

Antibiotic Resistance and Its Alternatives — Companion Dossier to FORSCH-0211

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Companion dossier to the work FORSCH-0211 “The Body as a Biotope System”

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Reading note: This is a research-based overview dossier, not medical advice. Sources are listed at the end and referenced in the text as [n]. Where the evidence is uncertain, this is stated explicitly.

0 · Why this dossier connects to the biotope work

FORSCH-0211 describes the body, for the control and supply question, as a **system of nested milieus** — “fields of condition instead of responsibilities” — with the point that the microbiome is foreign life *within* the body’s boundaries and that a milieu can **tip** into another stable state (§4.1, §8.1). This is the natural frame for the antibiotic question: a broad-spectrum antibiotic is an intervention not into “an organ” but into a **field of condition** (the gut milieu), which may lose its order and tip (dysbiosis). The alternatives — phages, narrow spectrum, personalised therapy — are the attempt to act *gently on the milieu* rather than across the board. This dossier works up the state of the science.

1 · The problem in numbers

Antimicrobial resistance (AMR) is one of the greatest global health threats. The most comprehensive estimate to date (GRAM project, *The Lancet* 2022) puts the 2019 toll at **1.27 million deaths directly attributable to bacterial AMR** and **4.95 million deaths associated with AMR** [1]. Six pathogens — *E. coli*, *S. aureus*, *K. pneumoniae*, *S. pneumoniae*, *A. baumannii*, *P. aeruginosa* — accounted for 929,000 of the attributable deaths [1]. A follow-up analysis (1990–2021, with projection to 2050) confirms the rising trend [2].

The **WHO Bacterial Priority Pathogens List 2024** (BPPL) groups 15 pathogen families into “critical / high / medium”. The **critical** group contains carbapenem-resistant *Acinetobacter baumannii* (CRAB), carbapenem-resistant Enterobacterales (CRE) and third-generation-cephalosporin-resistant Enterobacterales; carbapenem-resistant *K. pneumoniae* tops the ranking, while carbapenem-resistant *P. aeruginosa* was downgraded from “critical” to “high” [3][4]. The acronym **ESKAPE** (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *Enterobacter*) bundles the clinically most dangerous multidrug-resistant germs.

2 · Biochemistry and genetics of resistance — and the evolution behind it

2.1 How antibiotics act

Antibiotics attack a few conserved bacterial targets: **cell-wall synthesis** (β -lactams such as penicillins/cephalosporins/carbapenems inhibit peptidoglycan cross-linking; glycopeptides like vancomycin bind D-Ala-D-Ala), **protein synthesis at the ribosome** (aminoglycosides, tetracyclines, macrolides, oxazolidinones), **DNA replication** (fluoroquinolones inhibit DNA gyrase/topoisomerase IV), **folate synthesis** (sulfonamides, trimethoprim) and the **cell membrane** (polymyxins such as colistin) [general knowledge; cf. 3].

2.2 How resistance arises (mechanisms)

Four basic strategies:

1. **Enzymatic inactivation** — β -lactamases cleave β -lactams; especially critical are **ESBLs** (extended-spectrum β -lactamases) and **carbapenemases** (KPC, NDM-1, OXA-48), which render almost all β -lactams ineffective [3].
2. **Efflux pumps** — active export of the drug (e.g. MexAB-OprM / MexXY in *P. aeruginosa*); often multidrug pumps [9].
3. **Target modification/protection** — alteration of the binding site (e.g. *mecA*/PBP2a in MRSA; gyrase mutations against quinolones; ribosomal methylation against macrolides).
4. **Reduced permeability** — loss/modification of porins (e.g. OmpK36 in *Klebsiella*).

2.3 Genetics: mutation, selection, horizontal gene transfer

Resistance arises through **spontaneous mutation + selection** (the antibiotic kills the susceptible, the resistant multiply) and — crucially — through **horizontal gene transfer (HGT): conjugation** (plasmids), **transformation** (free DNA) and **transduction** (via phages). Mobile genetic elements — **plasmids, transposons, integrons** — bundle resistance genes and spread them between species. The totality of all resistance genes in a community is the **resistome**; soils and waters are its natural reservoirs [7][8].

