THE AMOUNT, ECONOMIC VALUE AND ENVIRONMENTAL EMISSION OF CEPHAPIRIN AT DRY-OFF IN HOLSTEIN AND SIMMENTAL DAIRY COWS BY HERD SIZE

Boris Ljubojević¹, Ranko Gantner², Zvonimir Steiner³, Dragan Solić⁴, Vesna Gantner⁵ *Corresponding author E-mail: boris.ljubojevic@hrsume.hr

ARTICLE INFO

Original Article

Received: 03 October 2025

Accepted: 20 November 2025

doi:10.59267/ ekoPolj25041343L

UDC 636.09:636.23

Kevwords:

mastitis; selective dry cow therapy; cephapirin; environmental antibiotic emission: herd size

JEL: Q12

ABSTRACT

The research aim was to quantify the use of cephapirin in dry cow therapy, to estimate the economic value and potential environmental emissions regarding the herd size. The analysis included a 307,531 test-day records from Holsteins and 383,208 from Simmental. Udder health status at the last milk recording before dry-off was classified according to SCC criteria, and the scenario assumed universal use of BDCT, 1.2 g cephapirin per cow (300 mg per quarter × 4). The estimated total amount of cephapirin was 369.0 kg in Holsteins and 459.8 kg in Simmentals. The economic cost of the application was €7.85 million in Holstein and €9.78 million in Simmental herds, with healthy cows generating the largest share of the cost due to their large numbers. The estimated environmental release was 221.4 kg for Holstein and 275.9 kg for Simmental, with PEC/PNEC ratios high above the risk threshold, RQ 4,428.41 and 5,518.19, respectively.

¹ Boris Ljubojević, MSc Forestry Engineer, Croatian Forests Ltd., Directorate, Ulica kneza Branimira 1, 10000 Zagreb, Croatia; Phone: +38598447043, E-mail: boris.ljubojevic@hrsume.hr, ORCID ID (https://orcid.org/0009-0005-8334-278X)

² Ranko Gantner, Full Professor, Faculty of Agrobiotechnical Sciences Osijek, J.J. Strossmayer University of Osijek, Vladimira Preloga 1, Osijek, 31000, Croatia; Phone: +385992074490, E-mail: rgantner@fazos.hr, ORCID ID: (https://orcid.org/0000-0001-5426-4886)

³ Zvonimir Steiner, Full Professor, Faculty of Agrobiotechnical Sciences Osijek, J.J. Strossmayer University of Osijek, Vladimira Preloga 1, Osijek, 31000, Croatia; E-mail: zsteiner@fazos.hr, ORCID ID (https://orcid.org/0000-0002-4007-2231)

⁴ Dragan Solić, dr.sc., Croatian Agency for Agriculture and Food, Vinkovačka cesta 63c, Osijek, 31000, Croatia; E-mail: drago.solic@hapih.hr, ORCID ID (https://orcid.org/0000-0002-8877-921X)

⁵ Vesna Gantner, Full Professor, Faculty of Agrobiotechnical Sciences Osijek, J.J. Strossmayer University of Osijek, Vladimira Preloga 1, Osijek, 31000, Croatia; Phone: +385992074490, E-mail: vgantner@fazos.hr, ORCID ID (https://orcid.org/0000-0002-1962-3131)

Introduction

Mastitis is the most common disease of dairy cows and one of the main causes of economic losses in the dairy sector. The consequences include reduced milk yield, increased somatic cell count, reduced milk quality and an increased risk of premature culling (Seegers et al., 2003; Green et al., 2002). The economic burden includes direct treatment costs, milk loss and additional labor, but also indirect effects on long-term herd productivity and farm sustainability (Halasa et al., 2007). Dry cow therapy (DCT) has been developed as a key strategy for treating existing intramammary infections and preventing new ones during the dry period. Cephapirin, commonly used in DCT, is rapidly metabolized to desacetylcephapirin, maintaining milk concentrations above MIC values for key pathogens, confirming its effectiveness but also the risk of residues (Stockler et al., 2009). The traditional approach, blanket dry cow therapy (BDCT), involves the routine treatment of all cows with antibiotics, regardless of their health status. Although this approach reduced the prevalence of infections, it also led to a high consumption of antibiotics, including the unnecessary treatment of healthy animals (Weber et al., 2021; Rowe et al., 2020). Alternatively, selective dry cow therapy (SDCT) involves the application of antibiotics only to cows with determined or suspected intramammary infection, while internal teat sealants are applied to healthy cows. Studies (Vanhoudt et al., 2018; McCubbin et al., 2023; Pavesi et al., 2023) have shown that SDCT can effectively reduce antibiotic use without increasing the risk of clinical mastitis or deteriorating udder health, provided that clearly defined selection criteria are met. Furthermore, Pavesi et al. (2023) showed that in healthy cows, antibiotic treatment at dry-off offers no additional udder health benefits and may disturb milk microbiota, while the use of sealant alone provides equivalent results in terms of somatic cell counts and the incidence of intramammary infections. Müller et al. (2023) concludede that antibiotics at dry-off have a limited effect on cure rates, and their actual benefit varies depending on the causative agent of the infection, further emphasizing the importance of a targeted approach. Excessive antibiotic use drives antimicrobial resistance (AMR), one of the major global health and environmental challenges (Bengtsson-Palme & Larsson, 2016). Resistant strains have been isolated from the most important mastitis pathogens, including Staphylococcus aureus, Escherichia coli and Streptococcus uberis (Maksimović et al., 2024). Analyses of antibiotic residues in manure have shown that a significant proportion of the applied doses are excreted in active form and are released into the environment through soil and water, where they can cause disruption of microbial communities and promote the spread of resistance genes (Berendsen et al., 2015; Thiele-Bruhn, 2003). Additionally, cephapirin has been detected in surface waters at concentrations up to 9 ng/L, where it is rapidly hydrolyzed, but its degradation products may be more stable and toxic than the parent substance (Ribeiro et al., 2018a). Environmental risks are evaluated using the PEC/PNEC ratio, where values above 1 indicate potential hazard and selection risk (Tell et al., 2019). Studies of MIC values for various cephalosporins, including cephapirin, have shown very low MIC thresholds for pathogen growth inhibition, supporting the use of conservative PNEC values in environmental assessments (Cortinhas et al., 2013). According to the WHO

