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Dermacentor variabilis Does Not Transstadially Transmit the U.S. Isolate of *Theileria orientalis* Ikeda: A Controlled Acquisition and Transmission Study

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Abstract: *Theileria orientalis* Ikeda, an emerging U.S. bovine hemoparasite, causes anemia, abortion, ill-thrift, and occasionally death. While *Haemaphysalis longicornis* is the primary vector, it is possible that other U.S. ticks are capable of parasite transmission and may contribute to disease spread. *Dermacentor variabilis* is highly prevalent in the U.S., exhibits a similar geographical distribution to *T. orientalis*, and is a competent vector of the related parasite, *Theileria equi*. Herein, we conducted controlled acquisition and transmission studies using splenectomized calves to assess whether *D. variabilis* can transstadially transmit *T. orientalis*. *D. variabilis* nymphs were applied to an infected, splenectomized calf for parasite acquisition and subsequently incubated to molt into adults. Freshly molted adults were applied to two splenectomized *T. orientalis*-naïve calves to investigate parasite transmission. Calves were monitored for 59 days, and no evidence of parasite transmission was detected using PCR for the *T. orientalis* Ikeda major piroplasm surface protein gene, blood smear cytology, complete blood counts, or physical examination. Salivary glands from a subset of *D. variabilis* adults were assessed for *T. orientalis* using PCR, and the parasite was not detected. These findings support the conclusion that *D. variabilis* is not capable of transstadial transmission of the U.S. *T. orientalis* Ikeda isolate.

Keywords: *Theileria orientalis*; ikeda; bovine; *Dermacentor variabilis*; competence; transstadial transmission

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1. Introduction

Bovine oriental theileriosis is caused by the tick-borne protozoan parasite *Theileria orientalis* [1,2]. Like other non-transforming *Theileria* species [1,3], the symptomatic phase of *T. orientalis* infection is characterized by infection of erythrocytes and resultant erythrolysis [1,4].

T. orientalis is classified into eleven genotypes based on targeted amplification and sequencing of the major piroplasm surface protein (MPSP) and small subunit (SSU) rRNA genes [2,3,5,6]. These genotypes include Chitose (type 1), Ikeda (type 2), buffeli (type 3), types 4 to 8, and types N1, N2, and N3 [2,5–9]. Most *T. orientalis* genotypes cause a relatively minor disease known as benign oriental bovine theileriosis [9,10]. The Ikeda and Chitose genotypes, in contrast, are more virulent, causing more severe clinical disease. These genotypes have been associated with relatively recent outbreaks in the U.S., Asia, Australia, and New Zealand [4,6,11–16].

Infection with virulent *T. orientalis* genotypes can cause severe hemolytic anemia, lethargy, anorexia, fever, icterus, abortion, stillbirth, inappetence, tachypnea, tachycardia,

and death in some cases [12,16–18]. The Ikeda genotype is associated with mortality rates of up to 6% in infected cattle [14,15,19]. Transplacental transmission of the parasite has been reported in up to 10% of infected cows, and abortions are sometimes a frequent occurrence during these outbreaks [20,21]. In this regard, *T. orientalis* Ikeda is associated with significant economic losses. For instance, the Australian beef industry suffers indirect costs of approximately AUD 19.6 million annually, and New Zealand suffers losses of more than NZD 400 per cow due to reduced meat and milk yields [22–24]. The lack of efficient diagnostic tests, efficacious treatment strategies, and vaccines for the control of the parasite further exacerbates these challenges.

The first *T. orientalis* Ikeda outbreak in the U.S. was reported in 2017 [4] and coincided with the detection of *Haemaphysalis longicornis* ticks in the same region [25–29], which were later shown to be competent vectors of the U.S. *T. orientalis* Ikeda isolate [26]. The source of *H. longicornis* introduction to the U.S. remains unknown, but, at the time of publication, it had spread to at least 19 U.S. states [30]. Control of *H. longicornis* is challenging because the tick species can withstand diverse climatic conditions [31], infests a wide range of host species, and reproduces via parthenogenesis, in which females do not require males to produce offspring [29,30,32]. It is therefore not surprising that since the tick's emergence in Virginia, *T. orientalis* Ikeda has spread within the U.S. and has also been reported in Tennessee, West Virginia, North Carolina, Pennsylvania, Arkansas, New York, Tennessee, and Kentucky [4,27,29,30,32,33].

