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Detour – Antimicrobial Resistance, Co-Extinction, and the Gut-Eye Axis (Part II)

Credit: Photos by Frank Cone and Mikhail Nilov (Edited, from Pexels)

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So ends AMR week 2025. Do consider: The gut, respiratory, and ocular microbiota in eye health & disease, antimicrobial contact lenses, rapid evolution and countering of antimicrobial resistance (AMR), and plagues of rabbits.

There are usually more microbial than human cells in your body. Advanced sequencing techniques have been uncovering much more about our assorted microscopic menageries within, built and cultured from birth. Unlike the kakapo, we have dozens of strains of bacteria, fungi, archaea, protozoans… Even ectoparasitic mites, viruses, and temperate phages. Some are crucial, some are beneficial, and some are little monsters. For the eyes, microbe communities and their metabolites have been tied to conditions as varied as myopia, dry eye disease, and glaucoma.

An appropriately populated gut microbiome is essential for long-term health and immune system function, but vulnerable to inappropriate use of antibiotics. Antibiotic misuse is also problematic because it is selecting for antimicrobial resistant (AMR) strains of bacteria, fungi, and parasites which are projected to cause millions more annual deaths in future (GRAM Project, 2024). Be ware – as it was the official week to do so – but fear not. Scientists are using machine intelligences and massive genetic databases to source for alternative antimicrobials, weapons forged by billions of years of itty-bitty biological antagonisms.

And Lord only knows what the rabbits will get up to in the Pacific…

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Detour – Antimicrobial Resistance, Co-Extinction, and the Gut-Eye Axis (Part II)

(Part 1: Parrot)

Part 2: Rabbit.

We begin with Eubiosis

Labetoulle et al. (2024) employ the term 'eubiosis' to describe the condition of a healthy gut microbiome, with no disruption to the barriers and layers of the gastrointestinal tract. Every commensal remains in it's appropriate place and proportion. Dysbiosis instead may result in colonising opportunities for pathogenic microbes, different circulating metabolites (products of gut bacteria), and altered immune system activity and inflammation.

Often used in reference to the gut which accounts for roughly 99% of the microbial mass within us, the term 'microbiome' applies to several specialised living communities of the skin (multiple), the ocular surface (multiple), lungs (multiple), and oral microbiome (Kammoun et al. (2024); H. Lee et al. (2025)). Even breast milk has its own, jump-starting a baby's immune system development, with certain gut bacteria possibly also beneficial for healthy pregnancies and births. There might even be a brain microbiome, though there remains uncertainty about this for a healthy nervous system. Instead, recent studies have supplied us with unnerving evidence of bacterial families residing in and perhaps cooperating with brain tumours.

Focusing on the gut, it is indeed richly populated by influential micro-organisms, including species of fungi (the mycobiome) that could be used to treat alcoholism or better understand genetic risks for cardiovascular disease. Archaea in cahoots with bacteria may play a role in infectious disease (Duller et al., 2024), cognitive performance (Fumagalli et al., 2025), and perhaps even healthy ageing (Mohammadzadeh et al., 2025). Although this article doesn't cover viruses, the gut virome's sub-population of temperate phages is another area of study. Their capacity to infect bacteria and influence their activity and/or resilience is thought to be a potential counter-AMR strategy (Bioengineer, 15/10/2025), albeit a much more complicated option. Unless we learn how to use Stevia doses for precision bacteriophage activation and predation of unwelcome strains. Slay.

Death, Disease, and Dysbiosis

According to global data from 2021, vascular and respiratory diseases are some of the leading causes of death along with respiratory cancers, dementia, diabetes, tuberculosis, and interrelated AMR and sepsis. Naturally the data differ greatly by country and region, with 'unintentional injury' at the third position for the United States (Ahmad et al., 2024). Sepsis, a host immune response to infection, is also technically around number 3 for the US, especially for hospital deaths, but not counted as an underlying cause (Morrissey et al., 2025). There is a complex relationship between sepsis late diagnosis, misdiagnosis, antibiotic prescriptions, and the rising rates of AMR in populations and hospitals. For tuberculosis, incidence and mortality is largely determined by regional underdevelopment and poverty, which is one amongst many factors that make the disease challenging to diagnose and treat.

Chronic stress, lack of regular exercise, and diets high in sugar and saturated fats can lead to dysbiosis (Kammoun et al., 2024), systemic diseases, and higher mortality risks post-infection. The antibiotics we use to treat infections (which are often misdiagnosed, but there's already several AI tools to help) can also negatively impact commensal microbes – and thus our health and immunity – over the long-term. Dysbiosis also features prominently in a growing body of literature on inter-organ axes in disease.

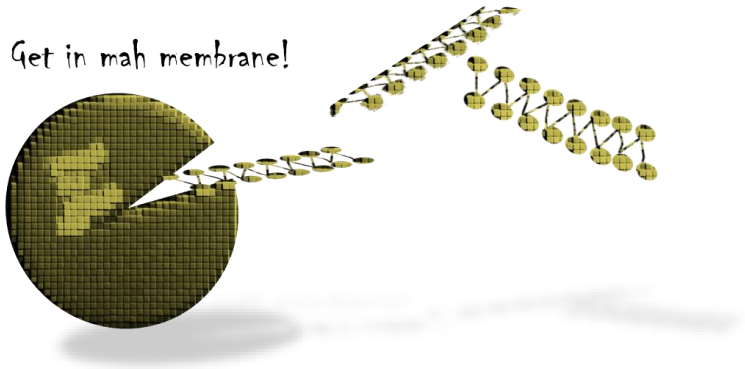
Multi-Omic, Ocul-Omic, Micro-Biologic

In research on some of the main mortality-causing conditions, it seems that what occurs in the respiratory tract, colon, or pancreas can end up affecting the brain and retina. The gut microbiome is proving to be a hotbed of causation, biomarkers, and therapeutic potential. This is somewhat aligned with the move towards multi-omic and non-invasive diagnostics for brain disease, and the nascent field of oculomics (See Weinreb et al., 2025) when it comes to the eye. Both have been facilitated by massive datasets as well as deep and machine learning for suprahuman analysis, tools similarly employed in building our understanding of microorganisms for the potential countering of AMR.

'Healthcare from the eye' aided by pre-screening, healthcare networks, and AI tools is a major new intiative by Topcon and the Institute of Digital Health (IDHea). Other types of artificial intelligence (AI) like latent diffusion and large language models (LLMs in biology reviewed by Lin et al., 2025) are also being used in the protein and chemical spaces for drug and material design. AI has become pretty handy for genetic analysis as well, scanning microbial codes for evolutionary relatedness and ideas. In future, as data-gathering and foundational knowledge improve for the different human microbiomes, AI might be utilised more for understanding eubiosis too (reviewed in Fonseca et al., 2025; Kim et al., 2025).

The Microbe Directory (TMD) by Oxford University demonstrates that at this stage, manual annotation by independent human volunteers with domain knowledge is still necessary (Sierra et al., 2025). The database is meant as a free, user-friendly resource for microbial phenotypes and ecology, pulling from other databases like the Human Microbiome Project and TARA Oceans, thus covering commensals and polar extremophiles. Despite the advantage of speed (versus 8-13 hours / week / 10 species / volunteer), Gemini AI had limited results matching with the TMD annotated data, especially for Archaea and Eukaryotes (Figure 4).

What does that mean? Well, that there is much we (and the machines) do not yet know about microbes, including those co-evolved within and their potential role in our novel healthcare technologies and natural bodily defence.



In a recent exploratory study using mice, researchers from the University of Cambridge found that certain strains of gut bacteria may be helping to clear our bodies of Perfluoroalkyl and Polyfluoroalkyl Substances (PFAS), engineered forever chemicals that are increasingly linked to endocrinological dysfunction and disease. Authors Lindell et al. (2025) found that they are able to do this without themselves being metabolically imperiled by squishing the artificial molecules into dense clusters, like a garbage press. If the same action is found in humans, anti-PFAS probiotics are an idea being floated around to deal with harmful bioaccumulation in our tissues.

