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Retrospective evaluation of excess death loss in feedlot cattle associated with in-feed tylosin application programs

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Abstract

Daily feedlot records from steer and heifer lots slaughtered between January 2015 and December 2020 were evaluated for timing of tylosin programs and death events. Tylosin applications were described as *Any*/*None* (1/0) in the first 30 days-on-feed, *Any* in the middle feeding period, and *Any*/*None* (1/0) in the last 30 days-on-feed. The final analysis included 125,520 lots of cattle with 18,814,224 head placed. By year, week of the year, week on feed, sex type, hundredweight at placement and tylosin program, weekly deaths were summarized as deaths per thousand head fed (Deaths_K). Using continuously fed tylosin lots as baseline for each summarized category, excess Deaths_K were calculated for each program. For each hundredweight group, mixed analysis of variance models were developed to assess differences in excess Deaths_K across tylosin programs. Overall, cattle not fed tylosin in the first 30 d in the feedlot experienced higher Deaths_K than cattle that were. Differences in excess death loss across tylosin programs were greater among cattle placed under 800 lb (363 kg) compared to heavier cattle.

Key words: antibiotic, tylosin, beef, feedlot, mortality

Introduction

The global concern over antimicrobial resistance has focused largely on animal agriculture and increasing the pressure to reduce agricultural reliance on antibiotics.[1,9,12] As part of the United States Food and Drug Administration's action plan to reduce antibiotic use, veterinary pharmaceutical companies voluntarily withdrew label claims for the use of medicated feed articles for growth promotion and, in 2017, the Veterinary Feed Directive (VFD) went into effect, requiring all therapeutic use of medicated feed articles to be used under the direction of a veterinarian.[14,15]

During this same time, consumer and interest groups continued to pressure the food service and retail sectors to force antibiotic reduction in supply chains.[19] One approach to achieve antibiotic reduction has involved the targeted removal of continuously fed medicated articles, under therapeutic label use, for a portion of the feeding period.[4,7,12,14,17]

The macrolide tylosin is 1 of the medicated feed articles approved for continuous feeding for the prevention and control liver abscesses.[8,13] Although tylosin itself is not used in human medicine, it has been designated as medically important because of its membership in the macrolide-lincosamide-streptogramin B superfamily since resistance to 1 member has the potential to confer resistance to others.[2] Despite its 4 decades on the market, associations between tylosin use and antimicrobial resistance in the feedlot environment are mixed in recent publications,[2,4,7,11,18] with Weinroth et al[17] reporting that sample location (region) has a significant role in fecal isolate microbiome observations.

In a retrospective study of feedlot death loss that accounted for antimicrobial use, an association was found between higher death loss and lots that used tylosin for less than 80% of the feeding period compared to lots with tylosin fed 80% or more of feeding dates.[10] The purpose of this study was to use retrospective data to understand if and how death loss differs according to when tylosin is delivered during the feeding period.

Materials and Methods

Data

A subset of data from an United States industry population database collected through feedlot accounting systems was summarized for daily tylosin use and mortality. Included were steer and heifer lots with complete daily feed records, microingredient ration inclusion information indicating use of tylosin in the form of any medicated feed article, and having been placed with average hundredweight (InWt100) between 400 and 900 lb (181 and 453 kg), fed less than 54 weeks and slaughtered between January 2015 and December 2020 in order to represent cattle on feed both before and after the VFD went into effect. By lot, each feeding date was assigned to week of the year (WeekNo) and week on feed (WOF). All mortality events included death dates and were assigned a corresponding WOF value. Tylosin use was categorized to approximate dietary transition from receiving to full finisher ration, the middle feeding period, and the beta-agonist feeding period. Accordingly, the in-feed tylosin program for each lot was described as *Any* or *None* for 3 time periods: the first 30 days-on-feed (DOF), the middle feeding period (>first 30 DOF and <last 30 DOF) and the last 30 DOF, defined as the last 30 d with 10 or more head fed, with the first and last periods represented as 1/0 to indicate *Any* or *None*. Year was assigned to each lot according to first feeding date of the week.