Assessment of the ability of other tick species, especially those native to the U.S. [34], to transmit *T. orientalis* Ikeda is key to comprehensively understanding the threat that the parasite poses to the American cattle population. *H. longicornis* belongs to the family Ixodidae [32], and evaluation of the competence of other U.S. ixodid ticks for *T. orientalis* Ikeda is key in the determination of its potential spread. Our group recently showed that the cattle fever tick (also known as the southern cattle tick), *Rhipicephalus microplus*, is likely not a competent vector of U.S. isolates of *T. orientalis* Ikeda [35]. In the present study, we assessed the competence of the American dog tick, *Dermacentor variabilis*, for the U.S. isolate of *T. orientalis* Ikeda using controlled acquisition and transmission studies in calves. *D. variabilis* was chosen for testing because: (1) It belongs to the Ixodidae family [32]; (2) it is the most widely distributed native north American tick species [36] and is well-established within the geographic range in which *T. orientalis* Ikeda is spreading [34,37]; and (3) it has been shown to transmit a related parasite, *Theileria equi*, to horses [38,39]. The findings obtained from this study are summarized herein.

2. Results

2.1. Theileria Orientalis Infection of Calf 1

Peripheral blood from Calf 1 became PCR-positive for *T. orientalis* Ikeda on day 16 post-infection and remained PCR-positive for the remainder of the experiment (Table 1). Merozoites were first detected within erythrocytes via blood smear cytology on day 38 post-infection. As noted previously [26,35], intraerythrocytic merozoites were pear-shaped and approximately 1–2.5 µm × 0.5 µm. The percent parasitized erythrocytes (PPE) varied from 0.06% to 1.57% for the remainder of the experiment (Figure 1). The packed cell volume (PCV) declined only mildly to a nadir of 28% on day 56 but returned to a pre-infection level of 32% by day 74 (Figure 1). Calf 1 did not develop any clinical signs of severe *T. orientalis*, and no other significant abnormalities were detected on the complete blood count (CBC) or serum chemistry panel.

Table 1. Weekly *Theileria orientalis* peripheral blood PCR results for Calves 1–3.

	1	2	3	4	5	6	7	8	9	10	11
Calf 1	–	–	+	+	+	+	+	+	+	+	+
Calf 2	–	–	–	–	–	–	–	–	–	N/A	N/A
Calf 3	–	–	–	–	–	–	–	–	–	N/A	N/A

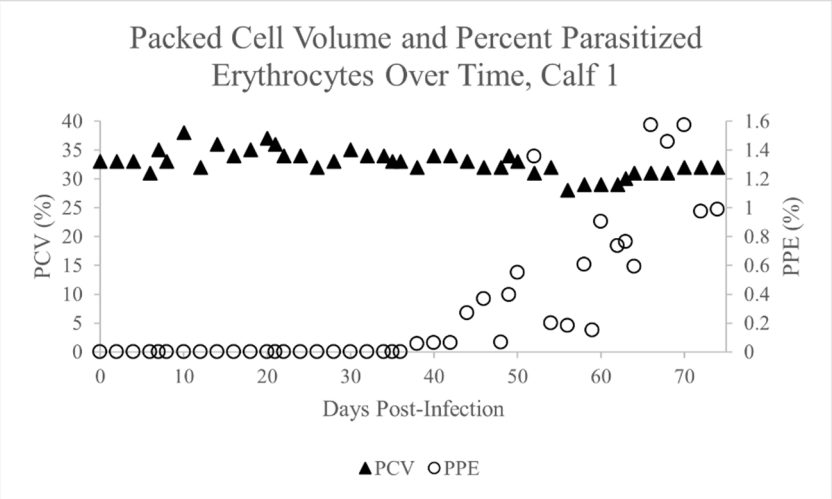

Figure 1. Packed cell volume (PCV) and percent parasitized erythrocytes (PPE) over time, Calf 1. Intraerythrocytic merozoites were first detected on day 38 post-inoculation, and from that point to the end of the experiment, PPE ranged from 0.06% to 1.57%. The PCV declined mildly to a nadir of 28% on day 56 but returned to pre-infection levels (32% by day 74).

2.2. Dermacentor variabilis Acquisition Feed on Calf 1

D. variabilis nymphs were applied to Calf 1 in two batches of 676 nymphs each. The first batch was applied on day 46 post-infection, and 467 replete nymphs from this batch were collected from 5 to 12 days post-application. The PPE during this time ranged from 0.07 to 1.36% (Figure 1). The second batch was applied on day 59 post-infection, and 213 replete nymphs from this batch were collected from 5 to 10 days post-application. The PPE during this time ranged from 0.59 to 1.57% (Figure 1). Replete nymphs were placed in an incubator and allowed to molt to the adult stage.

