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ANTIBIOTIC STABILITY ACROSS LABORATORY STORAGE CONDITIONS

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Abstract:

This analysis examines how laboratory storage conditions shape antibiotic stability, addressing the comparability of evidence used internationally in antimicrobial research. A descriptive secondary analysis evaluated 135 published condition estimates for ten beta lactam antibiotics from an experimental investigation published in 2024, retaining 84 numerical half lives and 51 lower bounds. Matched comparisons examined temperature, acidity and concentration within specified conditions. Increasing broth pH from 6.80 to 7.80 shortened estimated half-life for every antibiotic, with a median reduction of 61.50 percent. Warming aqueous solutions from 4°C to 25°C shortened half-life in 11 of 20 pairs, while increasing concentration shortened half-life in 13 of 30 pairs; remaining pairs shared reporting bounds. Frozen comparisons contained exceptions. Substituting a documented alternative imipenem estimate preserved the refrigeration versus room temperature direction but changed its magnitude. The contribution is a synthesis distinguishing directional consistency, proportional sensitivity and measurement resolution. The findings support compound specific storage assessment and explicit reporting of experimental conditions and bound to improve laboratory comparability.

Key Words: Antibiotic Stability; Beta Lactam Antibiotics; Storage Conditions; Matched Comparisons; Lower Bounds

1. Introduction:

Antibiotic degradation can change the exposure conditions of a laboratory experiment before its results are interpreted. When an active compound deteriorates during incubation or storage, its nominal concentration no longer describes the concentration available throughout the experiment. This creates a practical problem for susceptibility testing, preparation of experimental solutions and comparison of results across laboratories. Brouwers et al., 2020, demonstrated that beta lactam degradation can occur within the duration of bacterial growth assays, making chemical stability relevant to the interpretation of apparent bacterial regrowth. Stability therefore requires explicit consideration of the conditions under which an antibiotic is prepared, stored and measured. Chemical reaction kinetics explains why temperature, acidity and concentration may alter degradation half-life. Increasing temperature generally accelerates reactions within a given degradation pathway, while pH changes chemical speciation and the contribution of acid, neutral and base catalysed hydrolysis. Mitchell et al., 2014, documented temperature and pH dependent hydrolysis in three beta lactam antibiotics. Concentration introduces a competing expectation: an ideal first order process has a concentration independent half-life, whereas intermolecular reactions can produce concentration dependent degradation. Liebchen et al., 2021, discussed concentration related meropenem instability but found uniform degradation rates across the therapeutic concentrations examined in buffered serum. These findings establish that the direction and magnitude of stability relationships depend on the compound, concentration range and surrounding medium.

The closest empirical foundation is the investigation by Zhou et al., 2024, which estimated degradation half lives across broth, agar and purified water under different temperatures, pH values and concentrations. That investigation already established shorter broth half-lives at higher pH and differences associated with temperature and aqueous concentration. The present analysis builds directly on those published estimates. Its purpose is to examine how consistently the reported values establish an ordering within matched conditions, how proportional sensitivity differs from absolute stability, and how lower bounds constrain numerical comparisons. The contribution concerns the interpretation and transparent synthesis of existing evidence rather than the discovery of previously unreported degradation mechanisms. Measurement is central to this distinction. A numerical half-life estimate and a statement that half-life exceeds a reporting threshold contain different information. Two values reported above 500 hours cannot establish either equality or a precise difference. Similarly, an estimate pooled across several concentrations cannot be treated as several separate concentration observations. Fernández Rubio et al., 2022, organised antimicrobial stability evidence around drug identity, concentration, diluent, temperature and storage duration, demonstrating the importance of retaining experimental conditions when interpreting published results. The present analysis preserves these conditions and distinguishes numerical estimates from lower bounds throughout the comparisons.

This study aims to characterise variation in beta lactam antibiotic stability across temperature, acidity and concentration using matched descriptive comparisons. The central research question asks how reported degradation half-lives differ when one measured condition changes within an otherwise comparable antibiotic setting. The specific objectives are to compare aqueous half lives across temperatures within the same antibiotic and concentration, examine variation across reported pH levels under common broth conditions, and compare aqueous concentrations within the same antibiotic and temperature. These objectives require neither an assumed moderator nor a mediation pathway. The empirical setting comprises 135 unique condition estimates for ten antibiotics extracted from the source published in 2024. The dataset contains 84 numerical estimates and 51 lower bounds. It represents repeated laboratory condition estimates rather than an annual panel or a geographical sample. The acidity comparison uses 46 estimates at a common temperature, concentration and broth medium. The aqueous comparisons use 60 records organised into 20 temperature comparison groups and 30 concentration comparison pairs. Descriptive summaries retain the original units,

pooled concentration labels and reporting thresholds. An exploratory sensitivity calculation examines the documented alternative imipenem estimate to assess whether a source selection changes the direction or magnitude of a comparison.

