

THE IN A HURRY SERIES

Antibiotics *in a Hurry*

The miracle drugs, and the resistance problem

Max Brocklesby

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The Whole Thing in One Page

Antibiotics are remembered as a discovery story. A mould lands on Alexander Fleming's culture plate, bacteria disappear around it, penicillin follows, and lethal infections become curable. The image contains a truth large enough to deserve the word miracle. Before effective treatment, a cut, childbirth, pneumonia or an operation could end in fatal bacterial infection. Antibiotics changed what doctors could attempt and patients could survive.

The image also hides how the drugs work and why their success is unstable. The first requirement is selective toxicity: the drug must damage a bacterium more than the patient because bacterial cells differ from ours. Once administered, it also becomes a selective pressure on a multiplying population. Some drugs block construction of the cell wall. Others jam bacterial ribosomes, interfere with DNA, disrupt membranes or cut off an essential metabolic route. There is no single quality called antibiotic strength. A drug works when its target is present, the organism is susceptible, the medicine reaches the infected site at useful exposure, and the patient's immune system or a procedure can finish what chemistry began.

This makes treatment a race between populations. A dose does not confront one motionless enemy. It changes a multiplying bacterial population with variation. A rare mutation may alter a target, a plasmid may carry a resistance gene, an enzyme may destroy the drug, or a pump may throw it back out. Exposure removes susceptible competitors and leaves survivors room. Resistance is therefore neither a moral failure by bacteria nor the patient's body becoming accustomed to medicine. It is heredity under selection.

Fleming saw the effect in 1928 and reported it in 1929. Penicillin became a medicine because Howard Florey, Ernst Chain, Norman Heatley and a wider Oxford team purified and tested it, while governments and manufacturers learned to make it at scale during the Second World War. Streptomycin then opened a route against tuberculosis. The antibiotic age

was built by laboratories, fermentation vessels, trials, factories, hospitals and public systems, not by a fortunate plate.

Those systems now determine whether the miracle lasts. Poorly targeted prescribing, treatment when bacterial infection is unlikely, weak infection control, unreliable diagnostics or supply, routine use in healthy food animals and poorly controlled antibiotic discharge can increase selection or spread. Lack of access creates another failure: a transmissible infection may remain untreated, while delayed or unreliable therapy leaves clinicians and patients with worse options. Stewardship means choosing the right drug, route, dose and duration, then narrowing, switching or stopping when better information permits. It does not mean withholding necessary treatment.

The problem is serious without one doomsday date. WHO estimates that bacterial antimicrobial resistance was associated with more than 4.7 million deaths in 2021. Its 2025 surveillance report estimated resistance to antibiotic treatment in about one in six laboratory-confirmed bacterial infections worldwide in 2023. The mortality estimate and the surveillance estimate answer different questions, and neither is a census. They still show treatment failing at scale.

The loop is the book. Selective toxicity created the miracle; selection among living populations creates the resistance problem. A course can cure this patient while applying pressure to bacteria, so antibiotic effectiveness is not a stock of pills discovered once. It is a shared capability maintained through evidence, access, prevention, restraint and continued invention.

That is the book.

Why You Should Care

On 12 February 1941, doctors in Oxford gave penicillin to Albert Alexander, a policeman whose severe facial infection had spread through his body. The drug was so scarce that Norman Heatley recovered it from Alexander's urine and purified it for reuse. His temperature fell, his appetite returned and the infection receded. Then the supply ran out. He relapsed and died.

That episode contains the antibiotic age in miniature. A chemical could reverse an infection that ordinary medicine could barely touch, yet discovery was not enough. The drug had to be purified, dosed, manufactured and delivered in quantities large enough to outlast the bacteria. Penicillin became a miracle only when a fragile laboratory substance became an industrial and clinical system.

You depend on that system even when you are not taking an antibiotic. Caesarean sections, joint replacements, bowel surgery, intensive care, chemotherapy, transplantation and the care of premature babies all create moments when bacteria can cross damaged barriers or exploit weakened defences. Clean technique and infection prevention do much of the work, but many procedures remain safer because bacterial infections can be treated when prevention fails. Resistance therefore threatens more than a shelf of familiar medicines. It narrows the margin within which modern medicine operates.

The danger is easy to misunderstand because antibiotics create two different scales of benefit and cost. For the patient with a serious susceptible infection, prompt treatment can be life-saving. Across a ward, farm, town or river system, every exposure can favour resistant organisms or genes. The individual decision may be correct while the accumulated result weakens future treatment. That is why the subject cannot be reduced to blaming careless patients or reckless doctors. Prescribers, laboratories, hospitals, pharmacies, manufacturers, farmers, regulators, water systems and governments all shape the pressure and the routes by which resistance spreads.

Laboratory, supply and stewardship capacity vary within as well as between countries. One hospital may identify an organism, measure susceptibility and support a switch to a narrower drug; another may lack culture, a reliable supply of the first-line medicine or affordable care. Excess use and lack of access therefore coexist. The instruction to use fewer antibiotics is incomplete when some people die for want of the correct one while others receive them for illnesses the drugs cannot treat.

Numbers require care. A 2024 *Lancet* analysis estimated 4.71 million deaths associated with bacterial antimicrobial resistance in 2021 and 1.14 million attributable to it. The associated count uses no infection as the counterfactual; the attributable count replaces resistant infection with drug-susceptible infection. WHO's 2025 surveillance report drew on more than 23 million bacteriologically confirmed cases reported by 104 countries and generated adjusted estimates for common infections. Sampling, testing and coverage differ, so its one-in-six headline is not a census. It is still far too large to file under future risk.

The science is also more interesting than the slogan. Antibiotics expose how cells differ, how concentration changes effect, how populations evolve, how genes move sideways between organisms and how a treatment can alter the ecology around its target. They join chemistry, medicine, evolution, economics and public policy in one pill.

Once you understand that chain, the familiar arguments change shape. Broad spectrum stops meaning stronger. A laboratory result stops looking like a yes-or-no oracle. Course length becomes a question about following the current evidence-based plan rather than obeying a timeless maxim. A new drug stops looking like a permanent reset. The miracle becomes more impressive because you can see the machinery that makes it work, and the resistance problem becomes more tractable because you can see where pressure and spread can be changed.

The Core Ideas

The Miracle Is Selective Toxicity

A useful antibiotic commits a controlled act of discrimination. It reaches living cells in a patient and harms the bacterium more than the patient. That sounds obvious after a century of antibacterial medicine. Before the mechanisms were understood, it was a startling possibility. Many substances kill bacteria in a dish. Fire, bleach and concentrated alcohol do the job. They are poor treatments for a bloodstream because the patient is made of vulnerable cells too.

The opportunity lies in difference. Bacteria build rigid cell walls from peptidoglycan. Human cells do not. Their ribosomes share the task of making proteins with ours, but the machinery differs enough for some drugs to bind bacterial ribosomes preferentially. Bacteria copy DNA, manage folate and maintain membranes through structures and enzymes that can sometimes be attacked without causing equal damage to human tissue. Penicillins exploit the wall. Tetracyclines and macrolides obstruct protein synthesis. Fluoroquinolones interfere with enzymes that manage bacterial DNA. Trimethoprim and sulfonamides block steps in folate metabolism.

Selective does not mean harmless. A therapeutic window separates exposure likely to control infection from exposure likely to injure the patient, and that window varies among drugs and people. Aminoglycosides can damage kidneys and hearing. Some antibiotics disturb electrical conduction in the heart, injure the liver, suppress bone marrow or provoke severe allergic reactions. The patient's age, pregnancy, kidney and liver function, other medicines and genetics can change the balance. A safe drug for one infection may be a bad choice for another patient.

Selection is also ecological. An antibiotic taken for one pathogen reaches other susceptible bacteria in the gut, on the skin or in the mouth. Those communities can be disrupted even when treatment succeeds.

Clostridioides difficile disease is a clear example: antibiotics can remove organisms that normally help resist colonisation, giving a toxin-producing

bacterium room to expand. This collateral effect is one reason a narrow drug that fits the target can be preferable to a broad one.

The word antibiotic is often stretched to mean any medicine used against infection. Strictly, this book is about antibacterial agents. Viruses have no peptidoglycan wall or bacterial ribosome, so penicillin cannot treat influenza or a cold. Fungi and parasites are cellular organisms, but their biology demands different drug targets and often leaves a narrower safety margin because their cells resemble ours more closely.

The contrast with antisepsis clarifies the achievement. An antiseptic can be applied to skin or a wound because local exposure is controlled; a disinfectant belongs on objects and surfaces. A systemic antibiotic must travel through blood and tissue while preserving the organs carrying it. Paul Ehrlich's early twentieth-century hope for a chemical therapy that would strike a pathogen without striking the host became the image of a magic bullet. No antibiotic is that perfect. The phrase survives because selective toxicity came close enough to change medicine.

The first mental model is therefore not strong medicine against strong germs. It is a comparison among vulnerabilities. The target must matter to the bacterium, differ enough from the patient, and be reachable at an exposure the patient can tolerate. Every later success and failure begins there. The same discrimination that kills susceptible bacteria also determines which variants survive. Selective toxicity creates treatment. Selection among bacteria creates the bill.