Global Antimicrobial Resistance and Use Monitoring System (GLASS), consumption of beta-lactam antibiotics and fluoroquinolones is significantly correlated with an increase in resistance in E. coli and Klebsiella pneumoniae in the bloodstream, with each unit increase in consumption was associated with an increase in the proportion of resistant isolates of 11% to 40% in the countries analyzed (Ajulo & Awosile, 2024). Such findings confirm that antibiotic consumption patterns in veterinary practice have direct implications for public health, further emphasizing the need for their rational use. In addition to biological and environmental risks, economic aspects also play an important role. Studies have shown that the implementation of selective dry cow therapy (SDCT) can reduce the costs associated with antibiotic use and overall veterinary costs, especially on farms with a low prevalence of intramammary infections (Vissio et al., 2023; Navaei et al., 2025). Regional studies indicate significant differences in antibiotic use patterns and the occurrence of resistance among different production systems, with socioeconomic factors and herd size significantly influencing decisions on dry cow therapy (Popescu & Andrei, 2011; Kupczyński et al., 2024; Tomanić et al., 2024; Očić et al., 2022). At the European Union level, the Farm to Fork Strategy and the Green Deal envisage a 50% reduction in the use of antibiotics in agriculture by 2030, making rationalising antibiotic use in dry cow therapy a key measure for achieving sustainability goals, preserving public health and reducing environmental burden (McCubbin et al., 2023).

The aim of this study was to quantify the use of cephapirin in dry cow therapy of Holstein and Simmental dairy cows in Croatia, with an emphasis on three dimensions: the total amount of antibiotic administered, its economic value and potential emission into the environment regarding the herd size.

Materials and methods

The analysis was conducted on test-day records collected during the national milk recording of cows under breeding and selection programs in Croatia (HAPIH) for the period from January 1, 2013 to December 31, 2022, with sampling and analysis performed according to ICAR guidelines (in Croatia, AT4/BT4 methods with mathematical adjustment to the reference A4 method, SLKM HAPIH, accredited methods). After logical data validation (removal of records with extreme or inconsistent values of production and reproductive parameters), a total of 307,531 Holstein and 383,208 Simmental cows in production were included in the analysis. Herd size classes were defined as follows: for Holstein: < 5, 6-10, 11-50, 51-200, 201-500 and > 500cows, and for Simmental: < 5, 6-10, 11-50, 51-200 and > 200 cows. Udder health status at the last milk recording before dry-off was classified according to somatic cell count (SCC): healthy cows had <200,000/mL, subclinical mastitis 200,000-400,000/ mL, and clinical mastitis >400,000/mL. The assessment focused on the intramammary administration of Cefa-Safe (active ingredient: cephapirin) at dry-off. The standard dose was 300 mg per quarter, i.e. 1.2 g per cow. The total mass of active substance in the group was calculated according to the formula:

Amount
$$(g)$$
 = number of cows treated $\times 1.2 g$

The economic value was estimated based on the market price provided by the supplier (Medical Intertrade, 2025), where a package of Cefa-Safe (20 injectors \times 300 mg) contains 6 g of cephapirin at a price of \in 127.64, giving a unit price of \in 21.27/g. The value per group was calculated according to the formula:

The potential environmental emission was estimated using a scenario assuming that 60% of the administered dose is excreted in active form via urine and faeces, which enter the environment through manure. This value represents a conservative midpoint within the range of 40–80% reported in the literature (Berendsen et al., 2015; Thiele-Bruhn, 2003). The emission was calculated as:

Emission
$$(g) = Amount(g) \times 0.60$$

A simplified PEC/PNEC approach was used for the preliminary risk assessment. The predicted environmental concentration (PEC) was estimated using a homogeneous dispersion model in which 1 g of antibiotic was considered equivalent to 1,000 μ g/L in the aquatic environment, while the predicted no-effect concentration (PNEC) for cephapirin was set conservatively according to literature sources and the ECHA approach (Bengtsson-Palme & Larsson, 2016; Tell et al., 2019; Cortinhas et al., 2013). The low MIC values for cephapirin against the main mastitis pathogens support the use of a conservative PNEC threshold (Cortinhas et al., 2013), while pharmacokinetic data indicate rapid metabolism to desacetyl-cephapirin with prolonged retention of milk concentrations above the MIC value (Stockler et al., 2009). The risk quotient was calculated according to the formula:

RQ (risk quotient) = PEC (predicted environmental concentration) / PNEC (predicted no-effect concentration)

The results represent statistical calculations and scenario-based estimates of antibiotic use in the blanket dry cow therapy (BDCT) model, and not actual farm-level antibiotic use data. All calculations were performed descriptively (sums and proportions by group), while data validation, variable derivations and aggregations were carried out in SAS 9.4 (SAS Institute Inc., 2019), and graphical presentations were based on the same aggregated results.