The completed analysis contributes a distinction between consistent ordering, practical magnitude and measurement resolution. Higher pH corresponds to shorter half-life across all ten antibiotics under the common broth conditions. Refrigeration exceeds room temperature stability in every aqueous pair with an identifiable ordering, while frozen comparisons contain exceptions. Higher concentration corresponds to shorter half-life in every concentration pair whose ordering can be established. These results support condition specific interpretation rather than a universal storage ranking. Their broader relevance lies in identifying which comparisons can inform laboratory decisions and which require preservation of reporting bounds. Minichmayr and Friberg, 2024, demonstrated through pharmacokinetic and pharmacodynamic simulations that meropenem degradation can influence simulated exposure and bacterial killing. The present analysis addresses the preceding chemical evidence needed for such translation, without treating laboratory half-lives as direct evidence of clinical outcomes.

2. Theory, Conceptual Framework and Research Questions Development:

Antibiotic stability reflects the interaction between molecular structure and the chemical conditions surrounding the active compound. This analysis defines stability as degradation half-life, measured in hours, and examines its relationship with temperature, pH and antibiotic concentration. Chemical reaction kinetics provides the theoretical foundation: conditions that accelerate degradation should shorten half-life, although the magnitude depends on the antibiotic and medium. Brouwers et al., 2020, demonstrated that antibiotic degradation varies across bacterial growth media and responds to changes in temperature and pH. This evidence supports comparisons within the same antibiotic under specified laboratory conditions rather than treating stability as a fixed property of an antibiotic class. Temperature changes the energy available for chemical reactions. Within a stable reaction pathway, Arrhenius kinetics predicts faster degradation as temperature increases and therefore a shorter half-life. Mitchell et al., 2014, documented temperature dependent hydrolysis of ampicillin, cefalotin and cefoxitin, supporting this theoretical expectation. Their findings establish a mechanism for thermal sensitivity without implying that every antibiotic responds at the same rate. This analysis examines temperature through matched aqueous conditions, comparing each antibiotic at the same reported concentration. Keel et al., 2011, investigated doripenem, imipenem and meropenem at elevated room temperatures, reinforcing the relevance of examining thermal stability separately for individual compounds. The available estimates permit descriptive comparisons across refrigerated, frozen and room temperature conditions. Where half-lives are reported as lower bounds, the comparison preserves those bounds rather than assigning an exact degradation time.

RQ1: How do reported degradation half lives and their lower bounds vary with storage temperature within the same antibiotic and aqueous concentration?

Acidity influences degradation through chemical speciation and the relative contribution of acid, neutral and base catalysed reactions. Unlike a simple thermal acceleration mechanism, the relationship between pH and stability can change direction across the acidity range. Hirte et al., 2016, showed that pH influenced both amoxicillin hydrolysis and the formation of transformation products. This evidence supports a conditional relationship between pH and stability rather than a universal linear relationship across all aqueous environments. This analysis restricts the acidity comparison to the measured pH range from 6.80 to 7.80 in cation adjusted Mueller Hinton broth at 36°C and an antibiotic concentration of 8 mg/L. These conditions provide a common basis for describing variation within each antibiotic. Comparisons use the reported pH levels for each compound and do not extend the observed pattern to more acidic or alkaline conditions.

RQ2: How does degradation half-life vary across the reported pH levels within each antibiotic at a common temperature, concentration and broth medium?

Antibiotic concentration introduces a competing kinetic mechanism. Under an ideal first order process, increasing the initial concentration does not change half-life because degradation remains proportional to the amount present. However, reactions between antibiotic molecules can make the apparent degradation rate concentration dependent. Liebchen et al., 2021, discussed intermolecular aminolysis as a mechanism contributing to meropenem instability at higher concentrations, while finding no concentration dependent degradation across the therapeutic concentrations examined in buffered serum. The contrasting evidence indicates that concentration effects depend on the concentration range and surrounding medium. This analysis compares aqueous concentrations of 10 and 1,000 mg/L within the same antibiotic and temperature. The comparison describes differences in reported half-lives while retaining lower bound classifications. Estimates pooled across several concentrations remain pooled and do not represent separate concentration observations. This approach distinguishes evidence of concentration related variation from differences attributable to temperature or medium.

RQ3: How do reported degradation half lives and their lower bounds differ between aqueous concentrations of 10 and 1,000 mg/L within the same antibiotic and temperature?

The conceptual framework links three observed storage dimensions to one measured outcome: antibiotic stability expressed as degradation half-life. Antibiotic identity and medium define the comparison conditions. Temperature comparisons hold antibiotic identity and concentration constant, acidity comparisons use common broth conditions, and concentration comparisons hold antibiotic identity and temperature constant. These relationships guide descriptive comparisons of the available estimates and do not represent a jointly estimated causal model.

3. Data:

This analysis documents the provenance, selection and measurement of published antibiotic stability estimates. It preserves reported numerical estimates, lower bounds and pooled conditions to support reproducible descriptive comparisons.

3.1 Data Sources, Population, and Sample Construction:

The empirical dataset comprises estimates extracted from Tables 2 and 5 of Zhou et al., 2024, published in Antimicrobial Agents and Chemotherapy. The source identifier is DOI 10.1128/aac.01399-23, and the version of record provides the access route. The accompanying workbook retains the source extracts, table locations, condition notes and extraction timestamp. The publisher states that copyright belongs to the American Society for Microbiology, with all rights reserved. The workbook contains a secondary extraction of numerical results rather than the original experimental concentration measurements. The target

population comprises beta lactam antibiotics evaluated for chemical stability under laboratory storage and incubation conditions. The accessible sampling frame consists of the ten antibiotics represented in the extracted source tables: imipenem, biapenem, doripenem, meropenem, cefsulodin, cefepime, ceftazidime, piperacillin, ticarcillin and aztreonam. Selection follows compound eligibility and availability of a numerical half-life estimate or an explicit lower bound. Beta lactamase inhibitors and clavulanic acid fall outside this frame.