2.3. Failure of Adult D. variabilis Ticks to Acquire and Transmit T. orientalis to Calves 2 and 3

Amounts of 285–286 adult ticks from batches 1 and 2 were combined and applied to calves 2 and 3 as described above. After four days of feeding, five male and five female ticks were removed from each calf, dissected, and their salivary glands tested for *T. orientalis* via PCR. *T. orientalis* was not detected in the salivary glands of any of the assayed ticks (Table 2), suggesting that *D. variabilis* ticks did not acquire *T. orientalis* while feeding on Calf 1.

Table 2. Results of *Theileria orientalis* PCR performed on adult Dermacentor variabilis salivary glands.

Tick Batch	Females Tested	Males Tested	Number Positive
Group 1 Adults	5	5	0
Group 2 Adults	5	5	0

Of the 286 ticks applied to Calf 2, 197 (69%) were fed to repletion. Of the 285 ticks applied to Calf 3, 148 (52%) were fed to repletion. Calves 2 and 3 were monitored for evidence of *T. orientalis* infection for 59 days. Peripheral blood was assessed weekly for *T. orientalis* Ikeda using *T. orientalis* MPSP PCR, but *T. orientalis* was never detected in either calf. Furthermore, no organisms were visualized via blood smear cytology for the duration of the experiment (Figure 2A,B). Neither calf exhibited clinical signs consistent with *T. orientalis* (e.g., fever, icterus, inappetence, weakness), a decline in PCV (Figure 2A,B), or significant abnormalities in CBC or serum chemistry panel parameters during this time period. Since these calves were splenectomized and thus incredibly susceptible to hemoparasitic infections like *T. orientalis*, the lack of parasite detection via PCR or cytology, coupled with the complete absence of clinical signs of *T. orientalis*, strongly supports

the conclusion that adult *D. variabilis* ticks that had been fed as nymphs on a *T. orientalis*-infected calf failed to transmit *T. orientalis* in this experiment. This confirms that transstadial transmission from the nymphal tick stage to the adult tick stage failed to occur in this experiment. This conclusion is further strengthened by the fact that each splenectomized calf was infested by a large number of exposed adult ticks, increasing the likelihood of detection of even rare transmission events within the exposed tick population.

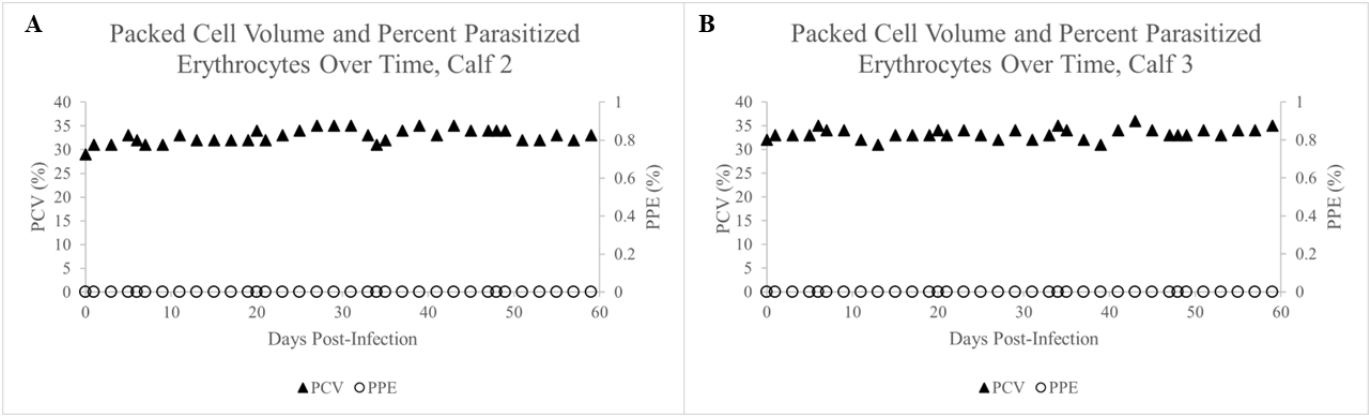

Figure 2. Packed cell volume (PCV) and percent parasitized erythrocytes (PPE) over time, Calves 2 (**A**) and 3 (**B**). In both calves, no parasites were detected, and the PCV remained normal during the monitoring period following tick application.