Some Inter-Organ Axes in Disease

The Gut-Brain Axis

As mentioned, humans have several different tissue-specific microbiomes. Each seem to have an optimal mix and ratio of microbial kingdoms (bacteria, fungi, archaea etc.) and strains that we're just starting to figure out. Upsets to that balance are analysed in disease pathways, with connections through anatomy, blood circulation, travelling microbes or metabolites, and the nervous and immune systems. In the past few months numerous articles have been published about the link between neurological development, neurodegenerative diseases, and the gut (e.g. in an issue of Inside Precision Medicine (IPM), Shafieinouri et al., 2025; Paul et al., 2025; Jabbari Shiadeh et al., 2025; Mukherjea et al., 2025).

Liu et al. (2025) at Duke University were able to link host feeding behaviour to levels of gut bacteria (only *Salmonella typhimurium* tested) in the colon through 'neurobiotic sense'. They refer to this gut-brain pathway as an additional sensory dimension, helping us respond to detected levels of flagellin in the colon, the latter a core feature of bacteria. Plant immune systems also rely on flagellin detection to mount a defence against pathogens, which some intend to supercharge with AI-mediated receptor design.

Gut-brain information flow is complex and bidirectional, involving the nervous system, hormones like serotonin, antioxidant short-chain fatty acids (SCFA), the immune system, and blood circulation. In a mouse model of Alzheimer's disease, Makhijani et al. (2025) found that neurodegeneration feeds back to colonic immune system, and that an inulin-rich diet could in turn be used to restore gut microbiome health, thereby attenuating certain aspects of Alzheimer's. There's also some promise in terms of improving mood disorders.

The Gut-Eye Axis

The gut linkage naturally extends to the retina, a part of the brain. Tirziu et al. (2024), Kammoun et al. (2024), and Labetoulle et al. (2024) have reviews on the link between gut dysbiosis and ocular disease. Notably, both the gut and eye have interrelated and interactive microbiomes. There's a fairly substantial list of eye conditions that are associated with and show some promise in being managed via the gut microbiome. That includes glaucoma, dry eye disease and uveitis, age-related macular degeneration, diabetic retinopathy, and even myopia. Dietary change, prebiotics, probiotics, and synbiotics with gut microbe and ocular targets may eventually become more common interventions.

Example: Sedentary lifestyles and diets high in saturated fats and sugar can imperil the function and survival of beneficial microbial strains in our gut, an opportunity for less benevolent species to thrive and secrete their own brand of toxic metabolites. A high fat diet through this sequence of events then raises the risks of choroidal neovascularisation (Ullah et al., 2024; Hui et al., 2025).

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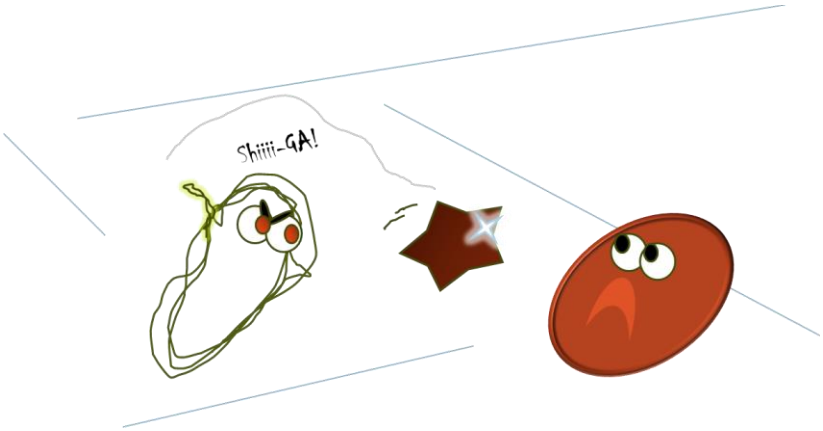
Ocular Surface Microbiota (OSM), Gut Microbiota (GM) -> Glaucoma

Some years ago a relationship was found between gut dysbiosis and glaucoma, traced to abnormal blood-barrier permeability and as a consequence, increased T-Cell reach and activity around the eye (Ullah et al., 2024). Later studies found elevated levels of the metabolite trimethylamine in galucoma-affected eyes, while a greater relative abundance of *Streptococcus, Staphylococcus*, and *Corynebacterium* were found in the OSM. By increasing the levels of butyrate, a 'good' metabolite, intraocular pressure could be lowered, summarised in Kammoun et al., (2024).

Glaucoma patients often have gut dysbiosis, e.g. from irritable bowel syndrome or a *Helicobacter pylori* infection, resulting in an elevated level of pro-inflammatory bacterial species and byproducts. This seems to lead to barrier disruption, inter-organ inflammation, and a tissue-damaging immune responses in the eyes (reviewed in Tirziu et al. (2024); Ullah et al., (2024)). However, this is less clear and direct than it may seem from a paragraph-length summary, as *hundreds* of gut microbe species were found to differ significantly between glaucoma patients and controls (Chen et al., 2022 cited in Ullah et al. (2024)). Hernandez-Zulueta et al. (2024) have a short and helpful list in Table 1, divided by the ocular, oral, and gut microbiome.

One of the main culprits implicated in the gut-glaucoma literature, first analysed for primary-open angle glaucoma by Gong et al. (2020), happens to be the species *Escherichia Coli* with their lipopolysaccharides potentially provoking an immune response. The specific strains were not identified.



There are hundreds of strains of E. Coli, a gram-negative bacteria. Some are commensal, for us and the kakapo. Some strains produce Shiga toxin (STEC) which causes lysis of red blood cells, kidney dysfunction, and disruption to protein synthesis and cell signalling that can be fatal. Contaminated alfalfa or even adorable animals in a petting zoo may harbour STEC.

GM -> High and Pathological Myopia

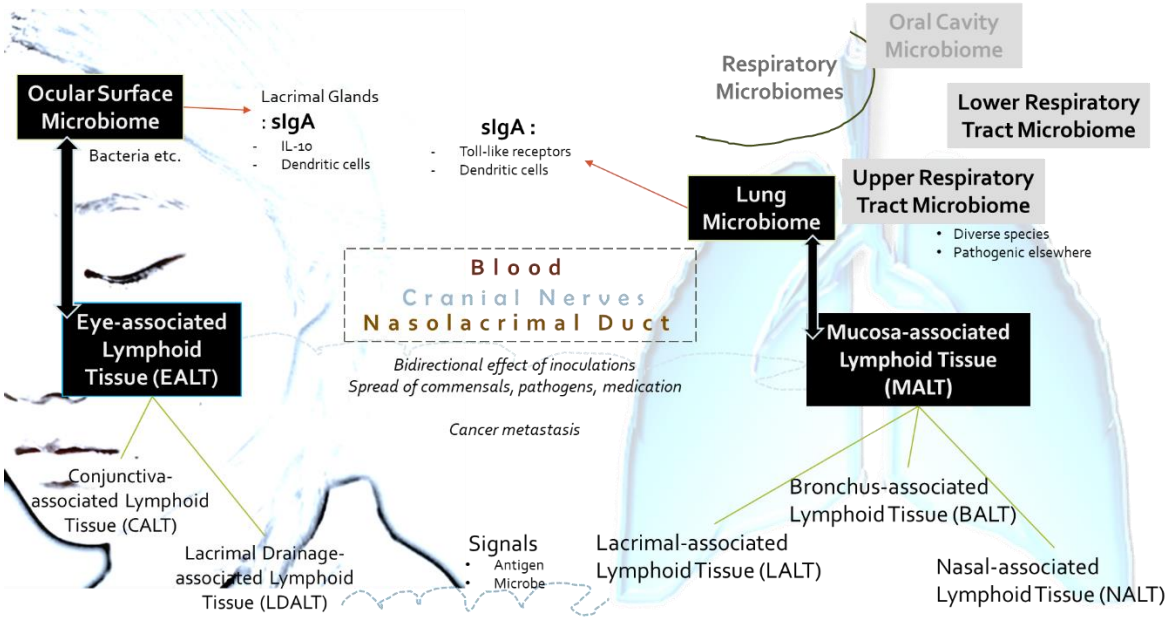
Experiments by Hui et al. (2025) and Li, H. et al. (2024) showed possible pathways for the influence of gut microbiota and their metabolites on myopia. Besides a 'reduction in probiotic abundance', the plasma of high myopia patients was found to have low levels of indole-3-acetic acid (3-IAA), a metabolite that seems to improve collagen type I alpha 1 (COL1A1) expression in the sclera and limit myopia progression (Li, H. et al., 2024). *Akkermansia* and its role in tryptophan metabolism and inflammation was found to be protective, which may also be true for diabetic retinopathy (in Tirziu et al., 2024).