The unit of analysis is one published antibiotic and condition estimate. The dataset is a collection of laboratory condition comparisons with repeated estimates within antibiotics. It is neither an annual panel nor a geographical sample. The eligibility window extends from 2010 to 2024, while the retained empirical estimates originate from the source published in 2024. Publication year does not identify the experimental measurement date. Experimental observation windows extend to approximately 26 hours in the broth acidity experiment, 72 hours in agar, 96 hours in room temperature broth, and 96 or 120 hours in water. The distinction between drug identity, medium and storage conditions is substantively necessary. Brouwers et al., 2020, examined stability in bacterial growth media, while Berthoin et al., 2010, investigated meropenem and doripenem solutions. Manning et al., 2014, and Foy et al., 2019, evaluated stability under infusion conditions. These publications inform the boundaries of comparability but contribute no additional observations to the analytical dataset.

Table 1: Sample construction and descriptive comparison samples

Stage	Antibiotics Represented	Records or Candidate Cells	Inclusion or Exclusion Rule
Extracted antibiotic frame	10	160	Fifty candidate cells from source Table 2 and 110 from source Table 5
Conditions not studied	3 affected	5 excluded	Four acidity conditions and one room temperature broth condition
Available entries before deduplication	10	155	Numerical estimates and explicit lower bounds
Repeated entries across source tables	10 affected	20 excluded	Identical broth conditions already retained from source Table 2
Final descriptive dataset	10	135	Unique antibiotic and condition combinations
Numerical estimate subset	10	84	Published numerical half-life estimates
Lower bound subset	10	51	Twelve bounds above 200 hours and 39 above 500 hours
Acidity comparison sample	10	46	Common broth medium, 36°C and 8 mg/L
Aqueous temperature comparison sample	10	60	Twenty matched groups defined by antibiotic and concentration
Aqueous concentration comparison sample	10	60	Thirty matched pairs defined by antibiotic and temperature

The final dataset contains 55 broth records, 20 agar records and 60 water records. Seven antibiotics contribute 14 records each, ticarcillin contributes 13, and cefepime and cefsulodin contribute 12 each. These differences reflect experimental coverage rather than annual attrition. The comparison samples overlap and must not be added together.

3.2 Data Integration, Cleaning, and Quality Assurance:

Integration appends the extracted source tables into one condition dataset. The identifying key combines antibiotic, medium, temperature, numerical pH where reported, and the documented concentration level or concentration set. Twenty repeated broth entries were retained once, using source Table 2 for the overlapping acidity conditions. The resulting dataset contains 135 distinct keys. Different conditions for the same antibiotic remain separate observations. The flat structure, consistent units and explicit identifiers follow the data organisation principles described by Broman and Woo, 2018. Missingness is recorded according to its substantive meaning. Numerical pH is available for 55 records and unreported for 80, comprising all 60 water records and 20 agar records. Each antibiotic therefore has eight records without numerical pH. Water is described as neutral, but no numerical value is assigned from that description. A single concentration value is available for 106 records. The remaining 29 estimates pool several concentrations: nine broth estimates combine 1 and 16 mg/L, while 20 agar estimates combine 1, 3, 10 and 30 mg/L. These estimates remain single records with their tested concentration sets preserved. Each antibiotic has three pooled records except ticarcillin, which has two. No missing condition is replaced with zero, interpolated or imputed. This treatment distinguishes unreported information from pooled measurement, consistent with the missing data distinctions discussed by Hughes et al., 2019.

The audit checked identifier uniqueness, positive half-life values, valid numerical pH and consistency between the estimate field and its comparator. All 135 half-life entries are positive, and all reported numerical pH values fall within the feasible scale. Numerical estimates remain distinct from lower bounds. No percentile trimming or winsorisation was applied. Large published estimates were retained rather than treated as errors solely because of their magnitude, following the distinction between erroneous and valid extreme observations discussed by Aguinis et al., 2013. Source notes preserve two interpretation choices. Refrigerated agar records use the source statement that estimated half-lives exceed 200 hours, while retaining the original table description of at least 90 percent remaining after 72 hours. The imipenem estimate of 83 hours in water at 4°C and 10 mg/L retains the source qualification that it represents the three less stable replicates. These are documented source interpretations rather than reconstructed experimental measurements. Original source entries remain separate from calculated workbook fields. Table identifiers, comparator labels and condition notes retain the path from each analytical record to its published origin. This

separation supports the traceability advocated by Sandve et al., 2013, and the distinction between computational reproducibility and independent experimental replication articulated by Peng, 2011.

