Biology Units 3 & 4

Chapter 8 — Emergence and treatment of disease

Aboriginal and Torres Strait Islander content has been excluded as accuracy cannot be guaranteed, and it is better to be respectful than cover the entire curriculum inaccurately.

Significant effort has been made to ensure this content is legal. Please send any areas of concern to admin@vwx.au with appropriate document/legal references so errors can be verified and changes be made.

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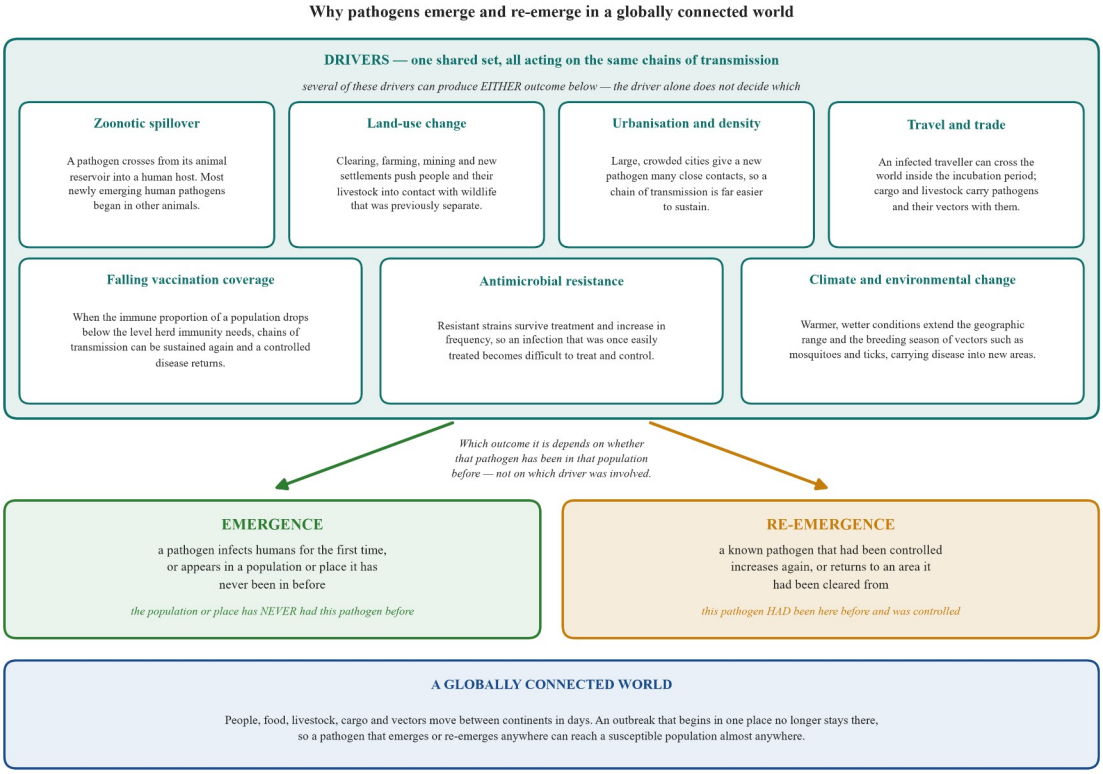
Chapter 8 Emergence and treatment of disease — 8A Emergence, re-emergence and disease containment

Theory

Chapter 7 dealt with defence inside **one body**. This subtopic moves up a level, to the **population**. A pathogen does not survive by infecting a single host; it survives by moving from host to host to host. Everything that follows — why new diseases appear, why old ones come back, and how outbreaks are stopped — is about that chain of transmission: what makes it easier to form, and how it can be broken.

Emerging and re-emerging pathogens. An **emerging pathogen** is one that infects humans for the **first time**, or a known pathogen that appears in a **population or geographic area it has never been in before**, or whose incidence rises rapidly in a place where it was previously unknown. The illness it causes is an **emerging infectious disease**. A **re-emerging pathogen** is a **known** pathogen that had been controlled, or was declining, and is now **increasing again** or returning to an area from which it had been cleared.

Notice that "new" is defined **relative to the population**, not relative to the pathogen. A pathogen that has circulated in one part of the world for centuries is still an **emerging** pathogen in a population that has never encountered it. That single idea explains both the danger of a novel virus today and the catastrophic effect of introduced diseases on Aboriginal and Torres Strait Islander peoples after European arrival.

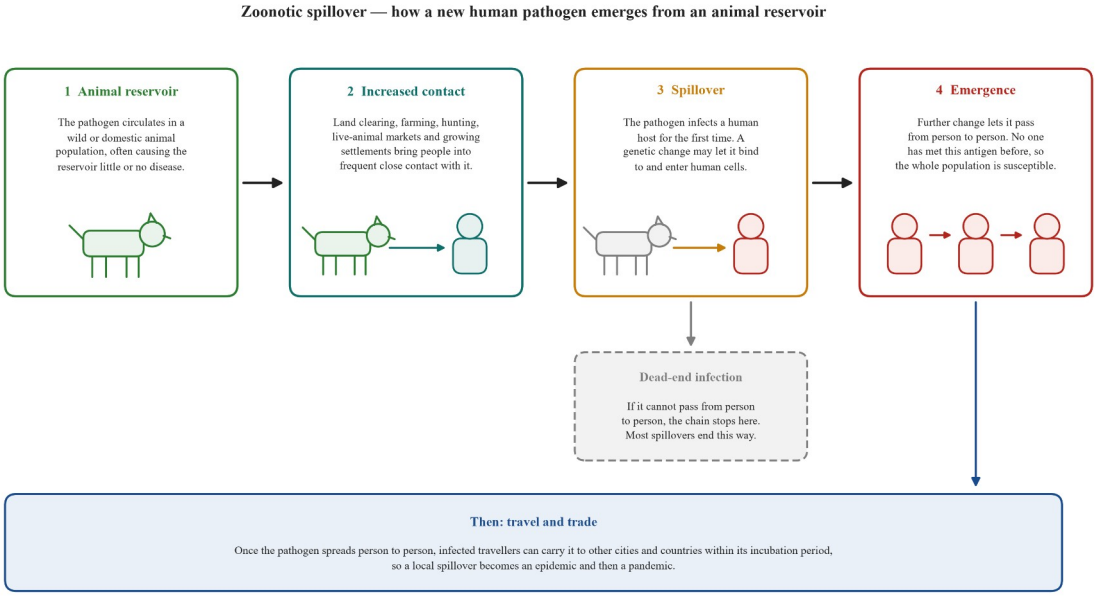


Why pathogens emerge and re-emerge in a globally connected world.

- **Zoonotic spillover.** A **zoonotic disease (zoonosis)** is one that can be transmitted from other animals to humans. The **reservoir** is the population or species in which the pathogen is normally maintained. Most newly emerging human pathogens began in other animals.
- **Land-use change.** Clearing forest, expanding farmland, mining and building new settlements bring people and their livestock into regular close contact with wildlife that was previously separate from them, creating many more chances for a spillover event.
- **Urbanisation and population density.** In a large, crowded city each infected person has many close contacts, so a chain of transmission is far easier to sustain. Crowded housing, shared water and limited sanitation add further routes of transmission.

- **International travel.** An infected person can cross the world **within the incubation period** — before they have symptoms and before anyone knows they are infectious — so an outbreak that starts in one city can seed outbreaks on other continents within days.
- **Trade and transport.** Live animals, meat, produce and cargo move between countries, carrying pathogens with them; **vectors** such as mosquitoes can also be transported in cargo (for example as eggs or larvae in water trapped in shipping containers or used tyres) and establish in a new country.
- **Climate and environmental change.** Warmer temperatures, changed rainfall and longer wet seasons extend the **geographic range and breeding season of vectors** such as mosquitoes and ticks, so vector-borne diseases appear in regions that were previously too cool or too dry for the vector.
- **Antimicrobial resistance.** Random mutation (and the transfer of resistance genes between bacteria) produces resistant variants. Using antimicrobials heavily — including using antibiotics when they are not needed, not completing a course, or using them routinely in agriculture — applies a **selection pressure**: susceptible bacteria are killed while **resistant** ones survive, reproduce and increase in frequency. A disease that was once easily treated becomes difficult to treat, so it re-emerges.
- **Falling vaccination coverage.** If the immune proportion of a population falls below the level herd immunity requires, chains of transmission can be sustained again and a controlled disease returns.

Zoonotic spillover in detail. Spillover is not a single event but a sequence, and most spillovers go no further than the first infected person.



The pathogen circulates in its animal **reservoir**, often causing that species little disease. Increased contact gives it repeated opportunities to enter a human host. A **genetic change** (usually a mutation altering a surface protein) may allow it to bind to and enter human cells. If it still cannot pass from person to person, the infection is a **dead end** and the chain stops. If further change allows **sustained human-to-human transmission**, the pathogen has **emerged**.

The human population is then extremely vulnerable, for one reason: **no one has met this antigen before**. Nobody has the matching **memory B and T cells**, so every person can mount only a slow **primary response**, and there is no pre-existing immunity in the population to slow the spread. Travel and trade then carry the pathogen far beyond where it began.

The impact of European arrival on Aboriginal and Torres Strait Islander peoples. Aboriginal and Torres Strait Islander peoples have lived on this continent for tens of thousands of years. Before European arrival from 1788, these populations had **never been exposed** to a number of pathogens that were long established in Europe and Asia, including those causing **smallpox, influenza, measles, tuberculosis** and **whooping cough**. When these pathogens were introduced, they were — by the definition above — **emerging pathogens in those populations**, even though they were old and familiar diseases elsewhere.

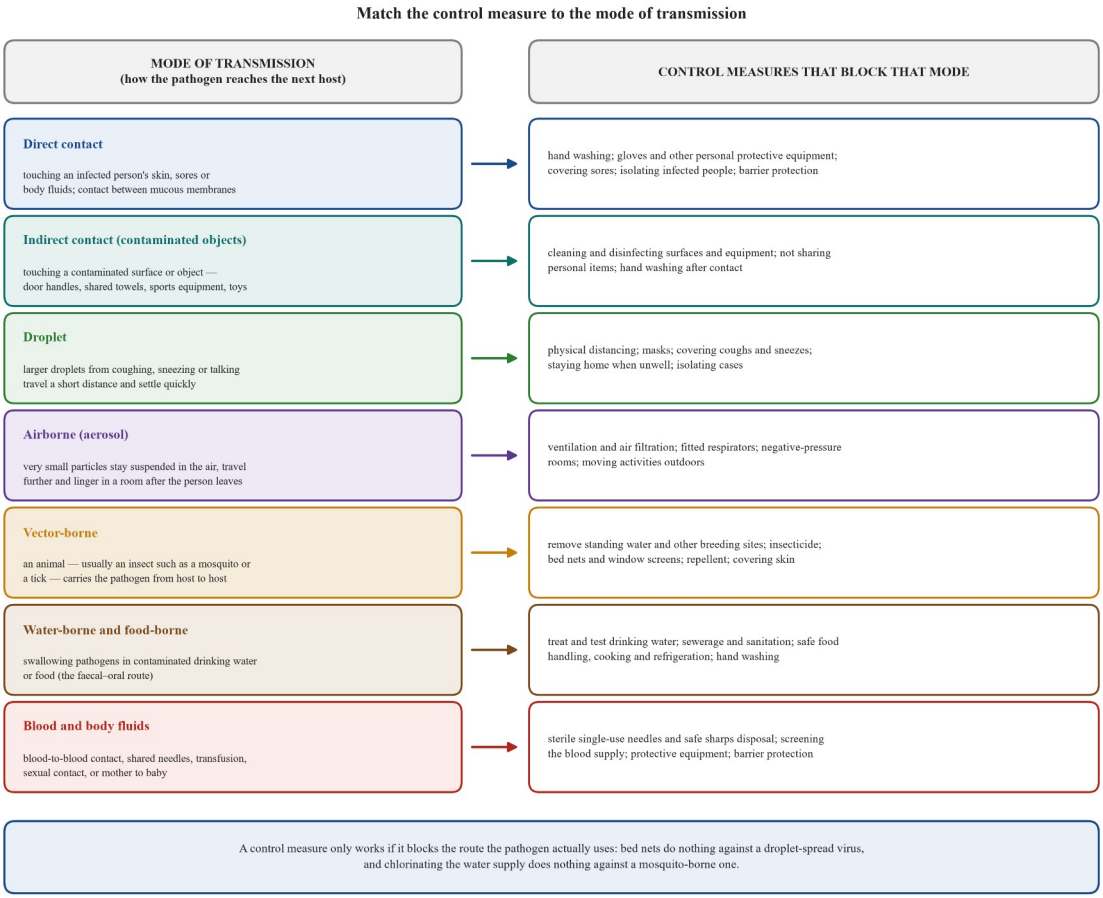
The consequences were devastating, for reasons that follow directly from the immunology of Chapter 7:

- **No prior exposure meant no acquired immunity.** Without previous exposure there were **no memory B or T cells** specific to these antigens. Every infection triggered only a **primary response**, which is slow (days to weeks) and produces relatively few antibodies, so the pathogen could multiply to very high numbers before the immune response took effect. Illness was therefore severe and mortality very high.
- **Every age group was affected at once.** Where a disease is long established, most adults were exposed in childhood and are immune, so outbreaks mainly affect young children. In a population with **no prior exposure**, adults, Elders and children were **all susceptible simultaneously**. In some communities a large proportion of people died within a very short period.
- **Care itself broke down.** Because whole communities became ill at the same time, there were too few well people to provide water, food, warmth and care to those who were sick — which increased deaths further, beyond what the pathogen alone would have caused.
- **The impact was compounded by dispossession and displacement.** Communities were dispossessed of Country and moved from their lands, often onto crowded settlements and missions. Crowding increased transmission; disruption of access to traditional foods, clean water and medicines weakened resistance to infection; and the disruption of established ways of living removed the social structures that communities relied on in a crisis. Introduced disease was one of several severe impacts of colonisation, and these effects reinforced one another.
- **Loss went well beyond the number of deaths.** Because the disease affected all ages, many **Elders and knowledge holders** died. Aboriginal and Torres Strait Islander knowledge — of language, Country, food, medicine, law and ceremony — is held and passed on by people, so these deaths caused losses of knowledge, language and cultural continuity that could not be replaced and that continue to be felt across generations.
- **The diseases travelled beyond first contact.** Communities were connected by long-established routes of travel, trade and ceremony, and an infected person can travel and infect others **before showing symptoms**. Introduced diseases therefore reached communities far inland, often **ahead of** the arrival of Europeans in those places — the same "globally connected world" effect described above, operating at a continental scale.

The health inequities experienced by Aboriginal and Torres Strait Islander peoples today have their roots in this history. Effective public health work with communities depends on genuine partnership, community-controlled health services, and communication that is developed **with** communities rather than delivered to them.

Identifying and controlling the spread of a pathogen. When an unusual cluster of illness is detected, public health investigators work through a standard sequence.

- **Identify the pathogen.** Samples are taken from patients (blood, swabs, faeces) and the organism is identified by **microscopy**, by **culturing** it, by **antigen or antibody tests**, or by **PCR and genetic sequencing** of its nucleic acid. Knowing what it is tells investigators whether it is bacterial, viral, fungal or protistan, whether an antimicrobial treatment or a vaccine already exists, and what it is likely to do next.
- **Identify the host and the reservoir.** Which people are being infected, and do they share an age, occupation or location? Is the **index case** (the first identified case) linked to an animal, a food, or a water source? Is there an **animal reservoir** in which the pathogen persists between outbreaks? A pathogen with an animal reservoir cannot be eliminated by treating and vaccinating people alone, because the reservoir keeps re-supplying it.
- **Determine the mode of transmission.** Investigators interview cases, map cases in **space and time**, carry out **contact tracing** (finding everyone a case has been near), and test water, food, surfaces and animals. The pattern of cases is the evidence: cases in everyone who ate one dish point to food; cases clustered near wetlands in summer point to a vector; cases in household and hospital contacts of a coughing patient point to droplets.
- **Control transmission.** Only now can the right controls be chosen — because a control measure works **only if it blocks the route the pathogen actually uses**.

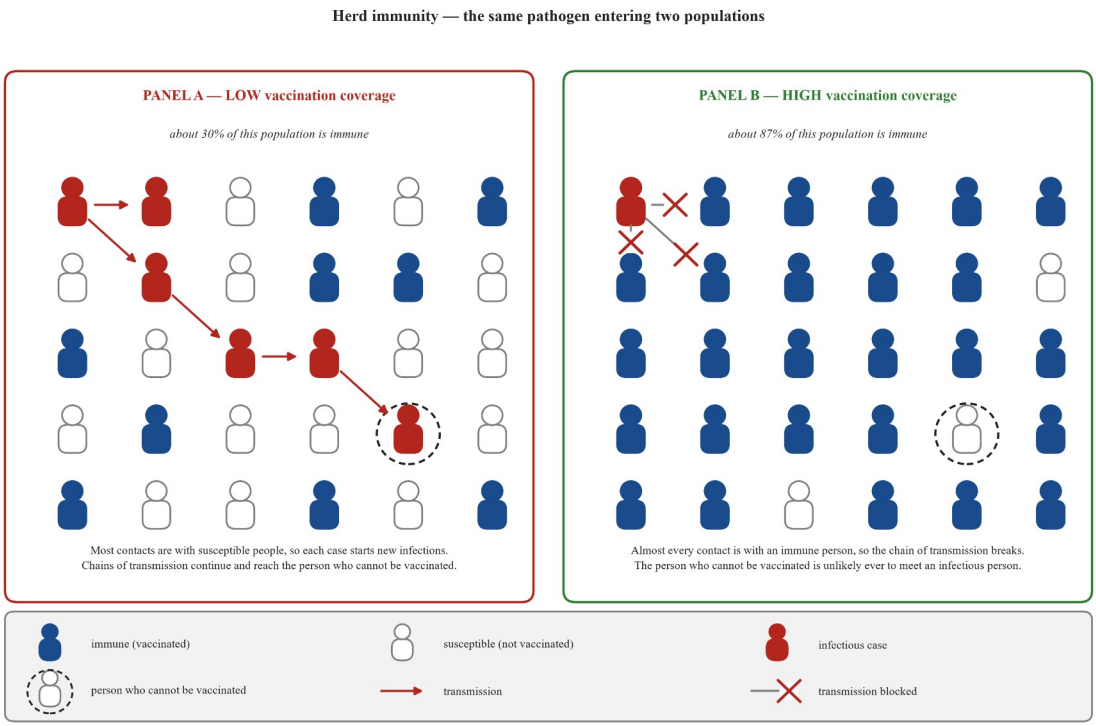


Two control measures are often confused. **Isolation** separates people who are **known to be infected** from others. **Quarantine** separates and restricts the movement of people who have been **exposed** and may be incubating the disease, but who are not (yet) known to be infected. Quarantine matters because a person can be infectious **before symptoms appear**, so waiting for symptoms would allow further transmission.