2.4 Evolution and adaptation under selection pressure

Resistance often carries a **fitness cost** (resistant strains grow more slowly without the antibiotic), which **compensatory mutations** then offset — after which resistance no longer disappears on its own even without further antibiotic pressure. One must distinguish **resistance** (heritable growth despite the drug) from **tolerance/persistence** (temporary survival without genetic resistance, e.g. in “persister” cells). Important for therapy strategy: **collateral sensitivity** — resistance to one drug can *increase* susceptibility to another; this can be exploited deliberately (see §4.3) [13][14].

Biotope link: Selection happens not “in the bacterium” but *in the milieu* — antibiotic concentration, pH, nutrients and neighbouring microbes form the field of condition that decides which variant prevails.

3 · Broad-spectrum antibiotics: pharmacology and side effects

3.1 Pharmacology (PK/PD)

Efficacy depends on **pharmacokinetics** (absorption, distribution, tissue penetration, excretion) and **pharmacodynamics**. One distinguishes **time-dependent** killers (β -lactams: time above the MIC matters) from **concentration-dependent** ones (aminoglycosides, fluoroquinolones: peak or AUC/MIC). This logic is exactly the **balance-across-the-boundary** logic from FORSCH-0211 §5.1: the effect closes where the conditions of the target milieu (concentration, binding) permit.

3.2 Collateral damage to the microbiome (dysbiosis)

Broad-spectrum antibiotics hit not only the pathogen but the whole gut flora. The result is **dysbiosis** with loss of **colonization resistance** — the healthy flora's ability to repel pathogens via nutrient and space competition, short-chain fatty acids (e.g. butyrate), bile-acid metabolism, bacteriocins and immune modulation [5][6]. A shift toward **Proteobacteria** is typical [6]. **This is the tipping of FORSCH-0211 §8.1 in the empirical record:** a field of condition passes into another, less protected state.

3.3 Clostridioides difficile infection (CDI)

The clearest clinical example: after antibiotics, *C. difficile* can expand into the emptied niche — severe colitis. Higher microbial diversity = higher colonization resistance [5]. **20-35 % of patients suffer recurrence after standard therapy (vancomycin/metronidazole)** [6] — the reason microbiome restoration (FMT, §5.5) works here.

3.4 Class-specific adverse effects

- **Fluoroquinolones** (ciprofloxacin etc.): FDA and EMA warn of **disabling, potentially permanent** damage to tendons, muscles, joints, nerves and the CNS; tendon rupture (esp. Achilles) can occur within 48 h; increased risk of **aortic aneurysm/dissection**. The EMA has **restricted** use and withdrawn some older quinolones; the FDA advises against use in uncomplicated infections (sinusitis, bronchitis, uncomplicated UTI) when alternatives exist [10][11].
- **Aminoglycosides:** oto- and nephrotoxicity. **Macrolides:** QT prolongation. **β -lactams:** allergy, CDI risk. **Tetracyclines:** photosensitivity, tooth discoloration in children.

Core point: the broader the spectrum, the greater the collateral damage to the inner milieu — the pharmacological case for **narrow spectrum and personalisation** (§6).

4 · Phage therapy

4.1 What phages are

Bacteriophages are viruses that infect only bacteria — the most abundant biological entities on Earth. Two life cycles: **lytic** (the phage replicates and bursts the cell — therapeutic

tically desired) and **lysogenic** (phage DNA integrates into the bacterial genome and rests — undesired, since genes, including resistance/toxin genes, can be transferred). Therapy uses **strictly lytic** phages. Advantages: **high specificity** (usually species/strain-precise, spares the rest of the flora), self-amplification at the site of infection, action on **biofilms**, few side effects [15][16].

