https://doi.org/10.31925/farmacia.2026.2.25 **ORIGINAL ARTICLE**

PRICE DYNAMICS AND SUPPLY DISRUPTIONS IN SYSTEMIC ANTIBIOTICS: A LONGITUDINAL ANALYSIS OF ATC J01 MEDICINES IN ROMANIA

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Abstract

Drug shortages represent a challenge for healthcare systems, particularly affecting essential medicines. This study investigates the relationship between long-term price dynamics and supply disruptions within the ATC J01 class in Romania. A retrospective observational analysis was conducted using wholesale price data (2008 - 2024) and official shortage notifications (2017 - 2025). Price erosion indicators were calculated, and their association with supply disruptions was assessed using comparative statistics and logistic regression. Results showed that antibiotics associated with shortages experienced significantly lower overall price erosion over the 2008 - 2024 period than those without disruptions ($p < 0.01$). Logistic regression confirmed an inverse association between price erosion and the probability of shortage (OR = 0.758). These findings suggest that market rigidity, rather than price compression alone, may represent a key determinant of supply vulnerability. Greater price flexibility may reflect competitive and adaptive market conditions that enhance supply resilience. The study highlights the need for balanced pharmaceutical policies integrating affordability with long-term market sustainability.

Rezumat

Discontinuitățile în aprovizionarea cu medicamente reprezintă o provocare pentru sistemele de sănătate, afectând în mod particular medicamentele esențiale. Acest studiu a investigat relația dintre dinamica pe termen lung a prețurilor și apariția discontinuităților în aprovizionare în cadrul clasei ATC J01 din România. A fost realizată o analiză retrospectivă observațională, utilizând date privind prețurile de distribuție (2008 - 2024) și notificările oficiale privind discontinuitatea (2017 - 2025). Indicatorii de eroziune a prețurilor au fost calculați și corelați cu apariția discontinuităților prin analize statistice comparative și modele de regresie logistică. Rezultatele au evidențiat că antibioticele asociate cu discontinuități prezintă valori semnificativ mai reduse ale eroziunii generale a prețurilor comparativ cu cele fără discontinuități ($p < 0,01$). Modelul de regresie logistică a confirmat o asociere inversă între eroziunea prețurilor și probabilitatea apariției discontinuităților (OR = 0,758). Astfel, s-a observat că rigiditatea pieței poate constitui un determinant important al vulnerabilității în aprovizionare. O flexibilitate mai mare a prețurilor poate reflecta existența unor mecanisme competitive și adaptive, favorabile stabilității aprovizionării. Astfel, este subliniată necesitatea unor politici farmaceutice echilibrate, care să integreze accesibilitatea economică cu sustenabilitatea pe termen lung a pieței.

Keywords: drug shortages, systemic antibiotics, price erosion, pharmaceutical policy, supply chain resilience

Introduction

Drug shortages are a recurring problem at the global and European levels, with a disproportionate impact on essential medicines (1). The causes are multifactorial and include, but are not limited to, the fragility of supply chains, dependence on a limited number of manufacturers and raw materials or imports, insufficiently flexible production capacities, and logistical disruptions (2). In recent years, European institutions have highlighted the "chronic" nature of shortages and the structural vulnerability of the supply chain for medicines critical to patient care (3).

The impact of shortages extends beyond the economic sphere. It translates directly into clinical and operational consequences, both for healthcare professionals, in which case shortages are associated with forced changes in treatment, the use of suboptimal alternatives, increased administrative burden, and therapeutic uncertainties, including in acute situations (4). For patients, shortages can mean delayed treatment, reduced adherence, substitutions with different efficacy or tolerability profiles, and, in certain contexts, an increased risk of complications or hospitalization. These effects are also consistently described in European professional reports, which define shortages as the inability of pharmacies to supply the necessary medication, necessitating substitution or treatment interruption (5-7).

Antibiotics constitute a therapeutic class that is particularly vulnerable to supply disruptions for two main reasons (8). First, a significant proportion of currently used antibiotics are mature drugs facing generic competition and price pressure, which can reduce their commercial appeal and limit investment in redundancy, alternative production capacities, or buffer stocks (9, 10). Second, antibiotics play a critical role in the management of acute infections and in preventing complications in complex medical care (surgery, oncology, intensive care), where prompt unavailability can disrupt standardized protocols (4, 11, 12). Furthermore, antibiotic shortages have been significant enough that European authorities have explicitly monitored the seasonal situation of antibiotics for respiratory infections and coordinated mitigation measures at the European Union/European Economic Area (EU/EEA) level (13, 14).

These pressures overlap with a major public health issue: the rise of antimicrobial resistance (AMR). Globally, AMR is recognized as one of the most significant threats, and the World Health Organization (WHO) estimates indicate a substantial burden on mortality and morbidity. In Europe, the European Center for Disease Prevention and Control (ECDC) reports persistently high levels of AMR and rising incidence rates for certain resistant infections, underscoring the importance of access to appropriate antibiotics and stewardship (15, 16). In particular, Romania has for several years been among the countries with concerning levels of resistance to indicator bacteria (17), a finding documented in ECDC assessments, which underscores the clinical relevance of stable access to antibacterial therapies (18). In this context, supply disruptions can have indirect effects on AMR by increasing the use of alternative broad-spectrum antibiotics or by deviations from local guidelines, with the potential to select for resistance (8, 19, 20).

In Romania, shortages are officially reported through national mechanisms, and authorities have developed, in recent years, monitoring and reporting tools for medicines, including systemic antibiotics (21). However, in pharmaceutical policy practice, one critical question remains open: to what extent are market economic dynamics, particularly long-term price trends, associated with supply stability. Possible mechanisms are plausible: price compression may reduce commercial sustainability and increase the risk of withdrawals or supply constraints, but, alternatively, active price dynamics may reflect a competitive market with greater capacity for adaptation and substitution among suppliers (22).

Against this background, the present study has three main aims. First, to characterize the long-term dynamics of wholesale prices for systemic antibiotics within ATC class J01 in Romania over the period 2008 - 2024, with particular attention to the patterns of price erosion across different regulatory phases. Second, to assess whether price erosion indicators are associated with the occurrence of officially reported supply disruptions in the NAMMDR database for the period 2017 - 2025. Third, to examine the direction and magnitude of this association using comparative statistical analyses and binary logistic regression to determine whether economic market rigidity, rather than price compression alone, represents a relevant marker of supply vulnerability. By integrating longitudinal economic data with a nationally validated indicator of therapeutic availability, the study aims to contribute empirical evidence to support more balanced pharmaceutical policies that reconcile affordability with long-term market sustainability, particularly for a therapeutic class of critical public health importance in the context of rising antimicrobial resistance.