The Drug Must Reach the Right Place

A culture plate can make an antibiotic look decisive. Place a paper disc soaked in drug on a lawn of bacteria and a clear zone may appear around it. The organism is inhibited where enough drug diffuses through the agar. Inside a person, the geometry is harder. A swallowed tablet must dissolve, cross the gut, enter blood, distribute through tissues and remain present long enough to affect bacteria at the site of infection. The laboratory result matters, but it is only one part of the route from dose to cure.

The minimum inhibitory concentration, or MIC, is the lowest tested concentration that prevents visible growth under specified laboratory conditions. A breakpoint combines that measurement with achievable exposure and clinical evidence to create a treatment category. Under current EUCAST definitions, S means susceptible at a standard dosing regimen, I means susceptible when exposure is increased, and R means a high likelihood of failure even with increased exposure. Dose, interval, infusion time, distribution and concentration at the infection site can all affect exposure. Other standards bodies may use different categories or thresholds. These are versioned decisions built from data, not permanent labels attached to a species.

Exposure has more than one shape. Some antibiotics work best when free drug concentrations remain above the MIC for enough of the dosing interval. For others, the height of the peak or total exposure relative to the MIC is more informative. This is why two medicines with the same laboratory susceptibility result may require different schedules. It is also why missing doses, shortening intervals by guesswork or doubling after a forgotten tablet can distort a regimen rather than repair it.

Place matters. A drug concentrated in urine may be useful for some urinary infections while reaching poor levels elsewhere. Penetration into cerebrospinal fluid, bone, prostate tissue, lung lining fluid or an abscess can differ. Protein binding, inflammation, blood flow and barriers between compartments alter the active concentration. Kidney or liver impairment can make a normal regimen accumulate; unusually rapid clearance can lower exposure. Intravenous delivery guarantees entry into the circulation, not entry into every infected site, and oral treatment can be entirely adequate when absorption is reliable and a suitable drug exists.

Chemistry may also be unable to reach the decisive problem. An abscess contains pus, damaged tissue and a walled-off bacterial population with poor blood supply. An infected catheter, prosthetic joint or heart valve can support a biofilm, a structured community attached to a surface. Growth may slow, local conditions change and drug penetration become uneven.

Draining pus, relieving an obstruction, removing dead tissue or taking out an infected device can therefore matter as much as choosing a molecule. Clinicians call this source control.

A report saying susceptible does not promise cure. The patient's immune response, infection burden, anatomy, timing and source control remain in the case. A report saying resistant does not mean the organism is invincible; it means the tested drug-regimen relationship is unlikely to succeed under the interpretive system used. The useful question is never whether an antibiotic is powerful in general. It is whether this regimen can create adequate active exposure at this site against this organism without imposing unacceptable harm.

A Few Targets Support Many Families

The pharmacy shelf suggests great variety. The underlying map is compact. Most antibacterial drugs interfere with a small set of indispensable bacterial jobs, and the families are best understood by the job they disturb rather than by memorising a catalogue of names.

Cell-wall synthesis is the classic target. Beta-lactams, including penicillins, cephalosporins and carbapenems, bind penicillin-binding proteins involved in cross-linking peptidoglycan. A growing bacterium continues to remodel its wall but cannot complete the structure reliably. Glycopeptides such as vancomycin obstruct wall assembly by binding a different part of the building process. These drugs do not share identical spectra or routes. Their family resemblance is mechanistic, not a guarantee of interchangeability.

Gram-positive and Gram-negative describe envelope patterns, not two levels of danger. Gram-negative bacteria have an outer membrane that can restrict entry and shelter enzymes in the periplasm; Gram-positive bacteria lack that outer membrane but usually expose a thicker peptidoglycan wall. The distinction helps with first-pass reasoning. Species, resistance mechanism, infection site and achievable exposure still decide whether a drug fits.

Protein synthesis supplies another large territory. Bacterial ribosomes

contain 30S and 50S subunits whose structures differ from human cytoplasmic ribosomes. Tetracyclines hinder delivery of amino acids to the ribosome. Aminoglycosides disrupt accurate reading and can promote faulty proteins. Macrolides, lincosamides and oxazolidinones interfere with different steps on the 50S subunit. The labels 30S and 50S do not add arithmetically to 80S because they describe sedimentation behaviour, not size in ordinary units. Biology keeps some jokes for the glossary.

Other agents target information and metabolism. Fluoroquinolones interfere with DNA gyrase or topoisomerase IV, enzymes that manage coiling and separation of bacterial DNA. Rifamycins inhibit bacterial RNA polymerase. Sulfonamides and trimethoprim block successive steps in folate metabolism, a pathway bacteria depend on to make essential cellular components. Metronidazole becomes chemically reactive in certain anaerobic organisms and damages DNA. Nitrofurantoin produces reactive intermediates inside susceptible bacteria and is useful chiefly in the urinary tract because of where the body concentrates it.

Membranes can be attacked too, but the safety problem becomes sharper because human cells also depend on membranes. Polymyxins bind components of the outer membrane of many Gram-negative bacteria and can injure kidneys and nerves. Daptomycin disrupts the membrane of susceptible Gram-positive bacteria but is inactivated by lung surfactant, so a drug active against an organism in blood is not automatically useful for pneumonia. Mechanism, organism and site remain tied together.

Spectrum describes the range of bacteria a drug can affect. It does not rank drugs from weak to strong. A broad-spectrum agent may be valuable before the organism is known or when several bacterial types are plausible. Once evidence identifies a susceptible pathogen, a narrower option may control it while exposing fewer bystanders. Broad treatment can also select resistance across a wider microbial community and increase other adverse effects. The right breadth is the breadth the case needs.

The distinction between bactericidal and bacteriostatic sounds more decisive than clinical evidence allows. In a specified laboratory test,

bactericidal drugs kill a defined proportion of organisms, while bacteriostatic drugs inhibit growth. The categories depend on organism, concentration and conditions, and trials do not support a universal rule that bactericidal agents produce better outcomes. Host defence can clear bacteria whose multiplication has been stopped. In selected infections and patients, killing dynamics matter, but the label cannot choose treatment by itself.

A small target map explains both abundance and fragility. Chemists can modify a molecular scaffold, alter absorption or evade one resistance mechanism, producing many drugs around a shared bacterial process. Bacteria need only protect a limited number of recurring processes to disable whole families. Variety on the shelf can conceal concentration underneath it.

Treatment Is a Race Between Populations

An infection is not a fixed quantity of bacteria waiting to be removed. It is a population changing through time inside a host whose defences are changing too. Bacteria multiply, die, move between compartments and vary in their metabolic state. Immune cells arrive, inflammation alters tissue, fever changes physiology, and damaged barriers may continue admitting organisms. Antibiotic treatment enters this moving contest.

For many infections, the drug need not eradicate every bacterium by itself. It may reduce growth or numbers enough for immune defence to regain control. That is why the same organism and MIC can produce different outcomes in a healthy adult, a premature baby and a patient with severe neutropenia. It also explains why lowering the bacterial burden through drainage or surgery can transform the odds. Treatment succeeds through the combined effect of drug, host and anatomy.

Timing creates a hard clinical problem. In septic shock or suspected bacterial meningitis, waiting for complete identification can be dangerous. Clinicians often begin empiric treatment based on the likely source, local resistance patterns, patient history and severity. Samples should be collected promptly when feasible, but therapy cannot always wait for culture.

Once results and clinical response narrow the possibilities, treatment can become definitive: change drug, reduce spectrum, adjust route, correct dose, address the source or stop if bacterial infection is no longer supported.

This sequence is easy to caricature. Starting broad can be rational because early uncertainty carries risk. Remaining broad after uncertainty has fallen can be wasteful or harmful. Stewardship is therefore not a command always to begin narrow. It is a discipline of making each decision with the information available, then revisiting it when the information changes.

Combination treatment shows the population logic most clearly in tuberculosis. A large population of *Mycobacterium tuberculosis* may contain rare mutants resistant to one drug before treatment starts. If a second active drug requires a different resistance change, the chance that the same cell already resists both can be far lower. Multiple agents also address bacterial populations in different physiological states and compartments. Poor adherence, inadequate regimens or interrupted supply can expose the organism to an effective monotherapy in practice even when several names appear on the prescription. Tuberculosis does not prove that more drugs are always better. It shows why resistance risk must be matched to population size, mutation routes and disease biology.

Duration belongs to the same model. Too little effective exposure can leave infection uncontrolled or allow relapse. More treatment is not automatically safer. Each extra dose adds adverse-effect risk and further selection among the patient's microbes. The best duration is the shortest regimen supported by good evidence for that syndrome, patient and source, not a universal number and not the moment symptoms first improve. Evidence has shortened recommended courses for many common infections, while deep, prosthetic, poorly controlled or immunocompromised infections may require longer treatment.

Colonisation complicates the race. Bacteria can be present on skin, in urine, airways or wounds without causing invasive disease. A positive test may detect carriage, contamination or dead bacterial material rather than the

cause of symptoms. Treating a result instead of an infection applies selection without assured benefit. Conversely, a negative test can miss an organism because sampling was poor, treatment began first or the pathogen sits in a compartment not sampled well.

