Effect of preweaning disease on the reproductive performance and first-lactation milk production of heifers in a large dairy herd

Angel Abuelo, Faith Cullens, and Jill L. Brester

ABSTRACT

Raising replacement heifers represents a substantial cost in dairy farms, with reproductive efficiency being one of the main factors driving the total rearing cost. Diseases during the preweaning period, such as diarrhea or bovine respiratory disease (BRD), are reported at high incidence risks worldwide. However, the long-term effects of disease before weaning on productive and reproductive performance remain controversial. This retrospective cohort study explored the extent to which diseases such as diarrhea or BRD during the preweaning period affected average daily gain (ADG), herd removal, reproductive indices, and 305-d mature equivalent milk production (305ME) of replacement heifers. The health, growth, and production records of 2,272 female calves from a large dairy herd were used; 487 and 926 of the calves had BRD and diarrhea, respectively, before weaning. The reproductive variables age at first service, age at successful service, age at calving, and pregnancies per artificial insemination were calculated. Associations of disease status with reproduction indices, removal from herd, ADG, and 305ME were evaluated by survival analysis and mixed models. Heifers with a history of BRD before weaning were less likely to be inseminated or achieve first calving than heifers without BRD. However, BRD status did not change the age at first insemination or calving among those being inseminated or reaching first calving, respectively. There were also no differences in ADG, 305ME, and pregnancies per artificial insemination between heifers with and without a history of BRD. A history of diarrhea preweaned was not associated with changes in the probability of being inseminated, having a confirmed pregnancy, or reaching first calving. However, heifers affected by diarrhea required more inseminations to become pregnant. Diarrhea status was also associated with a 325-kg reduction in 305ME in the first lactation and a 50 g/d reduction in ADG. Collectively, our results demonstrate some long-term effects of diseases before weaning on the reproductive efficiency of heifers and first-lactation 305ME production, but with limited effect on the time to achieve critical reproductive performance indicators.

Key words: dairy calf, pneumonia, diarrhea, neonatal disease, bovine respiratory disease

INTRODUCTION

Calf preweaning morbidity and mortality risks have been reported to be high (about 23–35% morbidity and 3.5–10.5% mortality) in several countries, including the United States, Canada, and Australia (NAHMS, 2014; Windley et al., 2014; Abuelo et al., 2019). Diarrhea and bovine respiratory disease (BRD) are the diseases most prevalent during the preweaning stage (NAHMS, 2007). Raising replacement heifers represents between 15 and 20% of total dairy production cost (Heinrichs, 1993). Thus, diseases during the preweaning stage significantly affect the economic viability of dairy operations due to the costs associated with calf losses, treatments, and potential long-term effects on performance (Lorenz et al., 2011).

The key indicator to reduce replacement costs is the age at first calving of heifers (Boulton et al., 2017), indicating that optimal reproductive performance of replacement heifers is essential for maintaining the economic viability of dairy farms. Similarly, greater milk production during the first lactation contributes to a faster offset of raising costs. Some controversy exists, however, regarding the effect of diseases during the preweaning period on heifer reproduction and first-lactation milk yield. Some studies report a lower risk of calving and a 6-mo delay in calving age in heifers affected by BRD (Correa et al., 1988), whereas others reported no differences in age at first service, at conception, or at first calving between calves with and without BRD (Aghakeshmiri et al., 2017). Similar differences between studies have also been observed for the effect of preweaning diarrhea on reproduction of
replacement heifers (Correa et al., 1988; Aghakeshmiri et al., 2017) and for the association of calf morbidity with subsequent first-lactation milk production (Warnick et al., 1995; Svensson and Hultgren, 2008; Teixeira et al., 2017).

Given the contrasting findings surrounding the effect of preweaning morbidity on subsequent performance, our objective was to explore the consequences of BRD, diarrhea, or both during the preweaning stage with subsequent reproductive and production performance using records from a large dairy farm. For this retrospective cohort study, we hypothesized that heifer calves with BRD, diarrhea, or both would have lower first-lactation 305-d mature equivalent milk production (305ME) and higher age at first insemination, at successful insemination, and at calving and would require more inseminations to become pregnant compared with herdmates without BRD or diarrhea.