Deaths by WOF were summarized across the entire dataset by tylosin program, sex type, InWt100, Year and WeekNo. For those same categories, the population at risk was summarized by taking the total head fed days from the feeding records (1 d per animal per feeding date) and dividing the value by 7000 (1000 head * 7 d/week) to approximate 1000 head at risk for death within each week. Death loss was calculated as death events/population at risk to create a value of deaths/1000 head (Deaths_K). In accordance with data privacy practice, categorical combinations with fewer than 3 lots or fewer than 500 head at risk were omitted from the final analysis.

In total, 125,520 steer and heifer lots of cattle, representing 18,814,224 head placed, were included in the final analysis. To compare mortality across tylosin programs, baseline death loss for each categorical combination of Year, WeekNo, WOF, sex type, and InWt100 was set as the observed Deaths_K value for continuously fed lots (*1-Any-1*). Excess Deaths_K were calculated for each categorical combination by subtracting the baseline value from the observed Deaths_K for each of the other 2 tylosin programs (*0-Any-1* and *1-Any-0*) across the first 26 WOF for InWt100 groups between 400 and 800 lb (181 and 408 kg) and first 24 WOF for InWt100 of 900 lb (408 kg). Excess Deaths_K for *1-Any-1* values were set to 0 (*1-Any-1* Deaths_K minus baseline).

Statistical analysis

Differences in Deaths_K across tylosin program and combination categories were evaluated for each InWt100 group through analysis of variance using commercially available software[a]. Data were transformed via hyperbolic arcsine to satisfy normality assumptions and analyzed using PROC MIXED, with WeekNo (Year) included as a random effect and 2-way interactions tested among tylosin program, sex type, InWt100 and WOF when the individual variables were significant at the level alpha=0.05. Final models were reduced to contain only those terms where P<0.05 and selected on the basis of lowest Bayesian Inclusion Criterion fit statistic. Differences in least-squared means estimates were used to compare differences between variable levels, with estimates and confidence intervals back-transformed for reporting and reported as LSMDiff (95% CI). Where WOF interactions were present, estimate statements were used to describe the differences across tylosin programs within the first 10 WOF, the second 10 WOF, and the remainder of the period.

Results

Table 1 contains information about cattle by tylosin program and closeout year, with in-weights and out-weights weighted by head sold. Figure 1 depicts the overall average death loss, weighted by average head fed, by week on feed, and tylosin program.

Table 2 reports least-squared mean differences across levels of statistically significant factors for each of the final hundredweight models. In the final model for 400-wt cattle, weekly Deaths_K differed across tylosin programs (P<0.0001). For 500-wt cattle, weekly Deaths_K differed across sex type (P=0.0012), WOF (P=0.0493), and tylosin programs (P<0.0001). With the model for 600-wt cattle, weekly Deaths_K differed across tylosin programs (P<0.0001), WOF (P<0.0001), and the interaction between the 2 (P<0.0001). Among 700-wt cattle, weekly Deaths_K differed across tylosin programs (P=0.0001), sex type (P<0.0001), and the interaction between the 2 (P<0.0001). For 800-wt cattle, weekly Deaths_K differed across tylosin programs (P<0.0001), sex type (P=0.0013), and the interaction between the 2 (P<0.0001). And in 900-wt cattle, weekly Deaths_K differed across tylosin programs (P=0.0461), WOF (P=0.0004), and the interaction between the 2 (P<0.0001).

Figure 2 shows the least-squared mean differences for the 2 InWt100 models with a significant tylosin program*WOF interaction.

Discussion

Core principles of antimicrobial stewardship in veterinary medicine include judicious use of antibiotics, including informed selection of product and regimen, and a commitment to stewardship that includes systematic assessment of the outcomes of antibiotic therapy.[9,14] For the feedlot sector, 1 measurable outcome to assess is mortality.