Alongside these **scientific** strategies sit the **social** strategies that make them work: clear and timely public health communication; education about hygiene, safe food and safe water; community engagement so that advice is trusted and culturally appropriate; surveillance and notification systems that detect outbreaks early; border screening and travel restrictions; closing schools or venues; and providing the sanitation, safe water and health services that make the recommended behaviour possible.

Vaccination programs and herd immunity. A vaccine gives **artificial active immunity** (7E): the person's own adaptive system responds to a harmless form of the antigen and forms **memory cells**, without the person having to suffer the disease. At the level of a **population**, vaccination does something extra. A vaccinated person is unlikely to become infected, and therefore unlikely to **pass the pathogen on** — so each vaccination removes a link from the chain of transmission.

Herd immunity is the protection that arises when a **large enough proportion of a population is immune** that the pathogen can no longer spread easily. An infectious person's contacts are mostly immune people who do not become infected and do not transmit further, so on average each case passes the pathogen on to **fewer than one** other person and the outbreak dies out.



Three points about herd immunity are examined repeatedly:

- **Who it protects.** It indirectly protects people who **cannot be vaccinated** — babies below the recommended age, people whose immune systems are weakened (for example by chemotherapy, an immunodeficiency, or medication taken after a transplant), people with a genuine severe allergy to a vaccine component — and people in whom the vaccine did not work.
- **What it is NOT.** Herd immunity does **not** make those people immune. They remain fully susceptible; they are protected only because the pathogen is unlikely to reach them. If an infectious person does reach them, they can still be infected.
- **The coverage needed depends on the pathogen.** The **more infectious** a pathogen — that is, the more people one case would infect in a fully susceptible population — the **higher** the proportion that must be immune before transmission collapses. For a highly infectious airborne disease such as **measles**, coverage of about **95%** is needed; for a less infectious disease the threshold is lower.

Vaccination programs exist to reach and hold that level of coverage: a funded schedule of vaccines offered free at set ages, immunisation registers and reminders, school-based programs, catch-up campaigns for those who missed doses, maintenance of the **cold chain** so vaccines remain effective, and clear public information. Sustained programs can **eliminate** a disease from a country and, in one case (smallpox, declared eradicated in 1980), **eradicate** it worldwide.

When coverage falls, the number of susceptible people grows. Once the immune proportion drops below the threshold, a single case — often imported by a traveller from a country where the disease still circulates — can start a chain of transmission that keeps going, and a controlled disease **re-emerges**. Because coverage is not spread evenly, a **community or school with low coverage** can suffer an outbreak even when the national figure looks high: herd immunity operates in the group where people actually mix.

Worked examples

Example 1 — scaffolded

In a rapidly expanding farming district, harvested grain is kept in open sheds that attract a local species of wild rodent. Over 18 months, 14 farm workers develop a severe fever caused by a virus that has never been recorded in humans. The same virus is later found in the rodents, which appear healthy. Six months later, cases occur in family members who had never entered the sheds.

(a) Explain how this virus emerged in the human population.

(b) Explain why the human population was highly susceptible to it.

Working	Comment
The rodents carry the virus without becoming ill, so the rodent population is the **reservoir** in which the virus is normally maintained.	Identify the reservoir first — "healthy carriers of the same virus" is the evidence.
Storing grain in open sheds in a newly expanded farming district is a **land-use change** that brings workers into repeated close contact with the reservoir species.	Name the driver and tie it to the scenario; contact is what creates the opportunity.
Repeated contact allowed a **zoonotic spillover**: the virus crossed from the rodents into a human host, most likely following a genetic change that let it bind to and enter human cells.	"Zoonotic" = transmitted from other animals to humans.
Cases in family members who never entered the sheds show the virus is now passing **from person to person**, so it is no longer a dead-end infection — it has **emerged** as a new human pathogen.	This is the evidence that separates an emerged pathogen from a dead-end spillover. Use the stimulus.
(b) No one in the population had ever encountered this virus, so **no one had memory B or T cells** against its antigens.	The reason must be immunological, not just "it was new".
Every infected person could therefore mount only a slow **primary response**, allowing the virus to reach high numbers before antibodies were produced — so illness was severe. There was also no herd immunity to slow transmission, so nearly the whole population was susceptible.	Two levels: severity in the individual, and spread in the population.

Example 2 — scaffolded

Over nine days, about 120 residents of a country town develop watery diarrhoea and vomiting. Cases occur in all age groups and in every suburb connected to the town reservoir, but not in the outlying farms that use tank water. Several visitors who stayed one night are also affected. The same bacterium is isolated from patient samples and from the reservoir, which received run-off from grazing land after heavy rain.

Identify the mode of transmission, justify your answer using two pieces of evidence, and describe two control measures that would block it.

Working	Comment
The mode of transmission is **water-borne** (a faecal–oral route): people are infected by swallowing pathogens in contaminated drinking water.	Name the mode precisely — "water-borne" not just "contaminated".
Evidence 1: cases occur in all age groups and across every suburb **supplied by the reservoir**, but not on farms using tank water. A shared water supply is the one exposure the cases have in common.	Person-to-person spread would produce clusters in households and workplaces, not a supply-area pattern.
Evidence 2: the **same bacterium** was isolated from patients **and** from the reservoir, which had received run-off from grazing land — a plausible source of faecal contamination. Overnight visitors were also affected, which fits a common source rather than long personal contact.	Link the microbiology to the epidemiology; both are needed.
Control 1 — treat and secure the water supply: disinfect (for example by chlorination) and filter the reservoir water, and issue a boil-water notice until	Say what the measure does to the transmission route, not just what it is.

Working	Comment
testing is clear. This kills or removes the pathogen before anyone drinks it.	
Control 2 — stop the contamination at its source and add hygiene measures: fence stock away from the catchment and divert run-off, and promote hand washing after using the toilet and before handling food to prevent secondary faecal–oral spread.	A second, genuinely different measure targeting the same route.

Example 3 — unscaffolded

A six-week-old baby is too young to receive the vaccine against a highly infectious respiratory disease. In her community, about 95% of people are vaccinated against it. Explain how the vaccination of other people protects her, and explain why this protection is not the same as her being immune.

Because about 95% of the community is vaccinated, almost everyone the baby (and anyone near her) comes into contact with has **memory cells** against this pathogen. A vaccinated person is unlikely to become infected, and therefore unlikely to **pass the pathogen on**, so vaccination removes links from the chain of transmission. If the pathogen is introduced into this community, an infectious person's contacts are mostly immune people in whom the chain **stops**, so on average each case infects fewer than one other person and the outbreak dies out. This is **herd immunity**: the baby is protected because the pathogen is very unlikely ever to reach her.

This is **not** the same as being immune. The baby has produced no antibodies and has no memory cells against this pathogen, so she remains **fully susceptible**. Her protection is indirect and depends entirely on the immunity of those around her: if coverage in her community fell, or if she were taken somewhere with low coverage, she could still be infected. ∴ herd immunity protects her by reducing transmission in the population, not by making her immune.

Example 4 — unscaffolded

Explain why pathogens such as smallpox, influenza and measles, introduced to the Australian continent following European arrival from 1788, had such a devastating impact on Aboriginal and Torres Strait Islander peoples. Refer in your answer to prior exposure and to the immune response.

These pathogens were long established in Europe but had **never been present** in Aboriginal and Torres Strait Islander populations, so they were **emerging pathogens** in those populations. Because there had been **no prior exposure** to these antigens, no one had the specific **memory B and T cells** that a previous infection or vaccination would have produced. Every person who was infected could therefore mount only a **primary response** — slow to develop and producing relatively few antibodies — so the pathogen multiplied to very high numbers before the adaptive response took effect. Illness was correspondingly severe and mortality was very high.

The effect was worsened because the **whole population was susceptible at the same time**. Where a disease is long established, most adults were exposed as children and are immune, so an outbreak affects mainly the young; here, children, adults and Elders were all susceptible together. With so many people ill simultaneously there were too few well people to provide water, food, warmth and care to those who were sick, so deaths were higher than the infections alone would have caused, and there was no herd immunity anywhere in the population to slow the spread. ∴ the absence of prior exposure — and therefore of any acquired immunity — meant these introduced pathogens met a population in which almost every individual was fully susceptible, producing severe illness and very high mortality.

Practice questions

Scaffolded

Q1. Define each of the following terms: (a) emerging pathogen; (b) re-emerging pathogen; (c) zoonotic disease, and the meaning of the term reservoir.

Q2. A previously unknown respiratory virus begins spreading in a city of 12 million people that has a major international airport. The virus has an incubation period of about five days. (a) Explain how international air travel can

turn a local outbreak of this virus into a global one. (b) Explain how the city's high population density makes the outbreak grow more quickly. (c) State one control measure that targets travel, and explain how it reduces spread.

Q3. Smallpox was long established in Europe before it was introduced to the Australian continent following European arrival from 1788. (a) Explain what is meant by saying a pathogen can be "emerging" in one population while being long established in another, using smallpox as your example. (b) Identify the mode of transmission by which respiratory pathogens such as smallpox and influenza pass between people, and state one control measure that blocks that mode. (c) Suggest why introduced diseases reached Aboriginal and Torres Strait Islander communities far from the places where Europeans first arrived.

Q4. Over three weeks, 11 members of a community sports club develop an infection producing red, crusted sores on the arms and legs. All 11 attend the same weekly training session, at which players share towels, wrestling mats and strapping tape. No cases occur in family members who do not attend training. (a) Identify the two most likely modes of transmission operating here, using the evidence given. (b) Explain why identifying which pathogen is causing the infection is important for controlling the outbreak. (c) Describe two control measures appropriate to the modes you identified.

Q5. Vaccination programs protect populations as well as individuals. (a) State which type of acquired immunity vaccination produces, and explain why the formation of memory cells is essential to it. (b) Define herd immunity. (c) Identify two groups of people who cannot be vaccinated, and state why each cannot.

Q6. A bacterial infection that was routinely cured with a common antibiotic is now causing outbreaks that do not respond to that antibiotic. (a) Explain how the heavy use of an antibiotic leads to a resistant strain of bacteria becoming common. (b) Explain how this causes a previously controlled disease to re-emerge. (c) State one measure that would slow the development of antimicrobial resistance.

Unscaffolded

Q7. International trade contributes to the emergence of disease in ways that are separate from passenger travel. Describe **two** ways in which trade or the transport of goods can introduce a pathogen or its vector into a country. *(2 marks)*

Q8. A virus has circulated for many years in a population of bats living in a forest that is being cleared for agriculture. Explain why such a virus may suddenly become able to infect humans, and explain why not every spillover event leads to an epidemic. *(3 marks)*

Q9. Distinguish between quarantine and isolation, and explain why both are used during an outbreak of a disease that is infectious before symptoms appear. *(3 marks)*

Q10. A virus is transmitted through blood and other body fluids. It is spreading in a regional health service. Three measures are proposed:

- **(i)** distributing insecticide-treated bed nets to patients;
- **(ii)** chlorinating the hospital's drinking water;
- **(iii)** using single-use sterile needles with safe sharps disposal, and gloves and gowns for staff.

Identify which measure would reduce transmission of this virus, explain how it does so, and explain why the other two would not. *(3 marks)*

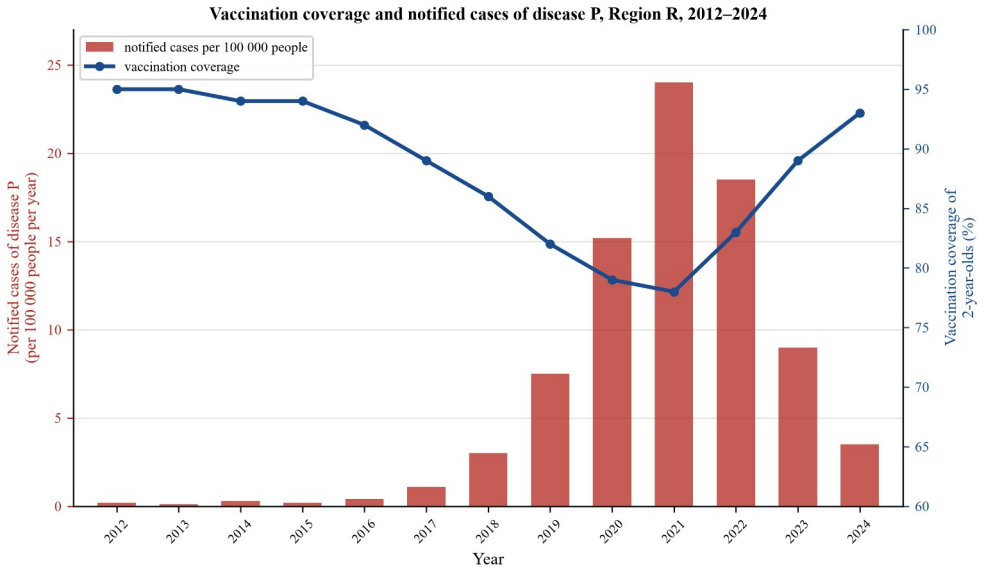
Q11. National vaccination coverage for a highly infectious childhood disease is 97%, yet a large outbreak occurs in one town. Suggest an explanation for this observation, with reference to herd immunity. *(3 marks)*

Q12. Explain why a more infectious pathogen requires a higher percentage of the population to be vaccinated before herd immunity is achieved. *(2 marks)*

Q13. The impact of introduced diseases on Aboriginal and Torres Strait Islander peoples following European arrival was made worse by factors other than the pathogens themselves. Describe **two** such factors and explain how each increased the impact, and explain one consequence of these epidemics that went beyond the number of deaths. *(4 marks)*

Q14. A mosquito-borne disease that had been restricted to tropical northern regions of a country begins to be reported in temperate southern areas, where it had never occurred. Suggest an explanation for this change, and describe **two** control measures that would reduce transmission in the newly affected areas. *(4 marks)*

Q15. *(Stimulus — data interpretation.)* The graph below shows vaccination coverage of two-year-olds, and notified cases of disease P, in Region R between 2012 and 2024.



(a) Describe the trend in vaccination coverage over the period shown.

(b) Describe the relationship between vaccination coverage and the number of notified cases.

(c) Explain, in terms of herd immunity, why the number of cases changed as it did.

(d) A student concludes from this graph alone that the fall in coverage caused the outbreak. State one limitation of drawing that conclusion from these data. *(5 marks)*

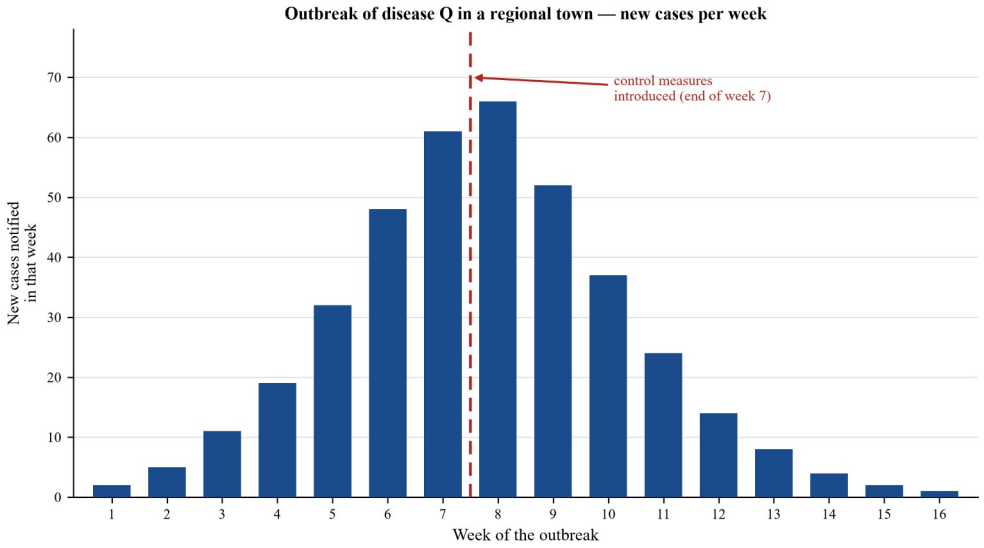
Q16. *(Stimulus.)* Three outbreaks were investigated in the same year.

Outbreak	Observations recorded by investigators
W	Residents of a poorly ventilated aged-care facility develop a lung infection. Cases include residents who were never within two metres of a known case but who spent time in rooms served by the same air-conditioning duct.
X	38 of 120 guests at a catered function become unwell 12 –36 hours afterwards. All of those affected ate the same chicken dish; none of the guests who did not eat it became unwell.
Y	A skin infection spreads among toddlers at a childcare centre. The affected children all used a shared play mat and the same set of toys; hand washing at the centre is inconsistent.

(a) State the most likely mode of transmission in each of outbreaks W, X and Y.

(b) Identify which of the three would be the most difficult to control, and justify your choice. *(4 marks)*

Q17. *(Stimulus — data interpretation.)* The graph below shows new cases of disease Q notified each week during an outbreak in a regional town. Control measures were introduced at the end of week 7.



(a) Describe the trend in new cases before the control measures were introduced.

(b) Describe the trend after they were introduced.

(c) Explain why the number of new cases continued to rise for a short time after the measures began.

(d) Explain how control measures reduce the number of new cases in an outbreak. *(4 marks)*

Q18. Explain why identifying the reservoir of a pathogen is important for the long-term control of a disease, and state what this means for a disease whose reservoir is a wild animal population. *(3 marks)*

Q19. *(Research method.)* A health department trials a mosquito-control program — removing standing water and fitting window screens — in Town 1, while Town 2 receives no program. The number of new notified cases of a mosquito-borne disease per 100 000 people is recorded each week in both towns for 20 weeks.

(a) Identify the independent variable and the dependent variable in this investigation.

(b) State one variable that should be controlled, and explain why.

(c) Evaluate this investigation as a test of whether the mosquito-control program reduces transmission. Refer to at least one strength and one limitation, and give a judgement. *(6 marks)*

Q20. *(Synthesis.)* A previously unknown virus, provisionally named virus H, is detected in a city of nine million people that has a large live-poultry market and an international airport. The first 30 cases all worked at or shopped in the market. Within four weeks, cases appear in people with no market contact, clustered in households and among staff on one hospital ward. Within eight weeks, cases are reported in six other countries. The virus is detected in poultry sold at the market, and in samples taken from the nose and throat of patients, most of whom have fever and a cough.