**MATERIALS AND METHODS**

Exemption from protocol review was granted by the Michigan State University Institutional Animal Care and Use Committee because only electronic records of the farm were used.

**Heifer Calf Management**

This retrospective cohort study was conducted using the herd health records of a large commercial dairy farm associated with the Michigan State University Training Center for Dairy Professionals (Elsie, MI). This farm has an average of 3,500 lactating Holstein cows with a rolling herd-average milk production of 12,250 kg/cow. The newborn care protocol included administering an oral vaccine against diarrhea pathogens (Calf-Guard, Zoetis Services), an intranasal vaccine against respiratory pathogens (Inforce 3, Zoetis Services), and 3 mL of a vitamin E and selenium complex subcutaneously (MU-SE, Merck Animal Health) immediately after birth. After 30 min, all calves received at least 3 L of >22% Brix fresh or frozen colostrum via an orogastric tube.

Calves were housed in in-house stalls and fed 3 L of milk replacer (Cow’s Match, Land O’Lakes Inc.) 3 times/d until 7 d of age. Subsequently, calves were raised either in groups with automatic feeding systems (Calf feeder CF1000S; DeLaval) or in individual in-house stalls and bucket-fed 3 L of milk replacer 3 times/d until weaning. A step-down weaning approach was used in both feeding systems. Water was available ad libitum from birth, and starter concentrate was available from 1 wk of age. After weaning, all heifer calves were managed under identical conditions. At the farm, heifers older than 12 mo of age and weighing more than 363 kg were inseminated by trained farm staff based on observed standing estrus. Pregnancy was confirmed via rectal ultrasonography 30 to 40 d after insemination.

**Records**

The complete records from 2,272 female calves were used. These data originated from a dataset of 4,489 calves born between January 2014 and April 2017 that had been randomly blood sampled at weekly intervals for serum total protein determination between 3 and 7 d of age (Figure 1). For each heifer, data regarding disease status, growth, reproductive and productive performance, and removal from the herd were extracted from the farm’s software database (DairyComp 305, Valley Agricultural Software). Disease diagnosis and treatment were performed by farm personnel following protocols designed by the herd veterinarians based on a validated health scoring system (McGuirk and Peek, 2014). Treatment for diarrhea included oral or intravenous fluid therapy and antimicrobial therapy based on the severity of the disease. Calves diagnosed with BRD were treated with gamithromycin (6.6 mg/kg s.c.; Zactran, Boehringer Ingelheim Animal Health USA Inc.). Average daily gain at weaning was calculated based on the recorded weights at birth and weaning [(weaning weight – birth weight)/age (d) at weaning]. The following indices related to reproductive efficiency were evaluated: age at first insemination, age at first successful insemination, age at calving, and pregnancies per AI (P/AI). The 305ME was used to compare milk production in the first lactation.

**Statistical Analyses**

All analyses were performed using the software R (R Core Team, 2015) and packages “plyr” (Wickham, 2011), “survival” (Therneau and Grambsch, 2000), “tidyverse” (Wickham, 2017), “survminer” (Kassambara et al., 2020), and “lme4” (Bates et al., 2015). Due to the presence of right-censored data (e.g., removal from the herd before the first insemination, failure to become pregnant, pregnancy losses), survival analysis methods were used. Particularly, Cox proportional hazard models were built to estimate the association of disease status preweaning with the reproductive indices age at first insemination, age at successful insemination, and age at first calving as well as removal from the herd before first calving, which included both mortality and culling. The following preweaning diseases were investigated as grouping variables: BRD, diarrhea, BRD and...
diarrhea (calves being diagnosed with both BRD and diarrhea), and “any preweaning disease” (BRD, diarrhea, or other disease before weaning, such as umbilical abscess). To account for potential confounders, the type of birth (singleton vs. twin), season of birth (fall, winter, spring, or summer), and feeding system (automatic vs. bucket feeding) were also explored as explanatory variables. Univariable and multivariable analyses were used. Variables with $P < 0.20$ in the univariable analyses were retained for multivariable analysis. The multivariable models were built using a backward Wald selection method, and explanatory variables with $P < 0.05$ were considered significantly associated with the outcome and retained in the final models. The proportional hazard assumption in Cox models was verified visually through plots of scaled Schoenfeld residuals against time. Results from Cox proportional hazard models are reported as hazard ratios and 95% confidence intervals, and the associated $P$-values are those adjusted for multiple comparisons via Bonferroni correction. A Kaplan-Meier survivor function was used to estimate the median time to each reproductive event investigated dependent on preweaning disease status, using the log-rank test to compare groups.