In their investigation, Hui et al. (2025) identified gut microbiotal taxa and metabolites that may have protective (*Bacteroides intestinalis A* only) or strong causal effects on myopia and pathological myopia, actions involving linoleic acid, albumin, and polyunsaturated fatty acids (Omega 3 and 6). Surprisingly the taxa identified as causal for myopia and pathological myopia did not overlap, with authors pointing to shared mechanisms between pathological myopia and glaucoma instead.

A Lung-Eye Axis – H. Lee et al. (2025)

Over 100 years ago, before the topics of dysbiosis in disease and the gut-eye axis became a thing, a connection between the lungs and eyes was noticed in cases of tuberculosis (across species) and cancer. H. Lee et al. (2025) describe this association as 'functional crosstalk' and 'dual-system pathophysiology' through mucosal, vascular, and microbe-linked inflammatory pathways. Based on severe acute respiratory syndrome (SARS) studies, transmission may also take place via cranial nerves. The lung-eye axis has further axis-type relationships with the gut and brain, and applies to both infectious and non-communicable disease.

Authors identify different ocular and respiratory microbiomes as well as sections of mucosal (lymphoid) tissue, pointing out that microbes with commensal roles in one space have pathogenic or inflammatory roles in others. Secretory immunoglobin A (sIgA) is common to both organs, perhaps mediating immune system communication dependent upon local microbes. Unfortunately, this means a history of dysbiosis or inflammation in one tissue, for example ocular uveitis, primes the response in others and may yield systemic inflammation. Microbe corpses from past infections in the lung may also travel to the eye and cause ocular inflammation. As for physical mechanisms: Coughing as a symptom of respiratory disease allows for transmission of viruses to ocular tissue through anatomical passages, called 'nasolacrimal reflux'. Conjunctivitis and keratitis thus become common co-occurrences with respiratory infections.



Summary diagram in not-cute aesthetic, based on text of H. Lee et al. (2025). Left background based on image by cottonbro studio (Pexels)

For viruses, as the receptor profiles of lung and ocular tissue are similar and the nasolacrimal duct acts as an anatomical bridge, they show similar vulnerabilities to viral infection and commensal shuttling. Blood ciculation to the choroid and conjunctiva provides another avenue, for spread of lung cancer and hematogenous spread of bacteria, especially *mycobacterium*. This was demonstrated in experiments on rabbits and zebrafish in the 1920s. As has been recently found in brain cancer, dysbiosis and certain microbes may then not only facilitate cancer progression, but cause inflammation and immunosuppression of other tissues.

The article's unexpectedly kawaii pastel-coloured diagrams clearly and simply depict the main anatomical pathways (Figure 1 and 2) and an example of shared disease mechanisms in the case of glaucoma and pulmonary diseases (Figure 3). The conclusion of paper points out that we don't know nearly enough about the ocular surface microbiome yet, which would be important for disease management and potentially diagnosis-from-the-eye for respiratory or systemic diseases.

Antimicrobial contact lenses

Perhaps more about this in a future article, but briefly for now in consideration of AMR:

Due to the rising prevalence of refractive errors and age-related eye disease, and therefore contact lens use and opthalmic surgery, novel antimicrobial characteristics are being sought for contact lens and other ocular implants and devices (See Tirziu et al., 2024; Qiang et al., 2024; Vivero-Lopez et al., 2022). Contamination of these surfaces can lead to eye infections (single or poly-microbial), inflammation, and possibly blindness if not handled in time. The risk is higher when our own ocular surface microbiota and homeostasis are already compromised, which can happen as a side effect of contact lens use (Vivero-Lopez et al., 2022; Zhu et al., 2024).

In the overview by Dziegielewska et al. (2025), MRSA is described as the dominant pathogen in conjunctivitis cases, with bacterial biofilms common for keratitis. Over 91% of contact lens-related microbial keratitis cases in Europe were caused by bacteria, the rest by fungal and Acanthamoeba infections (Zhu et al., 2024).

Drug delivery is identified as an issue, and figuring out how best to achieve this for the complex micro-environment of the eye. Biocompatibility is of course a major problem, highlighted by Zhu et al. (2024), along with user comfort and compliance. Some multi-modal objectives for the design of new contact lenses include being antimicrobial, bacteriostatic, prebiotic (for the OSM), mitochondria-supportive, anti-inflammatory, and anti-oxidant. Use of metals – but not mercury. We have learned – as well as phytochemicals (from plants) with surface properties that prevent microbe attachment and biofilm formation are major directions in research and experiments.

Vivero-Lopez et al. (2022) happened to test their resveratrol-releasing lenses on some New Zealand white rabbits.

Commensal microbes in a support role to our immune system are usually good at keeping pathogenic infestations in check, unaided by natural or synthetic antimicrobials. For example, up to one-fourth of the world population may already be infected with tuberculosis. Over 2 billion people may have the parasite *toxoplasmosis gondii*. But these are kept as latent infections, with few symptoms or damage to the host. Other resident microbes like the bacteria *S. aureus, C. difficile*, and the fungus *candida albicans* only become an issue when something is knocked out of balance in their microbiotic pocket.

Then we use drugs. But some resist.

We end with Resistance

The Rabbit Wars & Antimicrobials

The Global Research on Antimicrobial Resistance (GRAM) project by the University of Oxford gathers data on AMR and also assists countries with capacity-building. After estimating sepsis and AMR-associated deaths at 21.36 million and 4.71 million in 2021, their publication in September of 2024 predicted a significant increase in annual deaths, amounting to 39 million over the period of 2024 – 2050. Their empirical research on pathogens informs meetings of the United Nations General Assembly (UNGA) and global health policy, as does the data collected for the WHO's GLASS (Global Antimicrobial Resistance and Use Surveillance System) intitiative. The latest GLASS report is here, covering 22 antibiotics, 8 types of bacteria, and four types of infection.

Microbial evolution fuelled by a variety of converging factors is certainly fast, but it's not all nightmarish. First, a study published in April by Emons et al. (2025) showed that antibiotic resistance of some bacterial species tends to plateau over 20 years. Next: Multiple institutions and organisations aided by machine and deep learning have the pathogenic microbes in their sights, for example at MIT and GSK . There are also hopes that machine learning or large language models will assist in managing sepsis.

Accessible genomic testing of infections and perhaps AI are also expected to improve diagnostic accuracy and therefore antibiotic prescription precision. Availability, affordability, and cultural acceptibility of new tools and aproaches are thought to be crucial for reducing AMR risk in lower income territories.

Parellels, perhaps, might be useful too. Let us explore the history of a cute, non-microscopic mammal. The cute part gets struck off once you notice Hades follows close behind…

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Resistance: The Rabbit Wars

Strange that some heroes of conservation in the United Kingdom are dark-coated, devil-horned sheep (part 1). For 20th Century Australia, Tasmania, and New Zealand, there was once a sight portending ecological death and ruin: A silhouette not of devil horns, but grey, straight-eared, wild-type, European rabbits.

The Wild Rabbit. Based on CSIRO footage (1979; 2014)

"It's underlying substrate is biology.

Biology's core fundamental directive principle, whatever you want to call it, is to replicate and reproduce, not to make the product you want."

– Dugar, quoted from LeMieux (2022, timestamp 21:48)

Remember the weasals and stoats brought by European settlers that decimated kakapo and kea populations? Know why they brought weasels and stoats? Rabbits. A surprisingly illuminating case study for AMR. Those troubles for New Zealand and its beleaguered sheep farmers are covered in a documentary called *Apocalypse Down (2021)*. Perhaps even more hardcore than the Kea, New Zealand's invasive rabbits survived the harsh winter of 1991 by eating each other's ears (timestamp 8:57). Contemporary Australian populations dig up graves.

In Australia's long list of animal wars and defeats, the rabbit plagues are considered the most massive ecological disaster, with chance and deliberate viral outbreaks the heroes of the story. Similar to microbes, their 'biological superpower' is rapid reproduction and adaptation to things that used to kill them. This is extremely bad news for the region, considering funding for development of biological controls has run out, with novel deadly strains thought to be needed every ten to twenty years (Foley, 2025; CSIRO).