(a) Describe the scientific work investigators would carry out to identify the pathogen causing these cases and to establish which animal is acting as its host.

(b) Laboratory work alone will not stop the outbreak. Describe **two social strategies** the health authorities should use, and explain how each helps to control the spread of virus H.

(c) Identify the most likely mode of transmission between people, justify your answer using the evidence, and describe one control measure that would block it.

(d) A vaccine against virus H becomes available. Explain why the availability of a vaccine does not by itself end the outbreak. *(8 marks)*

Answers

Q1. (a) A pathogen infecting humans for the first time, or appearing in a population or area where it has not been before. (b) A known, previously controlled pathogen that is increasing again or returning to an area it had been cleared from. (c) A disease transmissible from other animals to humans; the reservoir is the population or species in which the pathogen is normally maintained. **Q2.** (a) An infected person can fly to another country within the five-day incubation period, before symptoms appear, and seed a new outbreak there. (b) More close contacts per person, so each case infects more people and the chain of transmission is easily sustained. (c) Quarantine of arriving travellers (or border screening / travel restrictions) — it separates people who may be incubating the disease so they cannot infect others. **Q3.** (a) "Emerging" is defined relative to the population: smallpox was long established in Europe but had never been present in Aboriginal and Torres Strait Islander populations, so on introduction it was new to those populations. (b) Droplet transmission (also direct contact with fluid from sores); isolating cases (or masks / distancing / covering coughs). (c) People moved between communities along established routes of travel, trade and ceremony, and an infected person can travel and infect others before symptoms appear, so the disease spread inland ahead of European arrival in those places. **Q4.** (a) Direct contact with the sores of an infected player, and indirect contact via contaminated objects (shared towels, mats, tape). (b) It determines whether the infection is bacterial (treatable with an antibiotic) or otherwise, how cases are diagnosed, and how long a person remains infectious. (c) Any two of: exclude players with sores or cover them; stop the sharing of towels, tape and drink bottles; clean and disinfect mats and equipment after every session; hand washing before and after training. **Q5.** (a) Artificial active immunity; memory cells are what remain after the response, allowing a fast and large secondary response on later exposure. (b) When a large enough proportion of a population is immune that the pathogen can no longer spread easily, so unimmunised people are unlikely to be infected. (c) Any two of: babies below the recommended age (immune system too immature / vaccine not approved for them); people whose immune systems are weakened by chemotherapy, immunodeficiency or transplant medication; people with a severe allergy to a vaccine component. **Q6.** (a) Mutation produces resistant variants; the antibiotic kills susceptible bacteria but resistant ones survive, reproduce and pass on the resistance, so resistant bacteria become common. (b) Infections can no longer be treated, so infected people stay infectious for longer and spread the pathogen, and case numbers rise again. (c) Any one of: prescribe antibiotics only when they are needed; complete the prescribed course; restrict routine antibiotic use in agriculture; improve infection control and hygiene. **Q7.** Live animals, meat or produce carrying a pathogen are imported; and vectors (or their eggs and larvae) are transported in cargo, containers or used tyres and establish in the new country. **Q8.** A mutation may alter a surface protein so it binds human cell receptors; land clearing greatly increases human–bat contact, giving more chances for this. Most spillovers are dead ends because the virus cannot pass person to person; an epidemic requires sustained human-to-human transmission. **Q9.** Isolation separates people known to be infected; quarantine separates and restricts people who have been exposed and may be incubating but are not known to be infected. Both are needed because a person can transmit before symptoms appear, so isolating only symptomatic cases would miss transmission. **Q10.** (iii) — sterile single-use needles, safe sharps disposal and protective equipment prevent blood and body fluids passing between people. (i) blocks vector-borne transmission and (ii) blocks water-borne transmission; neither is the route this virus uses. **Q11.** Coverage is not spread evenly: this town's coverage is below the threshold for this pathogen, so enough susceptible people are in contact for chains of transmission to be sustained locally once a case arrives. Herd immunity operates in the group where people actually mix, not in the national average. **Q12.** A more infectious pathogen means each case would infect more people in a fully susceptible population, so a larger proportion of contacts must be immune before each case passes it to fewer than one other person on average. **Q13.** Any two of: dispossession from Country and forced movement onto crowded settlements (crowding increased transmission); disrupted access to traditional food, clean water and medicines (weakened resistance and recovery); simultaneous illness leaving too few well people to provide care. Beyond deaths: the loss of many Elders and knowledge holders caused loss of language, cultural knowledge and continuity across generations. **Q14.** Warming temperatures and changed rainfall have extended the vector's geographic range and breeding season into the southern areas, so an imported case can now be transmitted locally. Controls: remove standing water and other breeding sites; use insecticide, window screens, bed nets, repellent and covering clothing. **Q15.** (a) Coverage was high and steady near 95% to 2015–2016, then fell steadily to about 78% in 2021, then rose again to about 93% by 2024. (b) Inverse (negative) relationship: as coverage fell, cases rose; as coverage recovered, cases fell. (c) Falling coverage increased the number of susceptible people; once coverage was below the herd-immunity threshold, chains of transmission could be sustained and cases rose sharply; restoring coverage broke the chains again. (d) Correlation does not establish causation — other factors (an imported case, increased testing or reporting, changes in the population) could contribute. **Q16.** (a) W = airborne (aerosol); X = food-borne; Y = indirect contact via contaminated objects (with direct contact also possible). (b) W — airborne particles stay suspended and travel beyond the immediate area, so

distancing and surface cleaning do not block it; it requires ventilation, filtration and fitted respirators. **Q17.** (a) New cases rose steeply from 2 in week 1 to 61 in week 7. (b) Cases peaked at 66 in week 8, then fell steadily to 1 by week 16. (c) People infected before the measures began were still incubating and became cases afterwards. (d) They break the chain of transmission by blocking the route the pathogen uses, so each case infects fewer than one other person on average and case numbers fall. **Q18.** The reservoir is the population in which the pathogen is maintained between outbreaks; unless it is identified and targeted, it keeps re-supplying the pathogen and outbreaks recur. A disease with a wild animal reservoir cannot be eradicated by treating and vaccinating people alone, so control must be ongoing. **Q19.** (a) IV = whether the mosquito-control program is carried out; DV = new notified cases per 100 000 people per week. (b) Any one of: the time period, the case definition and testing method, or comparable town size, climate and housing — so any difference in cases can be attributed to the program. (c) Strength: a comparison town measured over the same 20 weeks controls for season, and cases are expressed as a rate per 100 000 so the towns are comparable. Limitation: with only one town per condition and no random allocation, the towns may differ in rainfall, housing or population in ways that also affect case numbers (confounding). Judgement: the trial can show whether the two towns differ, but not that the program caused the difference; several matched towns allocated randomly would be needed. **Q20.** (a) Take patient swabs and blood and identify the agent by microscopy, culture, and PCR and genetic sequencing — the unmatched sequence shows it is a new virus and provides a specific diagnostic test. Apply the same testing to the market animals: the same sequence in the poultry, plus the market link shared by the first 30 cases, establishes poultry as the host. (b) Any two of: clear, timely public communication and education in the community's languages, so people recognise symptoms, get tested and stay home; surveillance and notification with contact tracing, so clusters are found early and contacts quarantined before they infect others; closing the market and other venues; border screening and travel advice; providing testing, sick leave and accommodation so isolation is possible. Each reduces the number of contacts an infectious person exposes. (c) Droplet transmission — fever and cough, virus in nose and throat samples, clusters in households and on a hospital ward; isolating cases (or masks, distancing, protective equipment for staff) blocks it. (d) A vaccine only works at population level once a high enough proportion is immunised; manufacture, distribution, the cold chain, the time needed for immunity to develop, doses required, access and hesitancy all delay reaching that threshold.

Fully-worked solutions

Q1. (a) An **emerging pathogen** is one that infects humans for the **first time**, or a known pathogen that appears in a **population or geographic area where it has not previously been found** (or whose incidence rises rapidly there). (b) A **re-emerging pathogen** is a **known** pathogen that had been controlled or was declining and is now **increasing again**, or returning to an area from which it had been cleared. (c) A **zoonotic disease** is one that can be **transmitted from other animals to humans**. The **reservoir** is the population or species in which the pathogen is **normally maintained**, often without causing that species serious disease.

Q2. (a) The virus has an incubation period of about **five days**, so an infected person can board a flight and arrive in another country **before they have any symptoms** and before anyone knows they are infectious. Modern air travel therefore moves infected people between continents faster than the disease declares itself, so an outbreak that begins in one city can seed outbreaks in many others. (b) In a city of 12 million, each infected person has a **large number of close contacts** each day — on transport, at work, in housing. Because a respiratory virus needs close contact to pass on, more contacts means each case infects more people, so the chain of transmission is easily sustained and case numbers rise quickly. (c) **Quarantine of arriving travellers** (border screening and travel restrictions are also acceptable): travellers who may have been exposed are separated from the community for the length of the incubation period, so that if they do become infectious they cannot pass the virus to others, and imported cases do not start new local chains of transmission.

Q3. (a) Whether a pathogen is "emerging" is judged **relative to the population it appears in**, not by how old the pathogen is. Smallpox had circulated in Europe for centuries, so it was long established there; but it had **never been present** in Aboriginal and Torres Strait Islander populations, and when it was introduced it was appearing in those populations **for the first time**. It was therefore an **emerging pathogen** in those populations while remaining an established one elsewhere. (b) Respiratory pathogens such as these pass between people mainly by **droplet transmission** — droplets released by coughing, sneezing and talking (smallpox also spread by direct contact with fluid from the sores and with contaminated bedding). A control measure that blocks the droplet route is **isolating infected people** (masks, physical distancing or covering coughs and sneezes are equally acceptable). (c) Aboriginal

and Torres Strait Islander communities were connected by **long-established routes of travel, trade and ceremony**, and colonists and their livestock also moved inland. Because a person can be **infectious before symptoms appear**, someone could travel and infect people in another community before anyone knew they were ill. Introduced diseases therefore moved from community to community and reached places far inland, in many cases **before** Europeans arrived there.

Q4. (a) The evidence — sores on the skin, and shared towels, mats and strapping tape at a single session — points to **direct contact** (touching the sores or skin of an infected player, for example during wrestling) and **indirect contact via contaminated objects** (a towel, mat or roll of tape touched by an infected player and then by another). That no household members are affected supports transmission occurring at training rather than by droplets in the wider community. (b) Identifying the pathogen tells investigators **what kind of organism it is** and therefore how to respond: whether it is a bacterium that can be treated with an antibiotic (and whether the strain is resistant), how it should be diagnosed and confirmed, how long a player stays infectious and so how long they must be excluded, and how the organism survives on surfaces, which determines the cleaning required. (c) Any two, described: **exclude players with active sores from training, or require the sores to be fully covered**, which removes the source of direct contact; **stop the sharing of towels, tape and drink bottles**, which removes the contaminated-object route; **clean and disinfect the mats and shared equipment after every session**; **hand washing before and after training**.

Q5. (a) Vaccination produces **artificial active immunity** — artificial because it is a deliberate medical intervention, active because the person's **own** immune system responds and makes its own antibodies. **Memory cells** are essential because they are what persists after the response ends: on a later exposure to the real pathogen they allow a **faster and larger secondary response**, so the person does not become ill. Without memory cells the vaccine would give only short-term protection. (b) **Herd immunity** is the protection that arises when a **large enough proportion of a population is immune** that the pathogen can no longer spread easily; chains of transmission break, so people who are not immune are unlikely to be infected. (c) Any two, with reasons: **babies below the recommended age**, because their immune systems are too immature to respond properly and the vaccine is not approved for them; **people whose immune systems are weakened** — for example by chemotherapy, an immunodeficiency, or medication taken after an organ transplant — because they cannot mount a proper response and a live vaccine could be dangerous for them; **people with a severe allergy to a vaccine component**.

Q6. (a) Bacteria vary: **random mutation** (and the transfer of resistance genes between bacteria) produces some individuals that are **resistant** to the antibiotic. Heavy use of the antibiotic acts as a **selection pressure** — susceptible bacteria are killed, while resistant ones **survive, reproduce and pass on the resistance**. Over successive generations the **proportion** of resistant bacteria in the population increases, until the resistant strain is common. (b) Once the strain is resistant, the antibiotic no longer cures the infection. Infected people **stay infected and infectious for longer**, so they transmit the pathogen to more people, and treatment can no longer be used to shorten outbreaks. A disease that was previously controlled therefore begins to **increase in incidence again** — it re-emerges. (c) Any one: prescribe antibiotics only when they are actually needed (not for viral illness); complete the prescribed course; restrict the routine use of antibiotics in agriculture; improve hygiene and infection control so fewer infections need treating at all.

Q7. One: live animals, meat or fresh produce that carry a pathogen can be **imported** — the pathogen arrives inside the traded goods and can then infect people or livestock in the importing country. **Two: vectors** can be transported as stowaways in cargo — for example mosquito eggs or larvae in water lying in shipping containers, machinery or used tyres — and can establish a breeding population in the new country, so the disease they carry can then be transmitted locally. *(1 mark for each of the two distinct, correctly explained routes. Total 2 marks.)*

Q8. A virus that has circulated in bats for years is adapted to bat cells, not human cells. A **random mutation** may alter one of its surface proteins so that it can **bind to and enter human cells**; clearing the forest for agriculture greatly increases how often people and bats come into contact, so there are far **more opportunities** for such a virus to enter a human host and for a variant able to infect humans to be transmitted. However, most spillovers are **dead-end infections**: the virus can infect the person who was exposed but **cannot pass from that person to another**, so the chain stops with them. An **epidemic requires sustained human-to-human transmission**, which needs further genetic change; until that happens, cases appear only in people directly exposed to the reservoir. *(1 mark: mutation allows the virus to infect human cells; 1 mark: increased contact from land clearing gives more opportunities; 1 mark: a spillover is a dead end unless human-to-human transmission is established.)*

Q9. Isolation separates people who are **known to be infected** with the pathogen from other people, so that they cannot pass it on while they are infectious. **Quarantine** separates and restricts the movement of people who have been

exposed to the pathogen and may be **incubating** it, but who are not (yet) known to be infected. Both are needed for a disease that is infectious **before symptoms appear**: isolation alone would only catch people once they were identified as cases, by which time they may already have transmitted the pathogen, so exposed contacts must also be quarantined for the length of the incubation period to stop transmission from people who are infectious but not yet visibly ill. *(1 mark: isolation defined; 1 mark: quarantine defined as exposed-but-not-confirmed; 1 mark: transmission before symptoms appear means isolating known cases alone is insufficient.)*

Q10. Measure (iii) would reduce transmission. The virus passes in **blood and other body fluids**, and in a health service the main risks are needle-stick injuries, re-used equipment and contact with patients' blood; **single-use sterile needles with safe sharps disposal** prevent blood from one person entering another, and **gloves and gowns** provide a barrier between staff and patients' body fluids, so the route the virus actually uses is blocked. **Measure (i)** targets **vector-borne** transmission and would only help if a mosquito or tick were carrying the pathogen, which is not the case here. **Measure (ii)** targets **water-borne** transmission and would only help against a pathogen swallowed in contaminated water. Neither blocks blood-to-blood or body-fluid contact, so neither would reduce transmission of this virus. *(1 mark: identifying (iii); 1 mark: explaining how it blocks the blood and body-fluid route; 1 mark: explaining that (i) and (ii) block different modes not used by this virus.)*

Q11. A national figure of 97% is an **average**, and coverage is **not spread evenly** across the country. Nationally that figure is above the roughly **95%** that a highly infectious disease requires, but the threshold has to be met **where people actually mix**. This town's coverage is very likely **below the threshold**, so within the town there are **enough susceptible people in contact with one another** for a chain of transmission to be sustained once a case arrives — for example imported by a traveller. Herd immunity depends on the immunity of the people an infectious person **actually mixes with**, so a local cluster of unvaccinated people forms a pocket in which an outbreak can occur even though the national average is comfortably above the threshold. *(1 mark: coverage is unevenly distributed / the town is below the threshold; 1 mark: enough susceptible contacts locally to sustain transmission; 1 mark: herd immunity operates in the mixing group, not the national average.)*

Q12. The threshold for herd immunity depends on **how many people one case would infect in a fully susceptible population**. A more infectious pathogen would infect **more** people per case, so a larger share of those contacts must be **immune** in order for the number of new infections per case to fall **below one**. If only the same proportion were immune as for a less infectious pathogen, enough of the remaining contacts would still be susceptible for transmission to continue. *(1 mark: a more infectious pathogen produces more infections per case; 1 mark: therefore a greater proportion must be immune to bring transmission below one new case per case.)*

Q13. Factor 1 — dispossession and displacement. Communities were dispossessed of Country and moved onto crowded settlements and missions. **Crowding increases contact between people**, so a pathogen spread by droplets or by contact moves through the population far more readily than it would in dispersed communities. **Factor 2 — disruption of access to food, water and care.** Removal from Country disrupted access to traditional foods, clean water and medicines; poor nutrition and the inability to care for the sick **weakened resistance to infection and worsened recovery**, so a given infection was more likely to be fatal. (Accept also: so many people ill at once that too few remained well to provide care.) **Consequence beyond deaths:** because the diseases affected all age groups, many **Elders and knowledge holders** died. Aboriginal and Torres Strait Islander knowledge of language, Country, food, medicine, law and ceremony is held and passed on by people, so their deaths caused **losses of language, cultural knowledge and continuity between generations** that could not be replaced and that continue to affect communities today. *(1 mark: first factor described and linked to increased transmission or a worse outcome; 1 mark: second factor described and linked; 1 mark: identifying the loss of Elders and knowledge holders; 1 mark: explaining the resulting loss of language, knowledge and cultural continuity. Total 4 marks.)*

Q14. Explanation: the pathogen is **vector-borne**, so it can only be transmitted where its mosquito vector lives. **Warming temperatures and changed rainfall** (climate change) have made the temperate southern areas warm enough and wet enough for the mosquito to **survive, breed and extend its season** there. Once the vector is established, an infected traveller arriving from the north can be bitten and the disease can then be **transmitted locally**, so cases appear in an area where the disease had never occurred. **Control measures:** (1) **remove standing water** — empty containers, gutters, tyres and pot-plant bases, and manage drains — because this removes the mosquito's breeding sites and so reduces the vector population; (2) **personal and household barriers** — insect screens on windows, bed nets, repellent and covering clothing (and targeted insecticide where appropriate) — because these stop mosquitoes biting people and so break the vector-to-human link. *(1 mark: climate change extends the vector's*

range/season; 1 mark: local transmission becomes possible once the vector is established; 1 mark each for two control measures correctly linked to blocking vector-borne transmission.)