Results

The analysis of udder health at the last milk recording before dry-off showed that slightly more than half of cows were healthy (SCC < 200,000/mL), while the rest showed subclinical (200,000–400,000 SCC/mL) or clinical mastitis (> 400,000 SCC/mL). In the Holstein breed (Table 1), 55.34% of cows (170,201) were healthy, 18.40% (56,571) had subclinical, and 26.26% (80,759) clinical mastitis.

Table 1. Health status of Holstein cows and total amount of cephapirin (Cefa-Safe) at dry-off by herd size.

		Last milk recording - Cefa-Safe								T. 4.1		
Herd size	Healthy			Subclinical mastitis		Clinical mastitis			Total			
Size	N	Amount	%	N	Amount	%	N	Amount	%	N	Amount	%
< 5	18631	22357,2	46,29	7898	9477,6	19,62	13718	16461,6	34,08	40247	48296,4	100
6-10	9622	11546,4	48,18	3973	4767,6	19,89	6378	7653,6	31,93	19973	23967,6	100
11-50	32461	38953,2	53,39	11358	13629,6	18,68	16985	20382	27,93	60804	72964,8	100
51-200	33861	40633,2	57,21	10691	12829,2	18,06	14631	17557,2	24,72	59183	71019,6	100
201- 500	34424	41308,8	56,23	11238	13485,6	18,36	15563	18675,6	25,42	61225	73470	100
> 500	41202	49442,4	62,33	11413	13695,6	17,27	13484	16180,8	20,4	66099	79318,8	100
Total	170201	204241,2	55,34	56571	67885,2	18,4	80759	96910,8	26,26	307531	369037,2	100

Health status was determined at the last milk recording before dry-off: healthy (<200,000 SCC/mL), subclinical mastitis (200,000–400,000 SCC/mL), and clinical mastitis (>400,000 SCC/mL). Amounts were calculated as number of treated cows × 1.2 g cephapirin per cow.

The total estimated amount of cephapirin (Cefa-Safe) under blanket dry cow therapy (BDCT) was 369,037.2 g. Antibiotic use differed by herd size: the largest herds (> 500 cows) had the highest estimated consumption (79,318.8 g), while herds with 6–10 cows had the lowest (23,967.6 g). The proportion of healthy cows increased with herd size, from 46.29% in herds < 5 cows to 62.33% in those > 500, while clinical mastitis decreased from 34.08% to 20.40%. In smaller herds a greater share of antibiotics was administered to mastitic cows, whereas in larger herds most were given to healthy animals.

Similar patterns were observed in the Simmental breed (Table 2). Healthy cows accounted for 55.83% (213,939), subclinical mastitis for 18.53% (71,015), and clinical mastitis for 25.64% (98,254). The total estimated cephapirin use reached 459,849.6 g, 25% higher than in the Holstein population. The highest antibiotic consumption occurred in herds with 11–50 cows (160,503.6 g), followed by herds with fewer than five cows (137,234.4 g), while the lowest was recorded in herds with more than 200 cows (2,503.2 g). As herd size increased, the proportion of healthy cows rose from 56.08% in herds with fewer than five cows to 66.35% in herds with more than 200 cows, whereas clinical mastitis decreased from 26% to 16%.

Table 2. Health status of Simmental cows and total amount of cephapirin (Cefa-Safe) at dry-off by herd size.

	Last milk recording - Cefa-Safe								Total			
Herd size	Healthy			Subclinical mastitis		Clinical mastitis			Total			
Size	N	Amount	%	N	Amount	%	N	Amount	%	N	Amount	%
< 5	64137	76964,4	56,08	21024	25228,8	18,38	29201	35041,2	25,53	114362	137234,4	100
6-10	45381	54457,2	54,21	15882	19058,4	18,97	22449	26938,8	26,82	83712	100454,4	100
11-50	74701	89641,2	55,85	24749	29698,8	18,5	34303	41163,6	25,65	133753	160503,6	100
51- 200	28336	34003,2	57,48	8993	10791,6	18,24	11966	14359,2	24,27	49295	59154	100
> 200	1384	1660,8	66,35	367	440,4	17,59	335	402	16,06	2086	2503,2	100
Total	213939	256726,8	55,83	71015	85218	18,53	98254	117904,8	25,64	383208	459849,6	100

Health status was determined at the last milk recording before dry-off: healthy (<200,000 SCC/mL),

subclinical mastitis (200,000–400,000 SCC/mL), and clinical mastitis (>400,000 SCC/mL). Amounts were calculated as number of treated cows × 1.2 g cephapirin per cow.

In both breeds, healthy cows constituted the majority of the population, but differences in antibiotic use by herd category were more pronounced in Simmentals, where small and medium herds accounted for the largest share of total cephapirin consumption.

The estimated economic value of cephapirin use at dry-off showed clear differences between breeds and herd size categories (Figures 1 and 2). In Holstein cows, the total value was $\[\in \]$ 7.85 million, with the highest cost recorded in herds with more than 500 cows ($\[\in \]$ 1.69 million) and the lowest in herds with 6–10 cows ($\[\in \]$ 0.51 million). The value increased with herd size, reflecting both the greater number of animals and the higher proportion of healthy cows in large herds. Healthy cows accounted for the largest share of the total value ($\[\in \]$ 4.34 million, 55.34%), while subclinical and clinical mastitis contributed $\[\in \]$ 1.44 million (18.40%) and $\[\in \]$ 2.06 million (26.26%), respectively, indicating that most antibiotics were used in cows without signs of mastitis due to their inclusion in blanket therapy.