Antibiotic decisions therefore occur under unequal costs of error. Missing a dangerous infection can be catastrophic. Treating every uncertain symptom guarantees unnecessary exposure. Good care does not abolish uncertainty. It changes the race through timely treatment, better samples, repeated review and the willingness to revise the first story.

Resistance Is Inherited Information

Resistance is often pictured as bacteria trying harder after being attacked. No intention is required. A bacterial population contains variation, and its members can acquire new genetic material. An antibiotic changes which variants leave descendants. The result looks purposeful because selection preserves whatever survives, but the mechanism is blind.

Some resistance is intrinsic. A bacterium may lack the drug's target, keep the drug outside, destroy it naturally or live in a physiological state the drug cannot affect. Acquired resistance appears when mutation changes the bacterium or when genes arrive from elsewhere. Vertical transmission then passes the trait to daughter cells. Horizontal gene transfer can move DNA between organisms through plasmids and other mobile elements, allowing resistance to cross lineages without waiting for ordinary descent.

The defensive moves mirror the target map. Enzymes can destroy or modify a drug. Beta-lactamases break the beta-lactam ring; some extended-spectrum enzymes disable many penicillins and cephalosporins, while carbapenemases can threaten drugs often reserved for resistant Gram-negative infection. A target can change, as altered penicillin-binding protein does in methicillin-resistant *Staphylococcus aureus*. Bacteria can reduce permeability, increase efflux, bypass a blocked pathway, protect a ribosome or produce more of the target. Several mechanisms can accumulate in one strain.

Mutation and gene transfer create possibilities. Exposure changes their frequency. Imagine, for illustration, one resistant cell among a million susceptible ones. Without drug, resistance may carry a growth cost and remain rare. With drug, susceptible competitors are removed and the resistant cell inherits the space. Later compensatory mutations can reduce the cost, so withdrawing the antibiotic does not guarantee rapid disappearance. The direction is clear even when the speed differs by organism, drug, setting and fitness effect.

Resistance predates clinical antibiotics. Microbes made antimicrobial compounds and evolved defences long before clinical medicine. Resistance genes have been recovered from environments remote from modern healthcare, including ancient permafrost. Human use did not invent every mechanism. It increased exposure, amplified selected organisms and genes, moved them through hospitals, farms, trade, travel and wastewater, and concentrated ecological contacts that let resistance circulate.

Not every survival phenomenon is inherited resistance. A biofilm can reduce penetration and alter growth. A small fraction of genetically susceptible cells may enter a tolerant state and survive transient exposure as persisters. Heteroresistance can place subpopulations with different susceptibility inside what appears to be one isolate. These states can cause failure or recurrence and create time for genetic resistance to emerge, but they should not be collapsed into one mechanism.

Resistance also differs from virulence. A resistant bacterium is harder to treat with particular drugs; it is not automatically better at causing severe disease. Some resistance changes reduce fitness, others carry little cost, and compensatory evolution can alter the balance. The public-health damage arises because common infections become harder, slower or more toxic to treat, hospital stays lengthen, second-line options cost more, and procedures depend on a narrower safety net.

The individual patient did not manufacture resistance by moral weakness, and one prescription cannot explain a population trend. Yet selection is cumulative. Human medicine, veterinary use, transmission, sanitation,

vaccination, infection control, travel, supply quality and environmental discharge all affect which genes appear, persist and spread. The right unit of explanation is a connected ecology of bacteria carrying information.

A Prescription Sits Inside a System

The visible object is a tablet or infusion bag. The working unit is a chain of decisions. Someone must recognise a possible bacterial infection, obtain samples, choose treatment, calculate exposure, supply an authentic product, administer it correctly, review the patient, receive a laboratory result, act on that result and prevent the organism reaching the next person. A failure at any link can look later like failure of the drug.

Diagnostic uncertainty is one driver of unnecessary use. Fever, cough, diarrhoea and urinary symptoms can arise from bacteria, viruses, inflammation or causes outside infection. A clinician weighs probabilities under time pressure, often without a rapid test that can identify both the organism and its susceptibility. The cost of delay may be high in a sick patient, while the cost of an unnecessary prescription is dispersed across adverse effects and future selection. Better diagnostics can change that calculation only if they are fast, affordable, sampled at the right time and trusted enough to alter decisions.

Antimicrobial stewardship organises the chain. Its questions are practical: Is bacterial infection likely? Are cultures or imaging needed? Does the patient need immediate empiric treatment? Which drug covers the plausible organisms while respecting allergies, organ function, pregnancy, interactions and local resistance? Is the route suitable? When should the decision be reviewed? Can intravenous treatment switch to oral? Can spectrum narrow? Is source control complete? What duration has evidence for this syndrome? Stewardship protects patients from undertreatment and overtreatment at once.

The World Health Organization's AWaRe system adds a population view. Access antibiotics are preferred first or second choices for many common infections and should remain widely available. Watch antibiotics have higher

resistance potential or narrower indications and need closer stewardship. Reserve agents are last-line options for selected resistant infections. The 2030 global target is for Access drugs to make up at least 70 per cent of human antibiotic use. Across the 2022 use data reported to WHO by 60 countries, Access agents made up about 53 per cent overall. That aggregate does not describe every country or its clinical needs.

Hospitals add transmission control. Hand hygiene, cleaning, screening in selected settings, isolation, safe devices and rapid removal of unnecessary catheters reduce the number of infections needing treatment and the spread of resistant organisms. Vaccination prevents bacterial disease directly in some cases and reduces secondary bacterial infection or antibiotic-seeking in others. Clean water, sanitation, nutrition and housing act earlier in the chain. The best antibiotic policy includes fewer infections.

Food production belongs in the same system without pretending every route contributes equally everywhere. Antibiotics can treat sick animals and protect welfare. WHO recommends ending routine use of medically important antimicrobials for growth promotion or disease prevention in healthy animals. That recommendation does not prohibit indicated treatment. Resistant organisms and genes can move through direct contact, food chains, waste and shared environments, but the contribution to a particular human infection varies by organism and setting.

Manufacturing also matters. Waste streams containing active antibiotic residues can expose dense environmental bacterial communities. Hospitals, households and farms contribute drugs, resistant bacteria and genes to wastewater too. Evidence of selection near high discharges is stronger than evidence tracing a particular clinical infection back to one source. Environmental pathways belong in the map, but they should not become a universal explanation for clinical resistance.

Access is the other half. A stewardship programme that restricts a drug without ensuring the right alternative can injure patients. Stock-outs, weak laboratories, substandard or falsified medicines and unaffordable care can delay effective treatment and, where infection is transmissible, prolong

spread. The aim is not fewer antibiotics in every place. It is less exposure without likely benefit, reliable access where benefit is likely, and systems strong enough to tell the difference.

Effectiveness Must Be Maintained

A barrel of oil is depleted when it is burned. Antibiotic effectiveness is stranger. The tablets can be reproduced, but the relationship between drug and bacterial population changes with use. A medicine can remain chemically identical while becoming less dependable because resistant organisms and genes have become common. Effectiveness therefore behaves like a shared capability: many people benefit from it, many activities can erode it, and no patient, hospital or country controls the ecology alone.

This creates an economic contradiction. Society wants new antibiotics ready for rare resistant infections, but it also wants clinicians to conserve them. A successful new drug may therefore be prescribed sparingly, generating less sales revenue than a medicine taken daily for years. Scientific risk is high, development is expensive, trials for resistant infections are difficult, and resistance can reduce useful life. Conventional payment by volume rewards the opposite of conservation. Subscription payments, public funding, market-entry rewards and international purchasing schemes try to pay for availability and value rather than encouraging maximal use. None has yet supplied a complete global answer.

Discovery is harder than screening another soil sample and waiting for a halo. The mid-century programmes found many classes by testing microbial products against bacteria. Repeated screening often rediscovered known compounds, while promising molecules failed because they were toxic, unstable, poorly absorbed or unable to cross the outer membrane of Gram-negative bacteria. A compound can kill a laboratory strain and still fail every condition described in the first six ideas.

The pipeline is broader than traditional antibiotics. Beta-lactamase inhibitors can restore activity to partner drugs against selected enzymes.

Bacteriophages attack bacteria with high specificity but raise questions about matching, resistance, immunity and manufacturing. Antibodies, anti-virulence agents, microbiome approaches and therapies that improve delivery or disable resistance mechanisms seek different leverage. Vaccines and rapid diagnostics can reduce demand for antibiotics. These tools may supplement antibacterial drugs; none permits the older drugs to be neglected.

WHO published its 2025 pipeline analysis in October using a data cut-off of 15 February 2025. It counted 90 antibacterial products in clinical development: 50 traditional agents and 40 non-traditional approaches. Only 15 met its innovation criteria, and for 10 of those the available data were insufficient to rule out cross-resistance. Pipeline totals also change as products enter, fail or leave development. A list of candidates is not a list of future cures.

Surveillance supplies the feedback. Laboratories identify organisms and resistance patterns; health systems then have to report comparable data, and analysts must distinguish infection from colonisation, community from hospital cases and tested patients from the population. WHO's latest report converted a large but uneven collection of routine results into adjusted estimates. The calculation improves the map without making the underlying samples representative of every infection.

