The Effect of Foot and Mouth Disease Morbidity Influencing Periparturient Diseases and Culling on Nir Yitzhak Dairy Cattle Farm

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ABSTRACT

Foot and mouth disease (FMD) is a contagious viral disease with major economic consequences. Information on the impact of the disease in vaccinated dairy cows kept under intensive management husbandry is poorly characterized. A FMD (virus serotype O\EA-3) outbreak which took place in a large-scale dairy farm in South-West Israel provided an opportunity to evaluate individual cow risk factors, the impact of clinical FMD morbidity on periparturient diseases and on culling. A retrospective cohort study was conducted on all cows and pregnant heifers at late pregnancy on the farm. Mortality among diseased cows was significantly higher in first calf heifers compared to older cows (OR=2.781; P<0.001). Lactating cows were at a higher risk to contract FMD compared to dry cows (OR=2.072; P=0.002). FMD in the dry period was associated with higher clinical metritis and retained fetal membranes incidence (OR=4.765; P=0.015 and OR= 6.951; P=0.001, respectively), but not with ketosis (OR=1.111; P=0.854). The risk of culling of FMD clinically affected cows was significantly higher in comparison to the healthy cows. The risk of culling of FMD affected cows differed between lactating and dry cow in comparison to the healthy cows 6 months after the outbreak (OR=2.698 and OR=4.616; P<0.001 and P=0.002, respectively). The pattern of culling differed between the clinically FMD cases and the healthy cows, as clinically affected cows were culled more hastily (log rank test=0.029) for up to 6 months from the beginning of the outbreak.

Key words: Foot and Mouth Disease; Dairy Cattle; Periparturient Diseases; Metritis; Retained Fetal Membranes; Ketosis; Culling.

INTRODUCTION

Foot and Mouth disease (FMD) is a highly contagious viral disease affecting cloven-hoofed species of wildlife and livestock (1,2). The disease is caused by a Picorna virus and was first described in Venice 1514 (3). The disease has major economic impact on cloven hoofed animals (4,5). Apart of the clinical implications of the disease, the major economic impacts of FMD stems from the control measures taken to prevent its spread such as trade and movement limitation (5) .

FMD epidemics in Israel occur almost every year and mostly affect cattle. The highest number of outbreaks occurs in beef cattle herds, followed by feedlots and dairy farms cattle (1,6,7). Differences in the management systems of the livestock sectors lead to differences in the level of possible exposure to the virus and vaccination coverage, hence may explain the differences (1). Most of the outbreaks in Israel occur between December and April (autumn and winter) and most of the outbreaks are caused by an O serotype virus (8).

The possibility of an endemic persistence of FMD within Israel is estimated as negligible to low, and past introductions of FMD viruses from surrounding countries have been demonstrated (1,2,8). In February 2017, FMD was diagnosed in the dairy farm of Kibbutz Nir Yitzhak, following FMD outbreaks in the Gaza strip (9). The outbreak strain was defined as serotype O of the EA-3 topotype (10). The isolated virus typically resembled those isolated in Sudan and Egypt (10). Although sufficient matching of the causative virus was found to be with one of the vaccine strains (R1=0.32 for strain O3039) (11), the extent of the outbreak was large, with young and adult vaccinated animals being effected, which was an atypical phenomenon in Israeli dairy farms (1).

The effects of FMD on dairy cattle in pastures have been described before (4, 12). However, there is a lack of data regarding FMD morbidity effects in intensive, zero-grazing management, high yielding dairy cattle, housed in loose housing systems. This study presents the effects of FMD morbidity periparturient diseases and calving traits, not demonstrated before. The described outbreak, therefore was an opportunity to analyze and quantify such an effect in large dairy industrial farms. The present study describes the 2017 Nir Yitshak outbreak; the risk factors for contracting FMD in the affected herd; the effects of FMD morbidity on periparturient diseases and the risk for culling after recovery.

MATERIALS AND METHODS

Study design and animals

The study was a retrospective cohort study conducted on all cows and pregnant heifers during late pregnancy present in an affected farm during the time of outbreak (February 6 to February 27 2017; N=511). The study population was followed for 180 days after the occurrence of the last FMD clinical case.