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It began harmlessly. Few perceived the risks despite historic records of island rabbit infestations that could be extreme enough to result in agricultural ruin, famine, and total territorial abandonment, as was the case for 15th century Porto Santo, Madeira. For the Balearic islands incident around 30 BC, none other than Roman emperor Augustus had to be called in to help. He sent some skilled hunters for tutelage and recommended ferrets. Thanks to these new tools and skillsets, the islanders were eventually able to eat their way out of the problem (in Hansley, 2019). See why a classical education matters? Although perhaps those societies didn't have such problematic meat and fur lobbyists (Foley, 2025).

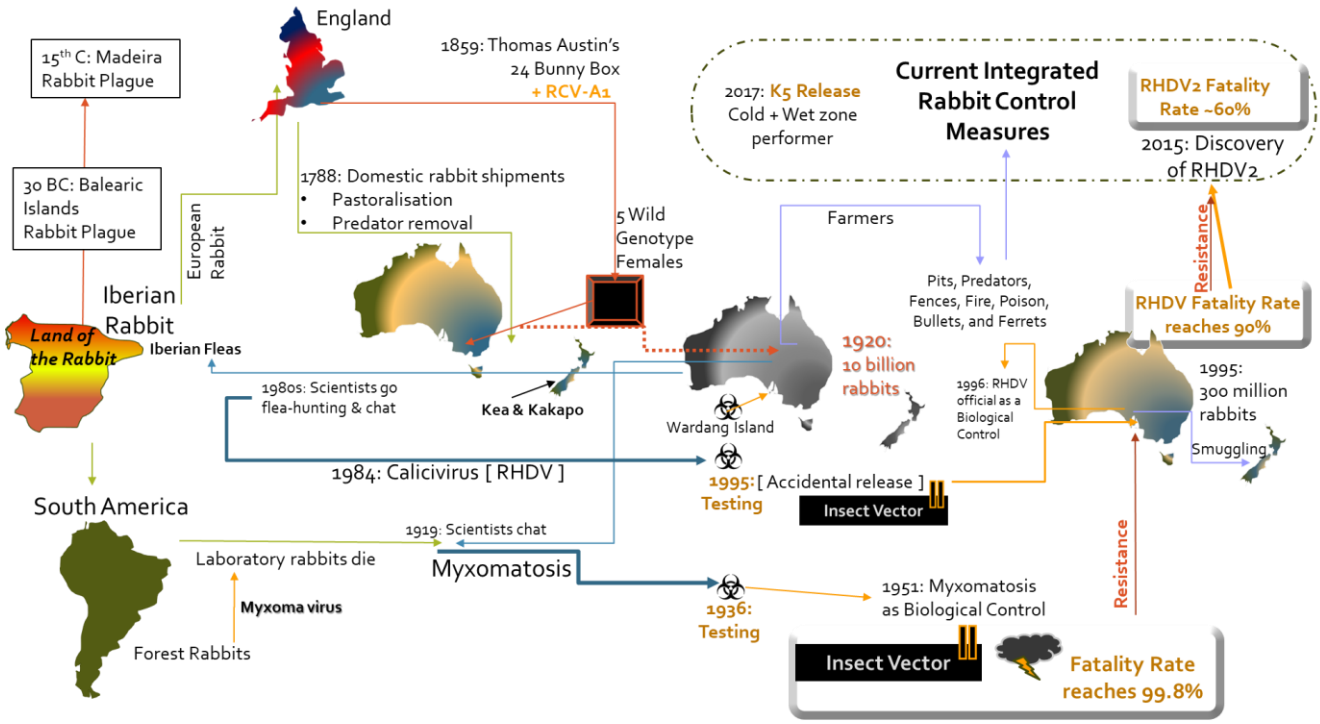
For mainland Australia, the first batch of domesticated bunnies that were tame, fancy-coated and floppy-eared arrived on the island in 1788, with 90 or more further imports until 1859 (Alves et al., (2022) provide a map of historic bunny translocations). Many were kept as pets in settled areas along the coast, others sent to Tasmania and New Zealand. Some escaped or were released and established small local populations. Still, all seemed well.

Until… Longing for the hobby-hunting of his homeland, a settler named Thomas Austin asked his family back in South West England to send some rabbits over for sport. The family assembled a package of 13 wild-caught and domestic rabbits, which upon arrival by ship had become 24, on the 25th of December 1859, ready for a festive shooting.

Despite Austin's expectations of environmental enrichment, this turned into a great misfortune for Australia and its neighbours. In combination with environmental changes like expanded farmland and removal of numerous predator species, these wild-type bunnies had an 'invasive genotype' (Alves et al., 2022) as well as distinctly less cute physical traits such as straight ears, and short grey coats. This new strain very much turned the tide against humans, crops, livestock, and much of the native wildlife. Traced by genetic analysis to 5 original females likely from the 1859 Christmas Day shipment (Alves et al., 2022), by the 1920s Australia was covered in a 'grey blanket' of *billions* of rabbits. Walls, poisons, and hunting in the millions had no impact. Footage from farms of the time show seething living swarms and smoke from piles of burning bunny bodies. A report in 1938 described the ground seeming to move as they came in their millions, by weight of numbers suffocating each other in the killing pits.

Understandably, this plague legitimised the release of the first ever deliberate-release virus for biological control in 1950, causing a rabbit-specific disease called myxomatosis. Initial test releases proved disappointing, as experimental strains seemed unlikely to spread. However, moving into 1951, rainy weather resulted in a boom of insect vectors for widespread transmission (Ward, 2011). Lethality post-infection reached 99.8%, but that didn't last long. Rapid reproduction and genetic recombination led to resistance, and numbers began climbing again. Experts in the 1990s and presently advise that even with biological controls, factors such as infection timing and hitting reductions above 95% through poisons and other synergistic measures are required to keep resistance from building and rabbit plague from re-blooming.

In the late 1980s, different types of fleas were being sourced to help increase infections. Spanish fleas, a historic pest-pair of the original Iberian rabbits, turned out to be the best candidate. While hunting for such useful fleas in Spain, Australian scientists heard of a new type of viral rabbit killer (CSIRO). The fleas were a bit of a bust, and so arose interest in calicivirus, a rabbit haemorrhagic disease (RHDV). A benign strain known as rabbit calicivirus Australia 1 (RCV-A1), residing in their gut and offering cross-protection, was in fact also introduced to Australia via Thomas Austin's wild shipment in 1859 (Jahnke et al., 2010). Careful preparations for release of bunny-Ebola began in 1995, but it was taking far too long for desperate farmers, with rabbit population estimated at 300 million and climbing.



A rough summary/timeline of events, compiled from references and linked sources. The 1920 estimate of 10 billion rabbits is from Foley (2025), majority of the other data from CSIRO, Ward (2011), and Alves et al. (2022).

Yet another miracle, once more borne by insects wings: In late 1995 experimental calicivirus escaped from Wardang Island's high security bio-testing site. While scientists, authorities, and other elements of society were somewhat uneased and displeased, farmers were *thrilled*. Some from New Zealand and Australia smuggled the infected corpses of rabbits over to their own land, blending up the bloody organs and marinating some carrots in the viral-hot stew, to spread amongst their own problem hordes (ABC Australia (2020, February 14); Newsroom NZ (2021, July 21); Anderson (1995)). Official release of RHDV was in 1996. In dry areas rife with flies as vector, fatalities hovered around 90%. Prior to evolution of rabbit resistance, a new strain evolved/arrived, dubbed RHDV2 which was confirmed in 2015, reportedly taking out 60% of the remaining wild rabbit population (CSIRO). Essentially natural viral evolution outpaced both rabbits and men.

The Korean strain K5 is the latest permutation. It was selected for its efficacy in cold, wetter climates (a gap for prior insect-vector viruses) and released in 2017, to be used in conjunction with other measures as the lethality rate is noticeably lower. There are clear use guidelines and protocols on integrated methods available for landowners (example). Whenever there is a scheduled RHDV release to control pest numbers, pet owners are advised to keep their rabbits out of harm's way, and a calicivirus vaccination is available for these domestic breeds. Successful island rabbit elimination programmes may prove to be an interesting read, and strangely a national rabbit database was only configured in 2019. Such tools are deemed essential for understanding and countering AMR as well, and ironically, rabbits were our very first animal source of antimicrobial peptides.

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Microbial Resistance: Crisis plus Feature

Where, What, How, and Have at you, AMR.