3. Discussion

This study assessed whether *D. variabilis*, a broadly distributed North American tick, could transstadially transmit the U.S. *T. orientalis* Ikeda isolate. We found that *D. variabilis* could neither acquire *T. orientalis* Ikeda while feeding as nymphs nor maintain infection through molting to the adult stage. Our findings suggest *D. variabilis* is unlikely to be a competent vector of *T. orientalis* Ikeda.

The assessment of intrastadial and transovarial transmission of *T. orientalis* by *D. variabilis* was beyond the scope of the current work. *D. variabilis* was shown to be competent to transmit *Theileria equi* intrastadially between horses [38–40]. Intrastadial transmission requires movement of adult ticks between infected and susceptible hosts; this can occur when partially fed female ticks are groomed off and subsequently reattach [41] or when male ticks move between hosts seeking females for mating [42–44]. *Anaplasma marginale* is routinely transmitted between infected and susceptible cattle [45,46] in this way. The ability of *D. variabilis* to intrastadially transmit *T. orientalis* should be assessed in future studies. Transovarial transmission was not assessed in the current study; however, as the lack of transovarial transmission is a defining characteristic of the *Theileria* sp. genus [47], it is incredibly unlikely that *T. orientalis* is transovarially transmitted.

Dermacentor variabilis ticks are known to be efficient vectors of both *Rickettsia rickettsii*, the causative agent of Rocky Mountain Spotted Fever, and *Francisella tularensis*, which causes tularemia [48]. *Rickettsia rickettsii* is a coccobacillary, obligate, intracellular organism that is transmitted transstadially between tick life stages and transovarially from adult females to their offspring [49]. *Francisella tularensis* is a gram-negative coccobacillus that is transstadially transmitted between tick life stages [50]. Interestingly, for both *R. rickettsii* and *F. tularensis*, most of the pathogen lifecycle occurs in the mammalian host as opposed to the tick vector [51]. In contrast, for *Theileria* species, the tick is the definitive host of the parasite since sexual stage development occurs within the tick, potentially highlighting the importance of tick-specific physiological processes for maintaining viable infection [1]. Given the marked differences between the tick-stage life cycle of *T. orientalis* Ikeda and that of most pathogens for which *D. variabilis* is a known competent and efficient vector, it is possible that *T. orientalis* Ikeda is incapable of completing its life cycle within the tick.

One notable exception to consider is the ability of *D. variabilis* to intrastadially transmit the related parasite, *T. equi* [38,39]. Although experimental studies have revealed this form of transmission is possible in *T. equi*, the epidemiological significance of intrastadial *T. equi* transmission by *D. variabilis* has yet to be shown. The overall efficiency, or capacity, of a given tick vector is influenced by several factors, including its competence to transmit the pathogen, host preferences, tick and host behavior, tick prevalence, and the life cycle characteristics of each pathogen [47]. Thus, although *D. variabilis* is a competent intrastadial vector of *T. equi,* it likely has a low overall vector capacity for that parasite. As stated above, further studies to assess whether *D. variabilis* is capable of intrastadial transmission of *T. orientalis* are warranted.

Furthermore, host use per life stage of *D. variabilis* may limit its ability to successfully transmit *T. orientalis* Ikeda to cattle. *Dermacentor variabilis* is a three-host tick, requiring three different hosts for blood meals to complete its life cycle [52]. Larval *D. variabilis* are known to feed on small mammals such as mice, voles, chipmunks, shrews, and rabbits, while nymphs and adults are likely to feed on medium and large mammals such as raccoons, domestic pets (dogs and cats), coyotes, humans, and cattle [37,53–57]. Given that the larval stages of *D. variabilis* are not known to feed on cattle or hosts that naturally carry *T. orientalis* Ikeda, it is unlikely that transstadial transmission between the larval and nymphal stages of *D. variabilis* will occur in nature.

Because *D. variabilis* is a multi-host tick and transstadial transmission of *T. orientalis* Ikeda between nymphs and adult stages does not occur, this tick is unlikely to contribute more than minimally, if at all, to transmission of *T. orientalis* Ikeda in the U.S. Despite this, several caveats should be considered. Our study used ticks obtained from a long-term captive-bred colony of *D. variabilis*. Despite occasional introductions of wild-type ticks into these colonies, there are likely minimal genetic differences among colonies of ticks and wild-type *D. variabilis,* which, although unlikely, might impact vector competence. The strain of *T. orientalis* Ikeda used for this study was obtained from a recent case of *T. orientalis* Ikeda [4,26] and is likely representative of field strains. Although our study was conducted in vivo and as close to natural conditions as possible, field conditions may vary, and factors such as co-feeding events next to infected ticks, local adaptation among tick populations, and variable pathogen strains might impact the ability of *D. variabilis* to transmit *T. orientalis* Ikeda. Finally, it is possible that *D. variaibilis* can transmit *T. orientalis* intrastadially, as this form of transmission was not assessed in the current study. Although *D. variabilis* is unlikely to influence transmission patterns of *T. orientalis* Ikeda, future work should address the capacity of other native tick species to carry and transmit *T. orientalis* Ikeda in the U.S.