Given the nature of the theoretical mechanisms described above, and in line with the framing in the pharmaceutical economics literature linking price compression to reduced commercial sustainability, the working hypothesis of this study was that greater long-term price erosion would be associated with a higher probability of supply disruptions. This hypothesis was treated as exploratory rather than confirmatory, given the absence of prior empirical data specifically addressing this relationship within the Romanian regulatory framework.

Materials and Methods

Study design

A retrospective observational study was conducted to assess the relationship between long-term changes in antibiotic prices and the occurrence of supply disruptions in the Romanian pharmaceutical market. Systemic antibiotics classified under ATC code J01 were analyzed, using data on price trends and official notifications of supply disruptions from 2008 to 2024.

This analysis focused on the specific features of the regulatory framework governing the setting and updating of drug prices in Romania. The evolution of antibiotic prices was evaluated in relation to changes in pharmaceutical policy that may influence the market's economic behavior, such as the introduction of the clawback tax (23) and successive revisions of the pricing methodology, as these interventions by regulatory bodies have the potential to generate structural price adjustments, alter the commercial viability of products, and, implicitly, influence the stability of supply.

The time intervals used to calculate price erosion were defined to capture economically and normatively relevant stages. The 2008 - 2015 period was selected to illustrate price dynamics during a period characterized by the introduction of the clawback tax (starting in 2009) (23) and the strengthening of cost-control mechanisms. The 2015 - 2024 period was chosen to capture subsequent developments, including changes associated with the implementation of Ministry of Health Order No. 368/2017 (24), which redefined the methodology for setting prices of medicines for human use. Price erosion over the 2008 - 2024 period was used as an indicator of long-term price dynamics. The observation period for supply discontinuities (2017 - 2025) was determined by the availability of national-level data in the National Agency for Medicines and Medical Devices of Romania (NAMMDR) public database (25). Although the intervals for calculating price erosion partially overlap with the period for monitoring supply disruptions, in this study, the erosion indicators were analyzed as measures of long-term economic trends rather than as strict predictors of supply disruption events. Thus, the aim was to delineate distinct phases of market evolution to interpret the results in the context of regulatory and fiscal changes relevant to the Romanian pharmaceutical market.

Data sources, definition of the unit of analysis, and level of aggregation

The data used in the analysis were obtained from official national sources to ensure the accuracy, comparability, and relevance of the economic and therapeutic availability information. In this study, two main categories of data were analyzed: data on the wholesale prices of antibiotics (26) and data on official notifications of supply disruptions (25).

Pricing information was extracted from the official national price catalogs of medicines authorized for use in Romania (CANAMED) (27, 28). Wholesale distribution prices were analyzed, as they are considered appropriate for assessing economic dynamics because they do not include variations arising from fiscal or commercial components that affect the final retail price. Thus, it is possible to avoid distortions caused by changes in the value-added tax (VAT), commercial markups, or other factors external to the retail price formation mechanism. For each molecule included in the analysis, price values were collected for the reference years 2008, 2012, 2015, 2020, and 2024.

Data on supply disruptions were obtained from the NAMMDR public database. This database includes official notifications of discontinuation or shortages issued by marketing authorization holders, in accordance with the reporting obligations set out in national legislation. Notifications for the 2017 - 2025 period were included; this interval was chosen because it represents the longest continuous period for which systematic and comparable data were available at the time of the analysis. To enable (data linkage) between the constructed price databases and the supply disruption registry, a binary indicator of exposure to discontinuities was constructed for each INN, which takes the value 1 if at least one discontinuity notification was recorded for the respective active substance during the 2017 - 2025 period and 0 otherwise. This approach captures whether an active substance was affected by at least one supply disruption in the Romanian pharmaceutical market during the analyzed period, rather than discontinuities specific to individual commercial products.

This aggregation was deemed appropriate to reflect the clinical and therapeutic impact of shortages, as the unavailability of a specific brand does not necessarily imply the unavailability of the molecule, while discontinuities reported at the INN level indicate disruptions relevant to access to treatment.

Finally, the integration of economic data and discontinuity data ensures alignment of the unit of analysis between the independent variables (price level, price erosion) and the dependent variable (shortage indicator).

The data extracted from the national price catalog (CANAMED) initially included 162 medicinal products that remained on the market throughout the entire analysis period. Of these, 140 entries met the eligibility criteria and were included in the analysis: each entry had to be identified by its INN (International Nonproprietary Name), trade name, ATC code, dosage form, strength, and package size. No price adjustments or estimates were made between different package sizes, as these may involve differences in the markup rates established under drug pricing regulation between the manufacturer's price and the distribution price. The 140 products analyzed correspond to 40 INNs in the ATC therapeutic class J01.

Eligibility criteria

This analysis included molecules (INNs) that cumulatively met the following criteria: belonging to ATC class J01 (systemic antibiotics); availability of wholesale price values for the reference years 2008, 2012, 2015, 2020, and 2024; and the possibility of unambiguous matching of INNs between the price database and the supply disruption database, ensuring consistent identification of the same active substance across data sources. Furthermore, only molecules with complete data available at all predefined time points were included.

On the other hand, molecules were excluded if price data were incomplete for one or more of the time points studied, if there were inconsistencies between data sources that prevented the comparable identification of products over time, or if the available information did not allow for a valid estimation of price erosion indicators. To ensure the comparability of price dynamics, price tracking was performed for equivalent products defined by pharmaceutical form, concentration, and package size.

Definition of variables

The price level was defined as the distribution price, expressed in national currency units, corresponding to each molecule (INN) and each reference year included in the analysis. To reduce the distributional asymmetry and heteroscedasticity, the prices were logarithmically transformed, yielding the *logPR* variable.

Price erosion was defined as the proportional change in the distribution price relative to the value recorded at the beginning of each analyzed period. The use of nominal distribution prices, without inflation adjustment, reflects a deliberate analytical choice grounded in the regulatory and commercial realities of the Romanian pharmaceutical market. Decisions regarding market withdrawal, supply continuity, and commercial viability are made by manufacturers based on nominal margins, as these directly govern contractual relationships, clawback contributions, and external reference pricing calculations under the national regulatory framework. From this perspective, nominal price erosion captures the metric that is operationally relevant to manufacturers' economic decisions. Moreover, since inflation affects all molecules included in the analysis uniformly over the same observation period, the directional differences in price erosion between the shortage and non-shortage groups, which constitute the primary comparison in this study, are not invalidated by the absence of inflation adjustment. Inflation introduces a common upward pressure across all INNs; consequently, between-group differences in nominal erosion reflect structural divergences in price dynamics rather than differential exposure to macroeconomic conditions. Therefore, in this study, erosion refers to the relative change in the nominal distribution price and does not include adjustments for inflation or purchasing power parity. Price erosion indicators were calculated for the periods 2008 - 2015, 2015 - 2024, and 2008 - 2024, according to the formula:

$$erosion_{t1-t2} = (PR_{t2} - PR_{t1})/PR_{t1},$$

where, PR_{t1} represents the distribution price recorded at the beginning of the analyzed period, and PR_{t2} represents the price observed at the end of the period. Negative values indicate a decrease in price compared to the base year, while positive values indicate an increase in price during the analyzed period.