A topical video was published last week on Youtube, titled 'Antibiotics are ending. We are all going to die' (Panchin, 2025). This actually sounds a bit less terrible in Russian. Anyway: Within were fun animations and a grim and gory look at bacterial diseases of medieval Europe, then the more encouraging human history of antibiotic discovery and use. Around 350 BC, the Nubians had unknowingly tetracycline-treated their food. In 1909, a chemical antibiotic derived from arsenic was deployed to counter syphilis. Specifically syphilis. Specificity was a new approach, according to the 'magic bullet' concept and also an advancement from its earlier 'treatment' which was mercury. By the 1940s, a biotic antibiotic derived from green mold (*Penicillium notatum,* a fungus) stole the show, becoming the drug of choice for numerous infections after A. Fleming observed how well it performed against the bacterial cell walls *Staphylococcus aureus (+)*.

In 1944, streptomycin was the first antibiotic administered for tuberculosis (*Mycobacterium tuberculosis*, ~+), which has been a leading cause of death for hundreds of years. Like myxomatosis-exposed rabbits, tuberculosis rapidly developed resistance to the antibiotic unless treated in conjunction with the chemical para-aminosalicyclic acid (PAS). Several more drugs followed soon after, and long, multi-drug treatment protocols have been designed to limit resistance evolution (Murray et al., 2015). Despite estimates that one quarter of the global population might have a TB infection, annual fatalities have ranged from 1.2 to 1.6 million over the past few years (Nardell, 2025). Hopes are that new tuberculosis antiotics like sorfequiline and vaccines could drop these figures and AMR risk (MIT news; WHO).

Broad-spectrum penicillin became a life-saver of millions, including the unfortunate sheep of New Zealand tormented by the kakapo and their *Clostridium (+)* contaminated beaks (Temple, 1994). Incidentally, Penicillin and *S. aureus* remain in a pretty active and innovative arms war.

From 1987 to present, evolution of drug-resistant strains has started to look like a real problem because antibiotic drug discovery hit a void. Meaning: The microbes are evolving at the same or greater pace, but supply of novel compounds and methods to counter them have slowed. Worse, we offer them an abudance of spaces and opportunities to lurk, learn, and coalesce as biofilms.

Vast hospital spaces serve as sources of supra-natural selection pressure and hub for horizontal transfer of genetic 'ideas' to the microbes within, notably MRSA (methicillin-resistant *S. aureus*) and the increasingly fatal multi-drug resistant *Acinetobacterium Baumani* (~–). The weakened immune systems of unhealthy and ageing populations, rising prevalence of systemic disease, improper antiobiotic use, and sub-optimal surface-cleaning techniques are some factors behind this.

A key concept from the 'we are all going to die' video is that antibiotics might be better conceived as *inter*-microbial weapons, ancient features forged by billions of years of competition and cooperation between microbe species, plants, and animals that we can discover and repurpose for our own defence. A crisis perspective might create urgency, but perhaps doesn't fully capture phenomenon and conceivable solutions. Frankly, as it is a feature of nature, the principle, tendency, and opportunity for AMR is everywhere. Behold, if you please, some enculturing environments:

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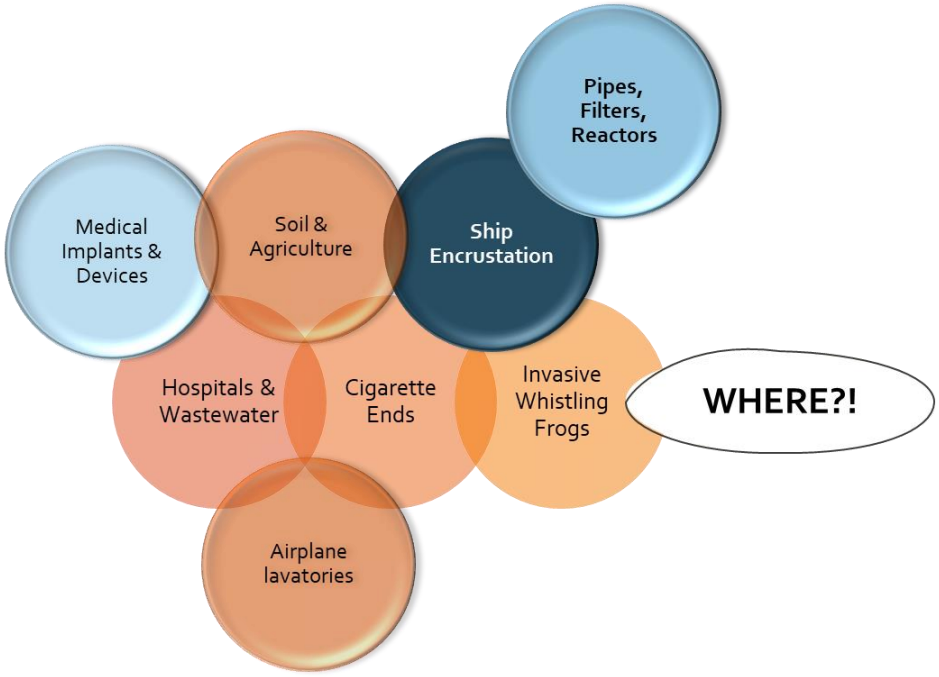
AMR where?



When Li, D. et al. (2025) analysed the genomes of a set concerning pathogens – the ESKAPE+E (listed in a figure below) – they found some strains had started to evolve resistance to heat and chlorine, thought to be dependable disinfecting agents. Hospital devices, surfaces, and wastewater are major sources of this risk (Li, D. et al., 2025; Bakon et al., 2025), in addition to surfaces that we take for granted in the built environment and everyday industry. Though not as relevant for AMR (or at least not as widely referenced) marine surface biofouling is a significant challenge in the shipping industry. Who knew microbes could slow ships in addition to mucking up contact lenses?

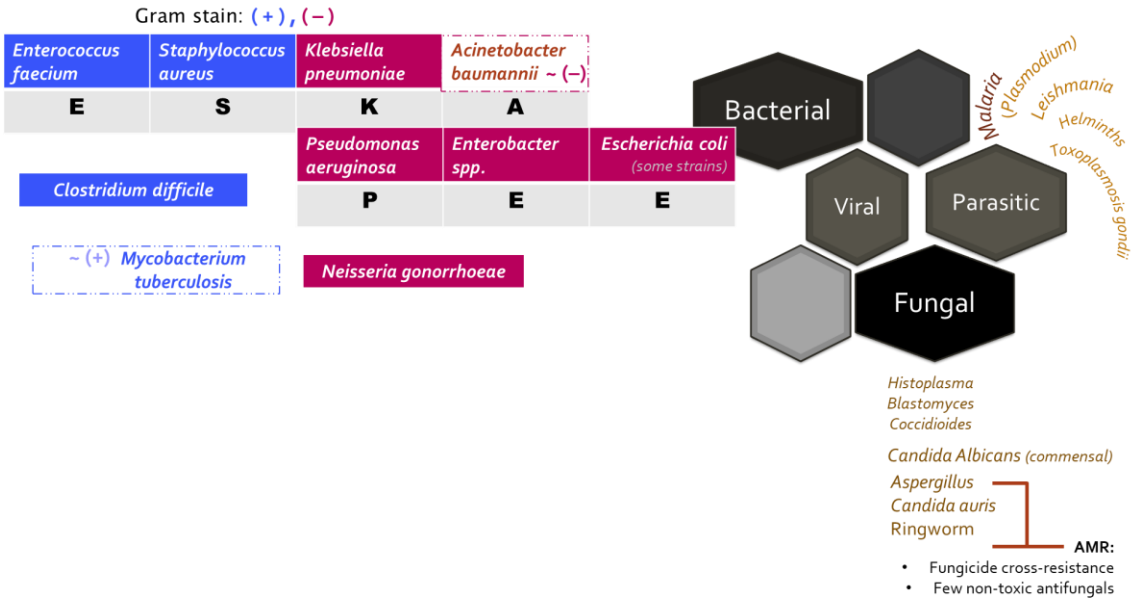
Most of us do know smoking isn't great for health. In addition, because the toxic particles from smoking make bacteria freak out, the stress response can enhance transfer of multi-drug resistant genes (Fang et al., 2025). Furthermore, discarded cigarette butts apparently acts as 'reservoirs and amplifiers of antibiotic resistance genes' in urban green spaces (Xu et al., 2025; nicely summarised here). In Latin America, invasive species of whistling frogs acts as reservoirs for Enterobacteriaceae (Abreu et al., 2025). According to a new sampling technique, aquariums may harbour problematic efflux pumps and human gastrointestinal tracts yet undiscovered streptothricin-resistant proteins. Aircraft lavatories harbour AMR pathogens too.