Maintenance therefore has no finishing date. Use evidence-based regimens, prevent infection, slow transmission, improve vaccination and sanitation, reduce avoidable exposure in humans and animals, control manufacturing waste, guarantee access, strengthen laboratories, reward useful innovation and revise policy as organisms change. Different settings need different priorities. A hospital facing carbapenem-resistant outbreaks, a district without microbiology and a farm system using routine group medication do not have the same first move.

The causal loop now closes. Selective toxicity works because bacteria possess attackable differences. Each treatment turns those differences into a filter through which a population passes. The survivors alter the next

treatment decision. Antibiotics did not fail by being miracles. They succeeded against living targets, and living targets do not hold still. Preserving the miracle means rebuilding effectiveness continuously rather than treating it as a historical gift.

How It Actually Works

Before the mould

At the opening of the twentieth century, germ theory had named many bacterial enemies but medicine could do little once they spread through living tissue. Antisepsis reduced contamination during surgery. Vaccination and sanitation prevented some infections. Surgeons drained pus and removed damaged tissue. Antitoxins helped against diseases driven by a known toxin. A patient with pneumonia, puerperal sepsis or an infected wound still depended heavily on immune defence and luck.

The first chemical successes were synthetic. Paul Ehrlich's laboratory screened numbered compounds against infectious agents, searching for selective chemotherapy. Arsphenamine, introduced in 1910 for syphilis, attacked the spirochaete inside the patient but required difficult preparation and carried serious toxicity. It was no clean magic bullet. It proved that a chemical could be chosen for a pathogen rather than used as a general antiseptic.

In the 1930s Gerhard Domagk found that the red dye Prontosil protected mice from streptococcal infection. A French team then showed that the active component released in the body was sulfanilamide. Sulfonamides became the first widely used systemic antibacterial drugs and reduced deaths from several common infections before penicillin was available. They also showed that an active molecule and a safe medicine were different achievements. In 1937 a sulfanilamide product made with a toxic solvent killed more than one hundred people in the United States and helped drive stronger drug-safety law. Chemistry needed formulation, testing and regulation.

The plate at St Mary's

Alexander Fleming was studying staphylococci at St Mary's Hospital in London when, in September 1928, he noticed that a contaminating *Penicillium* mould had prevented colonies growing around it. Chance supplied the contamination. Recognition supplied the result. Fleming had already worked on antibacterial substances and did not discard the spoiled plate. He cultured the mould, tested the liquid around it and called the active material penicillin.

His 1929 paper established that the filtrate inhibited some bacteria more than others and could assist laboratory isolation. It did not establish a usable systemic drug. Penicillin was dilute, unstable and difficult to purify. Mould broth contained many substances, while the desired compound lost activity during attempts to extract and store it. Fleming and others explored local uses, but no reliable dose reached patients' blood.

The distinction matters because discovery stories tend to stop when the photograph becomes good. A clear halo on agar answers whether something inhibits bacteria nearby. A medicine must survive purification, remain potent, avoid toxicity, reach infected tissue, be measured reproducibly and be made in quantities larger than a laboratory flask. For roughly a decade, penicillin was a clue without the system needed to carry it.

Oxford builds the drug

Ernst Chain encountered Fleming's paper while reviewing antibacterial substances at Oxford. Howard Florey led the pathology department and assembled a team that joined biochemistry, microbiology, pathology, clinical medicine and practical engineering. Norman Heatley devised extraction methods, assays and equipment. Edward Abraham worked on purification and chemistry. Many technicians and researchers maintained the cultures and repeated a process that failed easily.

In May 1940 the group infected mice with lethal streptococci. Animals receiving penicillin survived while untreated controls died. The experiment

made the therapeutic possibility visible inside a mammal, but it created a larger production problem. Human treatment needed far more material. Heatley designed shallow ceramic vessels with a large surface area for mould growth, and rooms became a small production plant. Broth was filtered, acidified, moved between solvents, returned to water and concentrated without letting the fragile compound decay.

Albert Alexander, an Oxford policeman with a severe facial infection, received the preparation in February 1941. He improved sharply. The team recovered active penicillin from his urine because much of the scarce drug was excreted unchanged. The supply still ran out, the infection returned and he died. Later patients were selected partly because smaller amounts could plausibly cure them. The clinical lesson and the production lesson arrived together: penicillin worked, and a university could not make enough.

Florey and Heatley travelled to the United States in 1941. At the Department of Agriculture laboratory in Peoria, researchers tested nutrient media and more productive mould strains. Corn-steep liquor, a by-product of maize processing, supported higher yields. Pharmaceutical companies adapted deep-tank fermentation, aeration, sterile handling and extraction to an organism that changed with its environment and contaminated easily. Engineers had to manage oxygen, mixing, heat and foam while chemists recovered the active product before it degraded.

By the later years of the Second World War, penicillin was available at industrial scale for military use and then for civilians. Potency could be standardised, batches checked and distribution organised. Dorothy Crowfoot Hodgkin's X-ray crystallography established the beta-lactam structure in 1945, helping chemists understand the molecule they were modifying. Fleming, Florey and Chain shared the Nobel Prize that year. Heatley did not. The famous plate remained the beginning, but the medicine was made by another decade of work.

The soil becomes a library

Penicillin covered only part of the bacterial world. Tuberculosis remained beyond its reach. Selman Waksman's group at Rutgers searched actinomycetes, soil bacteria that produce chemically diverse compounds while competing with other microbes. Albert Schatz carried out much of the culture and testing that identified streptomycin from *Streptomyces griseus*, working with Elizabeth Bugie and Waksman. Their 1944 paper reported activity against Gram-positive and Gram-negative bacteria.

Streptomycin's greatest early promise was activity against *Mycobacterium tuberculosis*. Patients could improve under treatment, yet resistance emerged readily when it was used alone. The British Medical Research Council's 1948 investigation compared streptomycin plus bed rest with bed rest alone through controlled allocation and blinded reading of chest radiographs. It became a landmark in the development of the randomised clinical trial. Benefit was visible, and so was the rise of streptomycin-resistant bacilli.

Combination therapy followed from population logic. A patient may harbour a mutant resistant to one drug before treatment begins. The chance that the same bacterium already carries independent resistance to several active drugs can be much lower. Using drugs with different targets reduces the opportunity for any one resistant subpopulation to take over, provided every component reaches useful exposure and the regimen is taken consistently. Tuberculosis treatment became longer and more complex because the organism grows slowly, occupies different compartments and can persist in different physiological states.

Credit for streptomycin later became a dispute. Waksman received the 1952 Nobel Prize, while Schatz sued over recognition and royalties. The lesson is not that one forgotten genius should replace one famous genius. Discovery depended on a laboratory programme, doctoral labour, clinical testing, manufacturing and institutions that decided whose name travelled. Antibiotic history repeatedly turns a network into a portrait.

The wider search programmes of the 1940s to the 1960s treated soil as a chemical library. Researchers collected samples, isolated microbes, fermented them, screened their products against test bacteria, purified promising compounds, determined structures and watched most candidates fail. The survivors included aminoglycosides, tetracyclines, macrolides, chloramphenicol and glycopeptides. Cephalosporins supplied another beta-lactam family. Medicinal chemists then changed natural scaffolds to improve stability, absorption, spectrum or resistance to bacterial enzymes. Fully synthetic classes such as fluoroquinolones extended the map.

The term golden age fits the number of major families found and misleads about ease. Screening repeatedly rediscovered known compounds. Many substances were too toxic, too unstable or too poor at entering the body. Chloramphenicol offered broad oral treatment but carried a rare risk of fatal aplastic anaemia. Aminoglycosides could rescue serious Gram-negative infection while damaging hearing or kidneys. Vancomycin spent years as a difficult reserve drug before resistant staphylococci increased its importance. Each gain arrived with a boundary.

The miracle becomes infrastructure

Once antibiotics became routine, they altered what medicine considered feasible. Surgery could breach the bowel or implant foreign material with a better rescue option if bacteria crossed the wound. Premature infants, people receiving cancer chemotherapy and transplant recipients could be supported through periods of weak defence. Obstetric infection became more treatable. Antibiotics did not make these practices safe on their own, but they expanded the margin around them.

Routine availability also changed behaviour. A prescription came to signify active care for many patients and clinicians. Broad-spectrum agents allowed dangerous uncertainty to be treated before identification. Where review systems were weak, that initial breadth could persist after the reason for it had passed. Agriculture adopted antibiotics to treat sick animals and, in many systems, to promote growth or prevent disease across healthy groups. Production rose, prices fell and selection pressure became ordinary.

Laboratories responded by standardising susceptibility tests. Naming a bacterium no longer answered which drug would work. Discs, dilution methods, control strains and interpretive breakpoints made results comparable. Hospitals tracked resistant organisms, built local antibiograms and introduced isolation or screening during outbreaks. Pharmaceutical companies produced successive derivatives to evade one enzyme, enter another organism or last longer in blood. Practice became a sequence of repairs.