4.2 Coevolution and phage resistance

Bacteria defend against phages via **receptor modification** (the phage no longer docks), **restriction-modification systems**, **CRISPR-Cas** (bacterial “immunity” against phage DNA) and **abortive-infection** systems [review 17]. Phages and bacteria thus coevolve — phage resistance is the rule, not the exception. Countermeasure: **phage cocktails** (several phages with different receptors) and combination with antibiotics.

4.3 Phage steering and collateral sensitivity (an evolutionary trick)

Especially elegant: one chooses phages whose receptor is a **resistance factor**. Classic example **ΦOMKO1** (Chan et al., Yale): the phage uses the **efflux pump MexAB/MexXY-OprM** of *P. aeruginosa* as its docking site. If the bacterium becomes phage-resistant, it *shrinks* this pump — and thereby becomes **antibiotic-susceptible again**. This **trade-off** is stable over ~70 bacterial generations, even under combined phage and antibiotic pressure [13][14]. This is “steering evolution” — driving the bacterium into a corner where every escape is costly.

4.4 Clinical evidence

The trigger of modern interest was the **Tom Patterson case (2016)**: a life-threatening carbapenem-resistant *A. baumannii* infection was successfully treated with a personalised phage cocktail (Texas A&M, US Navy) under an FDA **compassionate-use** authorisation; Steffanie Strathdee publicised the case and founded the **IPATH** centre (UC San Diego) [18]. A systematic cohort of **20 patients** with drug-resistant mycobacteria showed phage therapy is **safe and well tolerated** and can produce clinically meaningful improvement [18]. **Caveat (important)**: the evidence so far is mostly **case reports and small series**, not large randomised trials; several controlled trials are underway. Efficacy is therefore **promising but not yet proven at RCT scale** [16][18].

4.5 Regulatory status and limits

Phages fit poorly into the classic approval frame (a defined, unchanging molecule): they are biological, self-amplify, and often need to be **personalised** and updated. In **Belgium** a pragmatic route exists via **magistral preparation** (pharmacy-individual compounding); the **Eliava Institute (Georgia)** has treated with phages for nearly a century. In the **EU/USA**, compassionate-use single cases and trials dominate [15][16]. Limits: narrow host range (precise pathogen diagnostics required), phage resistance, immune response to phages, manufacturing and purity standards.

5 · Further approaches beyond classical antibiotics

5.1 Endolysins / enzybiotics

Endolysins are phage-encoded enzymes that cut the bacterial cell wall (peptidoglycan) from outside — especially effective against **Gram-positive** pathogens (exposed peptidoglycan). Advantages: **rapid bactericidal action, low resistance development**, biofilm activity. Against **Gram-negative** germs the outer membrane is a barrier; engineering tricks (fusion with membrane-penetrating peptides) help [19][20].

5.2 Antimicrobial peptides (AMPs)

Short (15–150 aa) peptides that mostly disrupt the bacterial membrane — **broad spectrum, fast action, low resistance tendency**; some are endogenous (part of innate immunity). Challenges: stability, toxicity, cost [19][20].

5.3 CRISPR-Cas as a “programmable” antibiotic

CRISPR-Cas can be repurposed to **specifically cut resistance or virulence genes** or to selectively kill only resistant bacteria — e.g. via phages as the vehicle. Still mostly preclinical; the delivery problem is unsolved [17].

5.4 Anti-virulence, anti-biofilm, antibodies, vaccines

- **Anti-virulence**: do not kill, but “disarm” (block toxins, quorum sensing, adhesins) → lower selection pressure.
- **Anti-biofilm**: break up biofilms, in which bacteria are up to 1000× more tolerant.
- **Monoclonal antibodies** against toxins/surfaces.
- **Vaccines**: prevention directly lowers antibiotic need — modelling studies show vaccination could avert a substantial share of the AMR burden [cf. 1].

5.5 Microbiome restoration: probiotics and FMT

Faecal microbiota transplantation (FMT) restores colonization resistance in recurrent CDI. Since 2022/2023 the first standardised FMT products are **FDA-approved** in the USA: **REBYOTA** (Ferring, rectal) and **VOWST** (Seres, oral) to prevent recurrent CDI [21][22]. In one analysis, success (no recurrence over 8 weeks) was **70.6 % for REBYOTA vs. 57.5 % for placebo** [21]. **Direct biotope link**: therapy as *re-erecting a tipped milieu*, not as another broad blow.