4. Materials and Methods

4.1. Cattle

All aspects of this study involving animals were approved by the University of Idaho Institutional Animal Care and Use Committee, protocol number 2021-37. Three 2–4-month-old Holstein-cross steers were utilized for this study. Steers were obtained from a local dairy were quarantined for two weeks to ensure adequate health prior to inclusion in the study. All three steers underwent splenectomy at the Washington State University Veterinary Teaching Hospital and were allowed to recover for 4–8 weeks following surgery. Splenectomy was elected to increase the likelihood of infection transmission and detection, even if *D. variabilis* is a less efficient vector. Once recovered, health status was verified via complete blood count (CBC) and serum chemistry panel, and calves were found to be negative for *T. orientalis* Ikeda via PCR for the *T. orientalis* Ikeda *MPSP* gene (referenced below).

4.2. Infection of Calf 1 and Tick Acquisition Feeding

Calf 1 was infected with the U.S. *T. orientalis* Ikeda isolate as described previously [26,35]. Briefly, 12 mL of cryopreserved *T. orientalis* Ikeda-infected erythrocyte stabilate was administered intravenously on day 0 (8.4 mL from stabilate batch 1804/3-2-22, parasitemia

2.5%; 2.4 mL from stabilate batch 1697/5-12-20, parasitemia 0.7%; and 1.2 mL from stabilate batch 1726/7-2-20, parasitemia 0.48%). Beginning one week after inoculation, temperature, pulse, respiratory rate, attitude, and appetite were assessed daily, and CBC, chemistry panel, and *T. orientalis* PCR were performed weekly. Blood was collected via jugular venipuncture. PCR for the *T. orientalis* major piroplasm surface protein (MPSP) gene was performed as previously described [35]. Packed cell volume (PCV) and percent parasitized erythrocytes (PPE) were assessed via blood smear cytology every 48 h using this equation: ((Total parasites in 5 fields)/(Erythrocyte count in ¼ of a field × 20)) × 100, as previously described [35]. To maximize the chance of *T. orientalis* acquisition by the ticks, *D. variabilis* nymphs were applied to the calf in two batches: the first batch of 676 nymphs was applied eight days after initial detection of merozoites via blood smear cytology (30 days after initial PCR-positive result), and the second batch of 676 nymphs was applied 21 days after initial detection of merozoites via blood smear cytology (43 days after initial PCR-positive result). Nymphs were applied to the back of the calf under separate fabric patches, as previously described [35], and allowed to feed to repletion. Replete nymphs were collected and placed in an incubator to molt to the adult stage. Following the collection of fed nymphs, Calf 1 was humanely euthanized via intravenous injection of sodium pentobarbital (Fatal Plus®, Vortech Pharmaceuticals, Dearborn, MI, USA).

4.3. Tick Transmission Feeding on Calves 2 and 3

Four to eight weeks after molting, *T. orientalis*-exposed *D. variabilis* adults from both batches of nymphs fed on Calf 1 were combined, applied under cloth patches to the backs of calves 2 and 3 (172 females and 114 males on calf 2 and 171 females and 114 males on calf 3), and allowed to feed to repletion. Four days after application, five male and five female ticks were forcibly removed from each calf, dissected, and their intact salivary glands removed, macerated, and tested via *T. orientalis* MPSP PCR for the presence of *T. orientalis* as described in [35]. Calves 2 and 3 were monitored for *T. orientalis* infection using the same protocol described above for Calf 1. Calves were monitored for 59 days and then humanely euthanized via intravenous injection of sodium pentobarbital. A monitoring period of 59 days was selected because it is approximately three times as long as the pre-patent period of the U.S. isolate of *T. orientalis* Ikeda when transmitted by *H. longicornis* ticks [26], thereby increasing the likelihood of parasite detection in the event that *D. variabilis* proved to be less efficient at parasite transmission.

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Conflicts of Interest: The authors declare no conflict of interest.

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