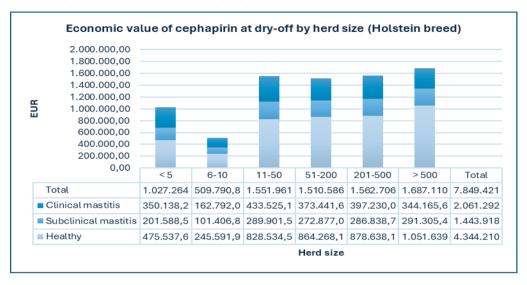


Figure 1. Economic value of cephapirin at dry-off by herd size (Holstein breed)

The total estimated economic value of the Simmental breed was higher than that of the Holstein population, amounting to 9.78 million euros.

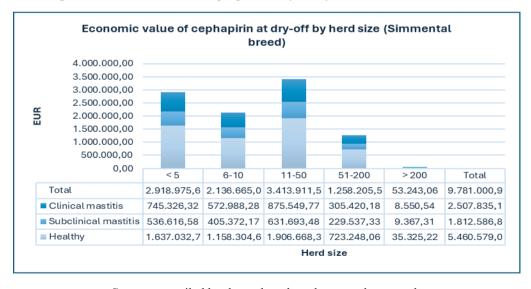


Figure 2. Economic value of cephapirin at dry-off by herd size (Simmental breed)

Source: compiled by the authors based on test-day records

The highest values were observed in herds with 11–50 cows (€3.41 million) and the lowest in herds with more than 200 cows (€0.05 million). The distribution pattern differed from Holsteins, as medium-sized herds accounted for the highest total costs, while small and large herds showed lower values. As in Holsteins, healthy cows

represented the largest share (€5.46 million, 55.83%), followed by subclinical (€1.81 million, 18.53%) and clinical mastitis (€2.51 million, 25.64%). A comparison of breeds shows that, despite similar proportions of healthy and mastitic cows, differences in total economic value resulted from herd size structure and animal numbers. In Holsteins, the highest costs were concentrated in large herds, whereas in Simmentals, medium herds dominated, confirming that herd size affects both the distribution of udder health categories and the overall cost of antibiotic use.

The estimated emission of cephapirin into the environment showed significant values in both breeds (Tables 3 and 4). In Holstein cows, the total emission was 221,422.32 g, resulting in a predicted environmental concentration (PEC) of 221.42 μ g/L. When compared to the predicted no-effect concentration (PNEC = 0.05 μ g/L), the PEC/PNEC ratio reached 4,428.41. These values clearly indicate a potentially high environmental risk, given that the risk quotient (RQ) in all herd categories was several orders of magnitude higher than the threshold value of 1. The highest emissions were recorded in herds with more than 500 cows (47,591.28 g), while the lowest emissions were in herds with 6–10 cows (14,380.56 g). However, regardless of herd size, all categories showed very high RQ values, ranging from 287.61 to 951.82.

Table 3. Estimated environmental emission of cephapirin (Cefa-Safe) and associated risk quotient (RQ) by herd size in Holstein cows

Herd size	Emission (g)	PEC (μg/L)	PNEC (µg/L)	RQ (PEC/PNEC)
< 5	28.977,84	28,98	0,05	579,55
6–10	14.380,56	14,38	0,05	287,61
11–50	43.778,88	43,78	0,05	875,57
51–200	42.611,76	42,61	0,05	852,23
201–500	44.082,00	44,08	0,05	881,63
> 500	47.591,28	47,59	0,05	951,82
Overall	221.422,32	221,42	0,05	4.428,41

Source: compiled by the authors based on test-day records

Emission calculated as Amount \times 0.60, representing a conservative scenario of 60 % excretion. PEC values were derived from emission assuming a homogeneous dispersion model (1 g = 1,000 μ g/L). The PNEC value of 0.05 μ g/L was used as a conservative methodological threshold based on published approaches to environmental risk/selection thresholds for antibiotics (see Bengtsson-Palme & Larsson, 2016; Tell et al., 2019).

In the Simmental breed, the total emission was higher, amounting to 275,909.76 g. The PEC value was 275.90 μ g/L, resulting in an overall RQ of 5,518.19. The highest emissions were recorded in herds with 11–50 cows (96,302.16 g), while the lowest values were in the largest herds (>200 cows), where the emission was 1,501.92 g. However, even at these lowest levels, the PEC/PNEC ratio was 30.04, which is still well above the ecologically acceptable threshold.

		•		
Herd size	Emission (g)	PEC (μg/L)	PNEC (µg/L)	RQ (PEC/PNEC)
< 5	82.340,64	82,34	0,05	1.646,81
6–10	60.272,64	60,27	0,05	1.205,45
11–50	96.302,16	96,30	0,05	1.926,04
51–200	35.492,40	35,49	0,05	709,85
> 200	1.501,92	1,50	0,05	30,04
Overall	275.909,76	275,90	0,05	5.518,19

Table 4. Estimated environmental emission of cephapirin (Cefa-Safe) and associated risk quotient (RQ) by herd size in Simmental cows

Emission calculated as Amount \times 0.60, representing a conservative scenario of 60 % excretion. PEC values were derived from emission assuming a homogeneous dispersion model (1 g = 1,000 μ g/L). The PNEC value of 0.05 μ g/L was used as a conservative methodological threshold based on published approaches to environmental risk/selection thresholds for antibiotics (see Bengtsson-Palme & Larsson, 2016; Tell et al., 2019).