6 · Personalised instead of standard therapy

6.1 The principle

Instead of an empirical broad-spectrum “shotgun”, a **precise, narrow-spectrum, pathogen-exact** therapy — guided where possible by rapid diagnostics. This spares the milieu (§3) and reduces resistance selection.

6.2 Diagnostics as bottleneck and lever

- **Rapid phenotypic susceptibility testing (rapid AST):** over 90 technologies in development that deliver an antibiogram faster than the classic overnight culture [23].
- **Metagenomic sequencing (mNGS):** hypothesis-free pathogen and resistance-gene detection straight from the sample; enables **early de-escalation of broad-spectrum antibiotics in over 30 % of cases** without worse outcome [23]. **But:** the **genotype-phenotype gap** is real — for many pathogen-drug pairs the actual susceptibility **cannot yet be inferred reliably enough** from the resistance gene for individual therapy [23]. Diagnostics does not yet replace the phenotypic antibiogram everywhere.
- **Personalised phage cocktails** (§4.4) and **microbiome-based** approaches (§5.5) are personalised therapy in the strictest sense.

6.3 Biotope connection

FORSCH-0211 supplies the rationale: each patient is an **individual inner milieu** (own microbiome, own fields of condition). A “standard antibiotic” treats an average that does not exist; “individual therapy” treats the actual milieu — and keeps it below the **tipping threshold** (§8.1 model: condition-dependent rates, hysteresis).

7 · Artificial intelligence: opportunities and dangers

7.1 Opportunities

- **Drug discovery:** a deep-learning model (Stokes, Collins, Barzilay et al., *Cell* 2020) identified **halicin** — a structurally novel antibiotic with broad activity (incl. *M. tuberculosis*, carbapenem-resistant Enterobacterales, *C. difficile*, pan-resistant *A. baumannii* in mouse models) [24]. In 2023 the same group used AI to find **abaucin**, targeted against *A. baumannii* (acting via disrupted lipoprotein trafficking) [25].
- **Phage-host matching, resistance prediction, diagnostic support:** ML models on mNGS data accelerate AST estimation [23].
- **Stewardship:** AI can support prescribing decisions and de-escalation.

7.2 Dangers

- **Dual use / biosecurity:** Urbina et al. (*Nature Machine Intelligence* 2022) showed that a simple sign-flip in a molecule generator’s reward term (rewarding toxicity instead of penalising it) generated **~40,000 toxic molecules in under 6 hours** — including the nerve agent VX and other known chemical-warfare agents [26]. The same technology that finds remedies can design poisons.
- **Reliability:** AI predictions from genotype data inherit the **genotype-phenotype gap** (§6.2) — misclassification can lead to under-/over-treatment.
- **Bias and data:** models are only as good as their (often Western/clinically skewed) training data.
- **Access equity & governance:** AI diagnostics/drugs risk widening the gap between rich and poor health systems; dual-use research is **still inadequately covered** by

regulation [26].

AI takeaway: large acceleration potential, but no substitute for phenotypic confirmation, and a serious dual-use risk that demands active governance.

8 • One Health: factory farming, water, environment

AMR is not a purely clinical problem. The **One Health** approach links humans, animals and the environment:

- **Factory farming & aquaculture** are now **major contributors to the global resistome** [7][8]. A substantial fraction of administered antibiotics is **excreted un-metabolised** and reaches soils and waters with manure.
- **Volumes:** estimates put **~3,000-27,000 tonnes** of animal drugs and bioactive intermediates released into the environment annually [7].
- **Water/wastewater: treatment plants** (municipal and hospital) are **hotspots** for the proliferation of resistant bacteria and the exchange of resistance genes; ARGs are found in sludge, river water, sediment, air and soil [7][8]. **Soil** is the primary natural reservoir of resistance genes.
- **Transmission routes** animal-human-environment are documented; AMR circulates in both clinical and natural environments [8].
- **Regulation:** the **EU banned growth-promoting antibiotics in 2006**; since 2022 stricter rules apply (ban on routine prophylaxis, reservation of critical antibiotics for humans). **Prevention rather than end-of-pipe remediation** delivers the most durable reductions [7].