The farm was a zero grazing dairy herd consisting of 500-520 Israeli Holstein cows. Cows were housed in loose housing systems in large, completely covered open sheds and fed total mixed ration (TMR). The cows were milked three times daily in a computer controlled milking PARLORS and the mean annual milk production was 13,800 kg per cow during the previous year. All cows were identified by ear tags and freeze marking.

The herd was treated by a single veterinarian, who provided a complete herd-health service. The herd was visited at least twice weekly during the study period. Clinical, reproduction, production and management data were computer recorded by the herd manager and the attending veterinarians.

Clinical examination

The dairy herd health manager recorded daily, all cows and heifers showing one or more clinical signs (mammary lesions; muzzle and mouth lesions; lameness) as “clinically affected” in the herd’s management software (“Noa”; Israeli Cattle Breeders Association, Caesarea, Israel).

For diagnosis of peripartuirent disease, all cows were examined routinely between 5 and 12 days after calving by the attending veterinarian, who also diagnosed, treated and recorded the periparturient disease conditions. At examination, all animals were body scored and comprehensively examined by intravaginal and trans-reactal palpation. Cases of retained fetal membranes (RFM) were defined as the presence of placental tissues 24 hours or more later after calving as observed by a trained farm employee or the attending veterinarian. Animals with observed or suspected RFM were submitted for veterinary examination on the next routine biweekly visit (1-4 days postpartum).

In animals without a history or diagnosis of RFM, the diagnosis of clinical metritis (CM) was based on the combined characteristics of vaginal discharge obtained by palpation per vagina and of cervical and uterine examination by palpation per rectum as previously described (13). Affected cows typically showed a flaccid, non-retractable uterus that was located in the abdomen and a watery, fetid vaginal discharge.

All cows with a lower-than-expected milk production and poor appetite were examined for clinical ketosis (CK) by placing a drop of urine obtained with a sterile disposable plastic catheter on a reagent strip (Ketostix, Bayer, Holland) and by comparing the color of the reaction after 5 seconds with a standardized color chart. Cows with urine acetoacetate (AcAc) concentration ≥ 15 mg/dl were recorded as ketotic.

Serology survey

The exposure of the cows on the farm to FMD virus was estimated by a serological survey of 25 cows for Non-Structural Protein antibodies (NSP) 30 days after the diagnosis of the index case. The sampled group contained heifers older than 16 months of age, lactating and dry cows groups. The samples were taken from clinically effected and healthy cows nine months after the beginning of outbreak. The serum samples were tested for FMD exposure using a Competitive Enzyme Linked Immunosorbent Assay (ELISA) for the qualitative detection of antibody to NSP (AniGen FMD NSP Ab ELISA; BIONOTE, Korea).

Table 1: Table describing the dairy herd milking and age groups at the beginning of the Foot and Mouth Disease outbreak and the morbidity in the group during the outbreak.

Group	Age	No.	Effected	Morbidity Rate
1st calf heifers	1st lactation	96	59	61%
young cows	2nd lactation	93	31	33%
Adult cows	3rd+lactation	90	34	38%
Adult cows	3rd+lactation	103	28	27%
low yielders	Mixed	44	18	41%
Dry cows	Mixed	45	1	2%
Close up	Mixed	40	11	28%
Hutches	0-2 months	41	4	10%
Young heifers	2-4 months	40	20	50%
Replacement heifers	4-18 months	80	6	8%
Pregnant heifers	18-24 months	103	41	40%
Overall		775	253	33%

Data collection

Milk production, reproduction data, culling dates as well as the calving traits, periparturient diseases, lameness, or other diseases and treatments were recorded using the herd's management software ("Noa"™; Israeli Cattle Breeders Association). For the data analysis, all data regarding calving, morbidity, mortality and BCS was collected from the farm management software and was transferred to Excel and SPSS (SPSS Statistics version 25, IBM). All cows and pregnant heifers that calved during the 3-week outbreak period were included in the primary data set.

Statistical analysis

For the analysis of the effect of FMD clinical disease on peripartuirent diseases, only cows that were dry during the outbreak and heifers pregnant 255 days or more were included in the data set (N=108). The analysis of FMD morbidity association with periparturient diseases included RFM, CM and CK. For analysis of FMD effects on culling, cows culled up to 180 days from the beginning of the outbreak were recorded as "Culled".