Q15. (a) Vaccination coverage was **high and stable at about 95%** from 2012 to about 2015, then **fell steadily** to a minimum of about **78% in 2021**, before **rising again** to about **93% by 2024**. (b) There is an **inverse (negative) relationship**: while coverage was high, notified cases stayed close to zero; as coverage fell below about 90% from 2017 onwards, cases **rose sharply** to a peak of about 24 per 100 000 in 2021; as coverage recovered from 2022, cases **fell** again. (c) Falling coverage means a **growing number of susceptible people** in the population. While coverage was above the **herd-immunity threshold**, any introduced case met mostly immune contacts and the chain of transmission broke, so cases stayed near zero. Once coverage fell **below the threshold**, an infectious person met enough susceptible contacts for each case to infect more than one other person, so **chains of transmission were sustained** and cases increased rapidly. Restoring coverage after 2021 pushed the immune proportion back above the threshold, breaking the chains again and reducing cases. (d) These data show a **correlation**, not causation: the two variables were only **observed**, not manipulated, so other factors could contribute — for example an imported case seeding the outbreak, increased testing or more complete notification, or changes in the population of Region R. *(a: 1 mark; b: 1 mark; c: 2 marks — susceptible pool grows, and transmission sustained once below the threshold; d: 1 mark. Total 5 marks.)*

Q16. (a) **Outbreak W — airborne (aerosol) transmission.** Cases occurred in people who were never within two metres of a case but who shared air through the same duct, which only small suspended particles could reach. **Outbreak X — food-borne transmission.** Illness is confined to those who ate one particular dish, with a delay of 12–36 hours typical of a pathogen or its toxin taken in with food. **Outbreak Y — indirect contact via contaminated objects** (direct skin contact is also plausible): the affected children shared a play mat and toys, and inconsistent hand washing allows the pathogen to pass from object to child. (b) **Outbreak W** would be hardest to control. Airborne particles remain **suspended in the air and travel beyond the immediate area**, and they persist in a room after the infectious person has left, so the measures that work for the others — excluding one food item, cleaning surfaces, hand washing, keeping two metres apart — do **not** block this route. Control requires **improved ventilation and air filtration, fitted respirators and negative-pressure rooms**, which are slow and expensive to put in place in an existing building, and the residents are elderly and at high risk. *(1 mark for each correct mode in (a) = 3 marks; 1 mark for a justified choice in (b). Total 4 marks.)*

Q17. (a) Before the intervention, new cases **rose steeply and continuously**, from 2 in week 1 to **61 in week 7** — roughly doubling every one to two weeks. (b) After the intervention, cases peaked at **66 in week 8** and then **fell steadily and continuously** to just **1 case in week 16**. (c) The measures cannot affect people who were **already infected**: those exposed in weeks 6 and 7 were still in their **incubation period** when the measures began and went on to develop symptoms, be tested and be notified in the following week. There is therefore a **lag** between blocking transmission and seeing the effect in the case numbers. (d) Control measures **block the route the pathogen uses to reach the next host**, so a smaller proportion of an infectious person's contacts become infected. Each case then passes the pathogen on to **fewer than one other person on average**, so each successive generation of infection is smaller than the last and new case numbers fall until the outbreak ends. *(1 mark each for (a), (b), (c) and (d). Total 4 marks.)*

Q18. The **reservoir** is the population or species in which a pathogen is **maintained between outbreaks** — it is the source that keeps re-supplying the pathogen to human hosts. If the reservoir is not identified, control measures aimed only at cases and their contacts will end the current outbreak but will not stop the pathogen returning, so **outbreaks recur** and the source of each new outbreak stays unknown. Where the reservoir is a **wild animal population**, the pathogen persists in that population regardless of what is done in humans, so the disease **cannot be eradicated by treating and vaccinating people alone**; control must be **ongoing** and must also target the animal–human interface (surveillance of wildlife and livestock, vaccinating domestic animals, reducing contact, and controlling markets or vectors). *(1 mark: reservoir defined as the maintaining population/source between outbreaks; 1 mark: control must target the reservoir or outbreaks recur; 1 mark: a wild animal reservoir makes eradication by human measures alone impossible, so control must be ongoing.)*

Q19. (a) The **independent variable** is **whether or not the mosquito-control program is carried out** in a town (the variable the health department manipulates — not "Town 1 and Town 2", which are its two levels). The **dependent variable** is the **number of new notified cases of the disease per 100 000 people per week**. (b) Any one, with a reason: the **time period over which cases are counted** must be the same in both towns, because case numbers vary seasonally with mosquito abundance and a difference in timing would produce a difference in cases that had nothing

to do with the program; **the case definition and testing method** must be identical, or a difference in cases could simply reflect a difference in how cases were detected; the towns should be as similar as possible in **size, climate and housing**, so that differences in cases can be attributed to the program. (c) **Strengths.** The design includes a **comparison (control) town** measured over the **same 20 weeks**, so a seasonal rise or fall in mosquito numbers acts on both towns and cannot on its own explain a difference between them. The dependent variable is a **rate per 100 000 people**, so the two towns can be compared even though their populations differ, and measuring **every week for 20 weeks** gives a trend — including whether the two towns diverge after the program begins — rather than a single snapshot. **Limitations.** There is only **one town in each condition** and **no random allocation**, so the towns almost certainly differ in other ways — rainfall, wetland area, housing quality, age structure, existing immunity — and any of these could also affect case numbers. This **confounding** means a difference between the towns cannot confidently be attributed to the program, and with a sample of one town per condition the result is also not readily generalised. Notification also depends on people seeking testing, and publicity about the program in Town 1 could itself change how many cases are detected. **Judgement.** As a practical field trial the design is sound enough to show whether case rates in the two towns **differ**, but it cannot establish that the program **caused** any difference; it should be treated as preliminary evidence. A stronger design would use **several matched towns in each group, allocated randomly**, with a baseline recorded before the program starts and the comparison run over more than one season. *(a: 1 mark for IV, 1 mark for DV; b: 1 mark; c: 3 marks — 1 mark for a strength, 1 mark for a limitation, 1 mark for a judgement about what the investigation can and cannot show. Total 6 marks.)*

Q20. (a) **Identifying the pathogen.** Samples are taken from the patients — **nose and throat swabs** and blood — and the organism in them is identified in the laboratory: it is examined by **microscopy**, an attempt is made to **culture** it, and its nucleic acid is amplified and read by **PCR and genetic sequencing**. The sequence matches no known agent, which identifies virus H as a **new virus** and provides the genome from which a **specific diagnostic test** can be built, so that later suspected cases — including those with no market contact — can be **confirmed** rather than assumed; **antibody tests** on patients' blood then show who has already been infected. **Establishing the host.** The same PCR and sequencing are applied to samples taken from the animals sold at the market and from the market environment. Finding the **same viral sequence in the market poultry**, together with the epidemiological finding that the first 30 cases all **worked at or shopped in the market**, establishes poultry as the animal host; testing other market species, farmed flocks and wild birds then shows how widely the virus is maintained and whether the market birds are themselves infected from a further reservoir. (b) **Strategy 1 — clear, timely public health communication and education.** People can only act on advice they have actually received and trust, so the authorities must tell the public what the symptoms are, to get tested, to stay home when unwell, to cover coughs and wash hands, and to avoid the market — delivered in the languages the community speaks and through **trusted community organisations**. Every person who follows that advice exposes **fewer contacts while infectious**, so the number of new infections per case falls. **Strategy 2 — surveillance and notification, with contact tracing.** An agreed **case definition** and a requirement that clinicians **notify** every case mean that new clusters — such as the one among staff on the hospital ward — are detected **early**, and the contacts of each case can be traced and quarantined **before they become infectious**, removing links from the chain of transmission rather than waiting for those people to fall ill. (Accept also: closing the live-poultry market and other venues; border screening and travel advice; and providing the testing, sick leave and isolation accommodation that make staying home possible.) (c) The most likely mode is **droplet transmission**. The evidence: most patients have a **fever and a cough**, virus is detected in samples from the **nose and throat**, and cases cluster in **households and on a hospital ward** — settings involving prolonged close contact — rather than being linked to a shared food or water source. A control measure that blocks this route is **isolating cases** (accept: masks for cases, staff and contacts; physical distancing; protective equipment and better ventilation on the ward), which prevents the droplets produced when an infectious person coughs from reaching another person's mucous membranes. (d) A vaccine protects a population only once a **high enough proportion of people are actually immunised** — for a virus this transmissible, a large majority. Reaching that level takes time: the vaccine must be **manufactured and distributed in enormous quantities**, kept viable through the **cold chain**, delivered through clinics with the staff to give it, and each person needs time (and possibly more than one dose) to develop protective immunity. Access, cost and vaccine hesitancy may also keep coverage below the threshold, and if coverage is uneven, low-coverage groups can continue to sustain transmission. Until the threshold is reached, the vaccine protects the individuals who receive it but does not stop the outbreak. *(a: 2 marks — laboratory identification of the pathogen (culture, PCR and sequencing); the same testing applied to market animals, with the epidemiological link, to establish the host. b: 2 marks — 1 mark for each social strategy described and linked to reducing transmission. c: 2 marks — droplet transmission justified from the evidence; one control measure that blocks that route. d: 2 marks — a threshold proportion must be immunised; practical reasons coverage is not reached quickly. Total 8 marks.)*

Theory

Most treatments for disease attack the problem with a chemical that has nothing to do with the immune system: an antibiotic kills the bacterium, and an untargeted cytotoxic drug poisons any cell that is dividing quickly. **Immunotherapy** works in a different way. It is treatment that **uses a component of the immune system — such as an antibody — or that changes how the body's own immune response behaves**, in order to treat a disease. Some immunotherapies **boost or direct** an immune response so that it **finds and destroys** cells it has been ignoring — this is the aim in cancer. Others turn a response **down**, because the immune system is attacking the body itself — this is the aim in autoimmune disease. Others again use an immune molecule purely as a **tool**: an antibody can block a signal a diseased cell depends on, or carry a drug to it, without raising or lowering the patient's immune response at all. The immunotherapy strategy you must know in detail is the use of **monoclonal antibodies**.

What "monoclonal" means. Recall from 7D that each B lymphocyte carries receptors of a single specificity, and that the antibodies its plasma cells secrete bind **one** complementary antigen.

A **monoclonal antibody (mAb)** is a population of **identical antibody molecules produced by a clone of cells derived from a single B lymphocyte**. Splitting the word apart: **mono** = one, **clonal** = clone.

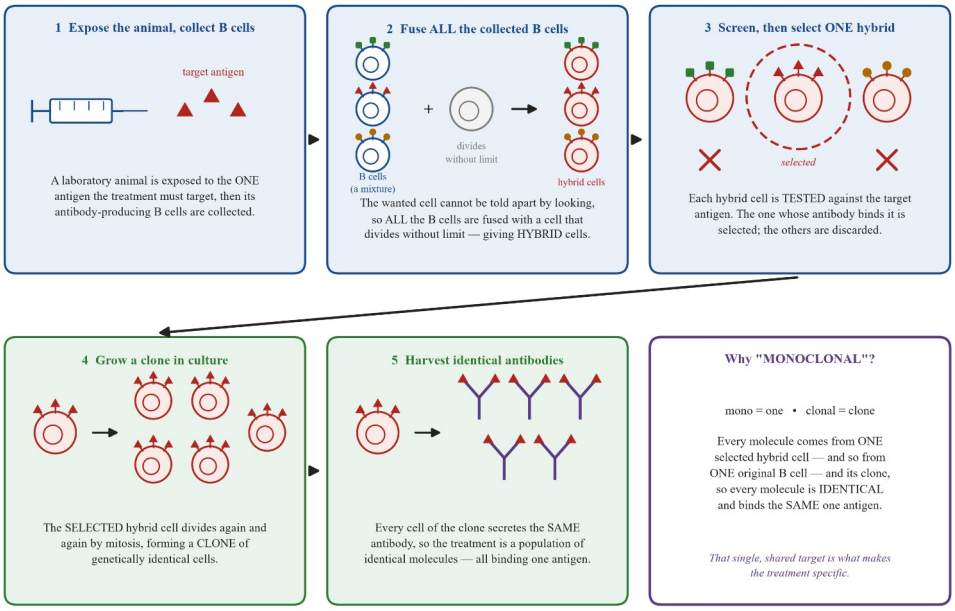
Because every molecule is made by cells descended from **one** original B cell:

- all the cells of the clone are **genetically identical**, so
- every antibody molecule has the **same variable region** and therefore the **same antigen-binding sites**, so
- every molecule binds the **same one antigen**.

That single shared target is the whole point of the treatment: a mAb is aimed at **one chosen molecule** and leaves the rest of the body alone. Antibodies collected straight from the blood of an immunised animal would instead be a **mixture** made by many different B cells, binding many different antigens — far less useful when a treatment must act on one target only.

How a monoclonal antibody is produced. Two problems have to be solved at once. A B cell making the wanted antibody does not, by itself, keep dividing in culture, so it cannot supply the huge quantities a treatment needs; and the one B cell making that antibody **cannot be picked out by looking at it**, because B cells that make different antibodies look the same. The general solution is:

1. **Choose the target antigen** — the one molecule the treatment must bind — and expose a laboratory animal to it, so that its B lymphocytes respond and produce antibodies against it. The antibody-producing B cells are then **collected** from the animal. They are a **mixture**: each makes one kind of antibody, and only a few of them make the one that fits the target.
2. **Fuse the collected B cells with cells that divide indefinitely.** Because the wanted cell cannot be identified in advance, the **whole population** is fused, not one chosen cell. Each fused (**hybrid**) cell both makes the antibody of the B cell it came from and keeps dividing without limit.
3. **Screen the hybrid cells, and select the one whose antibody binds the target antigen.** This is the step at which the choosing actually happens: the hybrid cells are **tested** against the target antigen, and hybrid cells making any other antibody are discarded.
4. The selected hybrid cell **divides again and again by mitosis** in culture, producing a **clone** of genetically identical cells.
5. Every cell of the clone secretes the **same antibody**, which is **collected and purified** — giving large quantities of one identical antibody, all specific to the chosen antigen.



Why specificity matters. An untargeted cytotoxic drug cannot tell a cancer cell from a healthy one; it acts on **any** rapidly dividing cell, which is why it also damages hair follicles, bone marrow and the lining of the gut. A monoclonal antibody binds **only** the cells or molecules carrying its target antigen, because only that antigen has a shape complementary to its binding sites. The treatment is therefore concentrated where the target is, and **far fewer healthy cells are affected** — the reason targeted treatments usually cause fewer and milder side effects.

Monoclonal antibodies in autoimmune disease — dampening a misdirected response. In an **autoimmune disease** the immune system fails to tolerate the body's own molecules: it treats a **self-antigen** as though it were foreign and mounts an adaptive response against the body's own cells and tissues. The result is **chronic inflammation and tissue damage**. Because the "invader" is the body itself, the aim of treatment is to **turn the misdirected response down**. A mAb can do this in two ways:

- **Neutralising an overactive signalling molecule.** Immune cells communicate using signalling molecules (cytokines); one important example is **tumour necrosis factor (TNF)**, which drives inflammation. In several autoimmune diseases far too much of one such molecule is released, keeping the response permanently switched on. A mAb made against that molecule **binds it and blocks it**, so it can no longer bind its receptor on the target cell. The signal is not received, the misdirected response is **dampened**, and inflammation and tissue damage are reduced.
- **Blocking the receptor.** Alternatively the mAb is made against the **receptor** for that signalling molecule and caps it, so the signal cannot be received even though the molecule is still present. The outcome is the same — the misdirected response is dampened.

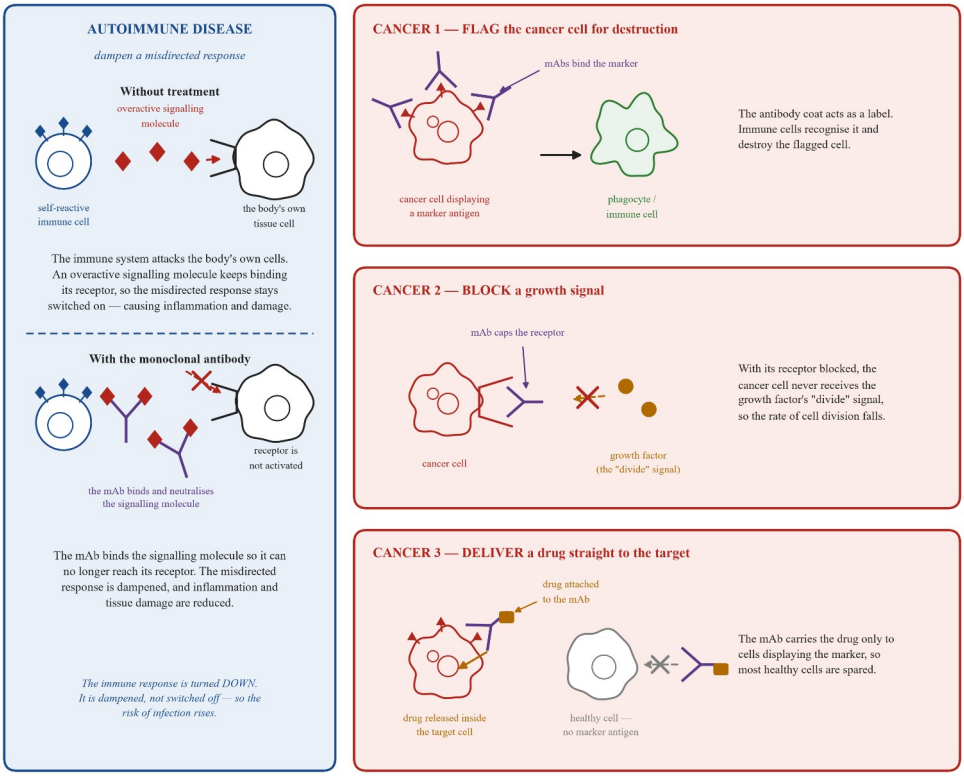
Two points follow. First, the treatment **manages the disease rather than curing it**: the self-reactive lymphocytes are still present, so treatment usually continues long term. Second, because part of the immune response has deliberately been turned down, patients face a **higher risk of infection**.