AMR what?

Brevity is very much in vogue these days, but it can be a little unhelpful to say 'antimicrobial resistance' when communicating about such an *enormous* swathe of living, interrelated organisms. Beyond the barely fathomable variations, microbes are also constantly adapting – which makes them rather alien to the notion of 'conservation' (Cohen, 2025) and more difficult for therapeutic design.

As a simple answer: The term AMR when used often refers to bacteria, especially gram-negative or the mixed group of ESKAPE+E pathogens that cause serious infection and mortality in hospitals (Zhu, Q. et al., 2024; Li, B. et al., 2025),

along with tuberculosis, gonorrhoeae, and some carried species like *C. difficile* or mouth-resident fungus *Candida albicans* that sometimes grow out of control, e.g. post antibiotic-use.



A casual selection of the main human-infecting microbes studied and mentioned re: AMR. Intrinsic and acquired resistance mechanisms, biofilm formats (especially involving mixed populations) and certain cellular states may reduce the efficacy of antimicrobials, immune system action, or hygiene protocols.

Strange that bacteria get so much publicity, because other domains of life are involved in AMR disease and death too, such as fungi, parasites, and viruses. Granted bacterial spread of resistance genes is faster, but fungal infections kill millions, estimated to be 3 – 8 million deaths in 2022, and mosquito-borne malaria caused by *plasmodium* parasites has been a leading cause of death for a very long time. All have been developing resistance, whether to a single, multiple, last-resort, or even all available drug classes, known as pan-drug resistance.

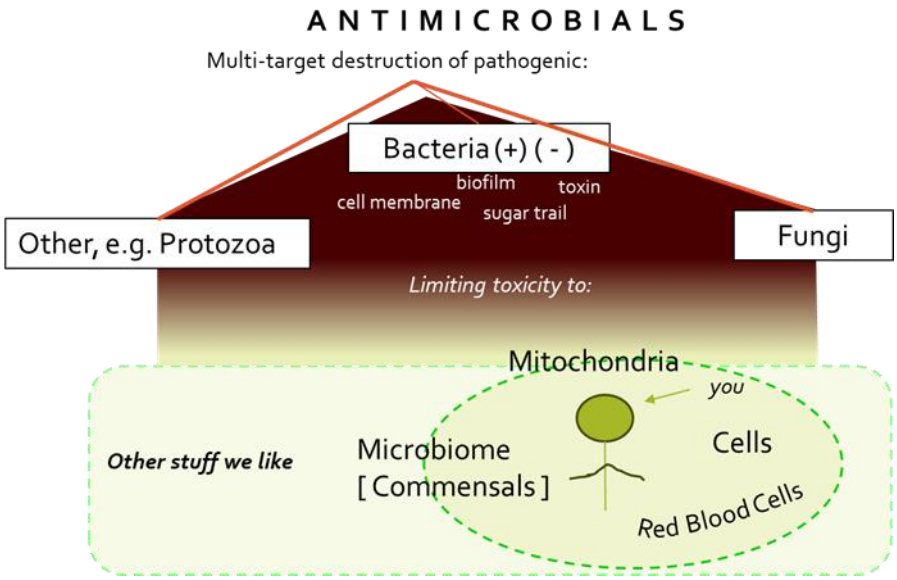
Our commensals are less experienced at managing fungal overgrowths or invaders, and AMR to the few available drug classes is growing in *candida, aspergillus*, and ringworm-causing species (See Guibelondo, 2025; Baid, 2022). The superfungus currently afflicting the nether regions of unfortunate souls in the United Kingdom is a type of drug resistant ringworm.

An antimicrobial could be an antibiotic (bacterial target) or not. It could be specific to gram-negative or gram-positive bacteria or both, the latter demonstrated by silver-chamomile nanoparticle contact lenses (Raptis et al., 2025). It could affect biofilm formation (biostatic) or virulence only, or it could be an anti-fungal, anti-parasitic, or anti-viral. Viruses are kind of sort of not counted in any domain of life, subject to ongoing debate. They have realms instead, which feels equivalently grand. Still, they matter in AMR as a concept, accordingly microscopically-sized, extremely clinically relevant, and phage varieties might serve as antibiotics.

Broadly speaking, something toxic to microbes could also potentially affect human cells (cytotoxicity), their mitochondria (mitotoxicity), red blood cells (hemolysis), or our commensal microbial species, adversely impacting health. A recent study showed – contrary to expectations – that fungicides, industrial chemicals and other pollutants

had 'anti-gut-bacterial activity'. *Bacteroidales* showed the highest sensitivity but fortunately(?), many commensal strains demonstrated resistance evolution to the xenobiotics. Nevertheless, changes to toxicology assessments and categorical labelling were suggested by authors Roux et al. (2025).

Antibiotics of last resort administered for drug-resistant infections, like polymyxins, may have significant toxicity to patients. Designing novel anti-fungals while mitigating toxicity to humans has been even more challenging, as fungi are eukaryotes like us. Testing for specificity, safety, and mutagenic risk are crucial parts of the research process for novel antimicrobials. Ideally, the compound precisely targets pathogens only, via multiple mechanisms or life stages to reduce the possibility of survival, selection, and next generation adaptation.



AMR how?

So. In the news: Raccoons got cuter and pathogens become deadlier. Same same. The highlights for modern microbial living and AMR development include :

- Partially fatal antimicrobial exposure
- Transmissible locus of stress tolerance (tLST) (Li, D. et al., 2025)
- Biofilms and sugar trails
- Metabolic state (Borrelli et al., 2025)
- Bioenergetic stress potentiation (Li, B. et al., 2025)
- Efflux pumps (Tarasenko et al., 2025)
- Climate change (Costa, 2024) e.g. temperature, natural disasters, vector availability

And even traitors in the gut microbiome (Miftode et al., 2025).

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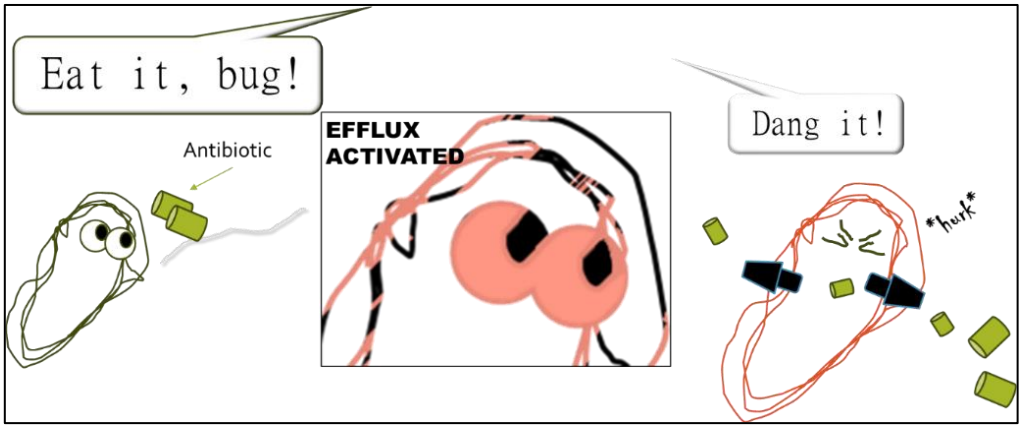
Detour – Antimicrobial Resistance, Co-Extinction, and the Gut-Eye Axis (Part II)

The *Financial Times* prepared a lovely little diagram of standard bacterial defence mechanisms here, while Y. Lee et al. (2023) and Guibelondo (2025) describes similar strategies for fungi. Fungi have the added skill of shape-shifting and mitochondrial support for 'active resistance' in adaptation to stressors.

Aside from quick transfers of adaptive genetic material, tools like β-lactamase production and efflux pumps mean bacteria are able survive what should be deadly doses of an antibiotic. Beta-lactamases are enzymes, and some of the best defences the gram-negatives evolved against man-made beta-lactam antibiotics that target and bring down the bacterial cell wall (Tarasenko et al., 2025; Hussain et al., 2021). Life may come at large metabolic cost, though. *Mycobacterium abscessus* have a single gene which can control over 100 proteins involved in resistance.