3.3 Variable Measurement, Construction, and Validation:

Antibiotic stability is measured as degradation half-life in hours. Higher values indicate slower degradation under the specified conditions. A numerical estimate and a lower bound represent different information: an entry above 500 hours identifies a threshold rather than an observed half-life of 500 hours. The dataset therefore stores the numerical value or threshold alongside an explicit comparator. Temperature is measured in degrees Celsius. Acidity is represented by reported numerical pH, with higher values indicating lower acidity. Concentration is measured in mg/L and remains separate from the concentration sets attached to pooled estimates. These dimensions correspond to mechanisms examined in hydrolysis research by Mitchell et al., 2014, and Hirte et al., 2016. Their evidence supports condition specific measurement rather than assuming uniform stability across antibiotics and media.

Table 2: Variable dictionary

Variable or Indicator	Analytical Role	Definition and Construction	Source and Identifier	Unit and Frequency	Transformation and Direction	Missing Value Rule	Coverage and Limitation
Degradation half-life	Outcome	Published numerical estimate or lower bound	Source Tables 2 and 5; half life h	Hours per condition	Higher values indicate greater stability	No substitution	135 records, including 51 bounds
Estimate comparator	Measurement qualifier	Distinguishes numerical estimates from greater than thresholds	comparator	Category per condition	Preserves the meaning of the outcome value	Complete	84 numerical estimates and 51 bounds
Temperature	Predictor	Reported storage or incubation temperature	Temperature C	°C per condition	Original scale	Complete	135 records, from minus 20 to 37°C
Numerical pH	Predictor	Reported acidity condition	pH	pH units per condition	Original scale; higher values indicate lower acidity	Retain unreported values as missing	55 records, from 6.80 to 7.80
pH status	Measurement qualifier	Identifies reported, unadjusted or qualitatively neutral conditions	pH status	Category per condition	No transformation	Complete	Explains 80 missing numerical values
Single concentration	Predictor	Concentration for estimates associated with one reported level	Concentration mg L	mg/L per condition	Original scale	Blank for pooled conditions	106 records
Concentration set	Design descriptor	Preserves all tested levels associated with an estimate	Concentrations mg L	mg/L levels per condition	No expansion into additional observations	Complete	Includes 29 pooled estimates
Medium	Comparison condition	Broth, agar or purified water	medium	Category per condition	Separate comparison settings	Complete	55 broth, 20 agar and 60 water records
Antibiotic identity	Matching identifier	Named compound associated with each estimate	drug	Compound per condition	Comparisons within antibiotics	Complete	Ten antibiotics
Log half-life value or bound	Calculated field	Natural logarithm of the reported value or threshold	Ln half life bound	Log hours per condition	Monotonic transformation	Complete	Comparator remains necessary
Degradation rate	Calculated field	Natural logarithm of two divided by a numerical half-life	Degradation rate h inv	Per hour per condition	Higher values indicate faster degradation	Blank for lower bounds	84 calculated values
Record and source identifiers	Provenance	Unique identifier, table, column, condition note and DOI	record id and source fields	Identifier per condition	No transformation	Complete	Supports record tracing

The workbook implements two transparent transformations.

$$L_i = \ln H_i$$

Here, L_i denotes the transformed value for record i, and H_i denotes its numerical half-life estimate or reported threshold in hours. Equation 1 does not convert a bound into an exact estimate.

$$k_i = \ln 2 \div H_i$$

Here, k_i denotes the calculated first order degradation rate per hour for record i, and H_i denotes a numerical half-life estimate. Equation 2 is applied only to the 84 numerical estimates. The rate field remains blank for the 51 lower bounds. Temperature and concentration comparisons retain antibiotic identity because thermal sensitivity and concentration dependence need not be uniform across compounds. Keel et al., 2011, examined temperature related stability in individual carbapenems. Liebchen et al., 2021, showed that concentration dependence can differ across solution conditions. These findings justify preserving the measured dimensions separately rather than combining them into an unvalidated storage index.

Table 3: Verified descriptive statistics

Measure	Valid Numerical Records	Mean	Sample SD	Median	Minimum	Maximum
Numerical degradation half-life, hours	84	208.71	332.64	93.40	10.00	1,824.00
Temperature, °C	135	18.30	20.20	25.00	Minus 20.00	37.00
Numerical pH	55	7.254	0.326	7.250	6.800	7.800
Single concentration, mg/L	106	289.32	448.63	10.00	8.00	1,000.00

The half-life summary describes only numerical estimates and does not estimate the distribution of all 135 records. Temperature, pH and concentration summaries describe the represented experimental conditions rather than their prevalence in laboratory practice. Reporting valid counts, dispersion and range alongside central tendency follows the emphasis on distributional transparency advanced by Weissgerber et al., 2015.

3.4 Analytical Framework, Identification, and Reproducibility:

The analytical framework is descriptive. It examines variation in published stability estimates within comparable antibiotic and condition groups. The 135 records represent repeated condition estimates across ten antibiotics, rather than 135 independent experimental replicates. This distinction addresses the pseudoreplication problem described by Lazic, 2010, and the separation of observational and experimental units explained by Lazic et al., 2018. The acidity comparison uses 46 broth estimates at 36°C and 8 mg/L. Temperature comparisons use 60 water records arranged into 20 groups defined by antibiotic and concentration, each containing three temperatures. Concentration comparisons use the same 60 water records arranged into 30 pairs defined by antibiotic and temperature. These groupings preserve the available matching structure without treating pooled concentrations as additional observations.