Biotope link: the environment is itself a biotope system of coupled milieus; the resistome flows across boundaries (barn → manure → soil → water → human) — exactly the “chain of milieus with filtered transitions” of FORSCH-0211 §4, here on the ecological level.

9 • Synthesis — what this means for the biotope work

1. **Antibiotics are milieu interventions, not organ interventions.** Their main harm (dysbiosis, CDI) is a **tipping of a field of condition** — the empirics of FORSCH-0211 §8.1.
2. **Broad spectrum = broad milieu damage; narrow spectrum/personalisation = milieu-sparing.** Pharmacology (§3) gives the rationale for personalised therapy (§6).
3. **The alternatives are all “milieu-oriented”:** phages (strain-precise), endolysins/AMPs (targeted), FMT (re-erect the milieu), diagnostics (hit the actual milieu).
4. **Evolution can be steered** (phage steering, collateral sensitivity) — therapy as intervention into the **field of condition of selection**, not as a command to “the bacterium”.
5. **AI** accelerates but does not replace the phenotypic antibiogram, and brings a **dual-use risk**.

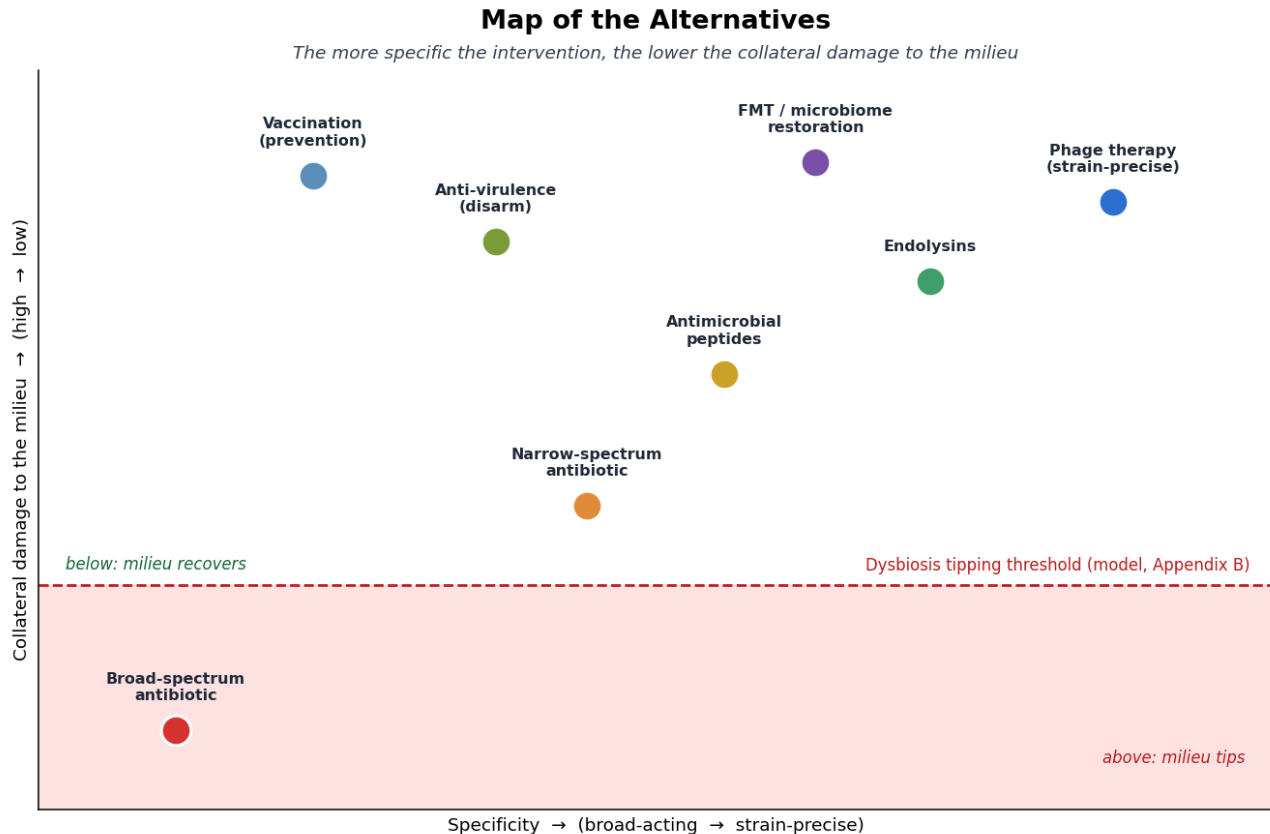


Figure 1: **Fig. 1** — Map of the alternatives: the more specific the intervention, the lower the collateral damage to the milieu. The broad-spectrum antibiotic is the only one below the dysbiosis tipping threshold (red; model, Appendix B) — it tips the gut milieu. Phages, endolysins and FMT act strain-precisely or restoratively and remain milieu-sparing. Vaccination and anti-virulence prevent or disarm rather than kill.