The highest RQ values were observed in herds with 11–50 cows (1,926.04), while the other categories also showed consistently high ratios. A comparison of breeds showed that, although the number of Simmental cows was higher, the average PEC/PNEC ratio was higher than in the Holstein breed. In both populations, blanket dry cow therapy (BDCT) was confirmed to generate significant amounts of antibiotic emissions into the environment, with values in all cases several-fold above the reference threshold of 1, indicating a potentially serious ecotoxic burden.

Discussions

This study analyzed the udder health status of dairy cows and the estimated antibiotic consumption at dry-off, emphasizing differences between breeds and herd size. In both populations, about half of the cows were healthy, while the rest showed subclinical or clinical mastitis, confirming that mastitis remains a leading health challenge in dairy farming, with prevalence ranging from 20 to 40% (Tomanić et al., 2024). The proportion of healthy cows increased with herd size, while clinical mastitis declined, indicating that larger herds, despite higher density, maintain better hygiene and veterinary control (Beggs et al., 2019). Consequently, estimated cephapirin use under BDCT differed by breed and herd size: Holstein cows showed higher consumption in large herds, whereas Simmentals had the greatest costs in medium herds. Although both breeds had similar proportions of healthy and diseased cows, total antibiotic use varied due to herd structure, highlighting the need to consider management organization and breed-specific factors when planning strategies for antibiotic reduction (Kupczyński et al., 2024; Vissio et al., 2023; Krogh et al., 2020).

The estimated economic value of cephapirin use at dry-off indicated that healthy animals accounted for the largest share of total costs. This was mainly a result of their high numbers and obligatory inclusion in blanket therapy (Lipkens et al., 2023; Vissio et al.,

2023). Such a cost pattern clearly demonstrates the fundamental limitation of BDCT, where considerable quantities of antibiotics are used without therapeutic justification, thereby raising production expenses and economic pressure on farmers (Halasa et al., 2007; Seegers et al., 2003). Earlier research has shown that mastitis costs extend well beyond the price of drugs, including substantial indirect losses through reduced milk yield, poorer quality, and impaired fertility, making it one of the costliest diseases in dairy production (Kharel et al., 2023; Halasa et al., 2007). Breed-related differences in the total value of antibiotic use arose primarily from herd structure and the distribution of health categories. In Holstein herds, the highest costs occurred on large farms, while in Simmental herds the burden was greatest in medium-sized systems. This pattern agrees with previous findings that herd size significantly influences both treatment and prevention costs (Smith et al., 2000; Stocco et al., 2023). It also supports the view that management quality and production organization can affect economic outcomes as much as, or even more than, the prevalence of mastitis itself (Tomanić et al., 2024). According to Gantner et al. (2023), environmental conditions such as temperature, humidity, and heat stress further modify production efficiency and cow health, adding complexity to the overall cost structure in dairy farming. Because healthy cows generated more than half of the total value of antibiotics used, they represent the main target for optimizing therapy (Lipkens et al., 2023). Implementing selective dry cow therapy (SDCT) can therefore substantially cut unnecessary costs while maintaining, or even enhancing, udder health and productivity (Vissio et al., 2023; Guadagnini et al., 2023). In addition, reducing blanket treatments contributes to lower antimicrobial resistance risk, a recognized global priority in livestock systems (Ajulo & Awosile, 2024; Peña-Mosca et al., 2025). Economic analyses consistently show that both clinical and subclinical mastitis lead to considerable financial losses (Halasa et al., 2007; Kharel et al., 2023). Yet, the results of this study emphasize that under BDCT, the majority of costs stem from cows that show no signs of infection. This finding further supports a targeted and selective approach to antibiotic use, particularly in herds where the proportion of healthy cows is high (Lipkens et al., 2023; Vissio et al., 2023).

The estimated emission of cephapirin to the environment revealed extremely high values, far exceeding the reference thresholds of acceptable risk. For Holstein cows, total emissions reached 221.42 kg, corresponding to an environmental concentration (PEC) of 221.42 µg/L. When compared with the conservative predicted no-effect concentration (PNEC = 0.05 µg/L), the PEC/PNEC ratio of 4,428.41 indicates a substantial ecological hazard. In this study, the threshold value of PNEC = 0.05 µg/L was adopted following established approaches for environmental risk assessment of antibiotics (Bengtsson-Palme & Larsson, 2016; Tell et al., 2019), taking into account the low MIC levels reported for mastitis pathogens (Cortinhas et al., 2013). As the official PNEC for cephapirin is not listed in the ECHA registration dossier, this value should be viewed as a methodological estimate used for comparative assessment. All herd categories exhibited RQ values well above 1. The highest risk was recorded in herds exceeding 500 cows (RQ = 951.82), and even the lowest, in herds with