Price erosion indicators, defined as relative price changes, were calculated for the periods 2008 - 2015, 2015 - 2024, and 2008 - 2024. The study's dependent variable was the occurrence of supply discontinuities. Shortage was operationally defined as the existence of an official discontinuity notification in the NAMMDR database. For each molecule (INN), a binary indicator was constructed: 0 = no discontinuity reported during the 2017 - 2025 period; 1 = at least one reported discontinuity. The 2017 - 2025 period was selected because it is the longest continuous period for which systematic, comparable public data on supply disruptions were available in the NAMMDR database (25).

Thus, the initial price level was treated as a potential explanatory variable for the magnitude of subsequent price erosion, and the overall price erosion during the 2008 - 2024 period was considered a possible factor associated with the incidence of supply disruptions.

The year 2012 was included as an intermediate observation point to enable the monitoring of price trends for systemic antibiotics. The inclusion of this time point facilitated the verification of the continuity of price trends and the identification of any intermediate variations. However, 2012 was not used as a cutoff for constructing parametric price-erosion indices, as segmenting the initial 2008 - 2015 interval into shorter subintervals would have resulted in subintervals that were insufficiently long to capture variations of economic or statistical significance. This approach is consistent with the study's objective of capturing structural trends in longer-term price dynamics so that fluctuations relevant to the market's economic sustainability and the risk of supply disruptions can be identified.

Statistical analysis

Statistical analyses were performed using JASP software (version 0.95.4) (29). The distribution of continuous variables was assessed using the Shapiro-Wilk test, followed by nonparametric (Mann-Whitney U) and parametric (t-test for independent samples) tests. The longitudinal evolution of prices was assessed using repeated-measures ANOVA, with appropriate corrections applied when assumptions were violated. Relationships between continuous variables were investigated using Pearson and Spearman correlation coefficients. The association between overall price erosion and the probability of supply disruptions was analyzed using a binary logistic regression model. The level of statistical significance was set at $p < 0.05$.

Results and Discussion

Market structure and portfolio dynamics in ATC J01 antibiotics

An analysis of the market structure for systemic antibiotics was conducted from a commercial perspective, based on the number of brand names *per* INN, using data prepared for price erosion analysis sourced from CaNaMed. Among the 40 INNs included in the study, a non-uniform distribution of the number of commercial products was observed. Some molecules were associated with a higher number of products, such as ciprofloxacin (7 trade names), amoxicillin and ampicillin (5 each), and clarithromycin (5), suggesting more competitive market segments. In comparison, a notable number of INNs are represented by a single commercial product, indicating low competition but also potential risks of supply disruptions. Intermediate situations were also identified, with 2 - 3 products *per* INN, for molecules such as azithromycin, cefuroxime, metronidazole, or the sulfamethoxazole/trimethoprim combination. Overall, this distribution, illustrated in Figure 1, reflects a mixed market structure, characterized by both competitive segments and highly concentrated niches, with potential implications for supply security (30-32).

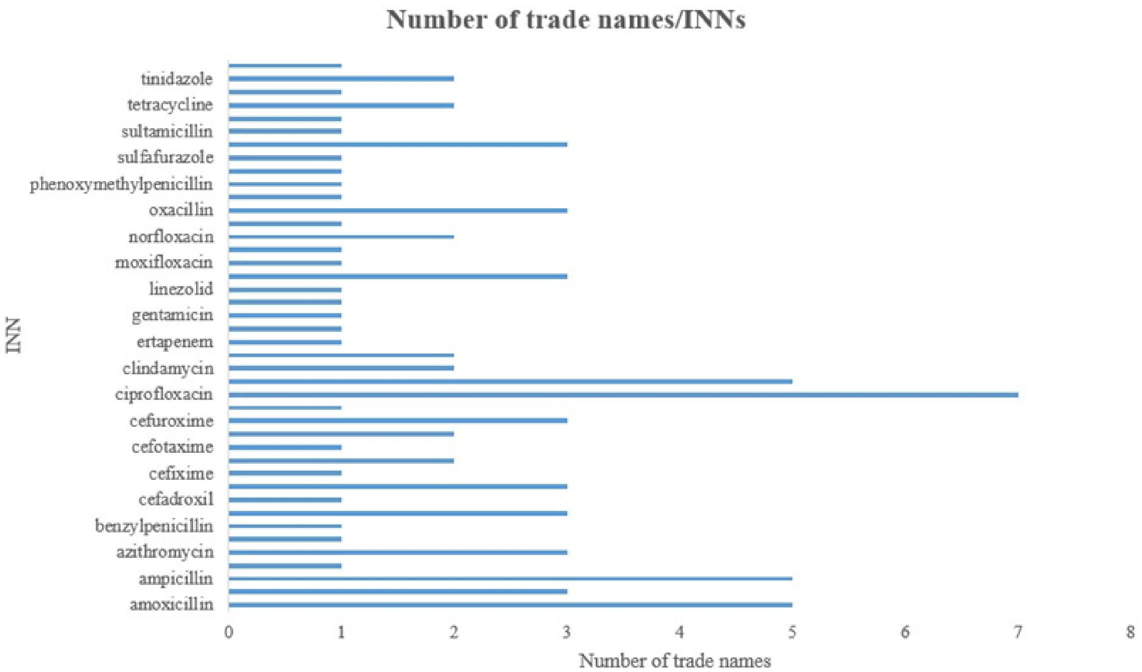


Figure 1.
Distribution of trade names/INNs in the analyzed data set

This diversity should be interpreted in the context of the structural changes in the market presence of systemic antibiotics during the period analyzed, 2008 to 2024. A descriptive comparison of the market presence of products in the ATC class J01 highlights changes in the composition of systemic antibiotics available on the Romanian market, marked by the discontinuation of certain established molecules and the introduction of newer therapies, as observed in an analysis of CaNaMed registries. Several INNs present in 2008 were no longer identified in the 2024 price catalog, including nalidixic acid, cefamandole, cefpirome, cefprozil, ceftibuten, kanamycin, lomefloxacin, netilmicin, roxithromycin, spectinomycin, and the ticarcillin/clavulanate combination. These molecules belong mainly to older generations of antibiotics, often characterized by limited clinical use, a less favorable safety profile, or low commercial appeal amid evolving treatment guidelines and market competition. In contrast, INNs not present in 2008 are included in 2024, such as aztreonam, ceftaroline fosamil, daptomycin, dalbavancin, eravacillin, or new beta-lactam combinations such as ceftazidime/avibactam and ceftolozane/tazobactam. These new entries may signify the addition of newer antibiotics, developed in part to tackle antimicrobial resistance (33-35).