The association of suspected risk factors with FMD morbidity and FMD morbidity with periparturient disease and culling was assessed by the use of Pearson χ^2 asymptotic 2-sided tests of significance. Values of P≤ 0.05 were considered statistically significant, and the Odds Ratios (OR) were calculated. FMD morbidity and culling association was evaluated using Pearson's chi-squared test and Kaplan-Meier survival analysis.

RESULTS

Descriptive statistics

During the study period, the herd consisted of 775 cows and heifers (Table 1). The herd was vaccinated a year before, and the young heifers were vaccinated during August 2016. Thirty three percent of the herd (253 cows and heifers) was recorded as clinically affected by FMD. New cases appeared from February 6th (1st case) until February 27th (last case; 22 days; Figure 1). The herd was under restrictions until the 5th of April, for 58 days. The farmer reported that the disease caused declined milk production, mortality, culling and animal welfare issues as a result of animal movement restriction and increased animal density.

Exposure of the cows to FMD virus

Out of 25 cows and heifers only one did not have NSP antibodies a month after the beginning of the outbreak on the farm (Table 2). In spite of the extensive exposure of all the animals in the study population, as indicated by the serology (96% sero-positivity; 100% of lactating cows; Table 2), and the extended interval since the cows were last vaccinated to the outbreak, only 36% of the cows and heifers in the relevant groups were clinically effected (Table 1).

FMD risk factors

Only cows that calved at least once were included in the analysis of parity as a risk factor (n=593; Table 3). Young age was associated with higher mortality rate; first calf heifers had higher mortality then older cows (OR=2.781; *P*<0.001. Table 3). The mortality of the second lactation cows did not differ from the older cows (Table 3). Lactating cows were