Monoclonal antibodies in cancer — aiming at a marker antigen. Cancer cells are the body's own cells that have lost control of cell division. Many of them display **surface marker antigens** that healthy cells either do not display at all, or display in far smaller numbers. Those markers give a mAb something to aim at. There are **three** strategies you must be able to describe. Only the first recruits the patient's immune system; the other two use the antibody as a targeting tool, and all three are immunotherapy because the antibody is itself a component of the immune system:

- **1 — Flag the cancer cell for destruction.** The mAb binds the marker antigen so the cancer cell becomes **coated in antibody**. The coat acts as a label the immune system recognises: **phagocytes and other immune cells** bind the coating and **destroy the flagged cell**. The antibody itself kills nothing; it makes the cell visible to the immune system.
- **2 — Block a growth signal.** Many cancer cells divide rapidly because they display large numbers of **receptors for a growth factor** — a signalling molecule that instructs the cell to divide. A mAb made against

that receptor **binds and caps** it, so the growth factor can no longer bind. The "divide" message is never received, the **rate of cell division falls**, and the tumour grows more slowly. (A mAb made against the growth factor itself works the same way, mopping up the signal before it reaches the cell.)

- **3 — Deliver a drug straight to the target.** A **cytotoxic drug or a radioactive isotope is attached to the mAb**, which then acts as a delivery vehicle. The antibody binds only cells displaying the marker antigen, so the drug is carried to those cells and acts there. Healthy cells that lack the marker are not bound, so most of them are spared.



Strengths and limitations — what to weigh up in an "evaluate" question.

Strengths:

- **Specific** — one target antigen, so far fewer healthy cells are affected than with an untargeted treatment, and side effects are usually fewer and milder.
- It can act on molecules no ordinary drug could reach, and it can **carry a drug** to exactly where it is needed.
- Because the cells of the clone are identical, huge quantities of **identical** molecules can be made, so every dose is the same.

Limitations:

- It works only if the diseased cells display a **suitable target**. Patients are usually tested first, and some are found not to be suitable for the treatment.
- A target antigen is rarely found **only** on the diseased cells, so healthy cells carrying it are affected too — some side effects still occur.
- Antibodies are **proteins**, so a mAb would be digested if it were swallowed. It must be given by **injection or infusion**, usually in a clinic.
- The patient's own body is not making these antibodies, and the injected antibodies are gradually broken down, so **doses must be repeated**.
- A mAb produced using another species' cells may itself be recognised as **non-self** and attacked by the patient's immune system, reducing how well it works; modern mAbs are altered to be more human-like to reduce this problem.
- Growing living cells in culture and purifying protein is **expensive**, which limits access.

- Cancer cells that **stop displaying** the target antigen are no longer bound, so a tumour may begin to grow again after a period of successful treatment.

Worked examples

Example 1 — scaffolded

A student is told that a new treatment uses "a monoclonal antibody". Explain what the word *monoclonal* tells the student about the antibody molecules in that treatment, and why they all bind the same antigen.

Working	Comment
Split the word: **mono** = one, **clonal** = clone. The molecules are all produced by **one clone of cells**, all descended from a **single B lymphocyte**.	Begin with the meaning of the term — this is what the question is really testing.
Every cell of a clone is **genetically identical**, so each one makes an antibody with the **same variable region**.	Link identical cells to identical antibodies.
The variable region carries the **antigen-binding sites**, so every molecule has binding sites of the **same shape**.	Apply what you know about antibody structure; do not re-describe the whole molecule.
∴ every molecule in the treatment is **identical**, and each binds the **one antigen** whose shape is complementary to those binding sites.	Finish with the consequence the question asks for: one target.

Example 2 — scaffolded

Two hundred patients with the same cancer took part in a trial. One hundred were given an untargeted cytotoxic drug (drug K) and one hundred were given a monoclonal antibody therapy. The table shows how many patients in each group reported each effect.

Effect reported	Untargeted drug K (100 patients)	Monoclonal antibody therapy (100 patients)
Hair loss	78	4
Low white blood cell count	61	12
Nausea and vomiting	70	21

Using the data, compare the two treatments, then suggest one reason why some patients given the monoclonal antibody therapy still reported these effects.

Working	Comment
For every effect listed, fewer patients reported it on the mAb therapy than on drug K: hair loss **4 compared with 78**, low white blood cell count **12 compared with 61**, and nausea and vomiting **21 compared with 70**.	Quote figures from the table. A general statement such as "the mAb was better" would not earn the mark.
The pattern is the same for all three effects, so overall the mAb therapy was **much better tolerated** than the untargeted drug.	State the overall trend as well as the individual figures.
Drug K acts on **any** rapidly dividing cell, so it damages healthy dividing tissues — hair follicles, bone marrow and the gut lining — as well as the cancer. The mAb binds only cells displaying its **target antigen**.	The comparison must be explained in terms of targeting, not just reported.
Some effects still occurred because a target antigen is **rarely found only on cancer cells**: healthy cells that also display it are bound and affected as well.	This is the "suggest" mark — no target is perfectly unique to the diseased cells.

Example 3 — unscaffolded

In an autoimmune joint disease, self-reactive immune cells release unusually large amounts of a signalling molecule called JX-1. JX-1 binds receptors on cells in the joint lining and keeps the inflammatory response switched on, damaging the joint. A monoclonal antibody that binds JX-1 has been developed. Explain how this treatment would reduce the damage to the patient's joints, and explain why it would not cure the disease.

Every molecule of the monoclonal antibody has binding sites complementary to **JX-1 only**, so when it is given it **binds the JX-1 circulating in the patient**. A JX-1 molecule held by an antibody can no longer bind its **receptor** on the cells of the joint lining, so the signal is **not received**. With far less JX-1 signalling reaching those cells, the misdirected inflammatory response is **dampened**, and the inflammation and tissue damage in the joint are reduced.

The treatment does not cure the disease because it acts on the **signalling molecule**, not on the cause. The **self-reactive immune cells are still present and still releasing JX-1**, and the injected antibodies are gradually broken down, so the symptoms would return if treatment stopped. ∴ the mAb controls the damage and must be given repeatedly, rather than curing the condition.

Example 4 — unscaffolded

The cells of a tumour display very large numbers of a receptor, GF-R2, which binds a growth factor carried in the blood. When the growth factor binds GF-R2, the cell is signalled to divide. A monoclonal antibody has been made against GF-R2. Explain how this antibody would slow the growth of the tumour, and state how this mechanism differs from a monoclonal antibody that flags cancer cells for destruction.

The monoclonal antibody binds **GF-R2**, the receptor displayed in large numbers on the tumour cells, and **caps** it. With the receptor occupied by antibody, the **growth factor can no longer bind** to it, so the "divide" signal is **never received** by the cell. The **rate of cell division falls**, and because new cells are produced more slowly the **tumour grows more slowly**.

The mechanisms differ in **what the antibody achieves by binding**. Here the antibody **denies the cell a signal it depends on** — nothing destroys the cell, its division is simply slowed. A flagging antibody instead **labels** the cell with an antibody coat so that the patient's **immune cells recognise and destroy** it. ∴ one blocks a growth signal, while the other recruits the immune system to kill the cell.

Practice questions

Scaffolded

Q1. Define each of the following terms: (a) immunotherapy; (b) target (marker) antigen, as used in monoclonal antibody therapy; (c) autoimmune disease.

Q2. Monoclonal antibodies are produced in the laboratory. (a) State why a laboratory animal is first exposed to the chosen target antigen. (b) Explain why the B cells collected from the animal must be fused with a cell that divides indefinitely. (c) Explain why the finished treatment would not work if the wrong hybrid cell had been selected.

Q3. The cells of a certain tumour display a marker antigen that healthy cells do not display. A monoclonal antibody against this marker is given to the patient. (a) State which part of the antibody binds to the marker antigen. (b) Describe how coating the cancer cells with these antibodies leads to their destruction. (c) Explain why no drug needs to be attached to the antibody for this strategy to work.

Q4. Some monoclonal antibodies are used as delivery vehicles. (a) State what is attached to the monoclonal antibody in this strategy. (b) Explain how the attached substance comes to act mainly on the cancer cells. (c) State one advantage of attaching the drug to a monoclonal antibody rather than giving the same drug on its own.

Q5. In one autoimmune disease, a signalling molecule keeps an inflammatory response switched on. A monoclonal antibody has been made against the **receptor** for that signalling molecule. (a) Explain how binding to the receptor dampens the misdirected response. (b) State one risk to the patient of dampening an immune response in this way. (c) Explain why this antibody has no effect on the many other kinds of receptor found on the patient's cells.

Q6. Monoclonal antibody therapies have practical limitations. (a) State one reason these therapies are expensive to produce. (b) Explain why a monoclonal antibody cannot be given as a tablet to be swallowed. (c) Explain why the doses usually have to be repeated.

Unscaffolded

Q7. A doctor describes a monoclonal antibody that flags cancer cells for destruction as "immunotherapy", but does not use that word for an untargeted cytotoxic drug. Explain the difference between the two treatments, referring to how the cancer cells are destroyed in each case. *(3 marks)*

Q8. Explain why a preparation of monoclonal antibodies is more useful as a treatment than a mixture of antibodies collected from the blood of an immunised animal. *(2 marks)*

Q9. A research team has chosen a target antigen and now needs large quantities of a monoclonal antibody against it. Outline, in order, the main steps they would follow. *(4 marks)*

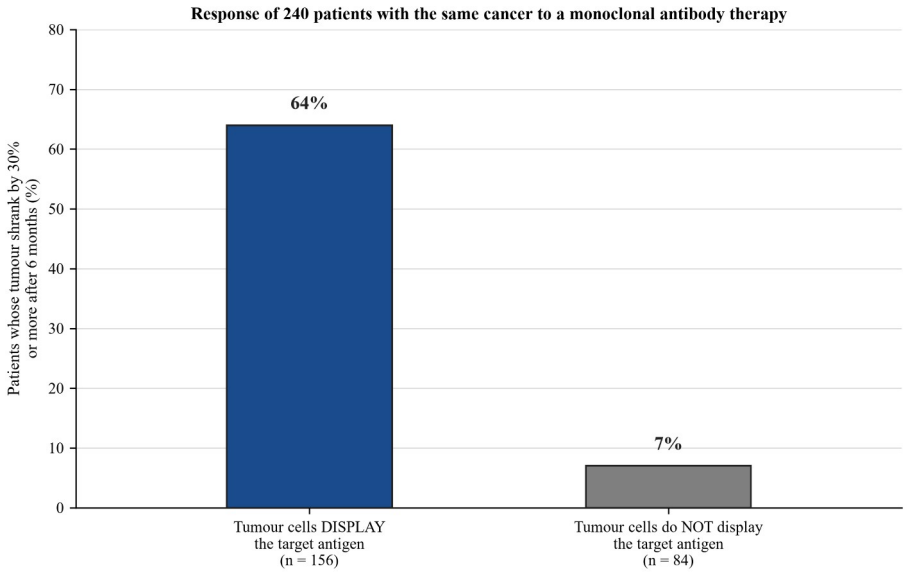
Q10. A monoclonal antibody has been developed against HB-9, a marker antigen displayed by the cells of a certain blood cancer. HB-9 is also displayed, in smaller amounts, by the patient's healthy B lymphocytes. Predict **two** consequences of giving this treatment, and explain each. *(3 marks)*

Q11. A second research team, working on the tumour described in Example 4, proposes a monoclonal antibody that binds the **growth factor itself** rather than its receptor. Explain how this antibody would also slow the growth of that tumour, and explain why it would have no effect on a different tumour whose cells divide without needing that growth factor. *(3 marks)*

Q12. Distinguish between the way immunotherapy is used to treat cancer and the way it is used to treat an autoimmune disease. Give one example of a monoclonal antibody strategy for each. *(3 marks)*

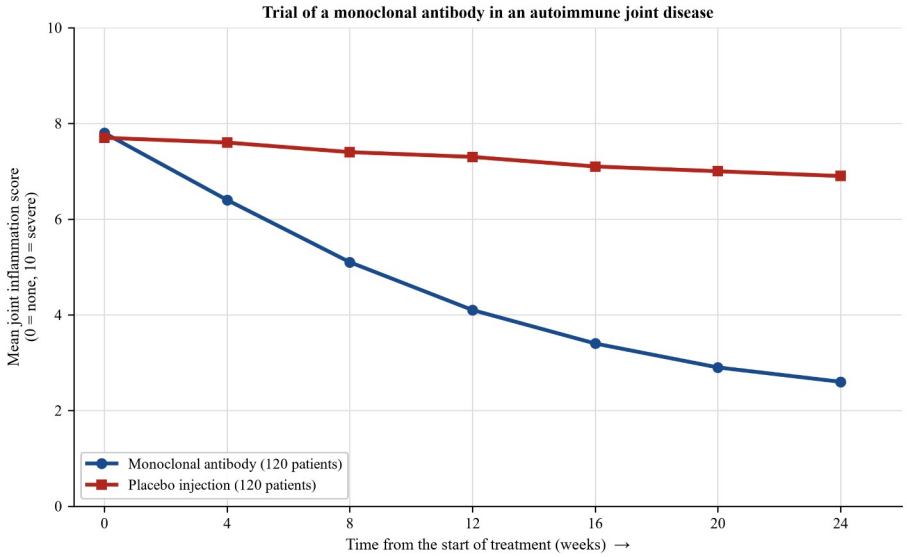
Q13. In a certain autoimmune disease, the tissue damage is caused by self-reactive lymphocytes that display a surface marker, CM-4. A monoclonal antibody against CM-4 coats these lymphocytes so that they are destroyed by the patient's immune system. Explain how this treatment would reduce the damage to the patient's tissues, and suggest why it might give longer-lasting relief than a monoclonal antibody that neutralises an inflammatory signalling molecule. *(3 marks)*

Q14. *(Stimulus.)* Two hundred and forty patients, all with the same type of cancer, were given the same monoclonal antibody therapy. Before treatment, a sample of each patient's tumour was tested to see whether its cells displayed the antibody's target antigen. The graph shows the results after six months.



(a) Describe what the graph shows.
(b) Explain, in terms of the antibody, why the two groups responded so differently.
(c) State what this result means for the way patients should be chosen for this therapy. *(4 marks)*

Q15. *(Stimulus.)* A monoclonal antibody developed for an autoimmune joint disease was trialled on 240 patients. Half were given the antibody by injection and half were given a placebo injection containing no antibody. The mean joint inflammation score of each group was measured every four weeks.



(a) Describe the trend shown by each group over the 24 weeks, quoting figures from the graph.

(b) Identify the independent variable and the dependent variable in this trial.

(c) Explain why the placebo group was included.

(d) State one conclusion that can be drawn from these results. *(5 marks)*

Q16. The first monoclonal antibodies used in medicine were produced using mouse cells. Patients given repeated doses often found the treatment became less effective over time. Explain why this happened, and suggest how the problem is reduced in modern monoclonal antibody therapies. *(3 marks)*

Q17. A patient's tumour shrinks steadily for eighteen months on a monoclonal antibody therapy, then begins to grow again even though the treatment is continued at the same dose. Suggest a biological explanation for this. *(2 marks)*

Q18. A biotechnology company must choose between two possible targets for a new monoclonal antibody against a solid tumour:

- **Antigen P** — displayed by about 90% of the tumour's cells and by no healthy cells;
- **Antigen R** — displayed by all of the tumour's cells and also by healthy heart muscle cells.

Evaluate which of these two targets the company should choose. *(3 marks)*

Q19. *(Synthesis.)* Cells of a certain solid tumour display a surface antigen, TX-4. A trial compared three treatments in patients whose tumour cells displayed TX-4. Drug D is an untargeted cytotoxic drug.

Treatment group (60 patients in each)	Mean reduction in tumour size after 6 months (%)	Patients in remission at 2 years (%)	Patients who stopped treatment because of side effects (%)
Drug D alone	31	18	33
Monoclonal antibody against TX-4 alone	27	22	5
Monoclonal antibody against TX-4 carrying drug D	58	42	10

(a) Using the data, compare the monoclonal antibody carrying drug D with drug D alone.

(b) Using the data and your knowledge of how each treatment works, explain why the monoclonal antibody given alone produced a smaller reduction in tumour size than the same antibody carrying drug D.

(c) Three in every ten patients screened for this trial could not take part because their tumour cells did not display TX-4. Explain why they were excluded.

(d) Evaluate whether the monoclonal antibody carrying drug D should replace drug D as the standard treatment for this cancer. *(8 marks)*

Answers

Q1. (a) Treatment that uses a component of the immune system, such as an antibody, or that boosts, directs or dampens the body's own immune response, in order to treat a disease. (b) A surface molecule displayed by the diseased cells that the monoclonal antibody is made to bind. (c) A disease in which the immune system attacks the body's own (self) antigens, damaging its own tissues. **Q2.** (a) So its B lymphocytes respond to that antigen and produce the wanted antibody. (b) Because a B cell alone will not keep dividing, and huge quantities of the antibody are needed; the whole collected population is fused because the wanted cell cannot be identified beforehand. (c) A different hybrid cell makes an antibody with a different variable region, which would bind a different antigen, not the target. **Q3.** (a) The antigen-binding sites at the tips of the two arms (the variable region). (b) The antibody coat labels the cell, and phagocytes and other immune cells recognise the coat and destroy it. (c) The antibody only has to make the cell visible — the patient's own immune cells do the destroying. **Q4.** (a) A cytotoxic drug (or a radioactive isotope). (b) The antibody binds only cells displaying the target antigen, so the drug is carried to and released at those cells. (c) Far fewer healthy cells receive the drug, so the side effects are fewer and milder. **Q5.** (a) The capped receptor cannot bind the signalling molecule, so the signal is not received and the misdirected response is dampened. (b) A higher risk of infection. (c) Its binding sites are complementary in shape to that one receptor only, so it does not bind others. **Q6.** (a) It must be made by growing living cells in culture and then purifying the protein. (b) It is a protein and would be digested before it could reach the blood. (c) The body does not make these antibodies itself and the injected ones are gradually broken down. **Q7.** The mAb works through the immune system — it labels the cancer cells so the patient's own immune cells destroy them; the cytotoxic drug kills any rapidly dividing cell directly, without involving the immune system. Of these two treatments, only the mAb uses a component of the immune system, so only it is immunotherapy. **Q8.** All the molecules in a monoclonal preparation are identical and bind one antigen, so the treatment acts on one chosen target; a mixture from blood contains many different antibodies binding many antigens. **Q9.** Expose an animal to the target antigen and collect its B cells → fuse them with cells that divide indefinitely, giving hybrid cells → screen the hybrid cells and select the one making the antibody that binds the target → grow a clone of that hybrid cell in culture → collect and purify the identical antibodies it secretes. **Q10.** The cancer cells display the most HB-9, so they are bound and destroyed; the patient's healthy B lymphocytes also display HB-9, so they are destroyed too, meaning fewer antibodies are made and the patient is more prone to infection. **Q11.** The antibody binds the growth factor before it reaches the receptor, so the "divide" signal is never delivered and division slows; a tumour that does not need that growth factor is unaffected because blocking the signal removes nothing it depends on. **Q12.** In cancer the aim is to increase or direct an attack on the cancer cells (e.g. flagging them for destruction); in autoimmune disease the aim is to dampen the misdirected response (e.g. neutralising an overactive signalling molecule). **Q13.** The antibody coats the self-reactive lymphocytes so the immune system destroys them; fewer self-reactive cells means less attack on the body's own tissues. It removes the cells causing the damage rather than mopping up one signal they release, so the attack is reduced at its source. **Q14.** (a) 64% of the 156 target-positive patients responded, compared with only 7% of the 84 target-negative patients. (b) The antibody can only bind cells displaying its target antigen. (c) Patients should be tested for the target antigen and only treated if their tumour cells display it. **Q15.** (a) mAb group: fell steadily from 7.8 to 2.6; placebo group: almost unchanged, 7.7 to 6.9. (b) IV = whether the patient received the monoclonal antibody or the placebo; DV = mean joint inflammation score. (c) For comparison, so any change caused by the injection itself or by time is accounted for. (d) The monoclonal antibody reduced joint inflammation in this disease over 24 weeks. **Q16.** The mouse antibody is non-self, so the patient made an immune response against it and removed it. Modern mAbs are altered to be more human-like so they are less likely to be recognised as non-self. **Q17.** Cancer cells that no longer display the target antigen are not bound by the antibody, so they survive, divide and come to make up the regrowing tumour. **Q18.** Antigen P — it is on no healthy cells, so healthy tissue is spared; antigen R would also bind heart muscle. P leaves about 10% of tumour cells untreated, but that is outweighed by avoiding damage to the heart. **Q19.** (a) The antibody carrying drug D almost doubled tumour reduction (58% compared with 31%) and more than doubled remission (42% compared with 18%), and far fewer patients stopped it (10% compared with 33%). (b) The antibody alone only binds TX-4; adding drug D delivers a cell-killing drug to the same cells. (c) Their cells had no target for the antibody to bind. (d) Yes for patients whose tumour cells display TX-4 — better on all three measures — but not for the roughly 30% whose tumours lack TX-4.