6-10 cows (RQ = 287.61), remained far beyond the safety limit. In the Simmental population, total emissions were even higher (275.91 kg) with an overall RQ value of 5,518.19. Medium-sized herds (11-50 cows) showed the highest discharge (96.30 kg, RQ = 1,926.04), while the largest herds (>200 cows) still exceeded acceptable levels (RQ = 30.04). These findings confirm that blanket dry cow therapy (BDCT) creates a considerable ecotoxic burden, largely independent of herd size or breed. The results align with established evidence showing that a substantial fraction of antibiotics used in livestock—estimated at 40-80%—is excreted unchanged into the environment (Thiele-Bruhn, 2003; Berendsen et al., 2015). Once released into soil or water, β-lactam antibiotics such as cephapirin alter microbial communities, reduce biodiversity, and foster the emergence of resistant strains (Peña-Mosca et al., 2025). Experimental data further demonstrate that cephapirin, despite rapid degradation, retains antimicrobial activity capable of affecting algae and bacteria, which supports the high PEC/PNEC ratios observed here (Ribeiro et al., 2018b). Other studies emphasize that data on the environmental behavior and ecotoxicity of cephalosporins remain limited, pointing to the need for continued research (Ribeiro et al., 2018a). Interestingly, Simmental herds exhibited even higher risk values than Holsteins, despite a nearly identical distribution of healthy and mastitic cows. This difference likely stems from herd structure and the distribution of animals across size categories, previously described as a critical determinant of antibiotic emissions at the farm level (Stocco et al., 2023). Comparable patterns have been reported elsewhere, confirming that herd organization and management practices directly influence antibiotic application and, consequently, the risk of environmental contamination (Smith et al., 2000).

The results clearly indicate that continuing the use of blanket dry cow therapy (BDCT) would substantially increase the environmental load within the dairy sector, running counter to the objectives of sustainable production and the EU strategy for reduced antibiotic use. Under the common EU risk assessment framework, RQ values greater than 1 are considered a signal of potential ecological risk and the need for management intervention (Tell et al., 2019). In this study, all recorded values exceeded that threshold several-fold, confirming that BDCT poses an unacceptable level of environmental pressure. These findings reinforce the importance of broader implementation of selective dry cow therapy (SDCT) and complementary preventive measures aimed at safeguarding both the environment and public health (Lipkens et al., 2023; Kupczyński et al., 2024). At the same time, the data reaffirm that mastitis remains the primary factor driving antibiotic use in dairy cattle, with nearly half of all cows in both breeds affected by subclinical or clinical forms of the disease (Tomanić et al., 2024). Economic analysis further demonstrated that healthy animals, although least in need of antimicrobial protection, generated the largest share of BDCT-related costs due to their high prevalence within the population (Halasa et al., 2007; Seegers et al., 2003). Differences between breeds in the cost structure were also evident: larger herds tended to have a higher proportion of healthy cows and better overall management systems, which reduced mastitis occurrence and improved cost efficiency (Beggs et al., 2019).

Finally, the estimated cephapirin emissions to the environment were several-fold above the acceptable threshold in all herd categories, confirming the environmental risk associated with BDCT (Ajulo & Awosile, 2024). These findings clearly support recommendations on the necessity of transitioning to SDCT, in order to reduce unnecessary antibiotic consumption, limit costs, and lower the environmental impact (Lipkens et al., 2023; Kupczyński et al., 2024).

Conclusions

The obtained results showed that although more than half of the cows in both populations were healthy, a significant proportion exhibited signs of subclinical or clinical mastitis, confirming that mastitis remains a major challenge in dairy farming. Herd size affects the cows' health status, with larger herds having a higher proportion of healthy animals and a lower incidence of clinical mastitis, reflecting the impact of better management and veterinary care. Economic analyses showed that healthy cows accounted for the largest share of total antibiotic costs due to their large numbers in the population, even though they would not require treatment under a selective approach. Differences between breeds were primarily related to herd size distribution: in Simmental cows, the highest costs were concentrated in medium-sized herds, whereas in Holsteins, large herds dominated. Environmental emission assessments indicated that cephapirin levels in all herd categories were several-fold above acceptable risk thresholds, confirming the considerable ecotoxic potential of universal therapy. Finally, the obtained results indicate the need to reduce unnecessary antibiotic use in healthy animals and to transition to selective dry cow therapy (SDCT) in order to align with the goals of animal health preservation, economic sustainability, and environmental protection.

Acknowledgements

The manuscript is the result of the activities conducted within the project "Optimization of the Sustainability of Animal Production under Climate Change Conditions: Integration of Genetic, Environmental, and Technological Factors", ("Optimizacija održivosti animalne proizvodnje u uvjetima klimatskih promjena: integracija genetskih, okolišnih i tehnoloških čimbenika").

Conflict of interests

The authors declare no conflict of interest.

References

1. Ajulo, S., & Awosile, B. (2024). Global antimicrobial resistance and use surveillance system (GLASS 2022): Investigating the relationship between antimicrobial resistance and antimicrobial consumption data across the participating countries. *PLOS ONE*, 19(2), e0297921. https://doi.org/10.1371/journal.pone.0297921