The associations between preweaning disease and ADG, P/AI, and 305ME were investigated using linear regression models. Univariable and multivariable models were constructed as described for the proportional hazard models for the same explanatory variables. Model assumptions were assessed by the evaluation of homoscedasticity and normality of residuals. To satisfy this assumption, the P/AI data were exponentially

Figure 1. Diagram representing the number of calves that reached each critical stage and reasons for their removal. STP = serum total protein.
transformed, and the resulting least squares means estimates were subsequently back transformed. Results from linear regression models are presented as the estimated mean or geometric mean and 95% confidence intervals. Tukey’s honestly significant difference test was used for post hoc comparisons.

RESULTS

Descriptive Statistics

The records of 2,272 heifer calves were analyzed for this study. Singleton births represented 97.2% (n = 2,209) of calves, and 2.8% (n = 63) were born from twin pregnancies. Most heifers in the data set were bucket-fed (n = 1,891; 83.2%), with only 16.8% (n = 381) being raised in automatic feeding systems. The births were similarly distributed across seasons, with 29.9% (n = 681), 24.0% (n = 546), 22.5% (n = 510), and 23.6% (n = 535) of calves being born in fall, winter, spring, and summer, respectively.

The overall incidence risks of BRD, diarrhea, and any preweaning disease were 21.4, 40.7, and 53.6%, respectively. Preweaning mortality risks for these diseases were 1.85, 1.30, and 1.15%, respectively. The median (interquartile range) age at weaning was 70 (13) d, and the median ages at first disease event diagnosis were 33 (51), 9 (3), and 9 (5) d for BRD, diarrhea, and any preweaning disease, respectively. A total of 283 calves experienced both diarrhea and BRD before weaning. A total of 2,045 heifers (90.0%) were inseminated at least 1 time, 1,964 (86.4%) had a confirmed pregnancy via ultrasonography, and 1,961 (86.3%) reached first calving (Figure 1).

Effect of Preweaning Disease on Reproductive Variables

The hazard of being inseminated or achieving first calving was 14% lower in heifers diagnosed with BRD before weaning compared with heifers that were not (Table 1). Similarly, heifers that were diagnosed with both BRD and diarrhea preweaning showed a lower hazard of insemination and calving compared with those without a history of both disorders. Conversely, being diagnosed with diarrhea did not affect the hazard of insemination, pregnancy, or first calving. Nevertheless, the heifers in the “any preweaning disease” group showed a decreased hazard of being inseminated, confirmed pregnant, or achieving first calving compared with their healthy counterparts. However, none of the disease statuses investigated increased the risk of removal from the herd before first calving.

<table>
<thead>
<tr>
<th>Disease</th>
<th>First insemination</th>
<th>Successful insemination</th>
<th>First calving</th>
<th>Removal before first calving</th>
</tr>
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<tr>
<td>Respiratory disease</td>
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<td>0.81</td>
<td>0.91</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Estimate</td>
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<td>0.84</td>
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</tr>
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<td>Respiratory disease and diarrhea</td>
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<td>0.97</td>
<td>0.89</td>
</tr>
<tr>
<td>Any disease</td>
<td>Estimate</td>
<td>0.91</td>
<td>0.91</td>
<td>0.94</td>
</tr>
</tbody>
</table>

Table 1. Hazard ratios and 95% CI of preweaning disease on heifer reproductive indices and removal from the herd before first calving from Cox proportional hazards multivariable model.
Among those heifers being inseminated, the median age at the time of insemination was not different between healthy and affected heifers for any of the studied disease categories (Table 2, Figure 2). Heifers diagnosed with diarrhea or any disease reached successful insemination later (Table 2) and needed more inseminations to become pregnant (Table 3) than unaffected heifers. A history of BRD, diarrhea, BRD and diarrhea, or any disease preweaning delayed first calving. However, the differences in time were only between 4 and 9 d.