Evolution of antibiotic prices over time

To assess longitudinal changes in the wholesale prices of systemic antibiotics in the ATC class J01 between 2008 and 2024, a repeated-measures ANOVA was performed. Mauchly's test indicated a violation of the sphericity assumption ($p < 0.05$), which is why the results were interpreted using the Greenhouse–Geisser correction. The analysis revealed a significant effect of time on the logarithmically transformed prices ($F = 19.44$; $p < 0.001$; $\omega^2 = 0.005$), indicating systematic price variation over the analyzed period. The effect size, estimated by the ω^2 index, suggests a small effect, indicating that, although temporal changes are statistically significant, the contribution of time to the total variation in prices is minor.

The variation in log-transformed wholesale prices for antibiotics in the ATC class J01 is presented in Figure 2. The mean log-transformed prices showed a steadily increasing trend over the analyzed period, from 2.795 in 2008 to 3.158 in 2024. In parallel, price variability, expressed as the standard deviation, showed a gradual decrease (SD = 1.732 in 2008 compared to SD = 1.434 in 2024). The same downward trend was observed for the coefficient of variation, which decreased from 0.619 to 0.454, suggesting a reduction in the relative dispersion of prices over time.

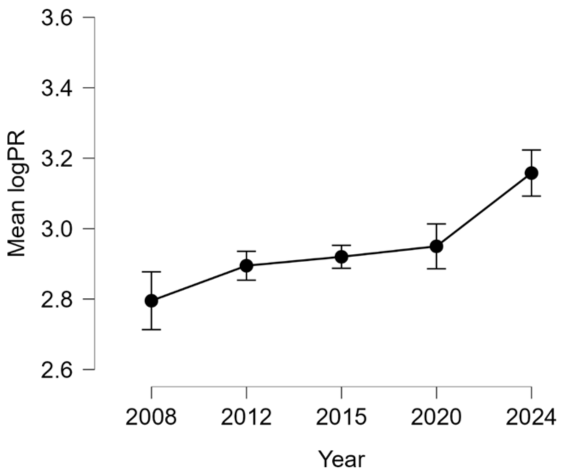


Figure 2.
Longitudinal evolution of the logarithmically transformed wholesale prices of antibiotics in the ATC class J01 during the period 2008 - 2024 (mean ± SE)

The longitudinal analysis revealed systematic variations in the distribution of antibiotic prices in the ATC class J01 during the period 2008 - 2024. Although the time effect was statistically significant, the small magnitude of the effect ($\omega^2 = 0.005$) suggests that the observed changes reflect gradual structural adjustments rather than abrupt shifts in price levels. The progressively increasing trend in log-transformed mean values, coupled with a decrease in relative variability, indicates a possible convergence of prices over time.

This seemingly paradoxical dynamic – the rise in the average price level in a context frequently characterized by downward pressure on generic drug prices – can be explained by several economic and regulatory mechanisms. First, aggregation at the molecule (INN) level may mask the heterogeneity of individual trends, with the average being influenced by changes in the structure of the analyzed portfolio (36). The withdrawal from the market of very inexpensive molecules or low-priced formulations can cause an artificial increase in the average value, even in the presence of price erosion at the individual product level (4). This phenomenon is well documented in economic analyses of regulated markets, where selective commercial withdrawals tend to disproportionately affect low-margin segments (37-39).

Second, changes in the regulatory framework can contribute to reshaping price distribution. The introduction of the clawback tax (23), the strengthening of external reference mechanisms, and the implementation of Order No. 368/2017 (24) have amplified pressure on the prices of mature medicines, though the effects are not uniform across therapeutic classes (40). On the other hand, price convergence can also be influenced by downward price adjustments applied to innovative medicines, which are typically positioned at the upper end of the price distribution. According to the national pricing methodology, following the expiration of market entry protection and the introduction of generic medicines, the maximum manufacturer price of the innovative medicine is reduced to a fixed percentage of the previously approved price (65% for generics), in accordance with the provisions of Order No. 368/2017 (24). This mechanism creates downward pressure on products with initially higher prices, resulting in a compression of the upper end of the price distribution. In certain situations, innovative medicines may be withdrawn from the market following the loss of exclusivity and a reduction in commercial profitability. The simultaneous compression of the lower and upper segments of the price distribution may explain the reduction in dispersion observed over time and the trend toward convergence of price levels. Antibiotics, characterized by episodic use, relatively unpredictable volumes, and intense generic competition, reiterating the points discussed in the first section, may exhibit different behaviors compared to other pharmaceutical segments (41). Price adjustments may be limited by minimum economic thresholds necessary to maintain commercial viability, leading to the stabilization or even a relative increase in prices of certain molecules remaining on the market (42).

The gradual decline in relative price variability suggests a possible homogenization of the market structure. This convergence may reflect both the effects of price control policies and processes of economic selection, through which products with extreme prices (very low or very high) are gradually eliminated. From an industrial perspective, this evolution may indicate a narrowing of the space for economic differentiation between products, with direct implications for positioning strategies, life cycle management, and supply chain sustainability (22).

For the pharmaceutical industry, the results suggest that the longitudinal dynamics of antibiotic prices cannot be interpreted exclusively through the lens of downward price erosion. Structural market changes, regulatory constraints, and selective withdrawals can reshape price distribution in complex ways. In this context, pricing strategies and decisions regarding commercial continuity must be evaluated in relation to long-term economic sustainability and the risks associated with supply disruptions (43).

Distribution of price erosion

Concerning the overall price erosion indicator for the period 2008 - 2024, classified according to the presence of supply disruptions between 2017 and 2025, the statistical analysis showed that molecules without episodes of shortage (Shortage = 0) exhibited higher values of overall erosion compared to molecules associated with shortages (Shortage = 1), both in terms of the median (0.695 *vs.* 0.264) and the mean (2.169 *vs*. 0.565). The variability of the erosion indicator was considerably higher in the group without discontinuities (SD = 5.066), with a wider range of values (-0.693 to 30.54), suggesting the presence of extreme values. In contrast, the group of molecules associated with scarcity exhibited lower dispersion (SD = 1.302) and a narrower range of variation (-0.733 to 7.907).

