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Antimicrobial Exposure Is Not Equivalent to Antimicrobial Success: A Veterinary Treatment Model Integrating Pathogen Susceptibility, Pharmacokinetics, Tissue Penetration, Pharmacodynamics, Host Response, Biofilm Biology, and Source Control

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ABSTRACT

Antimicrobial treatment is commonly interpreted through two linked observations: a pathogen is categorized as susceptible and an antimicrobial is administered at an accepted dose. Neither observation establishes that microbiologically active exposure occurs at the infection site or that bacterial control will follow. Veterinary patients introduce additional variation through species-specific disposition, disease-altered pharmacokinetics, anatomically protected compartments, biofilm growth, bacterial burden, host immune competence, foreign material, devitalized tissue, and the feasibility of delivering the intended regimen. This original non-empirical article develops a physiology- and mechanism-guided treatment model in which success is treated as a time-dependent state emerging from concordance among pathogen identity and phenotype, free-drug exposure, pharmacodynamic target attainment, site penetration, bacterial organization, host contribution, and source control. The model distinguishes drug delivery from effective exposure, effective exposure from bacterial effect, and bacterial effect from clinical recovery. It also separates remediable exposure failure from conditions in which dose escalation cannot compensate for inaccessible infection, protected bacterial states, uncontrolled sources, or an incorrect diagnosis. Reassessment is therefore framed as causal adjudication rather than automatic antimicrobial broadening. The proposed model may support more disciplined escalation, de-escalation, sampling, monitoring, and source-control decisions while preserving stewardship. It is not a validated prediction rule, additive score, or substitute for culture interpretation, clinical examination, imaging, surgery, or longitudinal response assessment. Its components require prospective testing across animal species, infection syndromes, production settings, antimicrobial classes, and clinically meaningful outcomes.

Keywords: Antimicrobial pharmacodynamics, Veterinary infection, Tissue penetration, Biofilm, Source control, Treatment failure

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Introduction

Veterinary antimicrobial treatment often begins with a plausible pathogen, an in-vitro susceptibility result, and a licensed or guideline-consistent regimen. This sequence is necessary but incomplete. Veterinary guidelines and evidence syntheses indicate that antimicrobial choice must follow a credible bacterial syndrome and feasible regimen, while treatment may add little when bacterial causation is weak or disease is self-limiting [1–3]. A susceptibility category estimates whether a defined exposure is likely to inhibit an isolate under specified

conditions; it does not measure free-drug concentration within diseased tissue, bacterial physiology in vivo, immune contribution, or removal of an infectious focus.

The clinical importance of those omitted domains is visible when outcome and susceptibility diverge. In surgically treated canine pyometra, favorable outcomes occurred despite frequent discordance between administered antimicrobials and in-vitro susceptibility, consistent with—but not proving—a major contribution from ovariohysterectomy and supportive care [4]. Conversely, apparent exposure can coexist with failure when penetration is inadequate, pharmacodynamic targets are missed, bacteria occupy protected states, or necrotic tissue and foreign material sustain burden.

This article therefore proposes an antimicrobial-success model that treats response as a changing configuration rather than a property of the drug–isolate pair. It integrates pathogen phenotype, pharmacokinetics, pharmacodynamics, infection-site access, intracellular protection, biofilm biology, bacterial burden, host response, source control, and dosing feasibility. The model is explanatory and decision-organizing; it does not claim prospective predictive performance.

Susceptibility is not equivalent to clinical success

Susceptibility testing compresses a laboratory observation into an interpretive category. Its clinical meaning depends on organism identification, test validity, breakpoint assumptions, exposure at the relevant compartment, and whether the cultured organism drives disease. A susceptible result supports one conditional proposition: under the embedded exposure assumptions, detected resistance does not preclude expected activity. It cannot establish diagnosis, adequate administration, site penetration, bacterial eradication, or recovery.

The reverse discordance is equally important. An isolate categorized as resistant may coexist with improvement when the sampled organism is incidental, host defenses dominate, drainage or excision reduces burden, or the infection resolves through source control. The pyometra evidence illustrates this interpretive boundary but should not be generalized to infections without removable foci [4]. Likewise, urinary guidelines link culture results to syndrome, sampling quality, recurrence status, and clinical evolution rather than treating susceptibility as a stand-alone outcome [1].