**Effect of Preweaning Disease on Preweaning Growth and First-Lactation Milk Production**

Neither ADG nor 305ME differed statistically between heifers with and without a history of BRD or BRD and diarrhea before weaning. However, heifers affected by diarrhea or any disease showed lower ADG at weaning and had a lower first-lactation 305ME. Nevertheless, the maximum differences between affected and unaffected heifers were 50 g/d for ADG and 325 kg for 305ME.

**DISCUSSION**

In this retrospective study we aimed to investigate the association between disease before weaning and growth, reproductive efficiency, milk production, and herd removal of replacement heifers in a large dairy farm. In the heifers enrolled in the study, the preweaning incidence risks of BRD (21.4%), diarrhea (40.8%), and any disease (53.6%) were higher than the 11.3, 18.9, and 33.9%, respectively, reported in the USDA’s
National Animal Health Monitoring System 2014 Dairy study (Urie et al., 2018). Conversely, this study’s pre-weaning mortality (1.19%) was lower than the reported 5.0% (Urie et al., 2018). Thus, the observed higher disease incidence associated with lower mortality could suggest that milder cases might have been identified and treated by farm staff; this needs to be considered when interpreting this study’s results because severity could influence the effect of disease on performance (Fulton et al., 2002).

**Effect of BRD Preweaning**

We found that the insemination hazard of heifers with a history of BRD was lower than that of heifers without a history, although without differences in the median age at first insemination. Two previous studies also found no differences in median age at first insemination in association with BRD preweaning (Aghakeshmiri et al., 2017; Teixeira et al., 2017).

In line with previous studies (Correa et al., 1988; Teixeira et al., 2017), a history of BRD was also associated with a delayed and lower probability of first calving. However, the magnitude of the effect documented in our study differed from previous reports. In 1988, Correa et al. (1988) showed that heifers without a history of BRD were twice as likely to calve and calved 6 mo earlier compared with those affected by BRD as calves. In 1994, Warnick et al. (1994) reported a similar hazard ratio but only a 3-mo delay in age at first calving. In contrast, we only detected a decrease of 14% in the probability of calving in association with a history of BRD—equivalent to unaffected heifers being 1.16 times more likely to calve—as well as a delay of 5 d in the age at first calving, which is in line with the average 7-d difference reported in 2017 (Teixeira et al., 2017). Thus, the effect of BRD on subsequent reproductive performance may have been mitigated by the improvement in calf management practices documented in recent decades in the United States (NAHMS, 2007, 2014). Moreover, previous economic analyses reported that a calving age <730 d (24 mo) is much more beneficial than older calving ages (Hoffman and Funk, 1992; Gabler et al., 2000; Boulton et al., 2017), and the median ages at calving observed in our study (704–699 d) indicate that this was achieved regardless of BRD history.

We found no differences in ADG between heifers with and without a history of BRD. This contrasts with the previous literature (Donovan et al., 1998; Curtis et al., 2018). However, the median age at first diagnosis of BRD in our study was after 1 mo of age, indicating that most calves were affected by BRD later in the preweaning period, which could have reduced the effect of the
disease on weight at weaning. Also, early identification and treatment of affected animals are paramount in reducing the effect of BRD (Nickell and White, 2010). The study farm has 2 dedicated herd veterinarians that oversee the implementation of treatment protocols by farm staff, which could have also contributed to the lack of differences in ADG between BRD-affected and unaffected heifers in our study.

Several previous studies reported no differences in milk production during the first lactation between heifers with and without a history of BRD (Britney et al., 1984; Warnick et al., 1995; Svensson and Hultgren, 2008; Closs and Dechow, 2017; Teixeira et al., 2017), which aligns with our findings. However, one study identified that calf health, determined by the number of days that calves had scours or coughing during the first 4 mo of life, negatively affected first-lactation 305ME (Heinrichs and Heinrichs, 2011). However, the negative effect reported in the aforementioned study may be due to assessing the combined effect of BRD and diarrhea; Svensson and Hultgren (2008) reported lower first-lactation milk yield in heifers with a history of diarrhea preweaning, which we also found here (Table 3). Another controversial aspect is the effect of BRD preweaning on survival before first calving. Closs and Dechow (2017) and our study found no differences in the risk of being removed from the herd between heifers affected and unaffected by BRD, whereas others documented an increased likelihood of removal (Teixeira et al., 2017). However, all of these studies were conducted on only one farm; thus, different disease definitions and farm factors such as culling decisions could explain these dissimilarities.