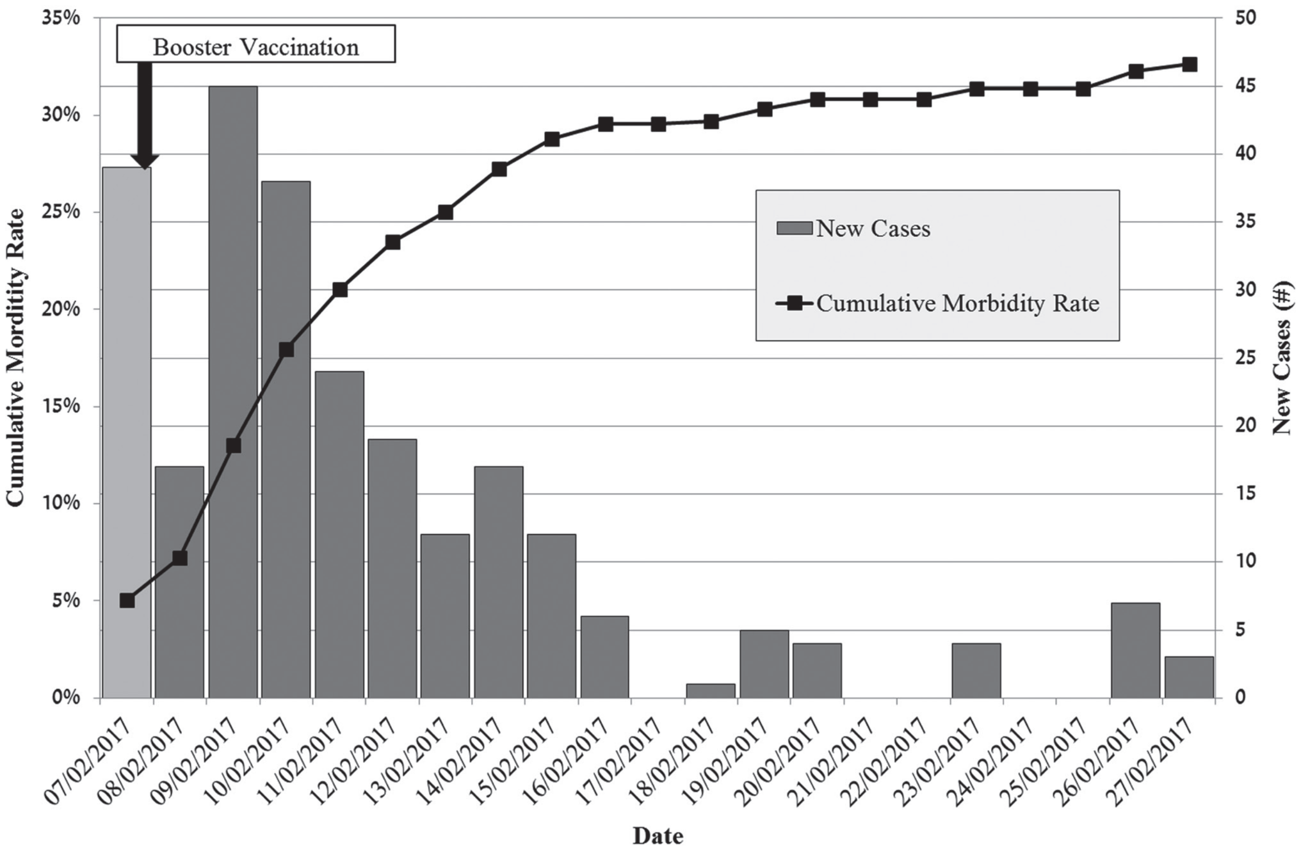

Figure Graph 1: A histogram describing new cases (bars) and the cumulative morbidity rate (curve) in the Nir Yitshak dairy farm Foot and Mouth Disease (FMD) outbreak. The light gray bar represents the new cases diagnosed at the time of the clinical suspicion of FMD and may represent the cumulative cases from the index case to the diagnosis.

found to be at a higher risk of FMD compared to dry cows (OR=2.072; *P*=0.002. Table 4).

FMD & Peripartuirent Diseases

Only dry cows and late pregnant heifers were included in the data analysis of the association of FMD morbidity with peripartuirent diseases (n=108). FMD morbidity during the dry and close-up periods was associated with higher RFM and CM Rates. (OR=4.765; *P*=0.015 and OR=0. 6.951; *P*=0.001 respectively. Table 5). The risk for CK was not associated with FMD morbidity (OR=0.9; *P*=0.854. Table 5).

Lameness

For the analysis of the association of FMD with lameness, all cows and pregnant heifers were included in the data set (n=593). Only 9 cases of lameness were recorded in the herd, 4 of them in FMD affected cows. FMD was not found to be

Table 2: Table describing the Non-Structural Proteins (NSP) antibodies prevalence in the different age groups 1 month after the beginning of the outbreak in relation to the clinical manifestation of Foot and Mouth Disease. The numbers in parenthesis represents the seroprevalence of NSP antibodies.

Age group	N	Healthy	Clinically affected	Overall NSPab[a]
Heifers	8	2 (66%)	5 (100%)	7 (87.5%)
1st calf heifers	9	3 (100%)	6 (100%)	9 (100%)
2nd lactation	1	—	1 (100%)	1 (100%)
Adult cows	7	5 (100%)	2 (100%)	7 (100%)
Over all	25	10 (91%)	14 (100%)	24 (96%)

NSPab- Non Structural Proteins antibodies.

Table 3: Table representing the difference of Foot and Mouth Disease morbidity within the different age groups of Nir Yitshak dairy farm cows.

Lactation No.	N	Morbidity Rate	OR	Sig.
1st calf heifers	236	45.3%	2.781	0.001>
2nd lactation	135	23.7%	1.042	0.874
3rd +lactation	222	23.0%	Ref	—

Table 4: Table representing the association between lactation stage and Foot and Mouth Disease Morbidity**.** The morbidity rates of Groups with different letters differ significantly (P=0.002)

Lactation stage	N	Affected	Morbidity Rate (%)
Lactating	485	168	34
Dry & Close-up[a]	108	22	20.4
Overall	593	190	32.0

[a] Dry and close-up group included dry cows and heifers ≥ 255 days pregnant.

associated with a higher lameness rate (OR=1.712; *P*=0.422. Table 5).

FMD & Culling

Cows affected by FMD had higher culling rate for up to 6 months after the resolution of the outbreak (Table 6). Lactating and dry cows affected by FMD did not differ significantly in culling rates for up to 6 months after the outbreak (OR=0.584; P=0.201. Table 6), but both groups had a higher culling rates compared to the healthy cows (Table 6; Figure 2; log rank test *P*=0.029). The effect of FMD morbidity on the culling lasted up to 75 days after the beginning of the outbreak (Figure 2). The culling pattern of both FMD affected cows and healthy cows was similar, that is 75 days or more post outbreak, as seen in Figure 2.