The distributions shown in Figure 3 reveal greater variability in price erosion for the group without shortages, as well as pronounced positive outliers. In contrast, products associated with discontinuities exhibit a more concentrated distribution around low values of price erosion.

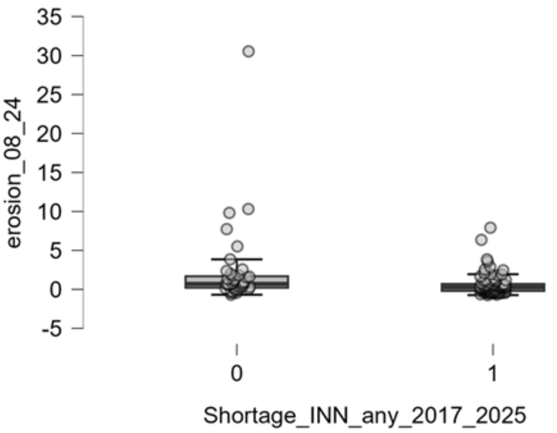


Figure 3.
Distribution of overall price erosion (2008 - 2024) based on the presence of antibiotic shortages (2017 - 2025). The boxplots illustrate the median values, interquartile ranges, and outliers

Analysis of the distribution of the overall price erosion indicator revealed clear differences between molecules associated with supply disruptions and those with no reported episodes. The working hypothesis of this study, that greater price erosion would be associated with a higher probability of shortage, through compression of commercial margins, was not supported by the data. Instead, molecules affected by shortages exhibited lower overall price erosion at both the median and mean levels, representing a finding that runs counter to the dominant theoretical expectation but is consistent with an alternative possibility: that active price dynamics may reflect competitive market conditions rather than commercial deterioration. At the same time, the substantially higher variability observed in the group without supply disruptions suggests marked heterogeneity in price dynamics, including the presence of large-scale price adjustments.

This seemingly counterintuitive finding may reflect the complex economic mechanisms characterizing the antibiotic market. Traditionally, price erosion is considered a risk factor for commercial sustainability, particularly for mature drugs, where margin compression can lead to voluntary market withdrawals. However, the results suggest that molecules with more pronounced price erosion were less frequently associated with shortages, indicating that the relationship between price dynamics and supply stability is not linear.

A plausible explanation is that more pronounced price erosion may serve as a marker of a functional competitive market. In segments with multiple competitors, price adjustments are more frequent, and competitive pressures may help maintain product availability by redistributing market share. In this context, price erosion reflects the adaptation of economic mechanisms to market conditions, rather than a deterioration in commercial viability. The economic literature indicates that markets with robust generic competition paradoxically exhibit greater resilience to disruptions compared to concentrated markets, where the withdrawal of a single manufacturer can generate significant shortages (30, 44). At the same time, disruptions are often influenced by structural vulnerable points in the active pharmaceutical ingredient (API) supply chain, as these are frequently produced by a limited number of manufacturers globally (4, 45). Continued pressure on the prices of mature medicines, including many systemic antibiotics, can reduce the economic incentives for maintaining alternative sources of supply or production capacity. Under these situations, any disruptions affecting a small number of API manufacturers can quickly ripple through the supply chain, especially when profit margins are already quite low. The intersection of price dynamics and the concentration of API manufacturing can therefore be a key mechanism linking economic sustainability to supply resilience (46, 47).

In contrast, molecules associated with shortages exhibited a more concentrated distribution in the low-erosion-value range, suggesting relative rigidity in price adjustments. In the existing context, market rigidity refers to the relatively limited ability of the price regulatory framework to adapt quickly to changes in costs or conditions within the supply chain. The entities directly involved, such as manufacturers and marketing authorization holders, must simultaneously adhere to regulatory requirements, including variations, GMP compliance, pharmacovigilance, supply continuity obligations (48), and additional supply chain security requirements introduced by the FMD Directive (49). These obligations entail additional operational costs (50), and must be proportionally aligned with pricing policies. However, the legislative framework for pricing and reimbursement does not permit adjustments proportional to the evolution of associated costs. Over time, this may reduce manufacturers' economic flexibility, increasing the risk of withdrawals and discontinuities for commercial reasons (51). This rigidity may signal pre-existing economic constraints, such as already compressed margins, reduced volumes, or limitations imposed by the regulatory framework. In such situations, the ability to adjust prices becomes limited, and products may become more vulnerable to supply chain disruptions, increases in production costs, or strategic decisions to withdraw from the market (2).

The presence of outliers in the non-shortage group suggests divergent price trajectories, possibly associated with commercial repositioning, changes in reimbursement status, manufacturer shifts, or portfolio reconfigurations. From an industrial- al perspective, this heterogeneity may reflect the flexibility of pricing strategies within a restrictive regulatory environment (47).

The practical implications of this finding are relevant for the pharmaceutical industry and for regulators. The data suggest that price compression alone does not directly explain shortages, and that economic rigidity may be a more important determinant of the risk of discontinuity. Consequently, price control policies should be evaluated not only in terms of cost reduction but also in relation to their impact on commercial sustainability and supply stability, particularly for critical therapeutic classes such as antibiotics. At the same time, these results must be interpreted with due consideration for the temporal scope of the analysis: price dynamics were assessed for the period 2008 - 2024, while supply disruptions were analyzed for the period 2017 - 2025 (25), in line with the availability of systematically reported national-level data. The 2008 - 2024 period reflects a time marked by major structural changes in Romania's pharmaceutical policy, including the post-EU accession phase (52), the effects of the 2008 economic crisis (53), and the introduction of the clawback tax (23), as well as the consolidation of price regulation mechanisms, including the methodology established by Order of the Minister of Health No. 368/2017 (24). These changes have impacted the economic viability of mature medicines, including systemic antibiotics, and may help explain the structural issues that later show up as supply shortages between 2017 and 2025. In this context, price erosion indicators should be understood as markers of structural economic circumstances that have evolved, rather than as direct short-term predictors of supply shortages.

Analysis of the association between overall price erosion and supply discontinuities

To assess the relationship between overall price erosion and the occurrence of supply disruptions, the price erosion indicator was analyzed for the period 2008 - 2024. The molecules were stratified according to discontinuity status for the 2017 - 2025 period (0 = no reported discontinuities; 1 = at least one reported discontinuity), and the variable compared between groups was overall price erosion (*erosion_08_24*).

Statistically significant differences were identified between the two groups. Molecules without shortages exhibited higher values of overall erosion compared to molecules associated with discontinuities. The mean erosion was 2.169 ± 5.066 in the group without shortages, compared to 0.576 ± 1.304 in the group with shortages. The considerably higher dispersion observed in the group without discontinuities suggests high variability in price dynamics and the presence of outliers.