Accordingly, susceptibility should function as one constrained input within a broader causal assessment. Persistent signs after "susceptible" therapy should trigger verification of diagnosis, regimen delivery, exposure, site access, burden, host state, and source control before being labeled antimicrobial resistance. This distinction prevents both false reassurance and reflexive escalation.

Pathogen identity and resistance phenotype

Species-level identification incompletely describes pathogenic potential. Lineages may differ in virulence determinants, resistance genes, host adaptation, biofilm capacity, and anatomical tropism. Nationwide surveillance of carbapenem-resistant Enterobacterales in companion animals demonstrates resistance across organisms and specimen contexts, but laboratory submissions cannot establish infection severity or outcome [5].

Genomic comparisons further show why syndrome and site matter. Multidrug-resistant *Escherichia coli* from canine pyometra and urinary infection can be genetically related yet distinct from isolates associated with prostatic abscesses, suggesting that anatomical ecology and pathogenic repertoire modify the meaning of species identity [6]. Comparative canine and human urinary isolates also contain host-associated populations with differing virulence, resistance, and biofilm capacities [7]. These findings support finer pathogen characterization, not automatic cross-host inference.

The proposed model separates four questions: Was the pathogen recovered from a credible sample? Is its phenotype technically reliable? Does it predict activity at the intended dose and site? Does a protected state alter that prediction? Resistance constrains options but does not identify the active lesion, quantify burden, or show that intensification will overcome an uncontrolled focus.

Antimicrobial pharmacokinetics

Antimicrobial pharmacokinetics determines the concentration–time profile presented to the pathogen, but the relevant profile is not always the plasma curve. Absorption may change with vomiting, feeding, formulation, gastrointestinal disease, or administration. Distribution varies with perfusion, binding, inflammation, edema, body composition, critical illness, and organ dysfunction. Clearance differs across animals and during treatment. Thus, an accepted dose is an input, not proof of comparable exposure.

The model distinguishes prescribed dose, delivered dose, systemic exposure, and infection-compartment exposure. Failure can arise at each transition. A missed oral dose is not a distribution failure; adequate plasma exposure with poor abscess access is not nonadherence; high total concentration with extensive binding is not necessarily high microbiologically active concentration. These mechanisms demand different corrections.

Single-sample concentration measurements also require restraint. They may verify gross underexposure or support pharmacokinetic modeling, but their interpretation depends on sampling time, assay, free versus total drug, and the compartment of interest. Repeated clinical and pharmacological observations are more informative when physiology is changing. Pharmacokinetics therefore supplies a time-varying exposure estimate that must be connected to susceptibility and pharmacodynamic effect rather than interpreted independently.

Pharmacodynamic target attainment

Pharmacodynamics links exposure to effect through indices based on time above the minimum inhibitory concentration, free-drug area under the curve, or peak concentration. The relevant target depends on antimicrobial class, organism, endpoint, immune state, and experimental basis. Veterinary PK/PD analyses demonstrate that regimen, MIC, and between-animal variability jointly determine modeled target attainment [8–10]. Attainment is probabilistic, not guaranteed by a conventional dose.

Three interpretive limits follow. First, a target derived from plasma exposure may not represent free concentration in diseased tissue. Second, a target associated with stasis or a specified bacterial reduction is not equivalent to clinical cure. Third, an MIC is measured under standardized conditions that may not reproduce bacterial density, nutrient availability, pH, oxygenation, intracellular residence, or biofilm physiology.

Within the proposed model, pharmacodynamic adequacy means that an evidence-supported exposure target is plausibly reached in the biologically relevant compartment for the organism and desired effect. A low probability of attainment supports regimen reconsideration when assumptions are applicable. A high probability narrows—but does not eliminate—exposure failure and should redirect reassessment toward diagnosis, penetration, protected bacterial states, host response, burden, and source control.

Tissue and infection-site penetration

Systemic availability becomes meaningful only when active drug reaches the pathogen's compartment for sufficient time. Penetration depends on perfusion, permeability, molecular properties, binding, transport, inflammation, pH, oxygen tension, tissue architecture, and inactivation. The destination may be extracellular fluid, urine, prostatic tissue, bone, an abscess, the ocular surface, or an intracellular niche. These are not interchangeable surrogates.