Gram-negative bacteria have complex and dynamic cell walls which make drug-targeting more difficult, as well as efflux pumps that can expel toxins/antibiotics. These mediate intrinsic and acquired resistance (Tarasenko et al., 2025). Fungi and parasites also commonly rely on this resistance mechanism, along with changes to enzyme and membrane protein expression.

Antibiotic misuse is seen as the major contributing factor to AMR. Poor health, improper hygiene, and inadequate sanitation amplify the risks, especially when combined with a lack of general knowledge and non-compliance. These are aspects of stewardship which require not just technological but cultural changes in numerous healthcare contexts, ranging from households to private practice to hospitals in Pakistan, India, and the United Kingdom. Agricultural use of antibiotics and fungicides are also seen as drivers of acquired AMR. In farming, the advised best practice is not parasite elimination, but selective use for infection damage-reduction. For humans, technologies to improve diagnostic accuracy are expected to mitigate AMR risks to some extent (Sinha et al., 2025; Bach, 2025), but only if prescribers and patients are compliant.

Poor health still matters as pathogenic species could be kept at bay by our own commensals. Tending to a healthy gut, oral, ocular etc. microbiome is therefore protective. Broad-spectrum or cytotoxic antibiotics that negatively impact commensal species may not just raise risks of AMR, but also long-term vulnerability to infections. Enterololin, a narrow-spectrum antibiotic option found with the help of AI, could protect the normal gut microbiome of Crohn's disease patients while targeting problematic *E. Coli*. Pro- and prebiotics are also rising in therapeutic favour.

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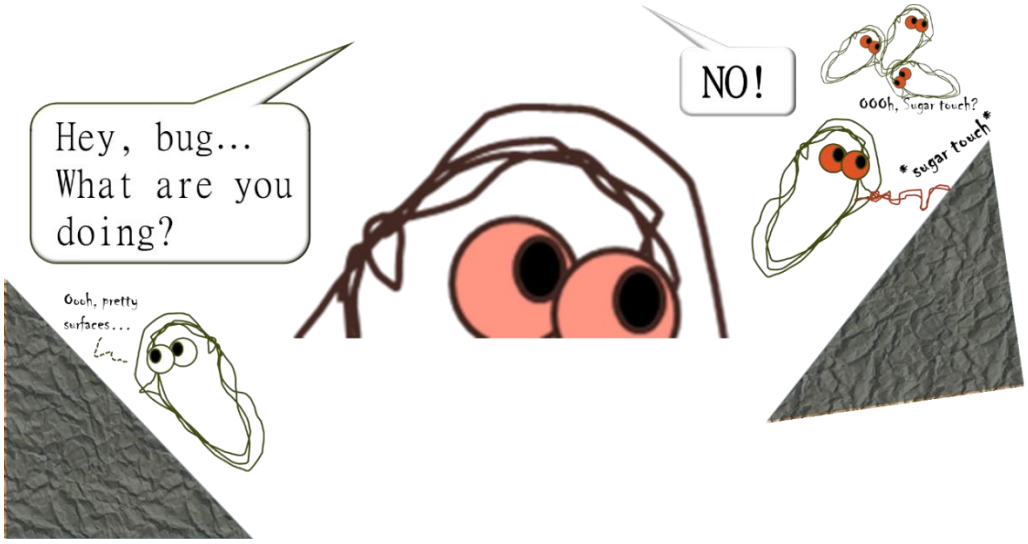
Detour – Antimicrobial Resistance, Co-Extinction, and the Gut-Eye Axis (Part II)

Microbial conditions matter too. Biofilms are organised bacterial community structures that offer greater chances of survival. In fact, up to 1000x greater. Layers and specialisation within mean that certain microbes are not as vulnerable to antibiotics, and genetic knowledge transfers are easier. You could think of a biofilm as a fortified Renaissance city for bacteria, with deeper cells free to sleep, philosophise, and survive attacks at the outer surface. This tends to be worse in hospitals, then termed nosocomial infections, offering hotbeds of weakened hosts and new pathogenic material every day, along with constant exposures to antimicrobials, disinfecting chemicals, and other selective pressures. This is partially how ESKAPEE pathogens may be acquiring resistance to other stressors, including strict sanitation protocols (Li, D. et al., 2025). An ominous acronym, because if they do in fact escape into the outside world with such a genetic repertoire, it will be challenging and unpleasant. Could be helpful if we figure out how to make hospital and other surfaces invisible to their grubby little grouping sensors.



A study by Schmidt et al. (2025) uncovered how Pseudomonas aeruginosa uses Psl polysaccharides and pili as sensors for surface attachment and biofilm formation. They describe this mechanism as 'chemosensing using mechanosensing' (p.2516). The cell thus achieves 'surface sentience' (Yu et al., 2025). Baulin et al. (2025) poignantly explain the 3.7 billion year history of microbe-surface interaction, and how it could be studied for mechano-bactericidal weaponisation.

The metabolic state of an individual bacterial cell affects whether an antibiotic kills them or not. Borrelli et al. (2025) recently found that dormant (stationary-phase) *E. Coli* cells are not killed by Polymyxin B (PmB), a membrane-targeting antibiotic of last-resort for gram-negative infections with major cytotoxic side effects for patients. While able to bind to the outer membrane of cells in all metabolic states, only active/expansionary E. Coli underwent a process of PmB-mediated lipopolysaaccharide loss that resulted in bactericidal disruption of both outer and inner membrane. Sleeper cells may reawaken up to years later to resume pathogenic activity. In an interview, the study authors mused that future combination treatments to first provoke all resident pathogens to arise, and thus produce outer armour for targeting, may help improve antibiotic efficacy.

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Detour – Antimicrobial Resistance, Co-Extinction, and the Gut-Eye Axis (Part II)

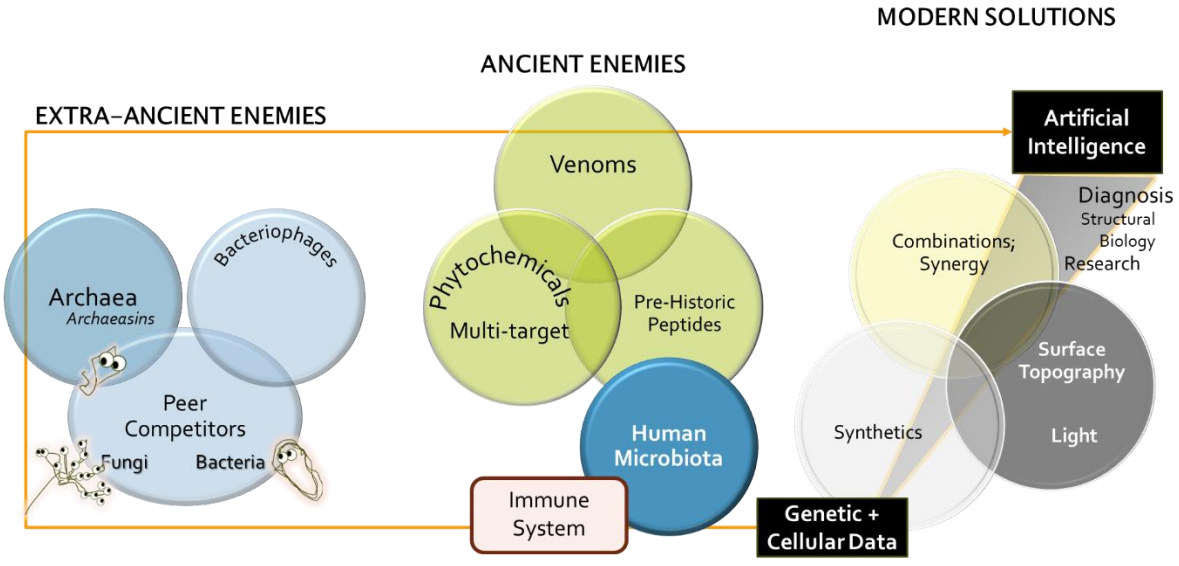
Countering AMR: Machine Brains and Old Enemies

We may not be able to replicate as wildly or rapidly as micro-bugs and bunnies, but historic humans are fairly good at leap-frogging trad evolution, i.e. cheating genes. Group living, impulses of curiosity and carnivorousness, role specialisation, and language, eventually resulted in exchange of ideas, hygiene practices, and tool use. Now we can use supercomputers to figure out how to turn the natural world against itself for our continuing benefit, unto the synthetic resurrection of mammoth and ancient penguin peptides with antibiotic properties.