Some repairs failed quickly. In 1940, before penicillin entered wide clinical use, Ernst Chain and Edward Abraham described a bacterial substance that destroyed it, later understood as a beta-lactamase. Penicillin-resistant staphylococci spread during the 1940s. Methicillin was designed to withstand common staphylococcal penicillinases; resistant strains were reported soon after introduction because they carried an altered penicillin-binding protein. The drug had blocked one defence and selected another.

Resistance moves

The same pattern appeared across families. Tetracycline resistance travelled on mobile genes. Macrolide targets were chemically modified. Gram-negative bacteria combined restricted entry, efflux pumps and drug-destroying enzymes. Carbapenems became valuable against organisms producing many beta-lactamases, followed by carbapenemases that compromised them. Vancomycin resistance spread among enterococci and later appeared in staphylococci. Introduction, selection, spread and countermeasure became the recurring sequence.

Plasmids made the timing harder to predict. A useful resistance gene could sit beside others on mobile DNA, so exposure to one drug preserved resistance to several. A successful strain could move between patients; a plasmid could move again into a different lineage. Hospitals joined high antibiotic use, vulnerable patients, invasive devices and frequent contact, creating conditions for both selection and transmission. Infection control therefore had to chase organisms while stewardship reduced the pressure

favouring them.

The traffic did not stop at hospital doors. Resistant bacteria moved through households, care homes, food systems, travel, sewage and animal contact. Antibiotic residues and bacteria entered wastewater from homes, hospitals, farms and manufacturing. The contribution of each route varies by organism and place, and a resistance gene found in a river cannot be assigned automatically to a human infection. The connections still matter because bacterial genes cross boundaries drawn for administrative convenience.

A prescription in motion

Modern treatment begins with a syndrome rather than a drug. A clinician asks where infection might be, how ill the patient is, which organisms fit, what exposures or devices change the risk and how dangerous delay would be. A stable patient with a mild illness can often be observed or tested. A patient with septic shock or suspected bacterial meningitis may need immediate empiric treatment after prompt samples because tissue damage can outrun the laboratory.

The sample has to represent the site. Blood cultures use bottles designed to detect microbial growth. Urine, sputum, cerebrospinal fluid, pus, tissue and swabs answer different questions. Skin bacteria can contaminate a blood culture during collection. Bacteria in urine can be present without causing symptoms. A wound surface may carry organisms unrelated to a deeper infection. Better detection increases the need for interpretation because finding biological material is not identical to finding the cause.

The laboratory makes the hidden population legible. A Gram stain gives early information about shape and cell-envelope type. Culture grows organisms on selected media, sometimes overnight and sometimes much longer. Identification can use biochemical reactions or protein patterns measured by mass spectrometry. Susceptibility testing exposes the isolate to defined antibiotics through discs, broth dilution or automated systems. Molecular tests can detect an organism or selected resistance genes faster, but a panel only sees what it was built to see.

Empiric therapy covers plausible dangerous organisms while evidence is incomplete. The opening choice reflects infection site, severity, previous cultures, recent healthcare, local resistance, allergy, kidney and liver function, pregnancy and interactions. Broad coverage may be correct at the start. It creates an obligation to review. Once culture, imaging and clinical response narrow the possibilities, continuing the widest regimen turns yesterday's uncertainty into today's avoidable exposure.

Dose and route shape exposure. Intravenous administration gives dependable entry to the circulation but does not guarantee penetration into every tissue. Oral treatment can be equally effective when absorption is reliable and a suitable medicine reaches the site. Kidney function changes clearance for many agents. Critical illness can alter body water, protein binding and organ perfusion. Selected antibiotics are measured in blood because too little risks failure and too much risks toxicity. A concentration without the time it was taken is a number with its clock removed.

England's Start Smart Then Focus toolkit calls for inpatient antimicrobial treatment to be reviewed within 48 to 72 hours. The team asks whether bacterial infection still looks likely, whether the patient is improving, whether results support a narrower agent, whether intravenous treatment can switch to oral, and whether an abscess, obstruction or device needs attention. Other systems use different review points, and some infections need earlier reassessment. Failure may mean resistance, poor exposure, missing source control, mixed infection or wrong diagnosis. Adding another antibiotic cannot repair every cause.

Duration is part of the same decision. Symptoms can improve before infection is controlled, and they can linger after bacterial growth has stopped. Evidence supports shorter treatment for many common infections than older custom required, while endocarditis, bone infection, tuberculosis and poorly controlled sources can need much longer regimens. The patient should follow the current plan and contact the prescriber or pharmacist before changing it. A revised plan made after review is updated treatment, not a failure to finish.

The repair job

At population scale, surveillance turns individual isolates into a map. Hospitals build antibiograms showing local susceptibility among tested organisms. National and international systems combine laboratory and use data, then adjust for some differences in reporting. The result remains shaped by who was cultured, which laboratories could test reliably and which infections entered care. A larger dataset narrows uncertainty without abolishing selection bias.

The response begins before prescribing. Vaccination prevents selected bacterial infections and reduces viral illnesses that lead to bacterial complications or unnecessary antibiotic demand. Clean water, sanitation, safe childbirth, sterile surgery, hand hygiene and careful device use reduce infections and transmission. Better animal husbandry and vaccination reduce the need for routine group medication. Manufacturing controls reduce exposure around antibiotic production. Prevention protects antibiotics by making fewer rescue attempts necessary.

Use also has to be reshaped. The WHO AWaRe framework encourages dependable supply of Access drugs for common infections, closer stewardship of Watch agents and guarded use of Reserve options. It is a classification for policy and stewardship, not a universal formulary: local resistance, disease burden, supply and clinical guidance still determine which medicine a patient needs.

New products remain necessary. WHO's October 2025 review found too little innovation for the hardest priority pathogens despite a sizeable candidate list. Attrition means many projects will not reach approval, and approval itself does not deliver affordable access, correct diagnosis or production capacity. Discovery is one link in the system, not its replacement.

The commercial model works against restraint. An antibiotic is often taken for days, and a valuable new drug may be reserved for rare resistant infections. High sales can signal poor stewardship. Subscription contracts, public research funding, market-entry rewards and pooled purchasing try to

pay for readiness rather than volume. These approaches remain experiments, but they acknowledge the central contradiction: society needs companies to develop medicines it hopes to use sparingly.

There is no final repair. Every new intervention enters a population capable of change. The task is to extend useful life, reduce infections, slow spread, detect failure sooner and keep effective treatment available where it is needed. Antibiotic policy is maintenance under evolutionary pressure.

How we know

The discovery story rests on Fleming's 1929 paper, the Oxford team's 1940 animal report, early clinical records and manufacturing archives. Together they separate observation, purification, experimental treatment, clinical use and scale. Accounts of Albert Alexander differ over the initiating injury and minor clinical details, so the narrative retains only the severe infection, early response, recovery of active penicillin from urine, exhausted supply, relapse and death.

Mechanisms are supported by genetics, biochemistry, structural work, susceptibility testing and clinical pharmacology. A laboratory result establishes behaviour under defined conditions; it does not reproduce the infected site, immune response or source control. Trials estimate average outcomes in selected patients, while uncommon resistant infections and severely ill groups can remain underrepresented.

Current figures require three dates. The GBD analysis was published in 2024 and estimated mortality for 2021. WHO's resistance report was published in October 2025 from 2023 surveillance data reported by 104 countries and converted into adjusted estimates. Its use report was published in April 2025 from 2022 data submitted by 60 countries. The pipeline review appeared in October 2025 but used a 15 February 2025 cut-off. None of these datasets is a live global census.

What People Get Wrong

"Antibiotics cure colds and flu"

Colds and influenza are caused by viruses. Viruses do not build peptidoglycan walls, use bacterial ribosomes or run the metabolic pathways targeted by antibacterial drugs. Giving amoxicillin to influenza is like presenting the correct key to a building that is not there. Greater antibacterial potency cannot create a viral target.

The confusion persists because respiratory illnesses produce overlapping symptoms and because some bacterial infections follow viral ones. A patient with influenza can develop bacterial pneumonia. A sore throat may be viral or caused by bacteria such as group A streptococcus. A clinician may prescribe under uncertainty, and the patient's recovery can then be credited to the antibiotic even when the illness would have improved on its own.

This correction does not mean every cough, fever or sore throat should be ignored. It means symptoms alone do not turn a virus into a bacterial target. Unnecessary treatment cannot shorten a viral infection, but it can cause adverse effects, disrupt the microbiome and select resistant bacteria carried by the patient. The useful question is whether there is a bacterial problem the drug can plausibly change.

"Resistance means your body has got used to the drug"

Your body can develop tolerance to some medicines, but antibiotic resistance belongs to bacteria. A resistant bacterium carries structural, regulatory or genetic features that let it survive an exposure that would inhibit a susceptible one. The patient is the environment in which selection may occur, not the organism learning to tolerate penicillin.

The wrong model feels intuitive because treatment failure is experienced by the person. It also borrows language from painkillers, sedatives and other drugs whose effects can change with repeated use. Yet the distinction has

practical consequences. A person who has never taken a particular antibiotic can acquire a resistant infection from another person, an animal, food, water or the wider environment. A patient who took an antibiotic years ago is not permanently resistant to the medicine; the bacteria involved in a future infection may be different.