**Effect of Diarrhea Preweaning**

A history of diarrhea before weaning was not associated with differences in hazards of insemination, pregnancy, or first calving in our study. However, heifers with a history of diarrhea required more inseminations to become pregnant, and they conceived and calved, on average, 5 and 7 d later than heifers without a history of diarrhea, respectively. Similar to our results, others also reported no differences in first calving hazard ratios (Warnick et al., 1994). Conversely, Aghakeshmiri et al. (2017) reported a 15 and 14% decrease in the likelihood of pregnancy and calving, respectively, between heifers with and without a history of diarrhea. Nevertheless, the differences in median age at these reproductive events were similar to those observed here, with an 8- and 10-d delay in becoming pregnant and calving, respectively. Thus, although a history of diarrhea negatively affects the reproductive efficiency as indicated by P/AI and delays reaching key reproductive performance indicators, heifers with a history of diarrhea are still able to achieve first calving before the critical 24 mo of age (Hoffman and Funk, 1992; Gabler et al., 2000; Boulton et al., 2017).

A history of diarrhea was associated with decreased ADG during the preweaning stage, which is in line with previous research (Donovan et al., 1998) but contrasts with other studies that found no association (Soberon et al., 2012). However, the latter study also reported that calves with a history of both diarrhea and antibiotic treatment showed approximately 50 g/d lower ADG, which is the same difference we observed here. Hence, it is possible that differences in disease definition and subsequent treatment can explain the diverging results between this study and ours, as antimicrobial therapy is recommended in calves more severely affected by diarrhea (Constable, 2009). Unfortunately, however, the retrospective nature of this study precluded us from segregating calves with diarrhea treated with and without antimicrobials, as this information was not recorded.

Last, being treated for diarrhea before weaning was associated with a 325-kg decrease in first-lactation 305ME. This is similar to the 344-kg reduction noted in Swedish herds for heifers with a history of diarrhea in the first 90 d of life (Svensson and Hultgren, 2008) and the 493-kg lower production in heifers that received antibiotics as calves compared with calves with no record of being treated with antibiotics (Soberon et al., 2012). However, other studies failed to detect differences in first-lactation milk yield between heifers with and without a history of diarrhea (Warnick et al., 1995; Aghakeshmiri et al., 2017). The differences in 305ME may be attributed, at least in part, to the effect of diarrhea status on preweaning ADG, as higher ADG increases milk yield (Zanton and Heinrichs, 2005; Soberon et al., 2012).

**Effect of Comorbidity and Overall Morbidity Preweaning**

A relatively high proportion (58.1%) of the heifers diagnosed with BRD also had a history of diarrhea. Thus, we also investigated separately the effect of having a history of preweaning comorbidity. Heifers diagnosed with both BRD and diarrhea showed a lower hazard of insemination and calving, reaching calving age 9 d later than heifers with no comorbidity history. Despite heifers with a history of diarrhea showing lower ADG, P/AI, and 305ME, these associations were not identified in the heifers with a history of both BRD and diarrhea. However, this can be attributed to the lower number of animals in this group compared with the other disease statuses investigated.
We also evaluated overall morbidity before weaning to determine the effect of being affected by any disease during this developmental stage on future performance. Heifers with a history of disease before weaning had lower insemination, pregnancy, and calving hazards, required more inseminations to become pregnant, and showed a 7- and 8-d delay in age at pregnancy and first calving, respectively. To our knowledge, no previous studies investigated the combined effect of preweaning disease on reproductive performance, impeding comparisons with the existing literature. Nevertheless, heifers with a history of disease before weaning showed a median (lower to upper 95%) age at first calving of 704 (700–709) d, which is lower than the previously reported critical cut-off of 24 mo (730 d). Thus, despite a history of disease preweaning being associated with worse reproductive indices, its effect did not have sufficient magnitude to cause substantial increases in cost.