Fully-worked solutions

Q1. (a) **Immunotherapy** is treatment that **uses a component of the immune system — such as an antibody — or that boosts, directs or dampens the body's own immune response**, in order to treat a disease. A monoclonal

antibody therapy is immunotherapy on either count: the antibody is itself an immune molecule, and it may also recruit the patient's immune cells to destroy the target. (b) A **target (marker) antigen** is a **surface molecule displayed by the diseased cells** — for example a marker found on cancer cells but not on healthy cells — which the monoclonal antibody is made to **bind**. (c) An **autoimmune disease** is one in which the immune system **fails to tolerate the body's own molecules** and mounts a response against **self-antigens**, damaging the body's own cells and tissues.

Q2. (a) Exposing the animal to the chosen antigen means its **B lymphocytes respond to that antigen**, so that among them there will be a cell producing the **exact antibody the treatment needs**. (b) A B cell taken from the animal will **not keep dividing** on its own, so it could never supply the large quantities of antibody a treatment requires. Fusing the collected B cells with cells that **divide indefinitely** gives **hybrid cells** that **both make their B cell's antibody and keep dividing**, so the wanted antibody can be produced in bulk. The **whole collected population** is fused, not one chosen cell, because B cells making different antibodies look identical — the cell that makes the wanted antibody cannot be picked out until the hybrid cells are screened. (c) Every B cell makes an antibody with a **different variable region**, and therefore binding sites of a **different shape**, and each hybrid cell inherits the antibody of the B cell it came from. If the wrong hybrid cell were selected at screening, the whole clone — and so every molecule in the finished treatment — would carry binding sites complementary to **some other antigen**. The treatment would not bind the **chosen target antigen**, so it would have no effect on the disease.

Q3. (a) The **antigen-binding sites at the tips of the two arms** — that is, the **variable region** of the antibody. (b) Each antibody binds the marker antigen, so the cancer cell becomes **coated in antibody**. The coat acts as a **label** marking the cell out as one to be destroyed: **phagocytes and other immune cells recognise the antibody coat**, bind to it and **destroy the flagged cell**. (c) In this strategy the antibody does not have to kill anything itself — its job is only to make the cancer cell **visible to the immune system**. The **destruction is carried out by the patient's own immune cells**, so no drug needs to be attached.

Q4. (a) A **cytotoxic (cell-killing) drug**, or a **radioactive isotope**, is attached to the antibody. (b) The antibody acts as a **delivery vehicle**: its binding sites fit **only the target antigen**, so it attaches to cells displaying that antigen and the drug is **carried to and released at those cells**. Healthy cells that do not display the antigen are not bound, so most of them do not receive the drug. (c) Because the drug is carried to the target cells instead of circulating freely, **far fewer healthy cells are exposed to it**, so the treatment causes **fewer and milder side effects** than the same drug given on its own.

Q5. (a) The antibody binds the **receptor** and **caps** it, so the **signalling molecule can no longer bind** even though it is still present. The cell therefore **does not receive the signal**, the misdirected inflammatory response is **dampened**, and inflammation and tissue damage are reduced. (b) The patient has a **greater risk of infection**, because part of the immune response has deliberately been turned down. (c) The antibody's binding sites are **complementary in shape to that one receptor only**. Other receptors have different shapes, so the antibody **cannot bind them** and they continue to work normally — this specificity is why the treatment acts only where it is meant to.

Q6. (a) They must be made by **growing living cells in culture** and then harvesting and **purifying the protein**, which is slow and costly (any one clear reason). (b) A monoclonal antibody is a **protein**. If swallowed it would be **digested (broken down into amino acids) in the gut**, so it could not reach the blood intact and would have no effect; it must therefore be **injected or infused**. (c) The patient's own body is **not producing these antibodies** — they have been given ready-made — and the injected molecules are **gradually broken down and removed**. As their concentration falls the effect wears off, so doses must be repeated.

Q7. The two treatments destroy cancer cells in **different ways**. The monoclonal antibody works **through the immune system**: it binds the marker antigen and **coats the cancer cell**, and the patient's **own phagocytes and other immune cells** then recognise the coat and destroy the cell — the antibody kills nothing itself. The untargeted cytotoxic drug works **directly and chemically**: it **poisons any rapidly dividing cell** it reaches, with no involvement of the immune system, which is why it also damages healthy dividing tissues. Of these **two** treatments, only the monoclonal antibody works through the immune system — it is itself an immune molecule and it recruits the patient's immune cells to do the killing — which is why it is called immunotherapy and the cytotoxic drug is not. *(1 mark: mAb flags/coats the cell; 1 mark: the patient's immune cells do the destroying; 1 mark: the cytotoxic drug kills dividing cells directly, without the immune system.)*

Q8. In a **monoclonal** preparation every molecule comes from **one clone** and is therefore **identical**, binding the **same single antigen** — so the whole dose acts on the one chosen target. A sample of antibodies taken from an immunised

animal's blood is a **mixture produced by many different B cells**, binding **many different antigens**; only a small fraction would bind the target, and the rest would bind other molecules. The monoclonal preparation is therefore far more **specific and predictable** as a treatment. *(1 mark: monoclonal = identical molecules, one target; 1 mark: a blood mixture contains many different antibodies binding many antigens.)*

Q9. Step 1: Expose a laboratory animal to the **chosen target antigen**, so that its B lymphocytes respond and produce antibodies against it, then **collect the antibody-producing B cells** from the animal. **Step 2: Fuse those B cells with cells that divide indefinitely**, giving **hybrid cells** that both make their B cell's antibody and keep dividing. The whole collected population is fused, because the cell making the wanted antibody cannot be identified beforehand. **Step 3: Screen the hybrid cells** against the target antigen and **select the one that makes the wanted antibody**, discarding the rest. **Step 4:** Let that selected hybrid cell **divide repeatedly by mitosis in culture**, forming a **clone** of genetically identical cells. **Step 5: Collect and purify** the antibody secreted by the clone — a large quantity of identical molecules, all specific to the chosen antigen. *(1 mark: animal exposed to the chosen antigen and its B cells collected; 1 mark: the B cells are fused with cells that divide indefinitely to give hybrid cells; 1 mark: the hybrid cells are screened and the one making the wanted antibody is selected; 1 mark: that hybrid cell is grown into a clone and the identical antibodies are harvested.)*

Q10. Consequence 1 — the cancer is treated. The antibody binds **HB-9 on the cancer cells**, which display it in large amounts, so those cells are **flagged and destroyed** and the cancer is reduced. **Consequence 2 — healthy B lymphocytes are also lost.** HB-9 is **not unique to the cancer cells**: the patient's healthy B lymphocytes also display it, so the antibody binds them as well and they are destroyed too. With fewer B lymphocytes the patient produces **fewer antibodies of their own** and so becomes **more prone to infection**. This illustrates that a target antigen is rarely found only on the diseased cells. *(1 mark: cancer cells bound and destroyed; 1 mark: healthy B cells also display HB-9 and are also destroyed; 1 mark: consequence of losing them — reduced antibody production / greater infection risk.)*

Q11. A monoclonal antibody made against the **growth factor itself** binds the growth-factor molecules **circulating in the blood**. A growth factor held by an antibody **can no longer bind GF-R2** on the tumour cells, so the "divide" signal is **never delivered**; the **rate of cell division falls** and the tumour grows more slowly — the same outcome as capping the receptor, achieved by removing the signal instead of blocking its receiver.

It would have **no effect** on a tumour whose cells divide **without needing that growth factor**, because those cells are not relying on the signal in the first place. Mopping up a signal the cells do not use takes nothing away from them, so their rate of division is unchanged. *(1 mark: antibody binds the growth factor so it cannot reach the receptor; 1 mark: signal not received, division rate falls; 1 mark: no effect if the cells do not depend on that growth factor.)*

Q12. The two uses aim in **opposite directions**. In **cancer**, the immune system is failing to deal with the patient's own abnormal cells, so the aim is to **direct and increase an attack on them** — for example a monoclonal antibody that binds a marker antigen and **flags the cancer cell so immune cells destroy it**. In an **autoimmune disease** the immune system is **attacking the body's own tissues**, so the aim is to **dampen the misdirected response** — for example a monoclonal antibody that **binds and neutralises an overactive signalling molecule** so that the inflammatory signal is not received. In both cases the same class of molecule is used, but in one the immune response is turned **up** or aimed, and in the other it is turned **down**. (Not every mAb used in cancer works through the immune system — one that blocks a growth signal or delivers a drug leaves the immune response unchanged — but the contrast this question asks for is between directing an attack and dampening one.) *(1 mark: cancer — direct/increase the attack; 1 mark: autoimmune — dampen the misdirected response; 1 mark: one correct example of each strategy.)*

Q13. Every molecule of the antibody binds **CM-4**, so it **coats the self-reactive lymphocytes** that display it. The antibody coat acts as a **label**, and the patient's **phagocytes and other immune cells recognise it and destroy those lymphocytes**. With **fewer self-reactive lymphocytes** left, the misdirected attack on the body's own tissues is reduced, so there is **less inflammation and tissue damage**.

It may give **longer-lasting relief** because it removes the **cells that cause the damage**, rather than mopping up **one signalling molecule those cells release**. An antibody that neutralises a signalling molecule only works while enough of it is present in the blood, and the self-reactive cells keep releasing more; destroying those cells reduces the attack **at its source**, so the benefit persists until the population of self-reactive lymphocytes is replaced. *(1 mark: the antibody coats the self-reactive lymphocytes and immune cells destroy them; 1 mark: fewer self-reactive cells means less attack*

on the patient's own tissues; 1 mark: it removes the source of the attack rather than one of its signals, so the effect outlasts the antibody in the blood.)

Q14. (a) Patients whose tumour cells **displayed** the target antigen responded far better than those whose cells did not: **64%** of the 156 target-positive patients had a tumour shrink by 30% or more after six months, compared with only **7%** of the 84 target-negative patients — a difference of 57 percentage points. (b) The monoclonal antibody can only act on a cell whose surface carries a molecule **complementary to its binding sites**. In the target-positive patients the antibody **binds the tumour cells** and acts on them; in the target-negative patients there is **nothing for it to bind**, so it passes by and the tumour is unaffected (the few responses seen are likely to reflect other treatment or natural variation). (c) Patients should be **tested for the target antigen before treatment**, and the therapy given only to those whose tumour cells display it — treating the others would expose them to the cost and side effects of a therapy that cannot work. *(1 mark: describes both figures with direction; 2 marks: explanation in terms of the antibody binding only its complementary target; 1 mark: patients should be screened for the antigen first.)*

Q15. (a) The **monoclonal antibody group's** mean inflammation score **fell steadily**, from **7.8 at week 0 to 2.6 at week 24** (a fall of 5.2), with the steepest fall in the first 12 weeks. The **placebo group's** score **stayed almost unchanged**, falling only slightly from **7.7 to 6.9** over the same period. (b) The **independent variable** is **whether the patient was given the monoclonal antibody or the placebo injection**; the **dependent variable** is the **mean joint inflammation score**. (c) The placebo group is a **control**. Its patients receive an injection but no antibody, so any change caused by the act of being injected, by the passage of time, or by the natural course of the disease shows up in that group. Comparing the two groups shows how much of the improvement is due to the **antibody itself**. (d) Over 24 weeks, the monoclonal antibody **substantially reduced joint inflammation** in patients with this autoimmune disease, whereas the placebo did not. *(1 mark: mAb trend with figures; 1 mark: placebo trend with figures; 1 mark: IV and DV both correct; 1 mark: purpose of the placebo control; 1 mark: valid conclusion.)*

Q16. An antibody produced using **mouse cells is not a human protein**, so to the patient it is **non-self**. The patient's own **adaptive immune response** therefore treats the injected antibody as an antigen: the patient makes **antibodies against the treatment**, which bind and **remove it from the blood** more and more quickly with each repeated dose, so less of it is available to act and the treatment becomes less effective.

The problem is reduced by **altering the antibody so that it is more human-like**, keeping only the small binding region needed to recognise the target. Being far closer to a human protein, it is **less likely to be recognised as non-self**, so it is not removed as quickly. *(1 mark: mouse antibody is non-self; 1 mark: the patient mounts a response against it and clears it, reducing the effect; 1 mark: mAbs are made more human-like to avoid this.)*

Q17. The antibody can only act on cells that **display the target antigen**. A tumour contains huge numbers of cells that are **not all identical**, and over eighteen months of treatment any cell that **stops displaying (or never displayed) the target antigen** is **not bound by the antibody** and therefore survives, while the cells that do display it are destroyed. Those surviving cells continue to divide, so the tumour that regrows is made up largely of cells the antibody cannot bind — which is why the same dose no longer works. *(1 mark: some cells no longer display the target antigen so are not bound; 1 mark: those cells survive and divide, so the regrown tumour is not affected by the antibody.)*

Q18. Antigen P — strength: it is displayed by **no healthy cells**, so an antibody against it would bind only tumour cells and healthy tissue would be spared; **limitation:** about **10% of the tumour's cells do not display it**, so those cells would not be bound and could survive and regrow. **Antigen R — strength:** it is displayed by **all** the tumour's cells, so none would be missed; **limitation:** it is also displayed by **healthy heart muscle cells**, which the antibody would bind and damage, causing serious side effects.

Judgement: the company should choose **antigen P**. Missing about a tenth of the tumour's cells is a real drawback, but it is far outweighed by avoiding an attack on the patient's heart muscle — and the whole advantage of a monoclonal antibody is its specificity for the diseased cells. *(1 mark: strength and limitation of P; 1 mark: strength and limitation of R; 1 mark: a clear judgement with reasoning.)*

Q19. (a) The **monoclonal antibody carrying drug D outperformed drug D alone on every measure**. Mean tumour reduction was almost double (**58%** compared with **31%**), the proportion still in remission at two years was more than double (**42%** compared with **18%**), and far fewer patients had to stop treatment because of side effects (**10%** compared with **33%**).

(b) Given **alone**, the antibody can only act **by binding TX-4** — flagging the cells so the immune system destroys them, and/or blocking a signal they depend on — so it depends on the patient's immune response and kills relatively few cells directly, giving only a **27%** mean reduction. When the **same antibody carries drug D**, it still binds TX-4 but now also **delivers a cell-killing drug into those cells**, adding direct destruction to the antibody's own effect. That combination doubled the mean reduction, to **58%**.

(c) The antibody has **binding sites complementary to TX-4 only**. In those patients the tumour cells **display no TX-4**, so there is **nothing for the antibody to bind** and neither the antibody nor the drug it carries would be delivered to the tumour.

(d) **Strengths:** it was better on all three measured outcomes — roughly double the tumour reduction and the two-year remission rate, and a much lower withdrawal rate from side effects (10% against 33%), consistent with the drug being delivered mainly to TX-4-positive cells rather than to every dividing cell. **Limitations:** it can only be given to patients whose tumour cells display TX-4, so drug D would still be needed for the roughly 30% who screen negative; 10% of patients still stopped because of side effects, since TX-4 is unlikely to be found only on tumour cells; and the trial was small (60 patients per group) and followed patients for only two years, with the cost of producing the antibody not considered. **Judgement:** it should replace drug D as the standard treatment **for patients whose tumour cells display TX-4**, but it cannot replace it for all patients with this cancer. ∴ the therapy should be adopted alongside screening for TX-4, not as a universal replacement. *(a: 2 marks — at least two measures compared with figures; b: 2 marks — antibody alone binds/flags only, versus antibody plus delivered drug, linked to the data; c: 1 mark — no TX-4 for the antibody to bind; d: 3 marks — one data-supported strength, one limitation, and a clear judgement.)*

Topic 3 Test A — Responding to pathogens

Reading time: 5 minutes. Writing time: 25 minutes. 20 questions, 20 marks. No calculator, no notes. This test covers Chapters 6, 7 and 8 (Unit 4 Area of Study 1). Choose the response that is correct or that best answers the question. A correct answer scores 1 mark; an incorrect answer scores 0. Marks are not deducted for incorrect answers. Diagrams are not drawn to scale.