The framework retains numerical estimates and lower bounds in their original categories. Numerical summary statistics use the 84 numerical estimates, while the complete dataset supports reporting of coverage and bound frequencies. The broth, agar and water estimates are not pooled into a joint causal specification because the available conditions do not provide a common experimental comparison across all three predictors. Interpretation concerns the direction and magnitude of reported differences under specified conditions. The dataset contains published estimates without the full covariance information needed to reconstruct their joint uncertainty. Accordingly, the descriptive framework does not attach newly calculated significance claims to these estimates. This distinction between numerical magnitude and statistical evidence follows Wasserstein and Lazar, 2016, and Greenland et al., 2016. Reproducibility rests on the retained source tables, explicit identifiers, documented exclusions, concentration sets, comparator fields and visible transformation formulas. The audit reconciles the sample construction counts with 135 unique records and verifies variable specific coverage. Stable source identification and readable metadata support the data stewardship principles set out by Wilkinson et al., 2016. Together, these features preserve consistent definitions and prevent unreported conditions or lower bounds from becoming fabricated numerical observations.

4. Methods:

4.1 Research Design and Comparison Strategy:

This analysis used a descriptive secondary analysis of published antibiotic stability estimates. The unit of analysis was one antibiotic and laboratory condition estimate. The quantities of interest were the direction and proportional magnitude of changes in degradation half-life between comparable conditions. The design examined variation within antibiotics rather than estimating a pooled relationship across chemically different compounds. The source investigation by Zhou et al., 2024, supplied estimates derived from experimental concentration profiles. The present analysis compared those estimates without refitting the original population models. Its conclusions therefore concern the ordering and magnitude of published estimates under specified conditions, rather than independently identified causal effects. Three comparison structures addressed the research questions. Acidity comparisons held antibiotic identity, broth medium, temperature and reported concentration constant. Temperature comparisons held antibiotic identity, aqueous medium and reported concentration constant. Concentration comparisons held antibiotic identity, aqueous medium and temperature constant. Numerical pH was unreported for the aqueous records and was not assigned an assumed value. Repeated condition estimates were not treated as independent experimental replicates. The distinction between observational records and independent experimental units follows Lazic et al., 2018. Accordingly, the analysis reports descriptive contrasts without significance tests based on an assumed sample of 135 independent experiments.

4.2 Analytical Samples and Measurement Alignment:

Table 1 documents sample construction, while Table 2 defines the variables and measurement qualifiers. The complete descriptive sample contained 135 records across ten antibiotics. Numerical estimates and lower bounds remained eligible for directional comparisons, but calculations requiring exact reported values used numerical estimates only. The acidity sample contained 46 broth estimates measured at 36°C and 8 mg/L. Endpoint comparisons paired pH 6.80 with pH 7.80 within each antibiotic. Additional comparisons sorted the available pH levels within each antibiotic and assessed the direction between successive reported levels. For cefepime and cefsulodin, successive comparisons used their three available levels without filling the unstudied intermediate conditions. The temperature sample contained 60 aqueous records organised into 20 groups defined by antibiotic and concentration. Each group contained estimates at minus 20°C, 4°C and 25°C. Comparisons examined each of the three temperature pairs separately. These comparisons reused observations and were not combined into an independent pooled sample. The concentration analysis reorganised the same aqueous records into 30 pairs defined by antibiotic and temperature. Each pair compared 10 with 1,000 mg/L. Broth and agar estimates pooled across multiple concentrations were excluded from this concentration comparison because they did not identify separate outcomes for individual concentration levels. Unreported numerical pH remained missing, while pooled concentrations retained their original concentration sets. No missing value was replaced with zero, interpolated or imputed. This preserved one condition estimate per record and avoided artificial replication, consistent with the spreadsheet organisation principles described by Broman and Woo, 2018.

4.3 Descriptive Calculations and Treatment of Lower Bounds:

Descriptive summaries reported valid counts, arithmetic means, sample standard deviations, medians and ranges. Sample standard deviations used the number of valid observations less one as the denominator. Half-life summaries included only the 84 numerical estimates. The 51 lower bounds were counted separately rather than entered as exact values. For pairs containing two numerical estimates, proportional change was calculated as:

$$D = 100 \times [1 - H_B \div H_A]$$

Here, D denotes the percentage reduction in half-life, H_A denotes the reference condition estimate in hours, and H_B denotes the comparison condition estimate in hours. Positive values indicate shorter half-life under the comparison condition; negative values indicate longer half-life. The reference conditions were the lower temperature, pH 6.80 and concentration of 10

mg/L, respectively. Equation 3 was evaluated separately for each eligible pair. Means, medians and ranges of proportional changes therefore summarised individual paired reductions, rather than percentage changes calculated from pooled group means. Each summary retained its own valid pair count. Directional classification also used lower bounds where they established an ordering. When the reference half-life exceeded a threshold and the comparison estimate was numerical and no greater than that threshold, the comparison condition was classified as having a shorter half-life. Conversely, a comparison lower bound at least as large as a numerical reference estimate established a longer half-life under the comparison condition.