Over the last decade, feedlot mortality has trended upward.[10,16] Vogel et al postulated that the increase in mortality observed between 2005 and 2014 could be attributed to increases in outweights and days spent in the feedlot.[15] More recent summaries of feedlot mortality describe continuation of this upward trend–despite the stabilization of outweights and days-on-feed.[10]

Simultaneously, other changes have also taken place in feedlot production. Among them are the increased representation of beef-dairy crosses in the general population, and changes to management practices, including how medicated feed articles are used.[10] An approach to assess the impact of a change is to perform a population-level analysis to determine excess or reduced death loss compared to the baseline expectation, where the baseline expectation is the observed event rate within a cohort population. Historical applications have included analyses of the effects of economic and social conditions on population-level death rates.[5,6] More recently,

Table 1. Descriptive data for tylosin programs regarding the number of lots (groups of cattle), cattle placed into and exiting from those lots, along with the weighted average body weights of cattle entering and exiting the lots, according to sex type (heifers or steers) and year for cattle marketed from beef feedlots in the United States from 2015 through 2020.

Tylosin Program	Sex type Year	Heifers 2015	Heifers 2016	Heifers 2017	Heifers 2018	Heifers 2019	Heifers 2020	Steers 2015	Steers 2016	Steers 2017	Steers 2018	Steers 2019	Steers 2020
0-Any-1	No. Lots	631	614	763	1077	1199	1056	860	803	823	1136	1254	973
0-Any-1	No. Head In	79,655	76,812	91,898	129,021	139,014	139,055	116,343	104,265	96,693	138,664	153,237	130,102
0-Any-1	No. Head Out	76,774	73,983	88,930	124,438	134,108	134,506	113,144	101,103	93,858	133,967	148,742	126,200
0-Any-1	In-Weight	626	656	630	622	621	631	713	709	667	655	672	665
0-Any-1	Out-Weight	1221	1240	1227	1235	1230	1277	1378	1378	1356	1355	1371	1401
0-Any-1	Death Loss %	3.617	3.683	3.230	3.552	3.529	3.271	2.750	3.033	2.932	3.387	2.933	2.999
1-Any-0	No. Lots	744	1,325	1,208	705	1,273	810	883	1,903	1,875	1,833	1,497	1,000
1-Any-0	No. Head In	157,996	228,493	196,500	123,545	285,979	212,941	172,996	339,623	310,264	320,482	296,058	250,036
1-Any-0	No. Head Out	155,853	225,692	193,646	120,845	279,845	207,190	170,607	335,076	305,510	314,590	290,329	245,199
1-Any-0	In-Weight	768	743	726	719	731	737	838	823	792	785	787	793
1-Any-0	Out-Weight	1281	1245	1233	1246	1253	1286	1476	1456	1422	1436	1432	1461
1-Any-0	Death Loss %	1.356	1.226	1.452	2.185	2.145	2.701	1.381	1.339	1.532	1.838	1.935	1.935
1-Any-1	No. Lots	6,903	7,314	7,831	7,794	8,709	9,080	8,356	8,228	9,179	7,879	8,588	9,414
1-Any-1	No. Head In	1,042,628	1,041,380	1,117,468	1,116,104	1,276,460	1,400,229	1,269,782	1,170,969	1,292,430	1,106,205	1,274,539	1,416,358
1-Any-1	No. Head Out	1,028,428	1,025,445	1,096,043	1,093,284	1,249,674	1,368,963	1,249,664	1,153,860	1,271,623	1,086,754	1,250,913	1,387,930
1-Any-1	In-Weight	751	757	743	741	731	732	802	811	803	790	786	786
1-Any-1	Out-Weight	1255	1272	1256	1264	1265	1297	1412	1418	1395	1393	1405	1443
1-Any-1	Death Loss %	1.362	1.530	1.917	2.045	2.098	2.233	1.584	1.461	1.610	1.758	1.854	2.007