Question 1

A wasting disease of farmed abalone is traced to an agent 90 nm across that consists of a single molecule of DNA enclosed in a protein coat. The agent cannot be grown on any nutrient medium, but it multiplies rapidly when added to a culture of living abalone gill cells. The agent is best classified as

A. a cellular pathogen, because it contains DNA and so must carry out its own metabolism.

B. a cellular pathogen, because it multiplies rapidly once it is added to the gill cell culture.

C. a non-cellular pathogen, and a prion, because it cannot be grown on any nutrient medium.

D. a non-cellular pathogen, and a virus, because it can multiply only inside a living host cell.

Question 2

A patient whose immune system has been weakened by cancer treatment develops a lung infection. Samples of the infected tissue contain an organism growing as branching threads, with cell walls containing chitin. It releases enzymes that digest the lung tissue and then absorbs the released nutrients. This organism is

A. a fungus, and a cellular pathogen, because it is made of eukaryotic cells with a metabolism of their own.

B. a protozoan, and a cellular pathogen, because it is a single eukaryotic cell.

C. a bacterium, and a cellular pathogen, because it has a cell wall.

D. a non-cellular pathogen, because it must obtain its nutrients from the host.

Question 3

Surgical instruments used on a patient later found to have a prion disease can still transmit the disease after being cleaned and heat-sterilised in the usual way. Which of the following best accounts for this, and for the way the prion increases in number in a new host?

A. The prion’s DNA survives heating because it is protected by the protein coat, and it is then copied by the new host’s own enzymes.

B. The prion is a misfolded protein with no membrane or nucleic acid to destroy, and it makes the host’s own proteins misfold.

C. The prion forms heat-resistant spores, which survive sterilisation and then germinate and divide inside the new host.

D. The prion is a very small heat-resistant virus, and it replicates by using the ribosomes and enzymes of the host’s nerve cells.

Question 4

A man receives a segment of liver donated by his identical twin. The graft is not rejected, even though he is given no medicine to suppress his immune system. The best explanation is that

A. liver cells do not display surface antigens.

B. the donated liver secretes antibodies that protect it from the recipient's immune system.

C. the twins carry the same self-antigens, so the graft displays no non-self antigen to the recipient's immune system.

D. the operation leaves the recipient permanently tolerant of any transplanted tissue.

Question 5

In one condition, a person's plasma cells secrete antibodies that bind a protein on the surface of that person's own thyroid cells, and the thyroid is progressively damaged. This condition is best described as

A. a failure of self-tolerance, in which a self-antigen is treated as though it were non-self.

B. a normal immune response to a non-self antigen that has entered the thyroid.

C. an allergic reaction, in which the immune system over-reacts to a normally harmless antigen.

D. a loss of the MHC self-markers from the surface of the thyroid cells, so they can no longer be recognised.

Question 6

A fungus gets past the outer surface of a leaf and begins to grow through the living tissue inside. In an animal, a pathogen that reached the tissues would meet the second and third lines of defence. Inside the leaf, the fungus meets

A. phagocytes that engulf it and carry its antigen to the nearest lymph node.

B. antibodies secreted by the leaf cells, but no memory cells, so no faster response next time.

C. a targeted response like an animal's, but a slower one, because the plant must first make defensive cells at the site.

D. chemical defences made by the leaf tissue, but nothing that targets this fungus in particular.

Question 7

For several months a patient takes a medicine that greatly reduces the amount of acid the stomach produces. During this time they suffer repeated bouts of gastroenteritis after eating food containing bacteria. The kind of barrier that has been weakened is

A. a physical barrier.

B. a microbiota barrier.

C. a chemical barrier.

D. a component of the third line of defence.

Question 8

A few hours after an ear is pierced, the tissue around the piercing is red, warm, **swollen** and sore. The **swelling** is caused most directly by

A. plasma leaking into the tissue from capillaries that histamine has made more permeable.

B. the increased flow of warm blood produced by vasodilation.

C. neutrophils engulfing bacteria and digesting them inside vesicles.

D. antibodies binding the bacteria and clumping them together.

Question 9

Plasma taken from a person who lacks one group of complement proteins is mixed in a tube with bacteria and with normal phagocytes. The phagocytes engulf far fewer bacteria than they do in normal plasma. The missing complement proteins were most likely acting by

A. making holes in the bacterial membranes so that the bacteria burst.

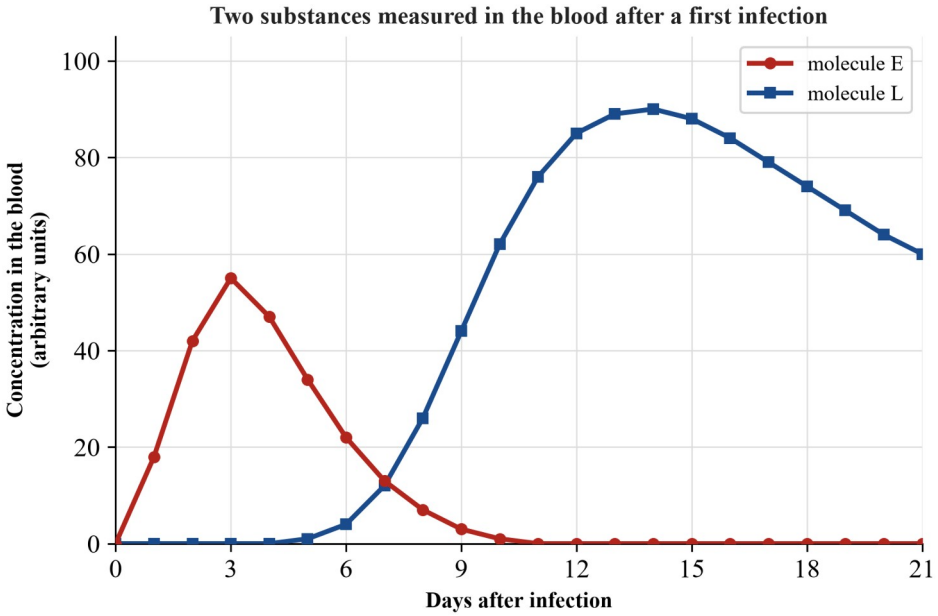
B. coating the bacteria so that phagocytes recognise and engulf them more easily.

C. producing antibodies against the bacteria.

D. releasing histamine, which makes nearby blood vessels dilate.

Use the following information to answer Questions 10 and 11.

A person is infected for the first time with a virus that infects cells of the airway lining. The concentration of two substances, **molecule E** and **molecule L**, was measured in the person's blood on each of the next 21 days.



Question 10

Molecule E is most likely to be

A. an antibody secreted by plasma cells.

B. interferon released by the virus-infected cells.

C. a complement protein, which the body begins to make only once a virus has been cleared.

D. histamine, which mast cells release within minutes of tissue damage and which is broken down within minutes.

Question 11

Two years later the same person is infected with the same virus. Compared with the graph, the level of molecule L would

A. follow exactly the same time course as before, because this kind of response has no memory of the first infection.

B. not rise at all, because the virus was cleared the first time.

C. begin to rise sooner and reach a higher peak, because memory cells for this virus already exist.

D. rise only if the person had been vaccinated in the meantime.

Question 12

A dendritic cell takes up viral antigen in the skin and later presents that antigen to lymphocytes in a lymph node. The dendritic cell reaches the node by

A. being pumped by the heart around the lymphatic circuit.

B. diffusing through the tissue fluid straight across to the node.

C. entering a blood capillary and leaving it again inside the node.

D. travelling in the one-way flow of lymph along the lymphatic vessels.

Question 13

A bacterium growing in food produces a toxin. A person eats the food, and the toxin — but not the bacterium — is absorbed into their blood. The part of the adaptive immune response that acts directly on the toxin in the blood is

A. cytotoxic T cells, which destroy the cells the toxin has damaged.

B. natural killer cells, which destroy any abnormal cell they detect.

C. interferons, which stop the toxin entering cells.

D. antibodies secreted by plasma cells, which bind the toxin and block its action.

Question 14

A laboratory worker is splashed in the eye with a culture of a dangerous virus. Within hours they are injected with purified antibodies collected from the blood of people who have recovered from that virus. This gives the worker

A. artificial passive immunity — immediate protection, but no memory cells.

B. artificial active immunity — slow to develop, but long-lasting.

C. natural passive immunity — immediate protection, and long-lasting.

D. natural active immunity, because the antibodies were made by other people's own immune systems.

Question 15

A virus circulates in a population of wild pigs without making them ill. Over two years, several people who work closely with the pigs become severely ill with this virus, but nobody who has had no contact with the pigs becomes ill. For this virus to cause an epidemic in the human population, the change most needed is

A. a change that allows the virus to pass from person to person.

B. an increase in the number of pigs carrying the virus.

C. a change that makes the illness the virus causes more severe.

D. the loss of the virus's outer envelope, so that it survives longer outside a host.

Question 16

A virus can be passed on from about two days before its first symptoms appear. When one resident of a share house tests positive for it, health authorities direct the other residents — all of whom feel perfectly well — to remain at home for ten days. This measure is

A. isolation, because everyone directed to stay at home has been shown to be carrying the virus.

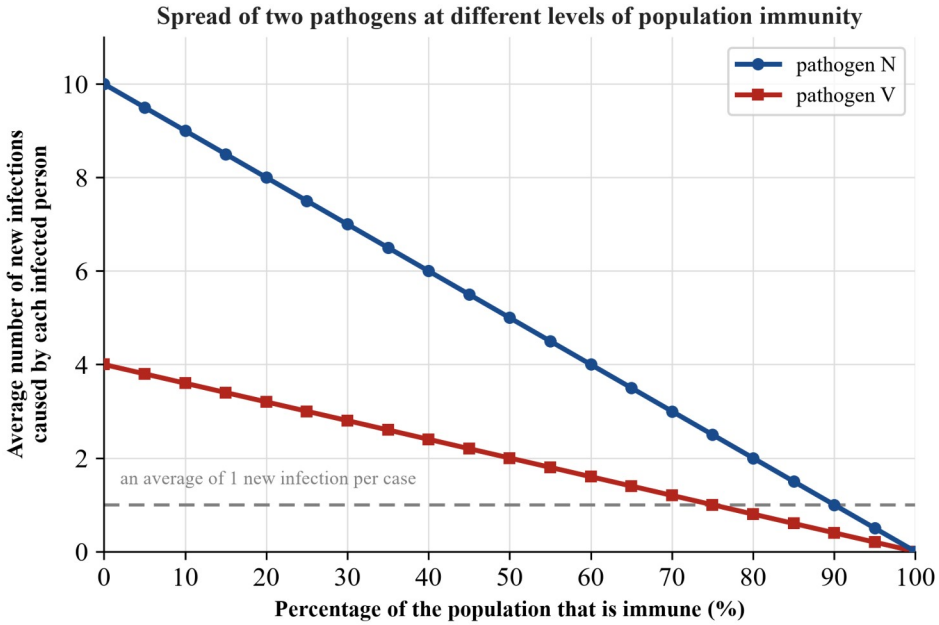
B. quarantine, because a well contact may already be passing the virus on.

C. isolation, because keeping the whole household at home removes the reservoir in which this virus is normally maintained.

D. quarantine, because ten days at home allows a person's own defences to build up against the virus.

Use the following information to answer Questions 17 and 18.

The graph shows, for two pathogens **N** and **V**, the average number of new infections caused by each infected person at different levels of immunity in a population. An outbreak dies out when this average falls below one.



Question 17

The smallest percentage of the population that must be immune before an outbreak of pathogen N dies out is closest to

A. 60%

B. 75%

C. 90%

D. 100%

Question 18

A patient receiving chemotherapy cannot be vaccinated against pathogen V and has no immunity to it. They live in a community in which 80% of people are immune to pathogen V. This patient is unlikely to catch pathogen V because

A. herd immunity has made this patient immune to pathogen V, even though they were never vaccinated.

B. pathogen V can no longer infect anybody in that community, so there is nothing left to catch.

C. chains of transmission die out before reaching them, since each case infects fewer than one person.

D. their innate defences have been strengthened by years of living among people who are immune to V.

Question 19

A monoclonal antibody used to treat an autoimmune joint disease binds a cytokine that the patient's own immune cells are releasing in excessive amounts. Patients given this antibody are told to report any fever or sore throat promptly. The reason for this advice is that the antibody

A. destroys the plasma cells, so the patient can make no antibodies of their own.

B. turns down part of the patient's immune response, so infections are harder to fight off.

C. is made using the cells of another species, so every dose produces a fever of its own.

D. also binds the receptor for the cytokine, which stops the joint-lining cells working normally.

Question 20

A bacterial disease of humans is maintained in a wild animal population, from which people are infected from time to time. Even if every person in the country were treated and vaccinated, the disease could not be eradicated. This is because

A. vaccines produce memory cells only against viruses, not against bacterial pathogens.

B. the bacterium would soon become resistant to the vaccine, as it does to an antibiotic.

C. herd immunity cannot be achieved against a bacterial pathogen, only against a viral one.

D. the wild animals are a reservoir that keeps re-supplying the pathogen to people.

End of Topic 3 Test A

Test A — solutions

Q	Ans	Q	Ans	Q	Ans	Q	Ans
1	D	6	D	11	C	16	B
2	A	7	C	12	D	17	C
3	B	8	A	13	D	18	C
4	C	9	B	14	A	19	B
5	A	10	B	15	A	20	D

Q1. D — genetic material inside a protein coat that can multiply only inside a living host cell is a virus, which is not a cell and so is non-cellular. A and B are wrong because having DNA and multiplying do not make something a cell; C is wrong because a prion carries no nucleic acid of any kind.

Q2. A — branching threads (hyphae) and a chitin cell wall identify a fungus, which is built from eukaryotic cells with their own metabolism, so it is cellular. B is wrong because a fungal mould is not a single cell, C because bacteria are prokaryotic and do not form hyphae, and D because being dependent on host nutrients does not make an organism non-cellular.

Q3. B — a prion is only a misfolded protein, so there is no membrane, cell wall or nucleic acid for ordinary sterilisation to destroy; its numbers grow because it acts as a template that forces the host's own normal proteins into the same misfolded shape. A and D wrongly give the prion genetic material, and C wrongly makes it a bacterium.

Q4. C — self-antigens are unique to an individual, but identical twins carry the same ones, so the graft displays nothing the recipient's immune system reads as non-self and no response is mounted. A is false (all nucleated cells display self-antigens), and B and D describe mechanisms that do not exist.

Q5. A — antibodies made against a molecule on the person's own cells means a self-antigen is being treated as non-self: self-tolerance has broken down (an autoimmune condition). C is wrong because an allergen is a non-self antigen from outside the body, and D is wrong because the thyroid cells still display their MHC markers.

Q6. D — a plant's defences are entirely non-specific. It has no adaptive immune response, so it makes no antibodies and no memory cells, and it has no defensive cells that can travel to the site of an infection; what the fungus meets in the leaf tissue is the plant's chemical defences, which act on pathogens as a class rather than on this one. A and B credit the plant with animal machinery it does not have — phagocytes and a lymph node in A, antibodies in B — and C is wrong because nothing a plant does is aimed at one pathogen in particular.

Q7. C — stomach acid is a chemical barrier: at about pH 2 it destroys most of the pathogens that are swallowed with food. Reducing the acid removes that chemical barrier; no structure and no resident microbe population has been removed, and the first line of defence is not part of the third line.

Q8. A — swelling is caused by fluid: histamine makes the capillaries more permeable, so plasma leaks out and collects in the tissue. B is the cause of the redness and heat, not the swelling, and C and D are not causes of swelling at all.

Q9. B — opsonisation is the complement role that makes phagocytosis easier, so losing it lowers the number of bacteria engulfed. If lysis (A) were missing there would be more intact bacteria, not fewer engulfed; complement does not make antibodies (C) and does not release histamine, and in a tube there are no blood vessels to dilate (D).

Q10. B — interferons are released by virus-infected cells within a day, act early and briefly, and are gone once the infection is controlled, which matches the curve for E. An antibody (A) would not appear until about a week; complement (C) circulates inactive from the start; histamine (D) acts locally over minutes, not over days.

Q11. C — molecule L is the antibody curve, so meeting this antigen a second time calls on the memory B cells left behind by the first infection, giving a secondary response with a shorter lag and a higher peak. A describes an innate response, B ignores memory, and D is wrong because natural infection also produces memory.

Q12. D — antigen-presenting cells that have taken up antigen in the tissues travel in the lymph along the lymphatic vessels to the draining node. A is wrong because lymph has no pump and is not a circuit, B because a cell cannot diffuse, and C because the dendritic cell uses the lymphatic, not the blood, route.

Q13. D — a toxin free in the blood is an extracellular threat, dealt with by the humoral arm: antibodies from plasma cells bind the toxin and neutralise it. A and B kill body cells rather than act on the toxin, and interferons (C) are innate proteins that act against viruses.

Q14. A — ready-made antibodies made by someone else give passive immunity, and delivering them by injection makes it artificial; protection is immediate but no memory cells form. D is the trap: what matters is who makes the antibodies protecting *this* person, not how the donors acquired them.

Q15. A — every case so far is a dead-end spillover from the pigs, so the missing step is sustained human-to-human transmission. More infected pigs (B) would give more dead-end cases but no epidemic; severity (C) and the envelope (D) do not determine whether a chain of transmission can be sustained.

Q16. B — restricting the movement of well people who have been *exposed*, but are not known to be infected, is quarantine. It is worth doing here because someone who still feels perfectly well may already be passing this virus on. Isolation (A, C) applies only to people confirmed to be carrying the pathogen, and D credits ten days at home with an effect on the immune system that it does not have.

Q17. C — read where the line for pathogen N falls to an average of one new infection per case: it reaches 1 at 90% immune, so immunity above about 90% is needed. 75% (B) is the corresponding value for pathogen V, and at 60% (A) pathogen N still causes an average of 4 new infections per case.

Q18. C — at 80% immune, pathogen V sits below the reference line, so on average a case gives rise to less than one further case and the chains of transmission peter out. A is the classic misconception — herd immunity protects this patient without making them immune; B overstates it (they can still be infected if an infectious person does reach them), and D is false.

Q19. B — the antibody is given in order to damp down one over-active part of the immune response, and that same damping leaves the patient less able to deal with an infection, so a fever or sore throat is treated as an early warning sign. A and D describe actions this antibody does not have — it binds the cytokine, not the plasma cells and not the receptor — and C confuses the loss of effectiveness that follows when an antibody is recognised as non-self with the reason for the warning.

Q20. D — a reservoir is the species that carries the pathogen along between human outbreaks, so while it persists in the wild animals it will keep re-infecting people however many people are treated or vaccinated. A and C are false, and B confuses vaccines with antimicrobials.

Topic 3 Test B — Responding to pathogens

Writing time: 50 minutes. Total 40 marks. No calculator, no notes. This test covers Chapters 6, 7 and 8 (Unit 4 Area of Study 1). Answer all questions in the spaces provided. Where more than one mark is available, full marks require the depth that the command term and the mark allocation ask for. Diagrams are not drawn to scale.