Two estimates above the same threshold were retained as sharing a reporting bound. They were not classified as equal and contributed no numerical percentage reduction. Other combinations that did not establish an ordering were likewise excluded from magnitude calculations. The logarithmic transformation and calculated degradation rate followed Equations 1 and 2. Logarithms retained the original comparator classification, while degradation rates were calculated only for numerical half lives. Neither transformation supplied an additional independent outcome or resolved an unknown value beyond a reporting threshold.

4.4 Verification, Sensitivity Analysis and Reproducibility:

Calculations used Python 3.12.14 with the standard library modules json, collections and statistics. Workbook extraction used zipfile and xml.etree. Element Tree. The procedures were deterministic and required no random seed, numerical optimisation or convergence settings. Records and matched pairs received equal weight within their respective descriptive summaries. Verification reconciled source table membership, sample counts, missingness and comparator frequencies. The identifying key combined antibiotic, medium, temperature, reported numerical pH and concentration level or concentration set. Checks assessed key uniqueness, positive half-life entries and feasible numerical pH. The audit also distinguished repeated conditions across source tables from genuine differences within antibiotics. Published extreme values were retained without trimming or winsorisation.

An exploratory sensitivity calculation addressed the documented alternative imipenem estimate at 4°C and 10 mg/L. The retained estimate of 83 hours was replaced with the source estimate of 582 hours based on all six replicates. All other records remained unchanged. The affected temperature and concentration contrasts were recalculated to determine whether the substitution changed their direction or magnitude. The alternative was evaluated separately and did not overwrite the primary dataset. The accompanying workbook preserves source extracts, record identifiers, table and column locations, condition notes, comparator labels and transformation formulas. Together with the explicit matching and calculation rules, these materials permit reconstruction of the descriptive comparisons. The method provides a transparent synthesis of published estimates using established procedures; its interpretive scope remains the represented antibiotics, conditions and reporting precision.

5. Findings:

This analysis examines how antibiotic stability varies with temperature, acidity and concentration through matched comparisons of published estimates. Numerical half-lives and reported lower bounds remain distinct throughout the analysis. The findings address the three research questions through comparative magnitudes, variation across antibiotics and sensitivity to a documented source estimate. The analytical sample contains 135 unique antibiotic and condition records covering ten antibiotics. Of these, 84 contain numerical half-life estimates and 51 contain lower bounds, representing 62.22 percent and 37.78 percent of the sample, respectively. These are published condition estimates extracted from Zhou et al., 2024, rather than independent experimental replicates. Table 4 shows that measurement completeness differs substantially across media.

Table 4: Analytical coverage by laboratory medium

Medium	Antibiotics	Records	Numerical Half-Life Estimates	Lower Bounds
Broth	10	55	55	0
Agar	10	20	8	12
Water	10	60	21	39
Total	10	135	84	51

Among the 84 numerical estimates, mean half-life was 208.71 hours, the sample standard deviation was 332.64 hours, and the median was 93.40 hours. Values ranged from 10.00 to 1,824.00 hours. The difference between the mean and median reflects an asymmetric distribution containing several long half-lives. These statistics describe the numerical subset only. They do not summarise the full sample because the lower bounds cannot be treated as exact observations. Numerical pH was available for 55 records, while 106 records contained a single concentration value. The remaining concentration records represented pooled experimental levels. Consequently, the acidity comparison used 46 common condition broth estimates, while the temperature and concentration comparisons used the 60 water records. This matching prevents differences in medium or pooled concentration coverage from being interpreted as changes in the focal predictor. Temperature comparisons provided the clearest directional evidence when refrigeration was compared with room temperature. Across 20 matched antibiotic and concentration pairs, moving from 4°C to 25°C produced shorter reported half-lives in 11 pairs. No pair showed a longer half-life at 25°C. The remaining nine pairs had lower bounds above 500 hours at both temperatures. Table 5 preserves these distinctions rather than interpreting shared thresholds as equal stability.

Table 5: Matched aqueous half-life comparisons across temperatures

Temperature Comparison	Matched Pairs	Shorter Half-Life at Higher Temperature	Longer Half-Life at Higher Temperature	Both Estimates Above 500 Hours
Minus 20°C to 4°C	20	4	2	14
4°C to 25°C	20	11	0	9
Minus 20°C to 25°C	20	10	1	9

Four pairs contained numerical estimates at both 4°C and 25°C. Their median half-life reduction was 43.27 percent, with reductions ranging from 11.20 percent to 78.91 percent. At 1,000 mg/L, imipenem declined from 69.7 to 14.7 hours,

corresponding to the largest reduction. Doripenem declined from 151.0 to 91.1 hours at 10 mg/L and from 112.0 to 59.5 hours at 1,000 mg/L. These comparisons are consistent with temperature dependent hydrolysis documented by Mitchell et al., 2014, while showing that the magnitude varies across the represented compounds and concentrations. The frozen comparisons did not establish a uniform temperature ordering. Piperacillin at 10 mg/L had a reported half-life of 354 hours at minus 20°C, compared with more than 500 hours at 4°C and 370 hours at 25°C. At 1,000 mg/L, its half-life was 321 hours at minus 20°C and more than 500 hours at 4°C. Therefore, RQ1 is answered conditionally: the reported estimates consistently favour refrigeration over room temperature wherever their ordering is identifiable, but the frozen comparisons contain exceptions. The acidity comparison showed a consistent ordering across all ten antibiotics. At 36°C and 8 mg/L in broth, increasing pH from 6.80 to 7.80 shortened every reported half-life. All 36 adjacent comparisons across available pH levels also showed decreases. The median endpoint reduction was 61.50 percent, with a range from 53.21 percent for meropenem to 69.70 percent for biapenem.