Values represent the population weighted mean unless otherwise indicated. Weights are reported as pounds. Tylosin Program is defined according to tylosin used (Any=1, None=0) in the first 30 days-on-feed, Any in the middle feeding period and (Any=1, None=0) in the last 30 days-on-feed.

this has been applied to the human population to estimate lives lost to SARS-CoV2, where the cohort population was defined by the prior year.[3] The size and nature of this dataset permitted comparisons between population cohorts that were in US feedlots at the same points in time, minimizing any seasonal impacts on Deaths_K.

This approach to excess death loss in the feedlot sector is not without potential sources of noise, however, as many forces drive feedlot capacity utilization and, therefore contributions to head fed and deaths within the category. Additionally, not all feedlots applied strategic tylosin reduction programs, nor was consideration given to how reduction programs were applied within yards (i.e., across the entire yard or to only a portion of its population). Even with these limitations, because deaths are a relatively rare event, a population-level analysis is a valuable approach to gain insight about outcomes that would not be detectable through typical study design due to a lack of power necessary to observe small differences.[4,17]

Although a number of investigations comparing tylosin feeding programs have been reported, they are generally powered to detect differences across the primary outcomes of interest, namely quantity and severity of liver abscessation.[4,7,17] Although no difference in mortality was reported by Davedow et al,[4] a study design that uses 10 replicates per treatment would reliably detect a 20-fold increase in mortality given alpha=0.05 and power=0.8.

The findings of this analysis are not without limitation, however. Categorizations of tylosin use were broadly intended to reflect common strategies employed by feedlots to reduce antibiotic use. However, the nature of "*Any*" in the middle feeding period means that a lot could have seen tylosin every day or only a single day during that time window. So while it is interesting that weekly Deaths_K were generally lower for *1-Any-0* compared to *1-Any-1*, it is also possible that some of that difference is attributable to within-feedlot programs and feedlot-specific populations. This potential artifact is further supported by the models containing significant interactions between the tylosin program and WOF. The models indicated *1-Any-0* cattle experienced lower weekly Deaths_K than *1-Any-1* cattle–even during the first 10 WOF and long before the final 30 d of the feeding period could have any impact. Additionally, limited representation of feeding programs among Sex Type *InWt100 combinations