Question 1 (6 marks)

Each morning, a baker begins to sneeze and cough within minutes of weighing out flour. Testing shows that the baker mounts a strong immune response to a protein present in wheat flour. A colleague who handles the same flour every day has no reaction to it at all. Some months later the baker develops a chest infection caused by a bacterium breathed in at work.

a. The wheat protein is not a pathogen, and the colleague who weighs out the same flour every day is unharmed by it. Explain why breathing in the flour nevertheless makes the baker ill. 2 marks

b. Name the type of cell that must act on the inhaled bacterium before any of the baker's lymphocytes can respond to it, and explain what that cell does and why the specific response cannot begin without it. 3 marks

c. Explain why the baker's own airway cells are not attacked during that response, even though the bacterium is in direct contact with them. 1 mark

Question 2 (7 marks)

A plant pathologist investigated the part played by the waxy cuticle in defending tomato plants against a fungus that causes leaf spot. Two hundred tomato seedlings of the same variety, age and size were grown side by side in one glasshouse. Every leaf of 100 of the seedlings (Group 1) was wiped gently with a fine powder that removed the waxy cuticle without damaging the cells beneath; the leaves of the other 100 seedlings (Group 2) were not wiped. All 200 seedlings were then sprayed with the same suspension of fungal spores.

Table 1 Percentage of leaves showing leaf-spot lesions

Days after spraying	Group 1 (cuticle removed)	Group 2 (cuticle intact)
3	14	0
6	43	2
9	71	5
14	86	6

a. Identify the independent and the dependent variable in this investigation. 2 marks

b. Describe the difference between the two groups over the 14 days, quoting figures from Table 1. 2 marks

c. Explain, in terms of the plant's first-line barriers, why removing the cuticle had this effect. 2 marks

d. After 14 days, 14% of the leaves in Group 1 still had no lesion. Suggest one reason, referring to another first-line defence of a plant. 1 mark

Question 3 (6 marks)

A virus infects cells of a person's liver. Some virus particles also travel free in the blood plasma.

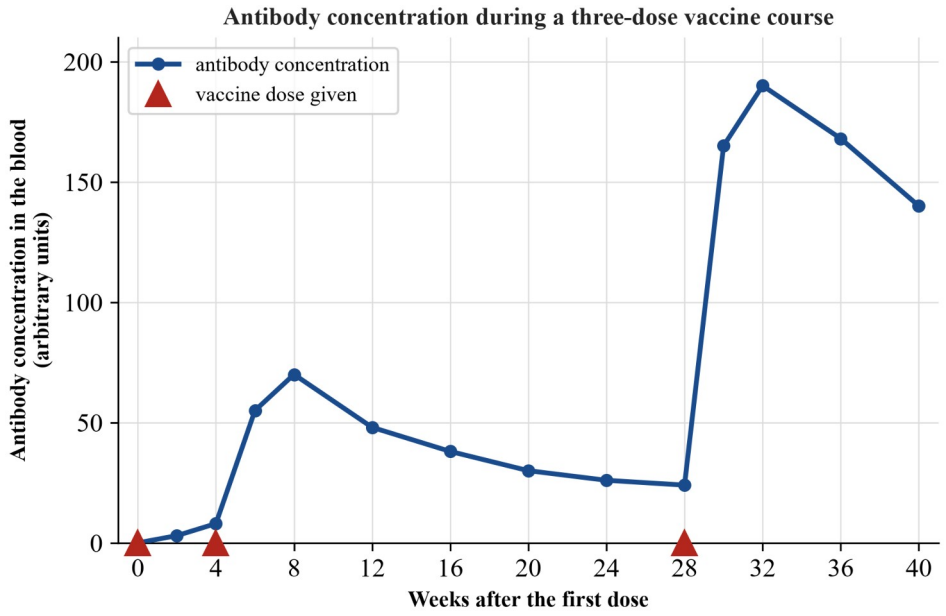
a. Explain how a liver cell that has already been infected makes it harder for the virus to establish itself in the liver cells around it. 2 marks

b. An antibody cannot follow the virus into a liver cell. Name the cell of the third line of defence that deals with the infected liver cells, and describe how it recognises and destroys them. 3 marks

c. State one feature of the response you described in part **a.** that places it in the second line of defence rather than the third. 1 mark

Question 4 (6 marks)

A new vaccine against a bacterial disease is given as a course of three doses. The graph shows the concentration of antibody against that bacterium in the blood of one person who had never met the bacterium before. Each triangle marks a dose; the doses were given at weeks 0, 4 and 28.



a. Using the graph, describe **two** ways in which the antibody response after the second dose differed from the response after the first dose. Quote figures in your answer. 2 marks

b. Explain why the second dose produced this different response, referring to the cells of the adaptive immune response. 2 marks

c. By week 40 the person's antibody concentration is falling. Explain why the person would still be protected if they met this bacterium several years later. 2 marks

Question 5 (6 marks)

Over four months, 23 patients in the surgical ward of a regional hospital develop wound infections caused by one strain of a bacterium. The strain is not killed by any of the three antibiotics the hospital normally uses; ten years ago, infections with this bacterium were reliably cured by the first of those antibiotics. Swabs taken during the investigation find the same strain on shared blood-pressure cuffs, on trolley handles and on the hands of several staff members, but not in the ward's water supply or food.

a. A junior doctor suggests that the antibiotics themselves changed these bacteria and made them resistant. Explain what is wrong with that account, and give the correct explanation of how a resistant strain came to dominate this ward. 3 marks

b. State the evidence in this scenario that makes this bacterium a re-emerging rather than an emerging pathogen. 1 mark

c. The ward introduces strict hand hygiene before and after every patient contact, but new cases continue. Using the swab results, suggest why, and state what further measure is needed. 2 marks

Question 6 (9 marks)

The cells of a certain lung tumour display very large numbers of a surface marker antigen, VN-4. Healthy cells of the lining of the airways display much smaller numbers of the same antigen. Antigen VN-4 is not a receptor and carries no signal into the cell. A biotechnology team has produced a monoclonal antibody, mAb-VN4, that binds antigen VN-4. Two preparations are being trialled: **preparation 1** is mAb-VN4 on its own, and **preparation 2** is mAb-VN4 with a cell-killing drug chemically attached to it. Many patients with this tumour have a badly weakened immune system as a result of earlier treatment.

a. Explain why mAb-VN4 concentrates its effect on the tumour cells rather than acting on the patient's cells in general. 2 marks

b. Explain how preparation 1 leads to the destruction of a tumour cell, and explain why a third possible approach — using the antibody to block a signal the tumour cell depends on — is not available with VN-4 as the target. 3 marks

c. Predict which of the two preparations would be less affected by these patients' weakened immune systems, and justify your answer. 2 marks

d. Healthy airway cells carry only a few VN-4 antigens each. Explain why these cells are nevertheless likely to be damaged by the treatment, and why the tumour cells are harmed far more than they are. 2 marks

End of Topic 3 Test B

Test B — solutions

Q1. (a) The wheat protein does the body **no direct damage of its own** — the colleague, who weighs out the same flour every day, has **no reaction at all** — so it is not a disease-causing agent. In the baker, though, it provokes a **strong, exaggerated response**: the sneezing and coughing are produced by the **baker's own immune system over-reacting** to this harmless foreign molecule, not by anything the molecule does to the tissue. The protein is therefore acting as an **allergen**, and the baker's illness is essentially **self-inflicted by an inappropriate immune response**. *(1 mark: the protein itself is harmless / does no damage — shown by the unaffected colleague; 1 mark: the symptoms come from the baker's own exaggerated (hypersensitive) reaction to it, i.e. it acts as an allergen.)*

(b) The cell is an **antigen-presenting cell** — a macrophage or dendritic cell in the airway lining. A lymphocyte is **not** switched on by a whole bacterium, nor by antigen loose in the tissue: it reacts only to antigen that has been **processed and put on display for it**. So the antigen-presenting cell must first **take the bacterium in and break it apart**, then hold **pieces of the antigen out on the MHC self-markers of its own surface** and carry them to the lymphocytes; only the lymphocyte whose receptor fits the displayed piece is then activated, and the specific response against the bacterium can begin. *(1 mark: names the antigen-presenting cell — macrophage/dendritic cell; 1 mark: a lymphocyte responds only to processed, displayed antigen, not to the free or intact bacterium; 1 mark: the cell engulfs and breaks down the bacterium and displays/presents its antigen, so the matching lymphocyte is activated and the response begins.)*

(c) The baker's own airway cells carry **self-antigens** — the MHC self-markers unique to the baker. As the immune system developed, any lymphocyte able to bind those markers was deleted or silenced, leaving the baker **self-tolerant**: every lymphocyte that survived that screening carries a receptor for a **foreign** shape only. Proximity is therefore irrelevant — what an activated lymphocyte responds to is the antigen it fits, so the bacterium is attacked while the airway cells pressed up against it, displaying nothing but the baker's own markers, are passed over. *(1 mark.)*

Q2. (a) The **independent variable** is **whether the waxy cuticle was removed from the leaves** (the variable the pathologist deliberately changed — not the two groups themselves, and not the powder). The **dependent variable** is the **percentage of leaves showing leaf-spot lesions**. *(1 mark: IV; 1 mark: DV.)*

(b) Group 1, whose cuticle had been removed, became infected **far more, and far sooner**: 14% of its leaves had lesions by day 3 and this rose steeply to **86% by day 14**. Group 2, with the cuticle intact, stayed **almost free of lesions**: 0% at day 3, rising only to **6% by day 14**. At every measurement Group 1 had the higher percentage, and by day 14 the difference between the groups was **80 percentage points**. *(1 mark: describes each group's trend with figures and direction; 1 mark: makes the comparison explicit, with figures.)*

(c) The **waxy cuticle** is a **physical barrier of the first line of defence** — a continuous, waterproof layer over the leaf epidermis that fungal spores **cannot easily penetrate**, and which keeps the leaf surface **dry**, so spores are less likely to germinate on it. Wiping it away leaves the epidermal cells directly **exposed**, so a spore landing on the leaf can now reach and enter the tissue and establish an infection — hence far more lesions in Group 1. *(1 mark: the cuticle is a non-specific physical barrier that blocks entry / keeps the surface dry; 1 mark: removing it lets the fungus reach and enter the tissue, so more leaves become infected.)*

(d) Any **one** of: every plant cell is still surrounded by a **rigid cellulose cell wall**, a further physical barrier that resists entry into the cells; the plant also produces **antimicrobial chemicals** (oils, resins and other toxic compounds) that kill or inhibit the fungus; the plant can **close its stomata**, blocking that route of entry into the leaf. *(1 mark: names a second first-line barrier of the plant and gives it as the reason that leaf escaped infection.)*

Q3. (a) Once the virus is inside it, the liver cell releases **interferons** — the signalling proteins a cell puts out when it has been infected. These reach the **liver cells around it that the virus has not yet entered** and switch them over to making **antiviral proteins**, which **obstruct viral replication** inside them. Such a cell is not made immune, but it is made a **poor host**: if the virus does reach it, few new virions are completed, so the infection **spreads more slowly** through the liver. *(1 mark: the infected cell releases interferon; 1 mark: the cells around it are switched over to making antiviral proteins that obstruct viral replication, slowing the spread.)*

(b) The **cytotoxic T cell**. An infected liver cell puts **fragments of the viral antigen on display on its surface MHC markers**, advertising that something foreign is inside it. The cytotoxic T cell that happens to carry a

receptor complementary to that fragment is **selected**, is switched fully on by **helper T cell cytokines**, and multiplies by **clonal expansion**. Its descendants then **dock onto each infected liver cell and release chemicals that trigger the cell's death**. Destroying the host cell **strips the virus of the machinery it was copying itself with**, so the virions inside are never finished and never released to reach other liver cells. *(1 mark: names the cytotoxic T cell; 1 mark: uses a matching receptor to recognise fragments of the virus held out on the surface markers of an infected cell; 1 mark: binds and releases chemicals that kill the cell, halting viral replication.)*

(c) Any **one** of: it is **non-specific** — interferons work against viruses as a class, not against this one virus; it has **no memory** — meeting the same virus again brings no faster or stronger version of it; it is **fast**, acting within hours because the cells that carry it out are already in place. *(1 mark.)*

Q4. (a) Any **two** of the following, each supported by figures:

- the response after the **second** dose was **much larger** — antibody peaked at about **70** arbitrary units, compared with only about **8** units after the first dose;
- it was **much faster** — two weeks after the second dose the concentration had already reached about **55** units, whereas two weeks after the first dose it was only about **3** units;
- it **lasted far longer** — 20 weeks after the second dose, at week 24, the level was still about **26** units, more than three times the highest level (8 units) ever reached after the first dose.

(1 mark for each of two correctly described differences, each with supporting figures.)

(b) The first dose produced a **primary response**. Only the **few B lymphocytes whose receptors matched** the vaccine's antigen could respond, and they had to be **selected (clonal selection)** and then **divide repeatedly (clonal expansion)** before any **plasma cells** existed to secrete antibody — which takes days to weeks, so antibody appeared **slowly and in small amounts**. That response left behind long-lived **memory B cells** specific to this antigen. The second dose delivered the **same antigen**, which the **memory cells — now present in large numbers — recognised immediately**, proliferating and differentiating into plasma cells straight away. This **secondary response** therefore produced antibody **sooner and in far greater quantity**. *(1 mark: the primary response is slow and small because the few matching B cells must first be selected and undergo clonal expansion; 1 mark: memory B cells formed then respond immediately to the same antigen, giving a faster, larger secondary response.)*

(c) Protection does **not** depend on the antibody concentration staying high. The course produced **active** immunity, so the **memory B and T cells persist** — often for years — long after the antibody itself has been broken down. If the person meets this bacterium, those memory cells **recognise its antigen at once** and rapidly proliferate into plasma cells, giving a **secondary response** in which antibody rises after a much **shorter delay** and to a much **higher level** than in the first response. ∴ the bacterium is usually cleared before it can cause illness. *(1 mark: memory cells persist even though the antibody level falls; 1 mark: they give a rapid, large secondary response that clears the pathogen before illness develops.)*

Q5. (a) The account is wrong about **where the resistance comes from**. An antibiotic has no power to redesign a bacterium; the variation is already there **before the drug is ever met**. A bacterial population is never uniform — a chance **mutation**, or a resistance gene picked up from a neighbouring bacterium, leaves a few cells with a version of the target the antibiotic cannot act on, and that would have happened whether or not anyone was ever treated. What the antibiotic does is **choose between** the cells already present: each course applies a **selection pressure** that kills the **susceptible** cells and leaves the **resistant** ones alive. Those survivors then **reproduce**, very rapidly by binary fission, and **hand the resistance on** to their offspring, so its frequency climbs with every further course until in practice the whole ward strain is resistant — and with three antibiotics in routine use, that has happened three times over on the same population. *(1 mark: the resistance arises by chance mutation or gene transfer independently of exposure — the antibiotic does not create it; 1 mark: the antibiotic acts as a selection pressure, killing susceptible cells and sparing resistant ones; 1 mark: the survivors reproduce and pass the resistance on, so its frequency rises.)*

(b) It is not new to this population: the **same bacterium was reliably cured by the first of these antibiotics ten years ago**, so it is a **known** pathogen that had been brought under control and is now causing cases once more. *(1 mark.)*

(c) Hand hygiene closes only **one** of the two routes the swabs identified. The same strain was found not just on **staff hands** but on **shared blood-pressure cuffs and trolley handles** — and a cuff wrapped around one patient's arm and then around the next patient's carries the bacterium **straight from wound to wound without any hand having to be contaminated**. The equipment is therefore an **independent link** in the chain, and it survives however well the staff wash. What is needed in addition is to **clean and disinfect shared equipment between every patient**, or to dedicate a cuff and the other shared items to a single patient, so that route is closed too. *(1 mark: the swabs also implicate shared equipment, which passes the strain between patients independently of hands; 1 mark: decontaminate shared equipment between patients, or use single-patient equipment.)*

Q6. (a) Every molecule of mAb-VN4 carries the **same binding sites**, shaped to fit **VN-4 and no other antigen**. The antibody therefore **attaches only to cells displaying VN-4** and passes by cells that do not — and the cells displaying it in very large numbers are the tumour cells. Whatever the antibody carries or triggers is thus delivered **wherever VN-4 is**, rather than spread over the body's cells at large. *(1 mark: every molecule binds VN-4 and nothing else; 1 mark: so it attaches to the VN-4-bearing tumour cells and not to cells lacking VN-4, concentrating the effect on the tumour.)*

(b) **Preparation 1.** mAb-VN4 binds the VN-4 all over the tumour cell's surface, so the cell ends up **coated in a layer of antibody**. That coat is a **label**: the patient's **own defensive cells attach to the bound antibody and kill the cell it is marking**. Nothing about the antibody is itself toxic — its whole contribution is to make **conspicuous** a cell the defences had been ignoring. **Why the third approach is unavailable.** Blocking a signal works only where the target antigen is a **receptor the cell depends on** — capping it then denies the cell the "divide" message it was receiving. VN-4 is **not a receptor and carries no signal into the cell**, so an antibody parked on VN-4 **takes nothing away from the tumour cell**: its rate of division would be exactly what it was before. *(1 mark: the antibody coats the tumour cell; 1 mark: that coat marks the cell out, and the patient's own defensive cells then kill it; 1 mark: VN-4 carries no signal, so capping it deprives the cell of nothing and cannot slow its division.)*

(c) **Preparation 2** would be the less affected. Preparation 1 kills nothing by itself: it only labels the tumour cell, and the **killing is then left to the patient's own immune cells**. In a patient whose immune system is badly weakened there is little left to answer that label, so most of the antibody's effect is lost. Preparation 2 does not depend on the patient's defences at all — the antibody works as a **delivery vehicle**, and the **cell-killing drug attached to it** acts on whichever cell the antibody has docked onto, however weak the immune response is. *(1 mark: predicts preparation 2; 1 mark: justifies it — preparation 1 needs the patient's own defensive cells to finish the job, whereas preparation 2's attached drug kills the bound cell directly.)*

(d) VN-4 is **not confined to the tumour**, and mAb-VN4 cannot tell a few VN-4 molecules on a healthy airway cell from very many on a tumour cell — it binds wherever its antigen is. The healthy airway cells are therefore **bound and labelled too**, and so are attacked or given the drug as well, producing **side effects in the lining of the airways**. The difference between the two is one of **degree**: a tumour cell displays far more VN-4, so it becomes **coated with far more antibody**, and because the damage a cell suffers rises with the **amount of antibody bound to it**, the heavily-coated tumour cells take the brunt of the treatment while the lightly-labelled healthy cells are harmed much less. *(1 mark: healthy airway cells display VN-4, so they are bound and damaged too — side effects in the airway lining; 1 mark: the tumour cells display far more VN-4, so bind far more antibody and are affected far more than the sparsely-labelled healthy cells.)*