Table 6: Changes in broth half-life between pH 6.80 and pH 7.80

Antibiotic	Half-life at pH 6.80, hours	Half-life at pH 7.80, hours	Reduction, Percent
Imipenem	23.7	10.3	56.54
Biapenem	33.0	10.0	69.70
Doripenem	59.7	23.3	60.97
Meropenem	62.4	29.2	53.21
Cefsulodin	36.8	14.9	59.51
Cefepime	80.9	28.1	65.27
Ceftazidime	266.0	102.0	61.65
Piperacillin	95.8	32.9	65.66
Ticarcillin	282.0	109.0	61.35
Aztreonam	1,824.0	685.0	62.45

The consistent direction coexisted with substantial differences in absolute stability. Aztreonam retained the longest half-life at both endpoints, despite a reduction exceeding 60 percent. Biapenem displayed the greatest proportional reduction and the shortest endpoint half-life at pH 7.80. Thus, relative sensitivity and absolute stability describe different features of the estimates. RQ2 is resolved descriptively within the measured interval: higher pH was associated with shorter half-life for every antibiotic under the common broth conditions. This pattern accords with the importance of acidity and medium documented by Brouwers et al., 2020. Because the extracted values originate from a shared population modelling framework, the uniform ordering describes those published estimates rather than providing independent experimental confirmation of a common pH response. Concentration comparisons also showed a consistent direction wherever the reported values established an ordering. Across 30 matched aqueous pairs, 13 showed shorter half-lives at 1,000 mg/L than at 10 mg/L. No pair established a longer half-life at the higher concentration. Seventeen pairs had lower bounds above 500 hours at both concentrations. Table 7 shows that most identifiable concentration differences occurred at 25°C.

Table 7: Matched aqueous comparisons between 10 and 1,000 mg/L

Temperature	Matched pairs	Shorter half-life at 1,000 mg/L	Longer half-life at 1,000 mg/L	Both estimates above 500 hours
Minus 20°C	10	3	0	7
4°C	10	2	0	8
25°C	10	8	0	2
Total	30	13	0	17

Eight concentration pairs contained numerical estimates at both levels. Their median reduction was 28.05 percent, ranging from 9.32 percent to 80.05 percent. At 25°C, imipenem declined from 73.7 to 14.7 hours when concentration increased from 10 to 1,000 mg/L. Doripenem declined from 91.1 to 59.5 hours, while piperacillin declined from 370 to 258 hours. Five additional antibiotics at 25°C had lower concentration estimates above 500 hours and higher concentration estimates below that threshold. These results answer RQ3 through a conditional concentration pattern: higher concentration corresponded to shorter half-life in every pair with an identifiable ordering. The pattern is consistent with the concentration related instability reported by Foy et al., 2019. The shared lower bounds for other pairs do not establish concentration independence. The concentration pattern also requires a defined environmental boundary. Liebchen et al., 2021, reported identical meropenem degradation rates across the therapeutic concentrations examined in buffered serum. The present aqueous comparison spans 10 to 1,000 mg/L and therefore describes a different concentration range and medium. Its findings cannot establish that the same proportional response applies in serum or across all formulation conditions.

An exploratory sensitivity calculation examined the documented alternative imipenem estimate at 4°C and 10 mg/L. Replacing the retained conservative estimate of 83 hours with the source estimate of 582 hours based on all six replicates changed the half-life reduction from 4°C to 25°C from 11.20 percent to 87.34 percent. The direction remained unchanged. However, the comparison between minus 20°C and 4°C reversed because the frozen estimate was 260 hours. The direction of the refrigeration versus room temperature comparison therefore survived this substitution, while its magnitude and the frozen ordering depended on the source estimate selected. Across the three research questions, acidity produced the most complete directional pattern under common conditions. Refrigeration exceeded room temperature stability in every aqueous comparison with an identifiable ordering, while higher concentration corresponded to shorter half-life in every identifiable concentration pair. Frozen comparisons contained exceptions. The empirical contribution is a matched descriptive synthesis that distinguishes consistent directional patterns from numerical magnitudes and shared reporting bounds.