DISCUSSION:

FMD is regarded as a disease causing severe economic damage to affected farms (5). Control and eradication efforts has eliminated the disease from most of developing countries (5). Hence, the disease is rarely encountered in modern intensive dairy farms. In the rare case of outbreaks in prosperous countries the affected herds are culled (5). This situation leads to a gap in the knowledge of the morbidity consequences on the modern dairy farm. In the majority of the developed countries, cattle are not vaccinated against FMD, hence cur-

Table 5: Table representing the association between Foot and Mouth Disease and periparturient diseases and lameness

Disease	Mortality rate (%)			OR	Sig.
	Overall	FMD	Healthy		
RFM[1]	9.3	22.7	5.8	4.765	0.015
CM[2]	55.6	86.4	47.7	6.951	0.001
CK[3]	21.3	22.7	20.9	1.111	0.854
Lameness	1.5	2.1	1.2	1.712	0.422

1-RFM – Retained Fetal Membranes.
2-CM – Clinical Metritis.
3-CK – Clinical Ketosis

Table 6: Table describing the effects of Foot and Mouth Disease (FMD) morbidity on culling of cows according to lactation stage of the cows. The risk of culling for affected lactating cows was not significantly higher than for the affected dry cows (*P*=0.201). All FMD affected cows had higher culling rate compared to the healthy cows.

Status	N.	Culled	Culling rate	OR	Sig.
Healthy	403	51	12.66%	–	–
FMD affected:					
Lactating	168	36	31.80%	2.698	>0.001
Dry & Close-up	22	7	21.40%	4.616	0.002
Overall	190	43	22.60%		

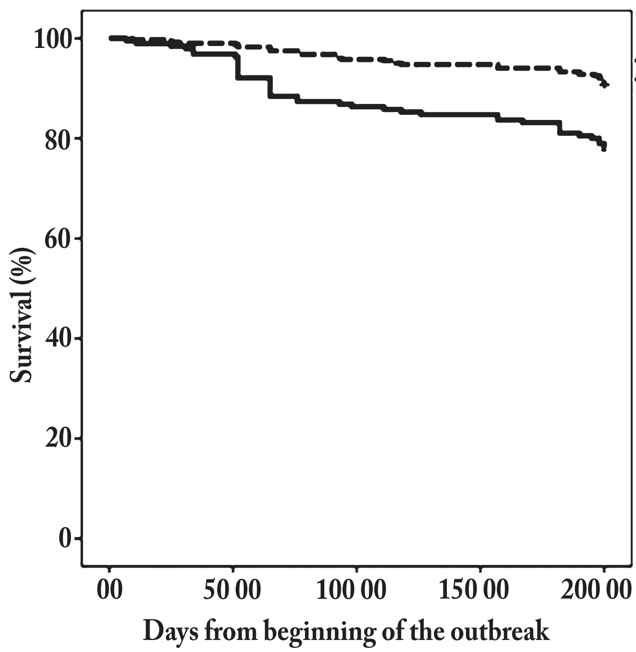

Figure 2: Survival graph of cows in Nir Yitshak dairy farm 6 months after the Foot and Mouth Disease (FMD) outbreak. The survival of the healthy cows (dotted line - - -) was higher than the FMD affected cows (solid line); Log rank test *P*= 0.029.

rent knowledge of the impact of FMD outbreak on modern, intensive dairy herds may be indicative of the damage to an unvaccinated herds. The present study analyzed the impacts of FMD on vaccinated dairy cattle in intensive management and production systems.

The cow's density, frequent contacts during milking times and the intensive usage of machinery may have contributed to a vast exposure of the cows and heifers in the farm, as demonstrated by the NSP antibodies prevalence. In an intensive, zero-grazing, modern dairy farm management affected by FMD virus, exposure of almost all animals to the virus is to be expected.

In the present study, older cows were more resistant to the disease, probably due to greater number of past vaccinations, as Israeli cows are vaccinated annually (14). It has been shown that cows vaccinated more than 3 (15) or 4 times (16) have a high, stable neutralizing antibodies titer. The fact that cows from 2nd lactation or more were relatively protected from FMD is consistent with previous reports in dairy cattle (12).