Selection still links use to risk. Exposure removes susceptible competitors and may favour resistant bacteria already present or acquired later. That is why unnecessary use matters. The transferable thing is the organism or its genes, not a resistant human body.

"Broad spectrum means stronger"

Spectrum describes range. A broad-spectrum antibiotic acts against a wider set of bacteria than a narrow-spectrum one. It does not strike each susceptible organism with greater force, penetrate every tissue better or create a higher chance of cure.

The language encourages the error. Broad sounds comprehensive, and comprehensive sounds safe when the cause is uncertain. In severe infection, broad empiric coverage can be rational while cultures are pending. Once the likely organism and site become clearer, breadth may become excess. A narrower agent can be the more reliable treatment because it has the right target, exposure and evidence while disturbing fewer bystander bacteria.

Breadth can also hide gaps. Vancomycin is important against many Gram-positive organisms but does not cross the outer membrane of Gram-negative bacteria. An agent described as broad may still miss atypical organisms, anaerobes or a local resistant strain. Conversely, a narrow drug can be ideal when it fits the pathogen precisely.

The correction matters because prescribing is selection, not escalation. The aim is adequate coverage of the organisms that plausibly cause the infection, then the least collateral range consistent with safe treatment and fewer bystander effects.

"Fleming found penicillin and medicine changed overnight"

Fleming noticed bacterial inhibition around a mould in 1928 and published in 1929. He did not purify penicillin into a stable systemic medicine, establish a dosing regimen, run the decisive animal work or build a factory. For roughly a decade, penicillin remained an interesting and awkward laboratory substance.

The one-man version survives because a contaminated plate is a perfect picture and industrial development is not. The Oxford team led by Howard Florey and involving Ernst Chain, Norman Heatley, Edward Abraham and others turned the observation into purified material, protected infected mice and treated patients. Government laboratories and pharmaceutical firms then solved fermentation, strain selection, aeration, extraction, sterility and scale. War supplied urgency and resources.

This does not diminish Fleming. It places discovery in its correct sequence. Observation, development, clinical proof and manufacture are different achievements. Antibiotics became dependable because many people converted a fragile biological effect into a standard product. The distinction also explains why identifying a promising molecule today does not mean a new medicine will arrive soon.

"Bactericidal always means better"

A bactericidal drug kills bacteria under defined laboratory conditions. A bacteriostatic drug inhibits growth under those conditions. The words sound like a ranking, and killing appears more decisive than restraint. A 2018 review of 56 randomised trials found no efficacy difference in 49, six favoured a static agent, and the single apparent cidal advantage involved a dosing problem. That pattern does not prove the categories never matter. It does show that the label cannot be treated as a general outcome hierarchy.

The categories depend on organism, drug concentration, test medium and time. The same agent may behave differently against another species or exposure. In a patient, immune function, infected site, source control,

toxicity and achievable concentration can matter more than the label. A static drug can stop multiplication long enough for host defences to clear infection. A cidal drug that fails to reach the tissue or cannot be tolerated is not rescued by its verb.

There are infections and clinical circumstances where guidelines prefer particular agents and where rapid killing may matter. That is an indication-specific judgement, not permission to rank every formulary by cidal status. Choose from evidence for the infection, organism and patient. Laboratory vocabulary is useful when it describes a mechanism and dangerous when it substitutes for an outcome.

"You must always finish every antibiotic course"

The old message joined a sound patient instruction to an over-simple biological story. Patients should not stop as soon as they feel better or change treatment on their own. It does not follow that every duration first written is optimal, or that shortening treatment after clinical review necessarily promotes resistance. Too little effective therapy can leave infection uncontrolled; treatment continued beyond the evidence-based duration adds adverse effects and selection without matching benefit.

The correct duration varies sharply. Some uncomplicated infections need short courses. Endocarditis, bone infection and tuberculosis can require much longer, often with several drugs. Source control, immune status, response and new test results can change the plan. Prescribers should therefore review duration rather than preserve an initial end date by reflex.

The practical rule is conservative. Take antibiotics according to the current instructions and contact the prescriber or pharmacist if symptoms change, doses are missed or side effects occur. A clinician may advise completing the original course, shortening it, switching it or stopping because the diagnosis has changed. The myth is the word always, not the need for an agreed plan or for the patient to follow it.

"A new antibiotic will solve resistance"

A new agent can rescue patients and close an important gap. It cannot repeal selection. If bacteria can survive through mutation, gene acquisition, reduced entry, drug destruction or target change, use will favour those routes. Some resistance is detected during development or soon after launch; other mechanisms spread years later.

The rescue story remains persuasive because past waves of drugs appeared to answer previous failures. Penicillinase-resistant penicillins followed penicillin resistance. Later cephalosporins, carbapenems and inhibitor combinations extended coverage again. Each advance was real. Each moved the contest rather than ending it.

New discovery is therefore necessary but insufficient. A useful product needs rapid diagnosis, susceptibility testing, appropriate exposure, infection control, surveillance, manufacturing quality, affordable access and stewardship. Reserving it too tightly can deny treatment; using it casually can shorten its useful life. The economic problem is equally awkward because developers need a return while health systems want low sales volume.

The durable aim is a renewing portfolio supported by prevention and controlled spread. There will be no final antibiotic. There can be a system that keeps more infections treatable.

Use It

Ask what would make bacteria the best explanation

An antibiotic decision begins with a causal claim: bacteria are contributing enough to the illness that suppressing or killing them should improve the outcome. Treat that claim as something to support, not something a prescription proves after the fact.

Evidence comes in layers. The pattern and duration of symptoms may shift

probability. Examination can locate a source. Imaging may reveal pneumonia, obstruction or an abscess. Culture can recover an organism. Molecular tests can detect selected pathogens or resistance genes. Inflammatory markers can support concern without naming the cause. Severity changes how much uncertainty can be tolerated before treatment begins.

Detection is not causation. A bacterium found in sputum, urine or a wound may be colonising the person or contaminating the sample. A negative result may miss the site, organism or timing. Ask what evidence would distinguish bacterial disease from alternatives, how dangerous delay would be, and what new result would change the plan. For your own illness, that judgement belongs with a qualified clinician using the whole case.

Read strength as fit, site and exposure

When someone calls an antibiotic strong, ask which property they mean. It may cover a wide range, have a low MIC against an isolate, reach a particular tissue well, achieve a high concentration or remain active against a resistance enzyme. Those properties do not travel together.

Use a compact check: organism, target, site, exposure and patient. Is the likely bacterium within range? Does resistance block the mechanism? Can the drug reach the infected compartment? Does the regimen create enough exposure? Can the patient tolerate and clear it? Failure in one dimension can outweigh success elsewhere.

This lens corrects escalation bias. Moving to a broader or newer drug feels decisive but can exchange a well-matched treatment for greater toxicity or ecological cost. It also corrects false reassurance from a susceptibility report. The laboratory cannot see an undrained abscess, infected implant or wrong diagnosis. A drug is capable only in relation to a defined problem under conditions that let its mechanism operate.

Follow the current plan, not folklore

Public rules about antibiotic courses became slogans because clinical detail does not fit on a packet. The safe instruction is narrower: take the medicine according to the current directions, do not share it, do not save it for another illness, and seek advice from the prescriber or pharmacist before changing the plan.

Feeling better does not always mean the infection is controlled. Feeling no better does not prove the medicine is weak. Symptoms may lag behind bacterial inhibition, the source may need drainage, the organism may be resistant, or the diagnosis may be wrong. Side effects range from nuisance to emergency. The answer is review, not improvisation.

An end date is part of a treatment plan rather than a moral test. Evidence may support a short course for one infection and prolonged combination therapy for another. Cultures, imaging, source control or response may justify revision. A clinician-directed change to the date is updated care, not non-adherence. Leftovers have lost the diagnosis, dose, timing and safety checks that made the original prescription intelligible.

Separate emergence from spread

Resistance discussions often collapse two events. A resistant bacterium or gene first becomes favoured within a population. It then moves between people, species or places. The controls overlap, but they are not identical.

Appropriate use reduces avoidable selection. It cannot by itself stop an established resistant strain passing through hands, equipment, food or unsafe water. Infection prevention can slow spread without changing the mechanism that first produced resistance. Surveillance can detect a cluster but does not treat it. A new drug can cure selected cases while leaving transmission untouched.

Use the distinction when a proposed solution sounds complete. A prescribing target may reduce exposure yet miss an outbreak driven by poor ward practice. Better sanitation may reduce infections while resistance

continues to evolve in those that remain. Banning one agricultural use may help while human prescribing or manufacturing discharge persists. A patient who acquires a resistant infection may have done nothing careless. Selection and transmission have routes wider than personal behaviour.

Count prevention as antibiotic policy

The best-preserved dose is often the one nobody needed. Vaccination, clean water, sanitation, safer childbirth, sterile surgery, hand hygiene, good device care and animal husbandry reduce infections or their spread. Their effect on resistance comes through fewer opportunities to prescribe and fewer resistant organisms reaching new hosts.