Population pharmacokinetic work in dogs shows substantial variability relevant to beta-lactam regimen design [8]. Healthy-dog PK/PD evaluation can establish baseline disposition and modeled adequacy, but it cannot reproduce every diseased tissue state [9]. Infection may increase permeability in one phase while thrombosis, necrosis, encapsulation, or declining perfusion later restricts delivery. Thus, "inflammation improves penetration" is not a stable rule.

The key clinical question is not whether drug is detectable, but whether unbound, microbiologically active exposure at the active lesion plausibly reaches the required temporal target. **Table 1** presents how infection-site compartments decouple systemic exposure from microbiologically active local exposure.

Table 1. How infection-site compartments decouple systemic exposure from microbiologically active local exposure

Infection-site question	Perfused extracellular infection	Excretory-compartment infection	Encapsulated, ischemic, or necrotic focus	Surface or protected microenvironment
Relation of plasma exposure to the site	Plasma exposure may approximate interstitial delivery	Local exposure may diverge markedly from plasma	Detectable systemic exposure may not reach the active burden	Contact, retention, and local conditions govern activity
Anatomic and physiological determinants	Perfusion, binding, edema, clearance	Urine flow, renal function, obstruction, pH	Capsule, thrombosis, debris, lesion age	Secretions, epithelial integrity, biofilm, cleansing

Site-specific evidence available	Clinical trajectory; timed concentrations when justified	Compartment-specific culture and physiology	Imaging, drainage findings, persistent focal signs	Site examination and correctly obtained samples
Treatment-planning use	Test regimen and target attainment before broadening	Interpret systemic concentrations cautiously	Prioritize source-access assessment over dose inflation	Match route and formulation to the compartment
Unresolved penetration question	Tissue exposure remains inferred unless directly sampled	High local concentration does not prove tissue eradication	Penetration failure and incorrect diagnosis may coexist	In-vitro activity may not represent local physiology
Evidentiary origin	Evidence-supported distinction	Evidence-supported distinction	Proposed adjudication state	Proposed adjudication state

Intracellular and protected infection sites

Some pathogens persist within host cells, poorly perfused cavities, epithelial recesses, secretions, or sequestered tissues. Protection can reduce exposure through limited cellular entry, vesicular trapping, altered pH, slow growth, or immune evasion. In canine corneal epithelial-cell experiments, *Staphylococcus pseudintermedius* produced intracellular and inflammatory effects modified alongside bacterial and biofilm measures; this supports mechanism, not clinical efficacy [11].

Canine otitis externa illustrates a different protected environment. Chronic inflammation, canal remodeling, exudate, local treatment delivery, and *Pseudomonas* biofilm biology can jointly shape response [12]. Laboratory characterization of resistant, biofilm-forming *Pseudomonas aeruginosa* from affected dogs confirms coexistence of relevant phenotypes, yet its small isolate set and absence of comparative outcomes prevent inference that any single determinant caused treatment failure [13].

Protected-site reasoning must therefore remain syndrome-specific. Intracellular activity cannot be inferred from extracellular MIC alone, and topical detectability cannot establish adequate contact across debris or biofilm. Reassessment should ask where viable organisms reside, which drug fraction reaches that location, whether local conditions preserve activity, and whether physical access can be improved. These questions identify failure mechanisms that antimicrobial spectrum alone cannot resolve.

Biofilms and bacterial burden

Biofilm is an organized bacterial state embedded in matrix and attached to tissue, debris, or foreign material. It can create concentration gradients, slow growth, phenotypic tolerance, and dispersal. These differ from heritable resistance. Canine otitis literature supports biofilm within a complex local environment [12], while resistant otic *Pseudomonas* isolates show that biofilm and acquired resistance can coexist without being equivalent [13].

Bacterial burden also alters treatment conditions. A large population increases heterogeneity and protected subpopulations; purulent or necrotic material may change pH, oxygenation, binding, and activity. Because practice rarely measures viable burden serially, “high burden” is a lesion-supported mechanistic inference, not a numerical threshold.

The model accordingly separates planktonic susceptibility, biofilm-associated tolerance, and burden-related persistence. Escalating spectrum may address undetected resistance but may not overcome matrix protection, inadequate contact, or continued seeding from a nidus. Useful reassessment therefore combines properly obtained culture with lesion examination, imaging or drainage when indicated, and longitudinal clinical response. Biofilm should neither become a universal explanation for failure nor be ignored when anatomy and recurrence make it plausible.