6. **One Health** shows: the biotope does not end at the skin — the resistome circulates through coupled environmental milieus.

Open / uncertain (honestly flagged): phage-therapy evidence still mostly case-based; mNGS genotype→phenotype not yet therapy-grade for all pairs; many alternatives (CRISPR-antibacterial, many AMPs/endolysins against Gram-negatives) preclinical; environmental volume figures span a wide range.

Appendix A • Minimal model of collateral sensitivity (phage steering)

To make the trade-off of §4.3 visible, a minimal, dimensionless population model (pure NumPy, no biological fit). A trait axis $e \in [0,1]$ denotes the **efflux-pump level**: high e = antibiotic-resistant (pump removes the drug) but phage-susceptible (the phage uses the pump as receptor); low e = phage-resistant but **antibiotic-susceptible**. Death rates: $d_{AB}(e) = A \cdot (1-e)$ (antibiotic kills low-efflux), $d_{phage}(e) = P \cdot e$ (phage kills high-efflux); a small growth/pump-cost term; weak mutational diffusion over the e grid.

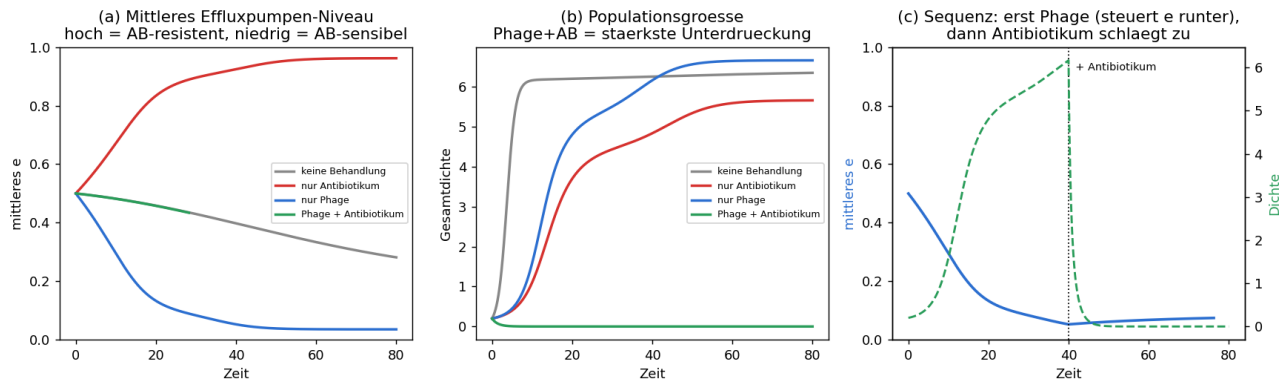


Figure 2: Phage steering / collateral sensitivity: (a) mean efflux level — antibiotic alone drives it up (resistant), phage alone drives it down (= antibiotic-susceptible again); (b) population size — only the combination phage+antibiotic eradicates the population; (c) sequential therapy — the phage first steers the trait down, then density collapses under antibiotic.