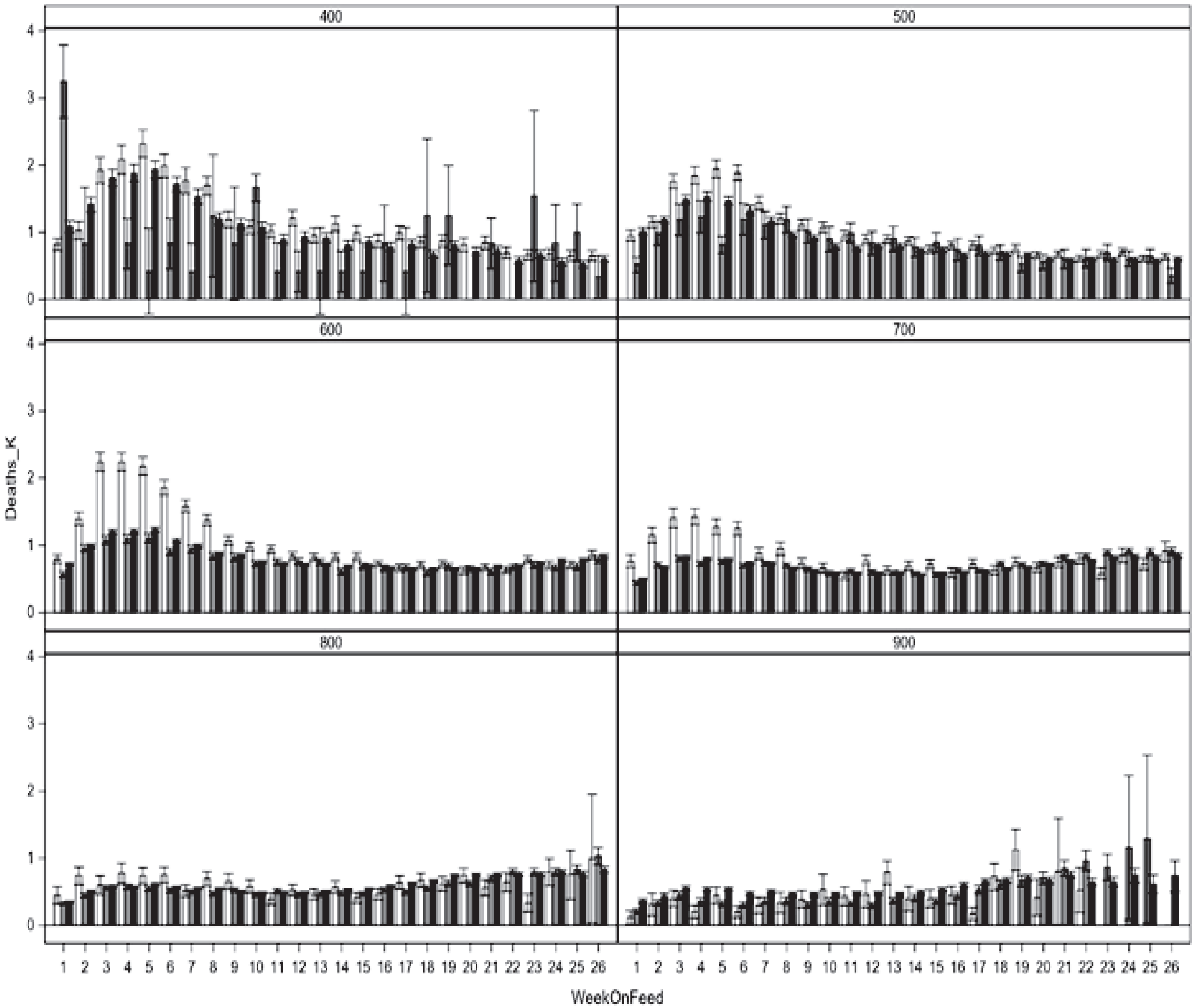

Figure 1. Bar graph summarizing the average number of deaths (±SE) per 1000 head fed (Deaths_K), weighted by head fed, by week on feed and InWt100 (lb) group for cattle fed tylosin throughout the entire feeding period (*1-Any-1*) (black bars), only in the middle and end of the feeding period (*0-Any-1*) (white bars), and only in the beginning and middle of the feeding period (*1-Any-0*) (gray bars).

(i.e., 800-wt *0-Any-1* Steers) contributed to noise. Even so, a conservative interpretation of these analysis would suggest that for 700-wt cattle and lower, omission of tylosin from the first 30 d of the feeding program has the potential to contribute another 0.1 to 0.2% in death loss across the entire feeding period.

Conclusions

The findings support the hypothesis that changes to the industry's application of tylosin in the feed may be a contributing factor to the continued increase in feedlot mortality observed across time. These results suggest that use of in-feed tylosin early in the feeding period impacts cattle survivability, with effects differing across sex type and in-weight. Analysis of additional data sources are needed to validate the repeatability of these findings, and further investigation is needed to understand the mechanism of action by which this may occur.

Endnote

[a] SAS 9.4; SAS Institute, Inc., Cary, North Carolina

Table 2. Least-squared mean differences in weekly deaths per 1000 head fed (Deaths_K) across factor levels.