Host immune contribution

Antimicrobials act within a host system that contains, clears, or amplifies infection. Innate recognition, phagocytosis, complement, barriers, perfusion, and adaptive immunity influence whether inhibition becomes eradication. *Staphylococcus aureus* mastitis research priorities identify gaps across pathogen adaptation, mammary immunity, and control [14]. Broader syntheses likewise identify animal, udder, pathogen, environmental, and management determinants [15].

Antimicrobial effect and immune clearance may be complementary. Bovine mastitis research describes how innate cellular responses shape bacterial control while contributing to tissue injury [16]. This supports a host-contribution domain but not a transferable immune threshold across species.

The same exposure may therefore yield different outcomes in an immunocompetent animal and one with neutropenia, endocrinopathy, systemic inflammation, malnutrition, or compromised barriers. The proposed model treats host response as dynamic: improving physiology may convert inhibition into clearance, whereas deteriorating reserve can reveal failure despite unchanged dosing. Host support, lesion control, and antimicrobial optimization are interacting interventions.

Necrotic tissue and foreign material

Necrosis and foreign material sustain organisms while restricting antimicrobial action. Devitalized tissue lacks reliable perfusion and supplies protected surfaces. Implants, sutures, sequestra, and debris can support attachment and continued inoculation. A canine fracture-related infection model provided a reproducible platform for studying early implant-associated infection, but cannot define clinical intervention thresholds [17].

Evidence that an alternative antibacterial modality reduced infection in that canine model reinforces the biological difficulty of implant-associated infection; it does not show that phage treatment or antimicrobial replacement will succeed across spontaneous veterinary cases [18]. Surgical-site infection literature also supports prevention, debridement, drainage, and management of contaminated material as complements to antimicrobial therapy, while most comparative outcome evidence is human and requires cautious veterinary transfer [19].

The proposed model therefore treats viable devitalized tissue and removable foreign material as potential exposure constraints and bacterial reservoirs, not merely background comorbidity. Their presence should prompt anatomical reassessment before dose escalation. **Table 2** presents joint influence of devitalized tissue and retained material on persistent infection and source control.

Table 2. Joint influence of devitalized tissue and retained material on persistent infection and source control

Tissue-viability configuration	Foreign-material configuration	Reservoir evidence	Source-control option	Risk constraining removal or eradication claims	Basis
Viable margins; no nidus identified	None evident	Improving perfusion and lesion trajectory	Continue exposure assessment and monitoring	Occult sequestrum or wrong diagnosis remains possible	Evidence-supported distinction
Suspected nonviable focus	None evident	Imaging, discoloration, nonhealing tissue, persistent discharge	Evaluate debridement or drainage feasibility	Tissue viability is clinically estimated	Proposed adjudication state
Limited necrosis	Retained removable material	Recurrent focal inflammation or implant-associated drainage	Compare removal, revision, and stabilization risks	Removal may threaten function or welfare	Proposed adjudication state
Extensive or inaccessible devitalization	Essential or nonremovable material	Persistent burden despite plausible exposure	Seek specialist source-control plan; reassess goals	Antimicrobials may suppress without eradicating	Proposed adjudication state

Source control

Source control reduces the anatomical process maintaining infection. It may comprise drainage, debridement, foreign-material revision, relief of obstruction, tissue excision, dental treatment, or correction of contamination. Its effects include lowering burden, restoring perfusion, disrupting protected niches, obtaining representative samples, and preventing reseeding.

The pyometra outcome pattern is consistent with a dominant contribution from ovariohysterectomy, although the retrospective design cannot isolate the effects of surgery, antimicrobial therapy, and supportive care [4]. Experimental fracture-related infection likewise demonstrates how implant stability, inoculum, debridement, and retained material define the treatment environment [17]. General surgical evidence supports timely control of contaminated or infected foci but does not establish one veterinary timing rule across organs and species [19].

Source control is neither a binary checkbox nor automatically curative. A procedure may be incomplete, delayed, anatomically impossible, or disproportionately harmful; some infections have no discrete removable focus. The proposed model therefore represents source control as a time-varying degree of reservoir reduction. When adequate antimicrobial exposure coexists with persistent focal disease, the next question is whether the source remains active, not simply whether broader therapy is available.