Result: antibiotic alone selects high efflux ($e \approx 0.96$, resistant, survives); phage alone selects low efflux ($e \approx 0.04$), rendering the population **antibiotic-susceptible again**; **phage + antibiotic** clamps the population from both ends → density → 0. The sequence “phage first, then antibiotic” shows the same: the phage **steers** the bacterium into a susceptible state in which the antibiotic bites again. This is the model illustration of phage steering (ΦOMKO1, §4.3) — and biotope logic: therapy acts on the **field of condition of selection**, not as a command to “the bacterium”. Reproducible: models/phage_steering_model.py. *Caveat (B14): shows that the trade-off is real as a dynamic — no claim about the concrete parameters of a real pathogen.*

Appendix B • PK/PD model of microbiome collateral damage

A second minimal model (pure NumPy) couples the antibiotic’s **pharmacokinetics** (daily dose over 7 days, elimination at rate k_e) to a **microbiome model** of commensals B_c and

a pathogen B_p (e.g. *C. difficile*) with **colonization resistance** (term $- \cdot B_c \cdot B_p$: the commensals suppress the pathogen). The antibiotic kills commensals at rate k_c (= **spectrum breadth**: high = broad-spectrum) and barely touches the pathogen (k_p small — the pathogen is largely resistant to the drug).

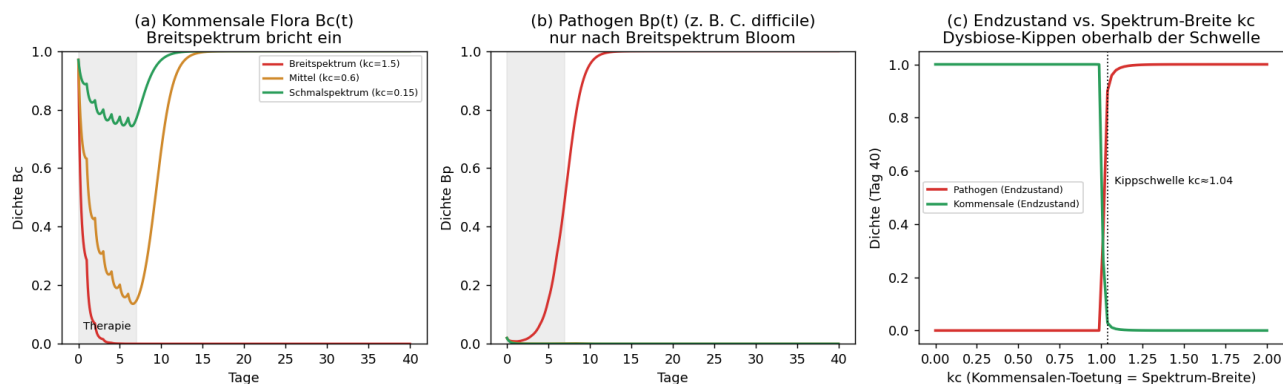


Figure 3: PK/PD microbiome model: (a) the commensal flora collapses durably only under broad spectrum; (b) the pathogen blooms only after broad spectrum (*C. difficile* logic); (c) final state vs spectrum breadth k_c with a sharp dysbiosis tipping threshold at $k_c \approx 1.04$.