- 2. Beggs, D. S., Jongman, E. C., Hemsworth, P. H., & Fisher, A. D. (2019). The effects of herd size on the welfare of dairy cows in a pasture-based system using animal- and resource-based indicators. *Journal of Dairy Science*, 102(4), 3406–3420. https://doi.org/10.3168/jds.2018-14850
- 3. Bengtsson-Palme, J., & Larsson, D. G. J. (2016). Concentrations of antibiotics predicted to select for resistant bacteria: Proposed limits for environmental regulation. *Environment International*, 86, 140–149. https://doi.org/10.1016/j.envint.2015.10.015
- 4. Berendsen, B. J. A., Wegh, R. S., Memelink, J., Zuidema, T., & Stolker, L. A. M. (2015). The analysis of animal faeces as a tool to monitor antibiotic usage. *Talanta*, 132, 258–268. https://doi.org/10.1016/j.talanta.2014.09.022
- 5. Cortinhas, C. S., Oliveira, L., Hulland, C. A., Santos, M. V., & Ruegg, P. L. (2013). Minimum inhibitory concentrations of cephalosporin compounds and their active metabolites for selected mastitis pathogens. *American Journal of Veterinary Research*, 74(5), 683–690. https://doi.org/10.2460/ajvr.74.5.683
- European Chemicals Agency (ECHA). (2024). Cephapirin sodium Registration Dossier. Retrieved from https://echa.europa.eu/registration-dossier/-/registered-dossier/29333
- 7. Filippone Pavesi, L.; Pollera, C.; Sala, G.; Cremonesi, P.; Monistero, V.; Biscarini, F.; Bronzo, V. Effect of the Selective Dry Cow Therapy on Udder Health and Milk Microbiota. *Antibiotics* 2023, 12, 1259. https://doi.org/10.3390/antibiotics12081259
- 8. Gantner, V., Šinka, D., Popović, V., Ćosić, M., Sudarić, T., & Gantner, R. (2023). The variability of microclimate parameters in dairy cattle farm facility. *In Sustainable agriculture and rural development: Thematic proceedings of the III international scientific conference*, December 2022, Belgrade (pp. 77–86). Institute of Agricultural Economics. https://www.iep.bg.ac.rs
- 9. Green, M. J., Green, L. E., Medley, G. F., Schukken, Y. H., & Bradley, A. J. (2002). Influence of Dry Period Bacterial Intramammary Infection on Clinical Mastitis in Dairy Cows. *Journal of Dairy Science*, 85(10), 2589–2599. https://doi.org/10.3168/jds.S0022-0302(02)74343-9
- Guadagnini, M., Gogna, C., Tolasi, C., Tolasi, G., Gnali, G., Freu, G., Masroure, A. J., & Moroni, P. (2023). Approach to Selective Dry Cow Therapy in Early Adopter Italian Dairy Farms: Why Compliance Is So Important. *Animals*, 13(22), 3485. https://doi.org/10.3390/ani13223485
- 11. Halasa, T., Huijps, K., Østerås, O., & Hogeveen, H. (2007). Economic effects of bovine mastitis and mastitis management: A review. *Veterinary Quarterly*, 29(1), 18–31. https://doi.org/10.1080/01652176.2007.9695224

- 12. Kharel, M., Timisina, K. P., Adhikari, S. P., Dhakal, C., Khanal, D. R., & Paudel, T. P. (2023). Does mastitis cause economic loss in dairy cattle in Nepal? *Nepal Agriculture Research Journal*, 15(1), 55–65. https://doi.org/10.3126/narj.v15i1.51064
- 13. Krogh, M. A., Nielsen, C. L., & Sørensen, J. T. (2020). Antimicrobial use in organic and conventional dairy herds. *Animal*, 14(10), 2187–2193. https://doi.org/10.1017/S1751731120000920
- Kupczyński, R., Bednarski, M., Sokołowski, M., Kowalkowski, W., & Pacyga, K. (2024). Comparison of Antibiotic Use and the Frequency of Diseases Depending on the Size of Herd and the Type of Cattle Breeding. *Animals*, 14(13), 1889. https://doi.org/10.3390/ani14131889
- 15. Lipkens, Z.; Piepers, S.; De Vliegher, S. Impact of Selective Dry Cow Therapy on Antimicrobial Consumption, Udder Health, Milk Yield, and Culling Hazard in Commercial Dairy Herds. *Antibiotics* 2023, 12, 901. https://doi.org/ 10.3390/antibiotics120509011
- 16. Maksimović, Z., Čengić, B., Ćutuk, A., & Maksimović, A. (2024). Antimicrobial Resistance of Cattle Mastitis-Causing Bacteria: How to Treat? In K. Petrovski (Ed.), *Veterinary Medicine and Science* (Vol. 19). IntechOpen. https://doi.org/10.5772/intechopen.112977
- 17. McCubbin, K. D., De Jong, E., Brummelhuis, C. M., Bodaneze, J., Biesheuvel, M., Kelton, D. F., Uyama, T., Dufour, S., Sanchez, J., Rizzo, D., Léger, D., & Barkema, H. W. (2023). Antimicrobial and teat sealant use and selection criteria at dry-off on Canadian dairy farms. *Journal of Dairy Science*, 106(10), 7104–7116. https://doi.org/10.3168/jds.2022-23083
- 18. Medical Intertrade d.o.o. (2025). Ponuda za antibiotike: Mastidry, Cefa-Safe, Orbeseal, Keraseal (Ponuda br. 12379/2025, 12. lipnja 2025.). Zagreb: Medical Intertrade d.o.o.
- Müller, S., Nitz, J., Tellen, A., Klocke, D., & Krömker, V. (2023). Effect of Antibiotic Compared to Non-Antibiotic Dry Cow Treatment on the Bacteriological Cure of Intramammary Infections during the Dry Period—A Retrospective Cross-Sectional Study. *Antibiotics*, 12(3), 429. https://doi.org/10.3390/antibiotics12030429
- 20. Navaei, H., Vodjgani, M., Khoramian, B., Akbarinejad, V., Gharagozloo, F., Garoussi, M. T., & Momeni, A. (2025). Evaluation of a new method of selective dry cow treatment using microbiological culture and antibiogram results. BMC *Veterinary Research*, 21(1). https://doi.org/10.1186/s12917-025-04767-z
- 21. Očić, V., Bobić Šakić, B., & Grgić, Z. (2022). Economic analysis of specialized dairy farms in Croatia according to FADN. *Mljekarstvo*, 73(1), 50–58. https://doi.org/10.15567/mljekarstvo.2023.0106
- 22. Peña-Mosca, F., Gaire, T. N., Dean, C., Ferm, P., Manriquez, D., Pinedo, P., Noyes, N., & Caixeta, L. (2025). Exploring the phylogenetic diversity and antimicrobial activity of non-aureus staphylococci and mammaliicocci isolated from teat apices of organic dairy cows. bioRxiv 2024.02.01.578391; https://doi.org/10.1101/2024.02.01.578391