Adherence and dosing feasibility

The delivered regimen can differ materially from the prescription. Owners must interpret instructions, administer formulations, coordinate dosing, manage adverse effects, and obtain refills. Communication research shows that dog and cat owners' knowledge and preferences influence antimicrobial decisions and explanations for treatment, testing, or non-treatment [20].

Veterinarians themselves navigate uncertainty when selecting drug, dose, and duration. Qualitative evidence describes interaction among clinical complexity, guidelines, experience, diagnostic access, owner circumstances, and practical administration [21]. Reported owner compliance with short veterinary antibiotic courses further supports treating delivery as a measured variable rather than an assumption, although self-report, setting, and regimen characteristics limit transferability [22].

The model separates feasibility at prescribing from execution during treatment. A regimen may be pharmacologically attractive yet fragile because of dosing frequency, formulation, palatability, cost, handling risk, monitoring requirements, or species-specific constraints. Reassessment should use nonjudgmental, specific questions about each dose, vomiting, refusal, technique, storage, and interruptions. If delivery is unreliable, simplifying an appropriate regimen may improve achieved exposure more plausibly than increasing spectrum.

A proposed antimicrobial-success model

The proposed model defines antimicrobial success as a time-dependent state in which four conditions remain sufficiently concordant: the causal pathogen is correctly represented; active drug reaches its biological location and attains a relevant pharmacodynamic target; bacterial burden and protected states are containable; and host response plus source control permit resolution. These conditions are conjunctive but not an additive score. Severe failure in one domain may dominate apparently favorable findings elsewhere.

The model separates three transitions. Delivery converts prescription into systemic exposure; biological access converts systemic exposure into active infection-site exposure; response converts that exposure into bacterial control and clinical recovery. PK/PD modeling informs the first two transitions [8]. Intracellular or biofilm states can weaken the second-to-third transition [11]. Source removal can improve response even when drug–isolate concordance is imperfect [4], whereas owner and administration constraints can interrupt delivery [20].

At each reassessment, observed trajectory is compared with the expected direction and timing for the syndrome. Improvement supports continuation or de-escalation without proving the proposed mechanism. Plateau or deterioration opens parallel checks of diagnosis, pathogen, delivery, exposure, site access, protected burden, host reserve, toxicity, and source control. The model's central claim is organizational: failure should be localized before therapy is intensified.

The temporal architecture below is needed because a static checklist cannot show reversible underexposure, accumulating protected burden, or repeated movement across reassessment and escalation boundaries.

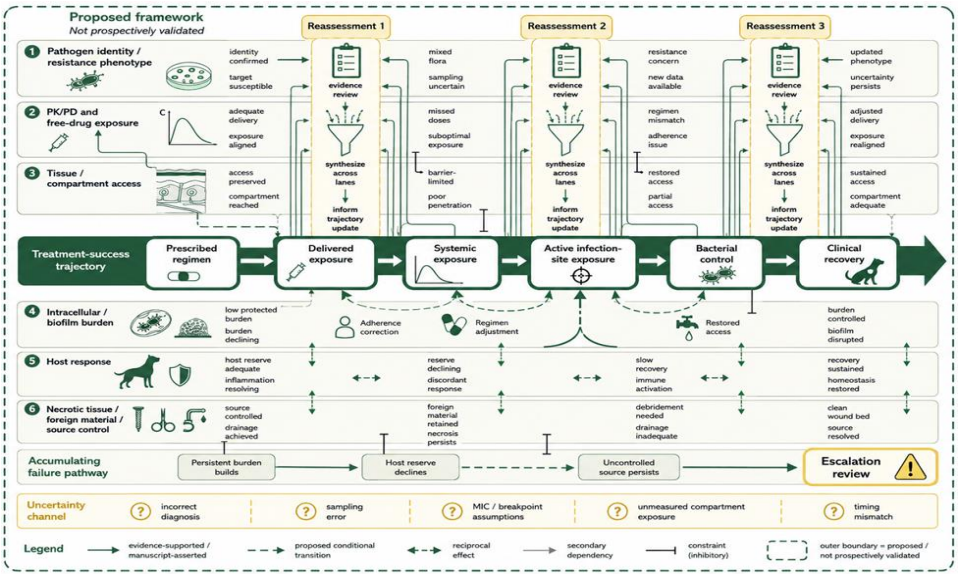

Figure 1. Treatment-success trajectories across exposure, biological access, bacterial persistence, and source-control boundaries