Result (day 40): narrow and medium spectrum $\rightarrow$ commensals recover ($B_c \approx 1.0$), pathogen stays low ($B_p \approx 0$). **Broad spectrum** $\rightarrow$ commensals to 0, pathogen to 1.0 — the milieu **tips** into the dysbiotic state and does not recover on its own. Panel (c) shows a **sharp threshold at $k_c \approx 1.04$** : only above this spectrum breadth does the system tip. This is exactly the **tipping/hysteresis logic of FORSCH-0211 §8.1**, here pharmacological: broad spectrum crosses the gut milieu’s tipping threshold, narrow spectrum stays below it — the quantitative case for personalised, milieu-sparing therapy (§6). Reproducible: `models/pkpd_microbiome_model.py`. *Caveat (B14): minimal illustration, not a clinical fit.*

Appendix C · One-Health resistome chain model (barn $\rightarrow$ water $\rightarrow$ human)

A third minimal model (pure NumPy): the spread of antibiotic resistance genes (ARGs) along a **chain of coupled environmental milieus** — barn $\rightarrow$ manure $\rightarrow$ soil $\rightarrow$ water $\rightarrow$ human — with **filtered transitions** (transfer coefficient $k < 1$ per boundary) and per-compartment decay. The barn carries the source s (antibiotic use $\rightarrow$ selection). This is FORSCH-0211 §4 at the ecological level: “a movement through a chain of milieus, filtered at each boundary”.

Result: relative to baseline, **source reduction** (e.g. the EU ban on growth-promoting antibiotics, -65% barn use) lowers the human-compartment ARG load by **$\sim 65\%$** ; a pure **end-of-pipe** measure (improving only the water $\rightarrow$ human transition, e.g. better wastewater treatment) achieves only **$\sim 56\%$** and leaves the entire upstream chain (barn, manure, soil, water) unchanged. This is the model form of the §8 statement: **prevention at the source beats end-of-pipe remediation** [7]. And it is biotope logic: the boundaries order the flow, but the most effective lever is the source, not the last filter. Reproducible: `models/resistome_chain_model.py`. *Caveat (B14): minimal illustration, no calibrated environmental parameters.*

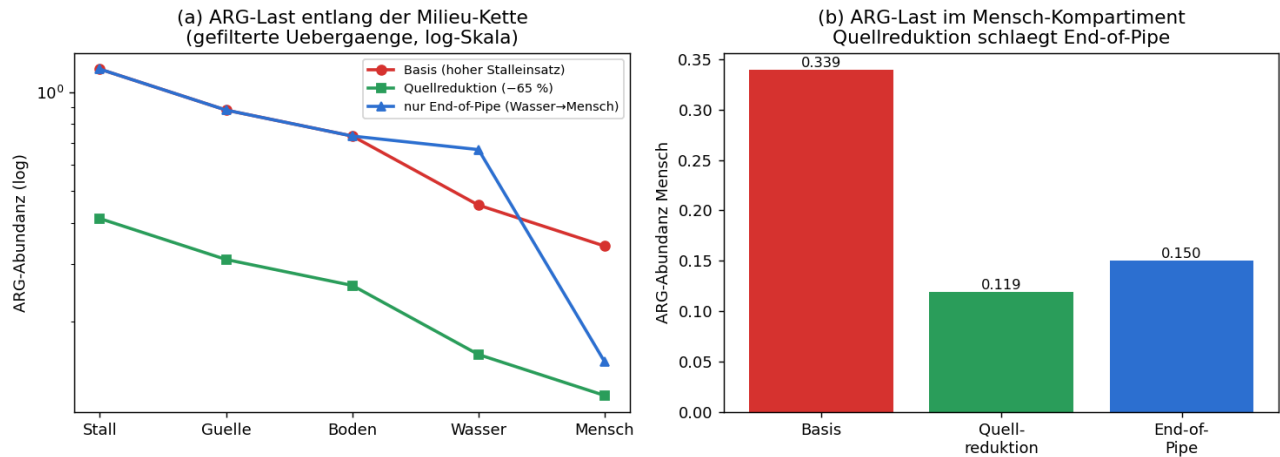


Figure 4: One-Health resistome chain: (a) ARG load along barn→manure→soil→water→human (log scale) for three strategies; (b) ARG load in the human compartment — source reduction (–65 %) beats end-of-pipe (–56 %).

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(Identical numbering to the German version.)

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