Given the asymmetric distribution of the erosion indicator, differences between groups were assessed using both the t-test for independent samples and the nonparametric Mann-Whitney U test, the latter being considered the primary analysis. The Mann-Whitney test indicated a statistically significant difference between groups (U = 2734.5; p = 0.002), with a moderate effect size (rank-serial correlation = -0.325). The mean rank for overall erosion was higher in the non-deprived group (85.59) than in the deprived group (63.02). Furthermore, these results were consistent with the parametric analysis, which confirmed the existence of a statistically significant difference (p = 0.004). The effect size estimated by Cohen's d was 0.53 (95% CI: 0.164 - 0.894), suggesting a moderate difference in magnitude between molecules with and without supply discontinuities.

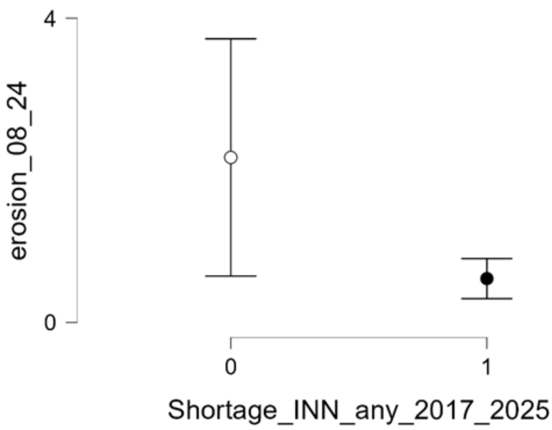


Figure 4.

Overall price erosion (2008 - 2024) by the presence of supply disruptions (2017 - 2025) for antibiotics in ATC class J01. Points represent group means of the price erosion indicator (erosion_08_24), while vertical bars indicate 95% confidence intervals

The comparative analysis revealed statistically significant differences between molecules associated with supply disruptions and those without episodes of shortage, with molecules without disruptions exhibiting higher values of overall price erosion. The moderate magnitude of the observed effect suggests that the identified differences are not only statistically significant but may also reflect structural economic mechanisms that affect supply stability.

This result reinforces previous descriptive observations and indicates an inverse relationship between the magnitude of long-term price adjustments and the probability of supply disruptions. Although the initial hypothesis assumed that sharp price erosion would increase the risk of shortages by compressing trade margins, the data suggest a different dynamic. Products characterized by larger price adjustments appear to be less vulnerable to supply disruptions.

One possible explanation is that overall price erosion may serve as an indirect indicator of the functioning of competitive mechanisms. In markets where there is active competition among producers, prices tend to be more dynamic, reflecting both competitive pressures and adaptive business strategies. This flexibility can help maintain supply continuity by redistributing market shares in the event of a temporary withdrawal of a market participant. The literature shows that shortages are more frequent in segments with a high degree of market concentration, where dependence on a limited number of suppliers amplifies systemic risk (43, 54).

In contrast, molecules associated with shortages exhibited lower levels of overall erosion and reduced dispersion, suggesting relative price rigidity. This rigidity may reflect pre-existing economic constraints, such as already-minimized margins, a lack of real competition, insufficient trade volumes, or limitations imposed by the regulatory framework. Under such conditions, the capacity for price adjustment becomes constrained, and products may become more sensitive to variations in production costs, logistical disruptions, or strategic delisting decisions.

From an industry perspective, the results suggest that supply stability may be more closely linked to economic flexibility than to the absolute level of prices. Products undergoing gradual price adjustments can benefit from continuous adaptation to market realities, while products with relatively rigid prices may accumulate economic imbalances that increase the likelihood of withdrawals or discontinuities (55).

The practical implications are relevant for both the pharmaceutical industry and regulatory authorities. Strict price control strategies, in the absence of mechanisms allowing for sustainable economic adjustments, can reduce market flexibility and amplify the risk of supply instability. In the case of antibiotics, an essential therapeutic class of major public health relevance, maintaining a balance between affordability and commercial viability is a critical element of pharmaceutical policies (44).

Correlation between initial price levels and price erosion

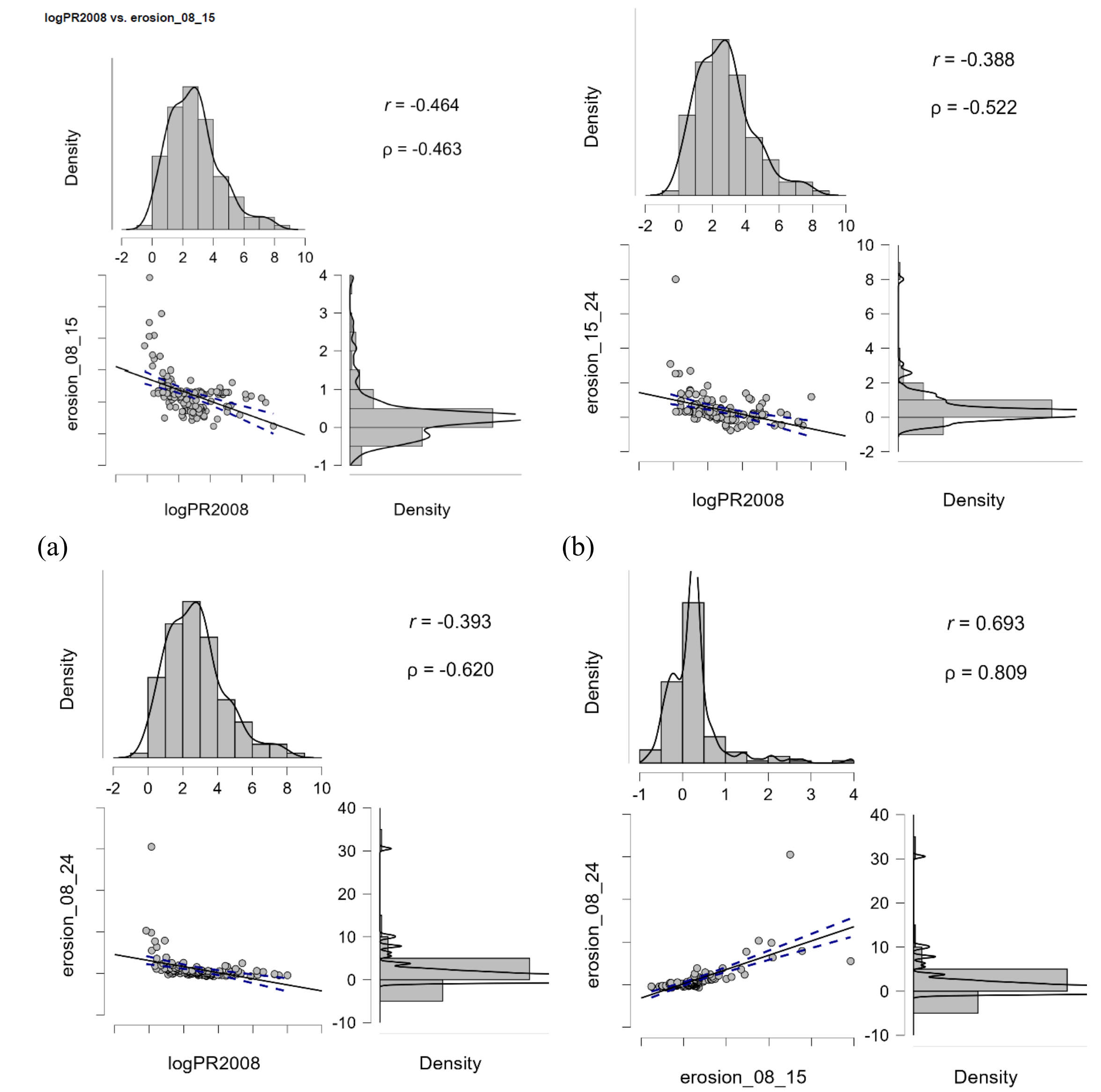
To assess the relationship between initial price levels and subsequent price dynamics, a correlation analysis was performed using Pearson and Spearman coefficients. The variable analyzed was the initial price level (*logPR2008*), and the associations were investigated relative to the price-erosion indicators for the periods 2008 - 2015 (*erosion_08_15*), 2015 - 2024 (*erosion_15_24*), and 2008 - 2024 (*erosion_08_24*). Pearson's correlation analysis revealed statistically significant negative correlations between the initial price level and all evaluated erosion indicators. For the 2008 - 2015 period, the correlation coefficient was $r = -0.464$ ($p < 0.001$), indicating a moderate inverse association. Similar negative correlations were observed for overall erosion from 2008 to 2024 ($r = -0.393$; $p < 0.001$) and for the period from 2015 to 2024 ($r = -0.388$; $p < 0.001$).