Discordance between laboratory susceptibility and clinical response

Discordance is informative only after its direction and denominator are specified. Susceptible-with-failure may reflect incorrect diagnosis, noncausal sampling, delivery failure, inadequate exposure, poor penetration, protected bacteria, excessive burden, impaired host response, an uncontrolled source, or an outcome assessed too early. Resistant-with-improvement may reflect source control, host clearance, high compartment exposure, mixed populations, incidental recovery, or limitations in testing and interpretation.

Evidence for shortening therapy in companion-animal urinary infection and pneumonia, together with work on interpretive surrogates, shows that laboratory categorization, treatment duration, and clinical outcome are related but nonidentical constructs [23–25]. These syntheses are constrained by heterogeneous regimens, syndromes, outcome definitions, and evidence quality. In dogs with lower urinary tract infection given nitrofurantoin, clinical and microbiological outcomes were not interchangeable, reinforcing the need to specify which response is being judged [26].

Table 3 presents laboratory susceptibility and clinical course as a concordance–discordance grid.

Table 3. Laboratory susceptibility and clinical course as a concordance–discordance grid

Laboratory result and clinical course	Explanatory pathways to test	Discriminating evidence	Regimen or source-control implication	Claim that remains unsafe	Basis
Susceptible; animal improving	Source control, host recovery, adequate delivery	Expected clinical trajectory	Continue or narrow when justified	Improvement does not prove eradication	Evidence-supported distinction
Susceptible; animal not improving	Exposure, penetration, burden, source, diagnosis	Dose history, examination, imaging, repeat sample	Localize failure before broadening	Timing and outcome definition matter	Proposed adjudication state
Resistant; animal improving	Incidental isolate, source removal, compartment exposure	Syndrome-specific clinical and microbiological follow-up	Verify causality before replacement	Relapse may expose unresolved infection	Proposed adjudication state
Result and course both ambiguous	Sampling or breakpoint uncertainty, mixed disease	Sample quality and competing diagnoses	Repeat or improve information first	Uncertainty must remain explicit	Proposed adjudication state

Reassessment of treatment failure

Treatment failure is an observed trajectory, not a diagnosis. Before attributing it to resistance, the clinician should define the failed endpoint: survival, fever, pain, discharge, organ function, bacterial clearance, recurrence, or expected time to improvement. Clinical persistence may lag behind bacterial control, while symptomatic improvement may precede microbiological eradication.

Reassessment begins with immediate threats and adverse effects, then revisits diagnosis and pathogen causality. It reconstructs administration, interval, interruptions, and relevant PK changes. It asks whether the target was plausible [8], anatomy permits site exposure, protected organisms or foreign material remain, and source control was complete. Discordant pyometra outcomes warn against equating laboratory mismatch with clinical failure [4]; canine urinary outcomes show that clinical and microbiological endpoints can separate [26].

Reassessment should be longitudinal and hypothesis-discriminating. Repeat culture is valuable when a representative specimen can distinguish persistence, relapse, reinfection, or contamination; indiscriminate resampling may instead amplify ambiguous colonization. Imaging, cytology, drainage, drug measurement, susceptibility confirmation, or surgical exploration should be selected for the mechanism they can adjudicate. If no observation could falsify the working explanation, “failure” becomes a label that invites uncontrolled escalation.

Escalation, de-escalation, and source-control decisions

Escalation should address an identified deficit: inadequate delivered exposure, insufficient spectrum for a credible pathogen, unstable disease requiring empirical coverage, or inaccessible/uncontrolled infection requiring procedural action. De-escalation becomes reasonable when diagnostic evidence narrows the pathogen, the animal stabilizes, bacterial infection becomes unlikely, source control is achieved, or continued exposure offers diminishing benefit relative to toxicity and selection pressure.