Interestingly, a history of preweaning disease was not associated with an increased likelihood of being removed from the herd, which in this study included both mortality and culling. This contrasts with previous research that showed that heifers with a history of being treated during the preweaning stage are more likely to die or be sold after weaning (Waltner-Toews et al., 1986). This previous study, however, was published more than 30 yr ago; therefore, we speculate that the improvements in calf management practices in the dairy industry in the last decades (NAHMS, 2007, 2014), along with the availability of more effective therapeutic options (O’Connor et al., 2016), could have improved recovery risks and subsequently minimized the effect of preweaning disease on removal from the herd. A more recent study also reported that the numbers of days ill before weaning did not significantly affect culling age (Heinrichs and Heinrichs, 2011), which further supports this contention.

In line with previous studies, a history of disease before weaning was associated with lower ADG at weaning (Donovan et al., 1998; Soberon et al., 2012). Impaired growth rates associated with disease could be attributed to decreased milk intake by sick calves, decreased nutrient absorption capacity of the affected intestines in cases of diarrhea, and increased nutrient demands by the immune system to fight infections. However, cause–effect relationships cannot be made given the study design used. An alternative explanation would be that slow-growing calves are at higher risk of disease before weaning. Nevertheless, previous studies support the hypothesis that disease adversely affects the growth of calves before weaning (Donovan et al., 1998; Soberon et al., 2012; Curtis et al., 2018). Heifers affected by preweaning disease also showed, on average, a 289-kg decrease in first-lactation 305ME, in line with previous studies (Heinrichs and Heinrichs, 2011), thus corroborating the importance of calf health on future productivity. Again, part of the differences in 305ME could be attributed to the effect of disease on ADG, as prepubertal ADG has been strongly associated with first-lactation milk yield (Zanton and Heinrichs, 2005; Soberon et al., 2012).

**Study Limitations**

Similar to some other previous studies (Aghakeshmiri et al., 2017; Closs and Dechow, 2017), records from only one farm were analyzed. Although this has some advantages in terms of homogeneity of disease diagnosis and treatment protocols and heifer reproductive management, the main disadvantage is that farm-dependent factors might have influenced the outcome. Thus, the findings cannot be broadly translated to other dairy farms or production systems. Also, this study focused only on preweaning disease; therefore, postweaning factors that might also affect reproductive indices cannot be identified using these data. For example, Stanton et al. (2012) showed that postweaning BRD also reduced reproductive efficiency in heifers. Nevertheless, the incidence risks of BRD (4.8%) and diarrhea (0.18%) from weaning to first calving were low in this data set, suggesting that disease during this period might not have greatly affected the study’s outcomes.

Also, the disease status of the animals was determined by farm staff using a standardized method based on health scores. However, this method is known to have only moderate sensitivity (55.4%) and specificity (58.0%) for identifying calves with lung lesions (Buczinski et al., 2014). Hence, the accuracy of the diagnostic method might have influenced the results, as some calves could have been misclassified as diseased or healthy.

Last, the sample size of this study was dictated by the number of full records available (n = 2,272) and the incidence of the different diseases during the study period. Thus, a sample size determination was not conducted to determine the number of animals needed. It is, therefore, possible that the study is underpowered for some of the studied outcome variables. In fact, a post hoc power calculation (Qiu et al., 2018) revealed only a power of 27.7% for the association between diarrhea and age at first insemination in our study. Therefore, the associations between preweaning health status and reproductive variables not identified in this study cannot be excluded.
CONCLUSIONS

A history of disease before weaning was associated with a reduced probability of heifers achieving key reproductive performance indicators and with lower reproductive efficiency, as indicated by lower P/AI. However, among those heifers reaching the indicators, disease status had no or limited effect on the time required to reach them. Also, diarrhea and any disease but not BRD were associated with lower growth rates preweaning and lower milk production in the first lactation. Collectively, our results confirm that health problems experienced early in life are associated with lower productivity and reproductive efficiency of heifers later in life.

ACKNOWLEDGMENTS

This research was funded by the USDA National Institute of Food and Agriculture Animal Health project number 1016161 and a grant from the Michigan Alliance for Animal Agriculture. The authors declare no conflicts of interest.

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