Adjusted LSMean Difference (95% CI) in Weekly Deaths_K	InWt100 (lb)					
	400	500	600	700	800	900
Steers vs Heifers	--	0.034 (0.013,0.055)*	--	--	--	--
0-Any-1 vs *1-Any-0*	0.374 (0.192,0.567)*	0.132 (0.092,0.173)*	--	--	--	--
0-Any-1 vs *1-Any-1*	0.067 (0.030,0.105)*	0.037 (0.015,0.058)*	--	--	--	--
1-Any-0 vs *1-Any-1*	-0.303 (-0.491,-0.124)*	-0.095 (-0.135,-0.056)*	--	--	--	--
0-Any-1 vs *1-Any-0* Steers	--	--	--	0.077 (0.054,0.100)*	0.016 (-0.010,0.042)	--
0-Any-1 vs *1-Any-1* Steers	--	--	--	0.065 (0.042,0.087)*	0.013 (-0.039,0.013)	--
1-Any-0 vs *1-Any-1* Steers	--	--	--	-0.012 (-.031,0.006)	-0.003 (-0.045,-0.014)*	--
0-Any-1 vs *1-Any-0* Heifers	--	--	--	0.088 (0.065,0.111)*	0.078 (0.028,0.129)*	--
0-Any-1 vs *1-Any-1* Heifers	--	--	--	-0.023 (-0.052,0.005)	-0.031 (-0.081,0.019)	--
1-Any-0 vs *1-Any-1* Heifers		--	--	-0.022 (-0.041,-0.003)*	-0.109 (-0.134,-0.084)*	--
0-Any-1 vs *1-Any-0* weeks 1-10	--	--	0.392 (0.360,0.426)*	--	--	0.051 (-0.012,0.114)
0-Any-1 vs *1-Any-1* weeks 1-10	--	--	0.229 (0.199,0.259)*	--	--	-0.050 (-0.113,0.013)
1-Any-0 vs *1-Any-1* weeks 1-10	--	--	-0.158 (-0.186,-0.129)*	--	--	-0.101 (-0.132,-0.070)*
0-Any-1 vs *1-Any-0* weeks 11-20	--	--	0.064 (0.034,0.094)*	--	--	0.091 (0.020,0.163)*
0-Any-1 vs *1-Any-1* weeks 11-20	--	--	0.023 (-0.005,0.051)	--	--	0.002 (-0.068,0.073)
1-Any-0 vs *1-Any-1* weeks 11-20	--	--	-0.041 (-0.068,-0.013)*	--	--	-0.088 (-0.120,-0.057)*
0-Any-1 vs *1-Any-0* weeks >20	--	--	0.014 (-0.026,0.054)	--	--	-0.052 (-0.297,0.139)
0-Any-1 vs *1-Any-1* weeks >20	--	--	-0.046 (-0.083,-0.010)*	--	--	0.039 (-0.199,0.278)
1-Any-0 vs *1-Any-1* weeks >20	--	--	-0.056 (-0.092,-0.020)*	--	--	0.071 (0.004,0.138)*

Values represent the adjusted least-squared mean differences (95% CI) in the number of weekly deaths per 1000 head fed (Deaths_K) by placement hundredweight category (InWt100). Factors included sex type (steers and heifer), tylosin program described under Table 1 (*0-Any-1*, *1-Any-0*, and *1-Any-1*), and weeks on feed (weeks 1-10, weeks 11-20 and weeks >20). *= P<0.05. -- =Variable was insignificant and not included in the final model.

Acknowledgement

All authors are employed by Elanco, manufacturer of the pioneer tylosin phosphate medicated feed article Tylan™. Data reflect feedlots that also use Elanco products, and findings may not be generalizable to the broader feedlot population.