The results were confirmed by Spearman's nonparametric correlation analysis, with the rho coefficients indicating the same inverse relationship: rho = -0.463 for erosion from 2008 to 2015, rho = -0.620 for erosion from 2008 to 2024, and rho = -0.522 for erosion from 2015 to 2024 (all $p < 0.001$). The consistency of results between parametric and nonparametric methods suggests the robustness of the observed associations.

In addition, the erosion indices calculated for different time intervals showed statistically significant positive correlations with one another. The strongest association was observed between erosion from 2008 to 2024 and erosion from 2015 to 2024 ($r = 0.903$; $p < 0.001$), indicating high longitudinal consistency in price variations. Positive correlations were also identified between the 2008 - 2015 erosion and overall erosion ($r = 0.693$; $p < 0.001$), and between the 2008 - 2015 erosion and the 2015 - 2024 erosion ($r = 0.464$; $p < 0.001$). This data is presented as a visual representation in Figure 5.

The relationship between overall price erosion and the probability of supply disruptions

To assess the relationship between long-term price dynamics and the probability of supply disruptions, a binary logistic regression model was constructed, with the dependent variable being the status of supply disruptions at the INN level for the period 2017 - 2025. A graphical representation of these results is illustrated in Figure 6. The predictor included in the model was overall price erosion for the 2008 - 2024 period. Compared with the null model (M_0), the model including overall price erosion (M_1) showed a statistically significant improvement ($\Delta\chi^2 = 9.552$; $p = 0.002$). The model's goodness-of-fit indicators suggested modest explanatory power (McFadden $R^2 = 0.056$; Nagelkerke $R^2 = 0.094$). The coefficient associated with the predictor *erosion_08_24* was statistically significant ($p = 0.014$), yielding an OR of 0.758, indicating an inverse association between overall price erosion and the probability of discontinuities. More specifically, higher price erosion values were associated with a lower probability of reporting scarcity episodes.



(a) (b)

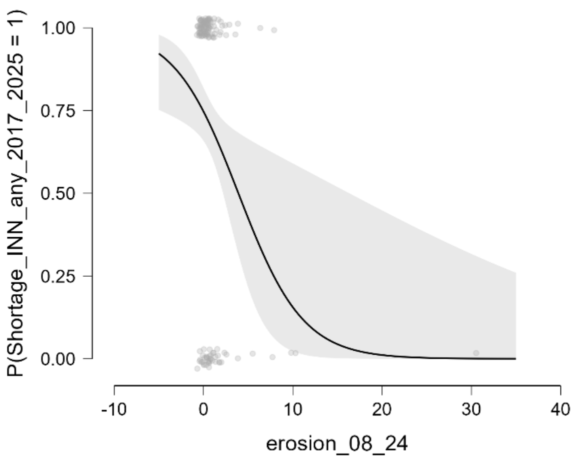
(c) (d)

Figure 5.

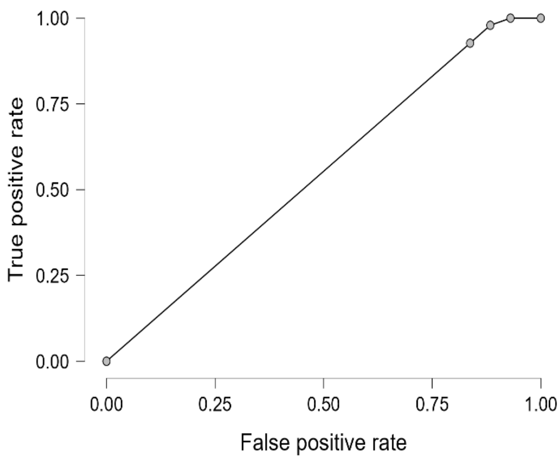
Relationships between initial price levels and price erosion indicators for antibiotics in the ATC class J01. Each panel shows a scatter plot with marginal distributions and the regression line. logPR2008 represents the log-transformed distribution price in 2008, and the indicators erosion_08_15, erosion_15_24, and erosion_08_24 represent the relative price changes over the periods 2008 - 2015, 2015 - 2024, and 2008 - 2024, respectively. (a) logPR2008 *vs*. erosion_08_15; (b) logPR2008 *vs*. erosion_08_24; (c) logPR2008 *vs*. erosion_15_24; (d) erosion_08_15 *vs*. erosion_08_24; (e) erosion_08_15 *vs*. erosion_15_24; (f) erosion_08_24 *vs*. erosion_15_24

The logistic regression model confirmed the inverse association observed in previous analyses, indicating that cumulative price erosion is significantly associated with the probability of supply disruptions. A sub-unit odds ratio (OR = 0.758) suggests that higher levels of long-term price adjustments are associated with a lower probability of reporting shortage episodes. Although the model's explanatory power is modest, the direction and statistical significance of the association are consistent with the results obtained in comparative analyses of erosion indicators between molecules with and without discontinuities.

