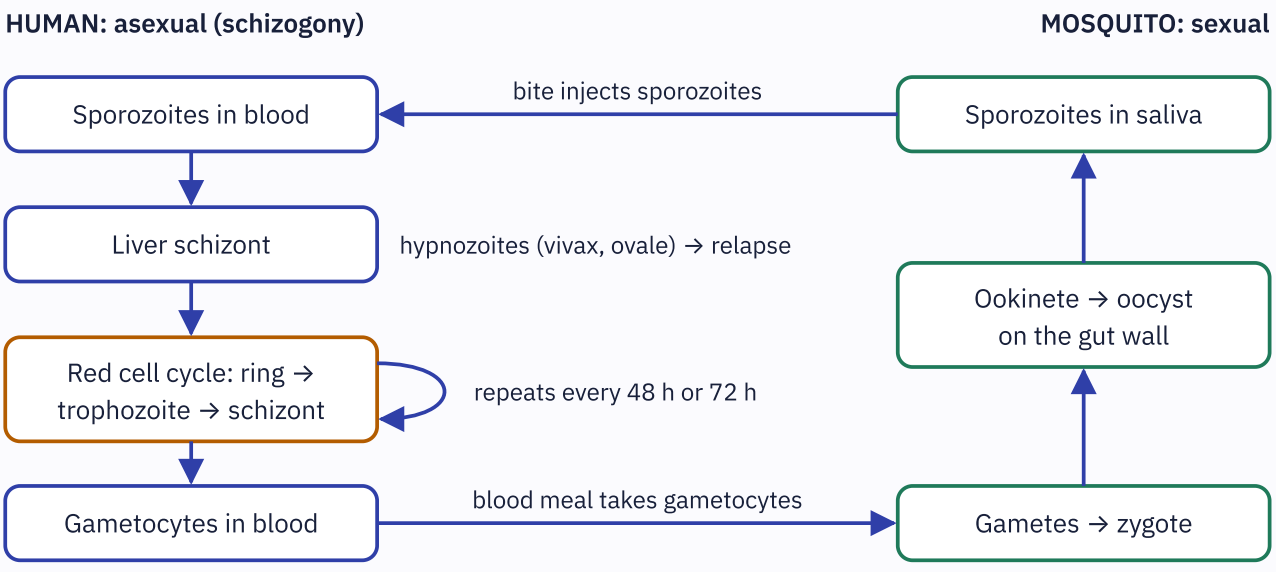


Figure 6.2.1 The malaria life cycle. Human stages are on the left (blue), mosquito stages on the right (green). Notice the loop in the red cell box: its timing sets the fever pattern, and only gametocytes can infect the mosquito.

P. falciparum is the most dangerous: it infects red cells of all ages, and infected cells stick to the walls of small blood vessels, blocking blood flow to the brain (cerebral malaria) and kidneys. *P. vivax* and *P. ovale* leave dormant liver forms called **hypnozoites**, which wake months later and cause relapse; primaquine kills them, but it can break red cells in people with G6PD deficiency, so that is checked first. Diagnosis uses Giemsa- or Leishman-stained blood smears (thick smear to find parasites, thin smear to name the species) or a rapid diagnostic test that detects parasite

antigens such as HRP2 (falciparum only) or pLDH. Falciparum malaria is treated with an artemisinin-based combination therapy (ACT).

Nipah is a bat-borne virus that caused outbreaks in Kozhikode, Kerala, from 2018. The viruses themselves are in Unit 3 (Human viruses: HIV and SARS-CoV-2).

WORKED EXAMPLE

Question (5 marks). On a Giemsa-stained thick smear, a technician counts 120 asexual malaria parasites while counting 200 white blood cells. On the thin smear, 25 of 2,500 red cells are infected, and many rings are seen with banana-shaped gametocytes. Calculate the parasite density (assume 8,000 white cells per µL) and the percentage parasitaemia, and name the likely species.

1. Parasites per µL = (parasites counted ÷ white cells counted) × white cells per µL = (120 ÷ 200) × 8,000.
2. = 0.6 × 8,000 = 4,800 parasites per µL of blood.
3. Parasitaemia = (infected red cells ÷ red cells counted) × 100 = (25 ÷ 2,500) × 100 = 1%.
4. Banana- or crescent-shaped gametocytes are typical of *P. falciparum*.

Answer: 4,800 parasites/µL, 1% parasitaemia, *P. falciparum*; treat with an ACT and watch for signs of severe malaria.

EXAM TRAPS

- A Widal test is not the first test in week one of fever; blood culture is. One positive Widal in an endemic area does not prove typhoid.
- Only the female *Anopheles* bites and transmits malaria; *Aedes* carries dengue and *Culex* carries filariasis.
- "Tertian" means every 48 hours (fever on day 1 and day 3), not every three days.
- Latent TB is not infectious; active pulmonary TB is. MDR-TB needs resistance to both isoniazid and rifampicin.
- Favourite question: "Describe the life cycle of *Plasmodium* with a neat diagram" and "Laboratory diagnosis of enteric fever".