Prevention lacks the drama of rescue because success is an event that did not occur. A hospital can celebrate a new agent while underfunding staffing, cleaning, laboratory turnaround or catheter removal that protects it. A country can publish a stewardship plan while unreliable water systems keep generating infections. The accounting is distorted when the prescription is visible and the avoided infection is not.

Ask whether an intervention lowers incidence, shortens transmission chains or reduces the need for broad empiric treatment. Ask who maintains it after launch. Prevention is part of the infrastructure that keeps difficult cases treatable, not a polite alternative reserved for easy ones.

Hold access and restraint together

Antibiotic policy can fail in opposite directions. Poorly targeted use increases harm and selection. Lack of access leaves treatable infections untreated. One service may need to reduce casual broad prescribing; another may lack the first-line medicine, diagnostic test or trained staff needed to treat severe infection well. Some systems face both failures in the same week.

Judge a policy by both questions. Does it reduce exposure without plausible benefit? Does it improve timely access where benefit is likely? A restriction that delays treatment for sepsis is not stewardship. Unsupervised access without diagnosis is not equity. Stock-outs that force repeated changes to

broader drugs can worsen care and resistance together.

The same balance applies to new agents. Reserve status should protect a medicine from casual use, yet a patient with a susceptible resistant infection must be able to receive it. Pricing and procurement should reward availability without rewarding volume. The objective is effective treatment delivered with enough discrimination that it remains effective.

The limits

This book cannot tell you whether your illness needs an antibiotic, which agent fits, what dose is safe or when a regimen should change. Those decisions depend on examination, medical history, local guidance, current resistance, organ function, allergy, pregnancy, interactions and the infected site. General mechanisms are not a substitute for clinical assessment.

The evidence has limits too. Laboratory susceptibility does not guarantee cure. Surveillance overrepresents infections and places that are sampled. Burden models depend on assumptions about what would have happened without resistance. A gene found in an environment does not establish a route into human disease. One Health is a necessary map of connected systems, not proof that each sector contributes equally to every case.

Stewardship cannot preserve each drug forever. Evolution has no obligation to respect a careful policy. Maintenance buys time, probability and options. It does not buy permanence.

The one thing to keep

Keep the relationship between the miracle and the problem.

An antibiotic works because it creates an unequal contest between bacterial biology and the patient's tolerance. That inequality is never a property of the molecule alone. It depends on susceptibility, exposure at the site, source control and the patient surviving both infection and treatment.

Every use then enters the next contest. Susceptible bacteria lose their place. Resistant cells and genes gain opportunities. The result may remain

inside one microbiome, move across a ward or travel through food, water and contact. Prevention, diagnosis and infection control alter those routes. Research supplies new options. Access determines who receives the benefit.

Stop seeing antibiotics as a finished invention stored in a cupboard. Their useful effect is rebuilt in a laboratory report, a dosing plan, a clean operating theatre, a vaccinated community, an effluent standard and the decision to drain an abscess rather than ask chemistry to do surgery's job.

The first antibiotic age taught medicine that bacteria could be selectively attacked. The resistance age adds the harder lesson: the advantage is conditional and can be spent. Every effective antibiotic is treatment for this patient and part of the capability inherited by the next one.

Terms

Antibiotic. A medicine that kills bacteria or restrains their growth at exposures a patient can tolerate. In ordinary clinical use the word covers natural, modified and fully synthetic antibacterial agents. Its clinical target is bacteria rather than every kind of microbe.

Antimicrobial. A broader category including agents against bacteria, viruses, fungi and parasites. Antibiotics are antimicrobials, but an antiviral or antifungal medicine is not an antibacterial antibiotic. The wider term is useful when several pathogen types are being discussed together.

Pathogen. An organism capable of causing disease in a host. Pathogenicity depends on organism, site and host; a harmless colonist in one place can cause infection in another. The label describes a relationship, not a fixed moral category.

Colonisation. The presence and growth of microorganisms without tissue invasion or disease requiring treatment. Confusing colonisation with infection can turn a positive sample into an unnecessary prescription. Colonised people can still carry and transmit resistant organisms.

Infection. Invasion and multiplication of an organism in a host with a damaging response or credible risk of disease. Detection alone does not establish that an infection is present. Symptoms, site and host response complete the interpretation.

Microbiome. The microorganisms, genes and surrounding conditions in a defined habitat such as the gut. Antibiotics can alter this community while treating a pathogen elsewhere. Many resulting changes are measurable before their health meaning is known.

Selective toxicity. Greater harm to the pathogen than to the patient at useful exposure. This relationship, rather than a drug being generally poisonous, makes systemic antibacterial treatment possible. The margin differs by drug, dose, patient and target.

Spectrum. The range of bacterial species or groups an antibiotic can affect. Broad spectrum means wider coverage, not greater force against every susceptible organism. Spectrum can also change when local resistance becomes common.

Gram-positive. Bacteria that retain the primary Gram stain because of their cell-envelope structure, usually including a thick peptidoglycan layer. The category helps guide early reasoning but does not determine treatment alone. Species, site and susceptibility remain decisive.

Gram-negative. Bacteria with a thin peptidoglycan layer behind an outer membrane. That extra barrier, porins and periplasmic enzymes can make entry and treatment harder. The category contains organisms with sharply different clinical behaviour.

Beta-lactam. A drug family defined by a beta-lactam ring, including penicillins, cephalosporins and carbapenems. Members inhibit bacterial cell-wall assembly but differ greatly in spectrum and enzyme stability.

Penicillin-binding protein. A bacterial enzyme involved in building and reshaping peptidoglycan. Beta-lactams bind selected members of this group; altered proteins can produce resistance.

Bactericidal. Killing bacteria under specified laboratory conditions. The label can matter in selected settings but does not create a universal clinical ranking above growth-inhibiting drugs.

Bacteriostatic. Inhibiting bacterial growth under specified conditions. Host defences can then clear the population; the category does not mean weak or incapable of curing infection.

Minimum inhibitory concentration. The lowest tested concentration preventing visible growth under standard conditions, abbreviated MIC. It is a measurement interpreted with exposure, breakpoints and clinical evidence.

Breakpoint. A threshold within a versioned interpretive system that helps classify an organism-drug pair under defined regimens. It combines MIC distributions, achievable exposure and clinical evidence; values can differ by standards body and change as evidence or dosing changes.

Susceptibility. The likelihood that a bacterial isolate can be treated successfully with an antibiotic at a specified exposure. It is a relationship, not a permanent species-wide property.

Intrinsic resistance. A built-in feature of a bacterial species or group that makes a drug ineffective, such as absence of the target or inability of the drug to enter.

Acquired resistance. Resistance gained through mutation or incoming genetic material. It can spread vertically to descendants or horizontally between bacterial lineages.

Mutation. A change in genetic sequence. Mutations arise without foresight; antibiotic exposure favours the rare changes that improve survival under that pressure.

Horizontal gene transfer. Movement of DNA between organisms outside ordinary parent-to-offspring descent. It allows resistance genes to cross strains and sometimes species faster than clonal spread alone.

Plasmid. A transferable DNA molecule separate from the main bacterial

chromosome. Plasmids can carry several resistance genes together, allowing one drug to co-select a larger package.

Beta-lactamase. An enzyme that opens the beta-lactam ring and disables selected drugs. Different enzyme families have different ranges, so an inhibitor effective against one may miss another.

Efflux pump. A transport system that exports substances from the bacterial cell. Increased pump activity can lower intracellular drug concentration and contribute to multidrug resistance.

Biofilm. A surface-attached microbial community embedded in a matrix. Altered growth, local chemistry and penetration can make biofilm infection persistent without every cell carrying genetic resistance.

Empiric therapy. Treatment chosen before the organism and susceptibility are fully known, using syndrome, severity, patient risk and local data. It should be reviewed as evidence arrives.

Definitive therapy. Treatment selected after microbiological and clinical information has narrowed the cause. It may be narrower, safer, oral, differently dosed or stopped if infection is unsupported.

Prophylaxis. Antibiotic use to prevent a defined infection risk, such as around selected operations. Effective prophylaxis depends on timing and indication, not prolonged treatment by default.

Antimicrobial stewardship. Organised improvement of diagnosis, drug choice, dose, route, review and duration. Its purpose is better patient care while reducing avoidable harm and selection.

One Health. A framework linking human, animal and environmental health. It helps map antibiotic use, bacterial movement and resistance without assuming every pathway contributes equally in every setting.

Go Deeper

The accessible history. William Rosen, *Miracle Cure: The Creation of Antibiotics and the Birth of Modern Medicine* (Viking, 2017). Rosen supplies a fast narrative from synthetic dyes through penicillin, streptomycin and the pharmaceutical industry. It is the easiest next step for a reader who wants people, laboratories and commercial decisions rather than a microbiology textbook. The book is strongest on sequence, personalities and the conversion of discoveries into products. Its sweep is also a warning: when a dramatic episode matters, follow Rosen's notes into primary papers or institutional archives rather than treating narrative compression as the final authority. Pair it with Bud when you want the cultural and institutional consequences.