In the present study, elevated clinical FMD morbidity rates were recorded in the milking cows groups compared to the dry cows. A lower FMD incidence in dry cow groups was demonstrated previously in an outbreak in Kenya, where the difference was not significant (17). The fact that dry cows, close-up cows and pregnant heifers were relatively protected from FMD may be explained by the facts that lactating cows are more exposed to the virus during herding for milking during which time they come into close contact with other infected cows within the modern milking parlor (18). The milking equipment may also serve as a vector (19) and milk production may induce metabolic stress, hence reducing the ability of the immune system to cope with infections (20).

Dry cows affected by FMD showed a higher risk for CM and RFM (uterine diseases, UD), which may have been as a result of immune-suppression or negative energy balance (NEB) during the dry period. FMD causes mouth and tongue lesions, which initiates pain and may lead to reduced feed intake (21,22). Reduced feed intake was noted on the farm as the early sign of the outbreak. NEB have been associated previously with UD (23-25). NEB in the postpartum cow causes fat mobilization and utilization, leading to the formation of ketone bodies and non-esterified fatty acids (NEFA) (26). Ketone bodies and NEFA were shown to cause immune suppression that may explain the higher UD rates in the clinically FMD affected dry cows (27). In contrast to this assumption, that NEB associated with FMD is the cause for higher UD rates, no difference in CK rates was found between the affected and healthy cows. This finding may be explained by the duration and intensity of NEB, as a transient FMD induced NEB during the dry period may cause a mild effect, affecting only the uterine health without inducing CK. It has been shown previously that the rates of CK in dairy herds are lower than the sub-clinical ketosis (SCK) rates (28,29), while both are caused by NEB (30,31). SCK was associated with UD in a previous study (29). As SCK was not monitored in this study, the frequencies in the different groups are unknown.

Another explanation for the rise in UD rates in the clinically FMD affected cows during the dry period may be due to a suppression of the immune system by the viral infection (23). Immune suppression following FMD infection has previously been demonstrated in pigs (32,33). However, infected cows were shown to be immune-competent during acute FMD disease (34) and in contrast to pigs, the natural infection induces natural killer cell activity (28).

In a previous study on FMD outbreak in a dairy farm, a prolongation interval of calving to conception interval (Open days) was demonstrated (12). As UD are recognized as important risk factors for reduced reproductive performance (13), the previously described increase in open days may be attributed to increased UD rates.

One of the prominent clinical signs of FMD in cattle is lameness (20, 22, 35). In the study population, a low lameness rate was recorded, and lameness was not associated with an increased culling risk. This finding correlates with a previous study (36), where low lameness incidence was associated with FMD in dairy cows.

As expected, the culling rate of the cows which were clinically FMD infected was higher significant compared to that of the healthy cows. This phenomenon was described in a previous FMD outbreak in a vaccinated dairy herd in Kenya (37). In contrast to the outbreak described by Lyones *et al.* (37), the pattern of culling in the described outbreak in this study was at the beginning of the follow-up period of the study. In the dairy herd that was infected in Kenya, the majority of FMD cases that were culled, exited the herd 5 and 9 months after the beginning of outbreak (37). The fact that the majority of the culled FMD clinically affected cows exited the herd by 75 days after the beginning of the outbreak, may be related to the fact that the herd was under movement restriction, and as a result all the cows that did not convalesce from the disease were culled in the weeks following the restriction removal. Another consideration is the costs of animal keeping. As this Israeli dairy farm operated as an intensive zero grazing system in opposition to the Kenyan dairy herd which was kept on pasture, the feeding costs in Israel were higher leading the farmers to take more rapid decisions regarding the fate of clinically FMD affected animals.

CONCLUSIONS

In modern intensive dairy farms, where cows and heifers are vaccinated against FMD, young cows were found to be more susceptible to FMD. Lactating cows were at increased risk for contracting FMD, compared to dry cows. Dry cows which were clinically affected, suffered from a higher UD incidence. The clinically FMD affected cow was at higher risk for culling, mainly after the FMD movement restrictions were cancellation.

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AUTHOR CONTRIBUTIONS

Conceptualization and Methodology, T. Goshen; Clinical Examination and Data collection, Z. Shmeiger, M. Miculitski and E. Vaxman; Laboratory Examination, B. Gelman; Data Analysis and Writing – Original Draft Preparation, Z. Shmeiger and T. Goshen.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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