Moving on from the discovery void, a change of pace for antimicrobial discovery/design, testing, and approval is expected through the use of different types of AI and availability of high-quality biological data. This is has been an approach for drug-resistant malaria, with at least one novel drug candidate found after screening 2.3 million molecules. Another example is MIT's Antibiotics-AI Project. There are many other organisations and AI platforms involved, engaged in a flurry of discovery, simulation, and early testing. As we gather more knowledge about the prehistoric and microscopic world, we can choose and use ancient enemies to fight our foes, as Australia tried to do with European fleas against invasive rabbits, hopefully with more success.

The 20th century selection of sheep victims by kea parrots in fact hinted at some of this hidden wisdom, because merino wool is thought to be antibacterial by virtue of its lanolin wax and fibre structure. Well, not quite true, but it was a decent jab at a beak-cleaning mechanism, since wool seems to pull biofims off other surfaces. To enhance any potential antimicrobial effects in the face of an AMR catastrophe, one could add silver or rare earth ions to woolly clothes. Make your investment decisions accordingly?

But perhaps we wont need futuristic antimicrobial attire. The diagram below loosely summarises and categorises recent research directions for countering AMR.



Detour – Antimicrobial Resistance, Co-Extinction, and the Gut-Eye Axis (Part II)

Antibiotic archaeasins (Torres et al., 2025a) and a miraculous 7-target antifungal mandimycin (Deng et al., 2025) were the eventual fruits of searches for biochemical weapons evolved in realms extra-ancient inter-microbial combat. The classical tactics of phages can be used synergistically with antibiotics to diminish the efflux-pump capabilities of resistant bacteria (Tarasenko et al., 2025), or entirely synthetic bacteriophages may be used against *mycobacterium* that cause leprosy and tuberculosis. This extra-ancient antagonistic biosphere was largely marine, so several novel tactics may come from marine or aquatic environments. Even fish eye wrinkles. No, really: (Vellwock et al., 2022). This is an enormous resource and subset of research, recently reviewed by Magalhaes et al. (2025) and Thomas & Antony (2024).

Our commensal microbes are also natural enemies, but a bit less ancient. Giving them a boost seems to be a decent alternative. Probiotics could be used as a defence against microbe-associated glaucoma (Ullah et al., 2024), dry eye disease (Song et al., 2024), or uveitis (Tirziu et al., 2024), and prebiotics could be integrated in contact lenses to nurture beneficial ocular flora (Vivero-Lopez et al., 2022). Probiotics given to pre-term infants to protect their gut microbiome also reduces their risk of antibiotic-resistant hospital infections (Kiu et al., 2025).

Of kin with the marine in terms of antimicrobial peptide (AMP) potential, plants and venomous animals are rich sources of bio-inspo. And humans have more AMPs than birds, according to the database (represented by Figure 1 in Magalhaes et al., 2025). Aided by the sequence-to-function deep learning model APEX – also used for archaeasins – 53 peptides based on snake, scorpion, spider, cone snail, sea anemone, and insect venoms showed 'potent' antimicrobial activity targeting bacterial cell membranes (Guan et al., 2025). Cytotoxicity was lowest for peptides derived from the lesser brown scorpion, the oak cone snail, and a species of burrowing wolf spider.

Phytochemicals are also proposed whether standalone or in combination with drugs and metal particles, but as covered by Dziegielewska et al. (2025) there are several challenges. Plant-derived compounds are quite a bit less potent and reliable, and therefore less likely to reach bodily targets or clinical trial stage without being substantially altered and/or paired with a fancy delivery system. Note there is less commercial incentive for testing a product that is not proprietary. Positives: Plants may seem static, but have long been engaged in chemical warfare against multiple types of microbe, especially fungi. Their mechanisms of action are naturally multi-targeted versus typical synthetics, offering synergistic effects and counter-AMR without needing to combine with other strategies (Dziegielewska et al., 2025).

Slithering into the now-times and technologies, besides AI assistance for several research stages and drug-to-market pathways there is also synthetic biology and new techniques for harvesting and documenting biological data. At a basic level, though not completely necessary, this can make the design of multimodal and/or synergistic therapeutics easier. AI-design and artificial production of entirely novel antimicrobials is possible (Torres et al. (2025b), but drug analogs with optimised modifications, even new polymers and nanomaterials (containing chitosan, silver, sulfur, plants etc.), also seem to show promise. Acting at scale, a key advantage of nanomaterials is that they bypass resistance mechanisms like efflux pumps and biofilm formation, but may not be without risk to human hosts (See Parvin et al., 2025). Well-crafted nanoparticles may be able to act simultaneously as supplements and antifungals (Huang et al., 2023).

Beyond synthetic imitation of the killing skillz of biological organisms, we can employ abiotic methods and compounds. That could be poisons or cytotoxic chemicals, ions like silver or copper, surface topography and electrical properties, and even microbe-specific biotoxic light wavelengths. Light is an interesting one, rarely mentioned in AMR reviews. In the focused review by Leanse et al. (2025), antimicrobial blue light seems to show specificity for bacterial species and supposedly low toxicity towards human cells in those wavelengths. Performance

against single and poly-microbial biofilms is encouraging, but the possibility of resistance evolution and emerging tolerance is unknown. Synergistic bactericidal effects are suggested by a study of phosphorus-based biomedical nanomaterials.

Surface topography that prevents the attachment of microbes through charge (e.g. zwitterionic) and/or textured patterns – of course aided in optimality by machine learning – seems to be a simple, non-toxic option that is perceived as having lower contribution to AMR. These may also be biomimetic. The sandwich version of Nobel prize-winning materials, metal-organic frameworks, have an unusual mechanism, that being nano-stabbing microbes to death. As described by the lead author on the first study of their bactericidal abilities when layered on top of each other: If distance-optimised, "These nanostructures can act like tiny spikes that physically injure the bacteria, quite simply puncturing them so that they die."

Sounds like a scene from tomb raider. Earlier studies offered the 'bed of nails' approach for medical implants, based on things like insect wings and gecko skin (See Chopra et al., 2021). Choice of nanotopographies for 'dominance over the surface' can and should be specific to bacteria, fungi, or viruses, reviewed by Baulin et al. (2025). There are images of each surface-type in this article, including microbe cartoon smiles of existential vacuity, perseverance, and futility (See Figure 1).

Conclusion

It is believed that the relationship between ocular microbiota and animal immune systems is extra ancient, since fish have it too. Not quite as far back as the magical endosymbiotic moment of mitochondria and the eukaryotic cell, but still, a relationship worth cherishing and deploying against drug-resistant pathogens and systemic disease. Biocompatibility is less of an issue, and it'll probably be cheaper. Related: The fine for keeping rabbits in Queensland is now AU$83,000. Still they breed. In the preparation of this article, it was very noticeable that depictions of drug-resistant microbes were often more charming, cute, and inviting than that of invasive rabbits. And: After all that on microbiome diversity and function, how on earth are kakapo – with guts close to exclusively dominated by *E. Coli* and *Shigella* as the theorised wild-type – still alive? An AMR week miracle!

To round up for AMR and its countering, as a few reigning principles: What *tries* to kill you but fails makes the survivors smarter and stronger. Mechanisms that do not exert strong selective pressure on pathogenic microbes are less likely to result in the development of resistant strains. Otherwise, synergistic therapies and simultaneous hits to different targets PLUS elimination are required. The literature on amplification of mutagenic power in the face of stress, potentially becoming resistant to chemicals and heat in hospital sanitation, is legitimately terrifying. Perhaps measures employing high-energy light and material-surface design are safer options, with longer anti-microbe histories than industrial chlorine.

Rather than just crisis, resistance may be conceptualised as a natural feature, conflict raging over billions of years with a wealth of data to mine. Supercomputers are employed to distill both evolutionary and supra-genomic options, so deliberate innovation could outpace natural mechanisms of resistance.

However. There is much we do not yet know about the violent microbial world within and around us, and it is imperative that one picks and preserves your allies wisely.

Now go wash your hands and eat some fibre.

End.

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