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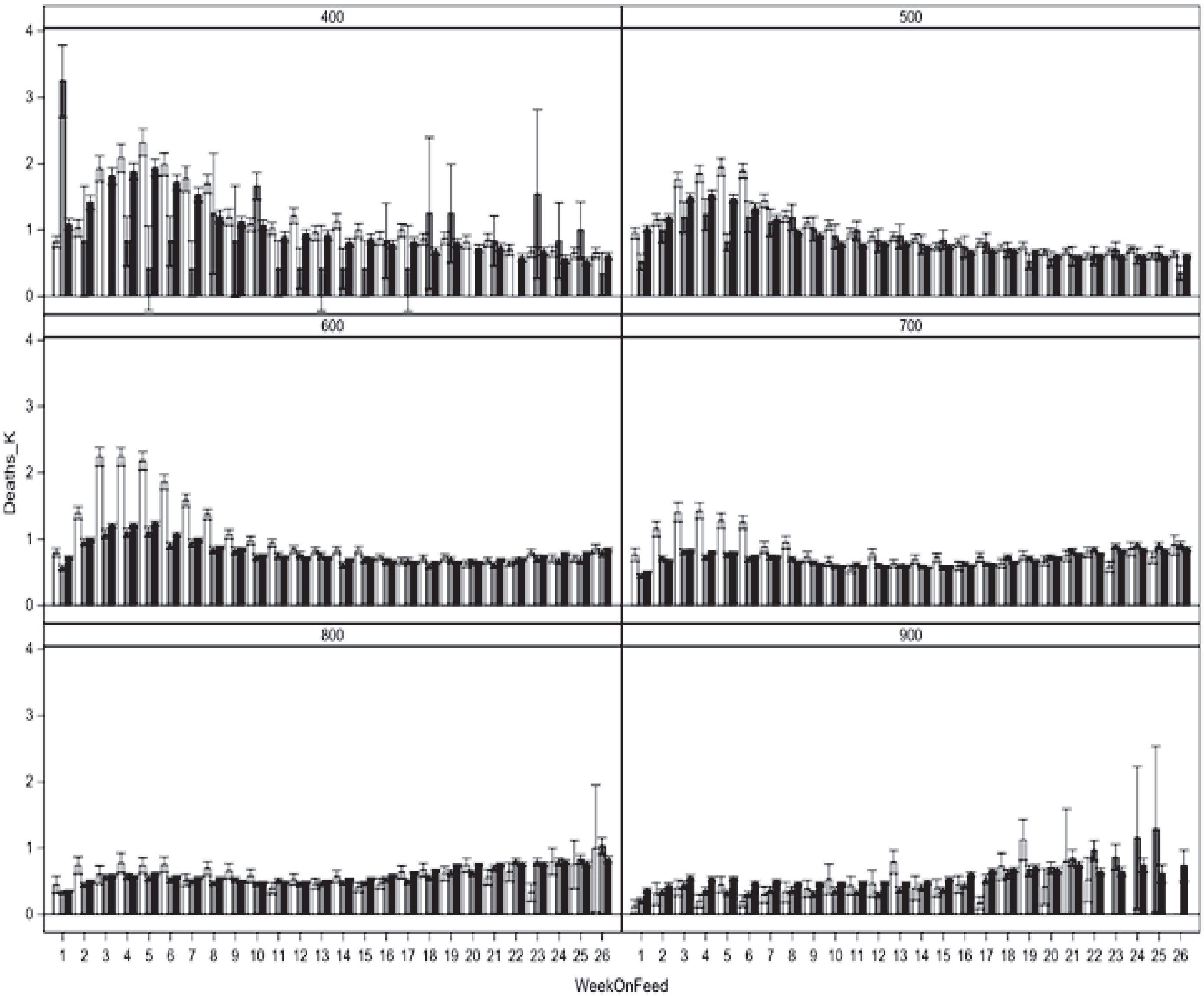

Figure 2. Bar graph summarizing the least-squared mean difference in deaths per 1000 head fed (95% CI) by tylosin program, week on feed and InWt100 group (lb) for InWt100 groups having interaction between tylosin program and InWt100. Statistically significant differences (P<0.5) are shown as black bars.

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