Institutional companion-animal stewardship guidance has been associated with reduced prescribing of critically important antimicrobials, demonstrating that decision architecture can change clinician behavior without establishing effects in every syndrome [27]. A scoping review of companion-animal surgical prophylaxis emphasizes heterogeneous practices and limited evidence, arguing against extending prophylaxis by habit [28]. Practice-level stewardship evaluation likewise supports feasible prescribing change while leaving durability and clinical-outcome attribution uncertain [29]. Fee-free urine culture and susceptibility testing shows that access to diagnostics can alter testing and treatment decisions, but the intervention's transferability depends on practice resources and owner populations [30].

The model therefore couples drug decisions with information and source decisions. Broadening without resolving obstruction, necrosis, an implant-associated nidus, or unreliable delivery may add exposure without adding success. Conversely, immediate narrowing is unsafe when instability and diagnostic uncertainty justify temporary coverage. Each decision should specify its target mechanism, review time, stopping condition, and welfare consequence.

Stewardship implications

Stewardship is often framed as choosing a narrower drug or shorter course. The model expands that frame to minimizing ineffective exposure. A susceptible result should not prolong therapy when the syndrome is nonbacterial, nor should repeated broadening substitute for drainage, debridement, adherence repair, or diagnostic revision. The relevant stewardship unit is the treatment episode: diagnosis, sampling, regimen, delivery, reassessment, source control, and stop decision.

Implementation must account for clinician workload, diagnostic cost, owner capability, production logistics, drug availability, withdrawal requirements, animal handling, and welfare. Veterinarians' accounts of regimen selection show why guideline availability alone does not dissolve these constraints [21]. Practice interventions can alter prescribing [27], and reduced diagnostic cost can change culture use [30], but neither finding establishes that the proposed model improves outcomes.

Practical use should therefore be light enough to support rather than delay care: a short causal checkpoint at prescription, an explicit reassessment interval, and documentation of the dominant uncertainty. Population-level benefits remain hypotheses. Reduced unnecessary exposure may lower selection pressure, but verifying that pathway requires linked antimicrobial-use, resistance, clinical, welfare, and production outcomes rather than dispensing counts alone.

Validation priorities

Validation should begin by operationalizing each model domain without pretending that all are directly measurable. Susceptibility categories depend on explicit methods, breakpoints, dosing assumptions, and continuing standards review [31]. Experiments using more physiological media show that conventional test conditions can misrepresent activity, but improved in-vivo prediction must be demonstrated pathogen by pathogen and syndrome by syndrome [32]. Differences between EUCAST and CLSI reporting principles further show that interpretive categories are constructed under distinct rules, not raw biological facts [33].

Prospective studies should enroll defined veterinary syndromes across species and settings, record prescribed and delivered doses, estimate free systemic and relevant compartment exposure, characterize pathogen and protected state, document host physiology and source-control timing, and measure both clinical and microbiological trajectories. External validation must test transport across practices, production systems, formulations, resistance prevalence, and diagnostic access. Contemporary network dispensing data can define candidate implementation contexts and prescribing baselines but cannot validate the model's mechanisms or benefits [34].

The framework should be challenged, not merely fitted. Useful tests include whether domain-informed reassessment improves causal classification, reduces unsupported escalation, or predicts recovery beyond susceptibility plus systemic exposure; whether omitted domains add value; and whether decision support causes delay, inequity, cost, or welfare harm. Calibration, inter-rater reliability, missing-data sensitivity, negative controls, and prespecified failure criteria are required before clinical deployment.

Conclusion

Antimicrobial administration creates an opportunity for success, not success itself. Susceptibility is conditional on pathogen, method, breakpoint, exposure, and compartment; systemic PK becomes clinically relevant only through site access and pharmacodynamic effect. Bacterial burden, intracellular residence, biofilm, host reserve, necrotic tissue, foreign material, source control, and feasible delivery can each redirect the trajectory.

The proposed model organizes these domains as changing, interacting conditions rather than an additive score. Its practical implication is disciplined localization of failure: verify diagnosis and causality, reconstruct delivery and exposure, examine biological access and protected burden, assess host response, and revisit source control before broadening therapy. Improvement may support narrowing without proving eradication; nonresponse may require a procedure or diagnostic revision rather than more antimicrobial exposure. This architecture remains unvalidated and cannot replace clinical judgment. Prospective, multispecies testing must determine whether it improves decisions, outcomes, welfare, and stewardship without creating delay or inequity.

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