Compared to the longitudinal analysis of price variation (RM ANOVA), which highlighted gradual structural adjustments and a trend toward convergence of price levels over time, the logistic regression model adds a supplementary perspective by quantifying the relationship between accumulated economic dynamics and the probability of discontinuities arising. Taken together, these results suggest that long-term price trends may reflect structural characteristics of the economic environment in which antibiotics are marketed. In this setting, overall price erosion should not be interpreted solely as an indicator of margin compression but can also serve as an indirect marker of the degree of economic adaptability of market segments. The consistency of the results obtained using different statistical methods highlights the fact that sensitivity to discontinuities may be more closely linked to regulatory restrictions that limit the ability to adjust in response to economic conditions than to the absolute magnitude of the price reduction (44, 56). This finding is congruent with the hypothesis that regulatory contexts characterized by limited flexibility in price adjustments may limit the ability of manufacturers to respond to cost pressures, including those arising from the active pharmaceutical ingredient (API) supply chain, logistics costs, or changes in production conditions (57-59). Thus, the results of the logistic regression should be interpreted as complementary to the descriptive and longitudinal analyses, collectively indicating that long-term economic dynamics can provide important signals regarding potential risks in the supply of systemic antibiotics (60). From a pharmaceutical policy perspective, these results support the need to evaluate price control mechanisms not only from the perspective of affordability but also in relation to their potential impact on supply capabilities, particularly for therapeutic classes of major importance to public health, such as antibiotics (61, 62).



(a)



(b)

Figure 6.

Relationship between overall price erosion and the probability of supply disruptions for antibiotics in ATC class J01 (a) Estimated probability of a supply disruption occurring as a function of price erosion during 2008 - 2024, estimated *via* logistic regression. The solid line represents the estimated probability, and the shaded area indicates the 95% confidence interval. (b) The ROC curve for the logistic regression model was used to assess the predictive capacity of the cumulative price erosion indicator for the occurrence of supply disruptions

Study limitations

Our study has several limitations that should be taken into account when interpreting the results. The dependent variable surprised only the existence of at least one official notification of shortage at the INN level, without reflecting the recurrence, time span, or intensity of the shortage incidents. Furthermore, the periods analyzed for price dynamics (2008 - 2024) and for shortages (2017 - 2025) do not fully overlap, so the erosion indicators should be understood as markers of long-term structural economic circumstances rather than as direct precursors of specific events.

Price erosion was calculated based on nominal distribution prices, without adjustment for inflation, production costs, exchange rate variations or other real economic pressures. Over the 2008 - 2024 period, Romania experienced significant cumulative inflation, including notable post-2020 acceleration driven by energy prices and the 2022 cost-of-living crisis. A product exhibiting a nominal price increase of 20% over this period may have undergone substantial real-terms compression, while a product with a stable nominal price experienced significant erosion in real value. This distinction is relevant when interpreting the magnitude of individual erosion values. However, since macroeconomic inflation constitutes a common factor affecting all molecules in the dataset over the same observation period, the between-group comparisons, retain their directional validity: systematic differences in nominal erosion between molecules with and without supply disruptions are unlikely to be explained by differential inflation exposure. Nonetheless, future studies incorporating real price indices or production cost deflators would allow for a more granular assessment of economic sustainability at the product level, and are recommended to confirm and extend the findings reported here.

Furthermore, the study did not include direct measures of important contributors to shortages, such as the concentration of API production, the number of suppliers, or the degree of market concentration. The results should therefore be interpreted within the specific context of the regulatory framework of the Romanian pharmaceutical market.

Implications for pharmaceutical policies and public health systems

When interpreting these results, the specific context of Romania's drug pricing regulatory mechanisms must be taken into account. Pricing that takes external referencing into account, in accordance with Order of the Minister of Health No. 368/2017 (24), involves aligning drug prices with the lowest level in a reference basket comprising 12 European Union member states (24). At the same time, a clawback tax applies to medicines included in the reimbursement system, which is a percentage contribution on the value of reimbursed medicines, currently set at 15% for generic medicines and 25% for innovative medicines, values applicable starting from the third quarter of 2023 (23). These mechanisms can exert significant economic pressure on manufacturers, particularly in the case of mature medicines, such as most antibiotics in the ATC class J01.

In this context, the inverse relationship identified between price erosion and the likelihood of supply disruptions may reflect the fact that markets characterized by a certain degree of price flexibility and competition among manufacturers have a greater capacity to adapt to economic conditions (63). In contrast, market segments where price adjustments are limited may indicate the existence of structural economic constraints, which can favor market withdrawals or supply disruptions (58, 64). From this perspective, the study's results suggest that the economic rigidity of the antibiotic market may represent a vulnerability factor for supply stability (20).

Given the essential role of ATC J01 antibiotics in the treatment of acute infections and in strategies to combat antimicrobial resistance, maintaining a balance between price control policies and the economic sustainability of the market may be an essential element in preventing supply disruptions.

Conclusions

This study evaluated, within the ATC J01 class of systemic antibiotics, the relationship between the long-term dynamics of wholesale prices and the occurrence of supply disruptions, as reported by the regulatory authority NAMMDR in Romania. The results showed that molecules associated with supply disruptions exhibited, on average, lower price erosion, and the logistic regression model indicated a statistically significant inverse association between price erosion and the probability of a shortage. These findings suggest that, in the J01 systemic antibiotics segment, economic and regulatory market rigidity may represent a more relevant marker of supply vulnerability than simple price compression. The results support the hypothesis that price dynamics may reflect, at least in part, the degree of market flexibility and adaptability. In a context characterized by external price referencing, fiscal pressure through the clawback tax, and the major clinical importance of antibiotics for the treatment of acute infections and for strategies to combat antimicrobial resistance, maintaining a balance between economic accessibility and commercial sustainability is particularly important. From a pharmaceutical policy perspective, monitoring economic indicators could help identify segments at high risk of discontinuity and develop more targeted preventive measures.

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Availability of data and materials

The data generated in the present study are included in the figures and/or tables of this article.

Ethics approval and consent to participate

Not applicable.

AI use disclosure

Not applicable.

Conflict of interest

The authors declare no conflict of interest.

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