CHECK YOURSELF

– REMEMBER **Name the four first-line TB drugs and the regimen code used in India.** 2 marks

Isoniazid, rifampicin, pyrazinamide, ethambutol; 2HRZE/4HRE (six months).

– REMEMBER **Which antigens does the Widal test use?** 2 marks

The O (somatic, LPS) and H (flagellar) antigens of *S.* Typhi, plus those of Paratyphi A and B.

– UNDERSTAND **Why is TB treated with several drugs at once for months?** 3 marks

A large bacterial population contains mutants resistant to any single drug; a combination kills them all. The slow-growing, partly dormant bacilli need months of exposure to be cleared.

– UNDERSTAND **Explain why vivax malaria can return months after the blood was cleared.** 3 marks

Dormant liver hypnozoites are untouched by blood-stage drugs; when they wake they release merozoites and start a new blood cycle (relapse). Primaquine is given to kill them.

– APPLY **A thick smear shows 300 parasites per 200 WBC. Find the density at 8,000 WBC/µL.** 2 marks

(300 ÷ 200) × 8,000 = 12,000 parasites/µL.

– APPLY **A patient has fever on day 6 of illness. Which sample would you send first to confirm typhoid, and why?** 2 marks

Blood culture: the bacteria are in the blood in the first week, before antibodies rise.

– ANALYZE **Compare how the immune system "fails" in TB and in typhoid carriers.** 4 marks

In both, bacteria survive in a protected niche. TB bacilli survive inside macrophages walled in granulomas and reactivate when immunity falls. Typhoid carriers harbour *S.* Typhi in the gall bladder (often on gallstones), out of reach of immune cells and many drugs. Both create silent reservoirs that sustain spread.

BEYOND THE SYLLABUS

This is not for the exam. Whole-genome sequencing of TB isolates now predicts drug resistance and tracks transmission. New all-oral regimens for drug-resistant TB (based on bedaquiline, pretomanid and linezolid) have cut treatment from years to months. Two malaria vaccines, RTS,S and R21 (the second made by the Serum Institute of India), are being rolled out in Africa. Search "WHO Global TB Report", "Ni-kshay portal" and "malaria elimination India 2030".

Key terms of this lesson

TERM	MEANING OR FORMULA	CHAPTER
Virulence (ID50, LD50)	Degree of disease; dose infecting or killing 50% of hosts (smaller = more virulent)	6.1
Device-associated infection rate	(infections ÷ device-days) × 1,000	6.1
Exotoxin vs endotoxin	Secreted protein, heat-labile, toxoid possible vs lipid A of LPS, heat-stable, no toxoid	6.1
TB regimen	2HRZE/4HRE; MDR-TB = resistant to isoniazid and rifampicin	6.2
Typhoid tests by week	Blood culture first; Widal (O, H) from week 2; stool and urine later	6.2
Parasite density	(parasites ÷ WBC counted) × 8,000 per µL	6.2

Glossary (terms used in this lesson)

Adhesin A microbial surface molecule that binds a host receptor.

BOD Biochemical oxygen demand: oxygen used by microbes oxidising organic matter in water, mg/L.

Chronic carrier A person who sheds a pathogen for long periods without illness, e.g. *S.* Typhi in the gall bladder.

Endotoxin Lipid A of Gram-negative lipopolysaccharide; causes fever and shock.

EPS	Extracellular polymeric substance: polysaccharides, proteins and DNA forming the biofilm matrix.
Exotoxin	Protein toxin secreted by a bacterium.
Granuloma	Organised ball of immune cells walling off *M. tuberculosis* (tubercle).
Healthcare-associated infection	Infection acquired in a healthcare setting, appearing 48 h or more after admission; also called nosocomial.
Hypnozoite	Dormant liver stage of *P. vivax* and *P. ovale* that causes relapse.
MDR-TB	TB resistant to at least isoniazid and rifampicin.
Opportunistic pathogen	Microbe that causes disease mainly when host defences are weakened.
Virulence	Degree of disease a strain causes; measured by ID50 or LD50.
Widal test	Agglutination test for antibodies to *Salmonella* O and H antigens.

The full unit book

Every chapter of Unit 6, the unit summary, the exam question bank with model answers and the full glossary: Microbiology · Unit 6 · Medical, Environmental and Industrial Microbiology (one file, works offline).

Sources and further reading

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- Stanbury, P. F., Whitaker, A. and Hall, S. J. *Principles of Fermentation Technology*. Elsevier. For industrial fermentation (from memory; check).

- Fertiliser (Control) Order, Schedule III (biofertilizer specifications), Department of Agriculture, Goa: agri.goa.gov.in, Schedule III of FCO. Source of the CFU standards in Chapter 6.6.
- General Standards for Discharge of Environmental Pollutants (Environment (Protection) Rules, 1986), copy at foundryinfo-india.org. Source of the BOD limit in Chapter 6.4.

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