- 23. Popescu, G., & Andrei, J. (2011). From industrial holdings to subsistence farms in Romanian agriculture. Analyzing the subsistence components of CAP. *Agricultural Economics*, 57(11), 555.
- 24. Ribeiro, A. R., Sures, B., & Schmidt, T. C. (2018a). Cephalosporin antibiotics in the aquatic environment: A critical review of occurrence, fate, ecotoxicity and removal technologies. *Environmental Pollution*, 241, 1153–1166. https://doi.org/10.1016/j.envpol.2018.06.040
- 25. Ribeiro, A. R., Sures, B., & Schmidt, T. C. (2018b). Ecotoxicity of the two veterinarian antibiotics ceftiofur and cefapirin before and after phototransformation. *Science of The Total Environment*, 619–620, 866–873. https://doi.org/10.1016/j.scitotenv.2017.11.109
- 26. Rowe, S. M., Godden, S. M., Nydam, D. V., Gorden, P. J., Lago, A., Vasquez, A. K., Royster, E., Timmerman, J., & Thomas, M. J. (2020). Randomized controlled trial investigating the effect of 2 selective dry-cow therapy protocols on udder health and performance in the subsequent lactation. *Journal of Dairy Science*, 103(7), 6493–6503. https://doi.org/10.3168/jds.2019-17961
- 27. Seegers, H., Fourichon, C., & Beaudeau, F. (2003). Production effects related to mastitis and mastitis economics in dairy cattle herds. *Veterinary Research*, 34(5), 475–491. https://doi.org/10.1051/vetres:2003027
- 28. Smith, J. W., Ely, L. O., & Chapa, A. M. (2000). Effect of Region, Herd Size, and Milk Production on Reasons Cows Leave the Herd. *Journal of Dairy Science*, 83(12), 2980–2987. https://doi.org/10.3168/jds.S0022-0302(00)75198-8
- Stocco, G., Cipolat-Gotet, C., Stefanon, B., Zecconi, A., Francescutti, M., Mountricha, M., & Summer, A. (2023). Herd and animal factors affect the variability of total and differential somatic cell count in bovine milk. *Journal of Animal Science*, 101, skac406. https://doi.org/10.1093/jas/skac406
- 30. Stockler, R. M., Morin, D. E., Lantz, R. K., & Constable, P. D. (2009). Effect of milking frequency and dosing interval on the pharmacokinetics of cephapirin after intramammary infusion in lactating dairy cows. *Journal of Dairy Science*, 92(9), 4262–4275. https://doi.org/10.3168/jds.2008-1916
- 31. Tell, J., Caldwell, D. J., Häner, A., Hellstern, J., Hoeger, B., Journel, R., Mastrocco, F., Ryan, J. J., Snape, J., Straub, J. O., & Vestel, J. (2019). Science-based Targets for Antibiotics in Receiving Waters from Pharmaceutical Manufacturing Operations. *Integrated Environmental Assessment and Management*, 15(3), 312–319. https://doi.org/10.1002/ieam.4141
- 32. Thiele-Bruhn, S. (2003). Pharmaceutical antibiotic compounds in soils a review. *Journal of Plant Nutrition and Soil Science*, 166(2), 145–167. https://doi.org/10.1002/jpln.200390023

- Tomanić, D., Samardžija, M., Stančić, I., Kladar, N., Maćešić, N., & Kovačević, Z. (2024). Mastitis challenges in Serbian dairy farming: A study on somatic cell counts and pathogen distribution. *Mljekarstvo*, 239–248. https://doi.org/10.15567/mljekarstvo.2024.0307
- 34. Vanhoudt, A., Hees-Huijps, K. van, Knegsel, A. T. M. van, Sampimon, O. C., Vernooij, J. C. M., Nielen, M., & Werven, T. van. (2018). Effects of reduced intramammary antimicrobial use during the dry period on udder health in Dutch dairy herds. *Journal of Dairy Science*, 101(4), 3248–3260. https://doi.org/10.3168/jds.2017-13555
- 35. Vissio, C., Richardet, M., Issaly, L. C., & Larriestra, A. J. (2023). Decision making on dry cow therapy: Economic evaluation using field data under Argentinian production conditions. *Ciência e Agrotecnologia*, 47, e016322. https://doi.org/10.1590/1413-7054202347016322
- Weber, J., Borchardt, S., Seidel, J., Schreiter, R., Wehrle, F., Donat, K., & Freick, M. (2021). Effects of Selective Dry Cow Treatment on Intramammary Infection Risk after Calving, Cure Risk during the Dry Period, and Antibiotic Use at Drying-Off: A Systematic Review and Meta-Analysis of Current Literature (2000–2021). *Animals*, 11(12), 3403. https://doi.org/10.3390/ani111234036