6. Discussion:

An antibiotic's reported stability is inseparable from its storage conditions and the precision of its measurement. Tables 5 to 7 distinguish three empirical patterns: consistent decreases across the measured pH interval, shorter half lives at room temperature wherever refrigeration comparisons establish an ordering, and concentration related reductions in the identifiable aqueous pairs. Equation 2 expresses the corresponding inverse relationship between half-life and calculated degradation rate, but adds no independent evidence. The contribution of this analysis lies in separating directional consistency, proportional magnitude and reporting limits within matched antibiotic comparisons. This distinction sharpens the interpretation of the heterogeneous stability evidence reviewed by Fernández Rubio et al., 2022. A stable ranking under one comparison does not establish a general storage rule across compounds, media and concentration ranges. The acidity findings identify the most consistently ordered relationship under common experimental conditions. In Table 6, every antibiotic shows a shorter estimated half-life at higher pH, with a median endpoint reduction of 61.50 percent. However, absolute stability and proportional sensitivity remain distinct: aztreonam retains the longest half-life despite a substantial relative decline. The chemical interpretation is consistent with pH sensitive degradation, while the shared source modelling framework limits interpretation of the uniform response as independent mechanistic confirmation. Jamieson et al., 2020, further demonstrated that buffering effects depend on formulation conditions and do not necessarily produce sufficient meropenem stability for prolonged administration. This comparison refines the theoretical interpretation of acidity: pH specifies the chemical environment in which stability is evaluated, rather than providing a universally transferable optimisation rule. Equation 2 preserves this conditional interpretation because its calculated rate remains specific to each reported half-life.

Temperature and concentration reveal a different form of consistency. Table 5 establishes an ordering favouring refrigeration over room temperature in 11 matched pairs, while Table 7 identifies shorter half-lives at higher concentration in 13 pairs. The greater number of identifiable concentration differences at 25°C shows where the available measurements distinguish conditions most clearly; it does not estimate a temperature and concentration interaction. Likewise, the descriptive comparisons provide no additive total effect that can be decomposed into independent pathway shares. Their theoretical value is the separation of conditional patterns that would be obscured by a pooled storage coefficient. Minichmayr and Friberg, 2024, incorporated concentration dependent meropenem degradation into pharmacokinetic and pharmacodynamic simulations and found consequences for simulated exposure and bacterial killing. The present synthesis contributes the preceding chemical comparison, identifying compound and condition combinations for which stability differences can be quantified without equating them with clinical effects. Measurement limits materially shape the apparent strength of storage relationships. Table 4 shows that lower bounds account for 65 percent of aqueous records, so comparisons based only on numerical estimates disproportionately represent conditions with shorter reported half-lives. Equation 1 preserves ordering through logarithmic transformation but cannot recover values beyond a reporting threshold. The imipenem sensitivity calculation illustrates a separate source of dependence: substituting the documented alternative estimate preserves the refrigeration versus room temperature direction while changing its magnitude and reversing the frozen comparison. These results establish that measurement completeness and estimate selection belong within the interpretation of stability, rather than being treated solely as data preparation details. Van Abel et al., 2023, similarly emphasised that antimicrobial stability must be considered alongside the practical conditions of continuous infusion. For laboratory reporting, the corresponding implication is to retain thresholds, concentration sets and source qualifications alongside numerical summaries.

International relevance rests on comparable chemical conditions rather than geographical labels. Japanese infusion experiments reported by Akahane et al., 2021, found differing stability among piperacillin, doripenem and meropenem under specified diluents and temperatures. Those findings reinforce the importance of compound identity, while their formulation conditions prevent direct numerical transfer from the aqueous and broth comparisons in Tables 5 to 7. The evidence therefore supports a practical change in laboratory interpretation: specify antibiotic, medium, temperature, pH and concentration together when comparing storage performance, and preserve reported bounds when exact rankings are unavailable. Refrigeration receives consistent descriptive support against room temperature in the identifiable aqueous comparisons, whereas freezing requires compound specific interpretation. The theoretical contribution is a conditional account of stability that distinguishes absolute persistence, proportional sensitivity and measurement resolution. This framework travels across laboratory settings through reproducible condition definitions, without requiring unsupported assumptions about national context or clinical benefit.

7. Conclusion and Implications:

Reliable antibiotic experiments depend on preserving the chemical exposure that their interpretations assume. This analysis shows that stability comparisons become informative when environmental conditions, preparation choices and compound identity are considered together while measurement limits remain explicit. The empirical contribution is a matched synthesis that separates consistent directional patterns from proportional sensitivity and absolute persistence. It refines the interpretation of reaction kinetics by showing why a broadly expected relationship cannot automatically become a universal storage ranking. Consistent ordering under specified conditions coexists with exceptions elsewhere, making transferability conditional on experimental comparability. Laboratory managers should therefore select storage procedures using compound specific evidence, retain preparation details and distinguish numerical estimates from reporting thresholds. Quality assurance policies should require traceable condition descriptions and prevent pooled measurements from being represented as independent observations. Operationally, recording preparation and storage conditions together would improve the comparability of experimental solutions and make departures from documented procedures easier to detect. These implications apply internationally because they concern reproducible chemical conditions rather than geographical assumptions. Their social relevance lies in strengthening the evidence base that supports antimicrobial research and laboratory interpretation. The contribution is therefore an approach to evidence interpretation, without claiming an independently established causal mechanism or clinical benefit.

The available evidence creates specific opportunities for extension. Published condition estimates can be complemented by original concentration measurements, replicate identifiers and uncertainty estimates to distinguish experimental variation from modelling assumptions. Longer observation windows could replace reporting bounds with measured degradation profiles.

Coordinated experiments across laboratories could test whether the observed ordering persists under comparable preparation and analytical procedures. Factorial designs could separate joint responses and evaluate whether surrounding conditions modify individual relationships. Direct measurements of degradation products would further connect comparative patterns with chemical pathways. Such extensions would strengthen generalisation while preserving the distinction between laboratory stability and clinical outcomes.

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