The primary clue. Alexander Fleming, "On the Antibacterial Action of Cultures of a *Penicillium*, with Special Reference to Their Use in the Isolation of *B. influenzae*" (1929). The paper is short and shows how far the famous observation remained from a systemic medicine. Read it to see the organisms tested, the limits Fleming reported and the laboratory emphasis removed by later retellings. Its old terminology is manageable, and the modest scope is instructive. The paper lets you compare what the discoverer claimed at the time with what public memory later assigned to him. It rewards slow reading because its omissions are part of the history.

The major interpretation. Robert Bud, *Penicillin: Triumph and Tragedy* (Oxford University Press, 2007). Bud follows penicillin as a scientific object, manufactured product, cultural symbol and model for later drugs. It is denser than Rosen and stronger on institutions, public expectation, regulation and the way success created patterns of use that later became liabilities. Read it after the narrative if the phrase miracle drug now feels too tidy. Bud's central strength is showing how a medicine can change culture and industry while its biological target continues changing beneath it. Its notes provide routes into production archives, policy history and earlier scholarship.

The current evidence map. World Health Organization, *Global Antibiotic*

Resistance Surveillance Report 2025. This is not a bedside guide or a smooth narrative. It shows what modern resistance surveillance measures, where the data come from and why global percentages require denominator discipline. Start with the executive summary, then inspect the methods, pathogen-drug combinations and country coverage before the headline tables. Notice which infections enter the system, which places have sparse data and how resistance differs by region. The gaps teach as much as the estimates because missing surveillance is not evidence of low resistance. Use the country annexes to see how national evidence quality and coverage differ.

Notes and Sources

The Whole Thing in One Page and Why You Should Care

The mortality discussion uses the WHO *Antimicrobial Resistance* fact sheet updated 16 July 2026 and the GBD 2021 analysis published in 2024. That analysis estimated 4.71 million deaths associated with bacterial AMR and 1.14 million attributable to it. The associated estimate uses no infection as its counterfactual; the attributable estimate replaces resistant infection with drug-susceptible infection. Neither figure is a surveillance count.

WHO's *Global Antibiotic Resistance Surveillance Report 2025* was published on 13 October 2025 and analyses 2023 data. It drew on more than 23 million bacteriologically confirmed cases reported by 104 countries and generated adjusted estimates for 93 infection type-pathogen-antibiotic combinations. The one-in-six headline refers to common laboratory-confirmed infections within that model, not every infection worldwide.

Albert Alexander's treatment date, clinical response, penicillin recovery from urine, exhaustion of supply and death are supported by the American Chemical Society's historical landmark account, Robert Bud and William Rosen. Accounts differ over the initiating injury and some clinical detail, so

the narrative does not rely on those disputed embellishments.

The dependence of surgery, intensive care, cancer chemotherapy, transplantation and neonatal medicine is stated as an enabling relationship rather than a claim that antibiotics alone made these practices possible. Sterile technique, anaesthesia, transfusion, imaging, immune support and procedural advances remain independent pillars.

The Core Ideas

Selective toxicity and the major target families follow standard antibacterial pharmacology and the reviews by Hutchings, Blair, and Munita and Arias. The discussion is organised by bacterial process rather than an exhaustive list of agents. Adverse-effect examples are class-specific and do not imply equal risk across all members.

The *Clostridioides difficile* example is retained as the clearest clinical case in which antibiotic disruption of colonisation resistance can cause disease. The manuscript does not generalise from it to claims that every microbiome change has a known long-term health consequence.

MIC and breakpoint language follows EUCAST's current definitions of S, I and R, checked 3 September 2026. S is “susceptible, standard dosing regimen”; I is “susceptible, increased exposure”; R indicates a high likelihood of failure even with increased exposure. Exposure includes mode of administration, dose, interval, infusion time, distribution and excretion. Breakpoints differ by standards body and version, so no numerical threshold is printed.

The pharmacokinetic-pharmacodynamic orientation uses the conventional time-above-MIC, peak-to-MIC and exposure-to-MIC patterns without assigning every drug rigidly to one index. General absorption, distribution and clearance remain within *Pharmacology in a Hurry*; this manuscript uses only what is needed to explain antibacterial success and failure.

The source-control examples reflect established surgical and infectious-disease practice. Drainage, debridement, relief of obstruction and

removal of infected devices are described as potentially decisive, not universally mandatory.

The bactericidal-bacteriostatic correction follows Wald-Dickler, Holtom and Spellberg's review of 56 randomised trials. Forty-nine found no efficacy difference, six favoured a bacteriostatic agent, and the one apparent bactericidal advantage involved a dosing concern. The manuscript rejects a universal hierarchy while preserving infection-specific guidance and exceptions.

The account of resistance mechanisms follows Blair and Munita and Arias. Extended-spectrum beta-lactamases, carbapenemases and altered penicillin-binding proteins are examples rather than a complete molecular catalogue. Resistance, tolerance, persistence, heteroresistance and biofilm protection are kept distinct because they involve different inheritance and measurement.

Ancient resistance is supported by D'Costa and colleagues, Forsberg and colleagues, and Larsson and Flach. Finding old or environmental resistance genes does not show that modern clinical prevalence would exist without human antibiotic use. The claim is narrower: defensive mechanisms predate medicine, while modern exposure amplifies and redistributes them.

Historical and clinical operation

Fleming's 1929 paper establishes the observation and its initial laboratory framing. Chain and colleagues' 1940 paper establishes the Oxford animal work. The American Chemical Society landmark, Bud and Rosen support purification, Heatley's role, early patients, the Peoria collaboration and industrial fermentation. Hodgkin's structure determination and the 1945 Nobel award are used only as chronological anchors.

The Prontosil and sulfanilamide sequence is supported by histories of antibacterial chemotherapy and Nobel material on Gerhard Domagk. The 1937 Elixir Sulfanilamide deaths and subsequent US regulatory response are documented by the US Food and Drug Administration. The episode concerns a toxic solvent, not failure of sulfanilamide as an antibacterial

compound.

Schatz, Bugie and Waksman's 1944 paper is the primary evidence for streptomycin. The credit dispute and royalty litigation are covered in modern histories. The text names the laboratory hierarchy without reducing discovery to a private motive that cannot be established.

The Medical Research Council's 1948 trial is described as a landmark in randomised clinical testing, not unqualified as the first randomised controlled trial. Its simultaneous demonstration of benefit and selection of streptomycin resistance supports the combination-therapy account.

The “golden age” dating is approximate and follows Hutchings, Truman and Wilkinson. Drug examples show the expansion of major families and associated limits; they do not imply that every listed compound was discovered by the same screening method or entered clinical use in the order presented.

The current clinical sequence is grounded in NICE guideline NG15, current NHS antibiotic advice, EUCAST definitions and standard laboratory practice. England's *Start Smart Then Focus* inpatient toolkit supports the 48-to-72-hour review wording. It is presented as one setting-specific operational standard, not a universal biological deadline or a requirement that every regimen change at that time.

What People Get Wrong and Use It

The virus correction concerns antibacterial drugs. Antivirals are outside this book. Secondary bacterial infection after viral disease explains why the presence of influenza does not exclude later antibacterial treatment.

The duration correction follows current stewardship guidance and the argument by Llewelyn and colleagues that “finish the course” is too absolute as a universal resistance message. The practical instruction remains conservative: patients should follow the current plan and contact the prescriber or pharmacist before stopping, extending, switching or reusing treatment. A clinician-directed revision is distinguished from self-directed

stopping.

The AWaRe categories and 70 per cent target follow WHO. The 53 per cent figure refers to the aggregate 2022 use data reported to WHO by 60 countries. It is not treated as a complete global census or as a target for an individual prescription.

The food-animal wording follows WHO's guidance against routine use of medically important antimicrobials for growth promotion or disease prevention in healthy animals. It preserves treatment of sick animals and does not assign a fixed fraction of human resistance to agriculture.

Environmental passages follow Larsson and Flach and WHO's 2024 manufacturing-waste guidance. Evidence for selection near high antibiotic discharges is stronger than evidence tracing any one clinical infection back to a particular environmental source. That limitation is explicit.

The pipeline report was published on 2 October 2025 but its clinical pipeline was cut off on 15 February 2025. It counted 90 products, 50 traditional and 40 non-traditional, and judged 15 innovative; for 10 of those the available evidence was insufficient to rule out cross-resistance. The manuscript distinguishes publication date from data date and candidates from approvals.

The WHO 2024 bacterial priority list contains 24 pathogens across 15 families. The book uses the list only to explain research priority and does not turn it into a ranking of danger for an individual patient.

The economic discussion uses the incentive logic behind delinked and subscription models. NHS England's antimicrobial products subscription model is treated as an example of paying partly for availability rather than volume, not as proof that one procurement design has solved the global development problem.

Scope

Microbiology in a Hurry owns the wider microbial world, methods and antimicrobial resistance across that discipline. *Pharmacology in a Hurry* owns general targets, dose-response, pharmacokinetics, development and drug adaptation. *Immunity in a Hurry* and *Vaccines in a Hurry* own host defence and vaccine mechanisms, while *The History of Medicine in a Hurry* owns the wider chronology. This book goes deeper only where antibacterial action, resistance, stewardship and history require it. It is explanatory and not a prescribing manual.

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