UNIVERSITI PUTRA MALAYSIA

EPIDEMIOLOGY OF HAEMOTROPIC Mycoplasma ovis IN SELECTED SMALL RUMINANT FLOCKS AND HOST CELL RESPONSES OF MICE TO M. ovis INFECTION

BURA PAUL THLAMA

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By

BURA PAUL THLAMA

Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfilment of the Requirements for the Degree of Doctor of Philosophy

March 2021

DEDICATION

Firstly, I dedicate this work to the love of God Almighty, my creator in whose arms I have been nurtured and raised to this height in life. I also dedicate this project to the love of my parents, siblings, wife, and children for their sacrifices. To all the poor children in Lassa community who struggle every day, my journey is a symbol of hope sunshine comes after the rain.

Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfilment of the requirement for the degree of Doctor of Philosophy

EPIDEMIOLOGY OF HAEMOTROPIC *Mycoplasma ovis* IN SELECTED SMALL RUMINANT FLOCKS AND HOST CELL RESPONSES OF MICE TO *M. ovis* INFECTION

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Chairman : Professor Faez Firdaus Jesse bin Abdullah, PhD
Faculty : Veterinary Medicine

Haemotropic *Mycoplasma ovis* is an emerging zoonotic epierythrocytic parasitic bacterium that causes haemolytic anaemia, decreased production outcomes and mortality in sheep and goats. Isolated clinical cases of haemotropic mycoplasmosis have been documented in Malaysian small ruminants since the early 1990s and recent survey of selected flocks in Selangor also reported an association between *M. ovis* and a severe nematode worm burden in goats. Although the assay of acute-phase proteins and cytokines offers cheaper and sensitive alternatives as early markers of infection, their role in haemoplasma diagnosis is unknown. This study was designed to investigate the epidemiology of *M. ovis* in selected small ruminant flocks and determine the clinical responses of cytokines, acute-phase proteins, and female reproductive hormones in mice model. Samples and data were collected by cross-sectional survey of 5 flocks in Negeri Sembilan, Malaysia. Giemsa-stained blood smears were examined to detect *M. ovis* and classify infection severity as mild (1-29% infected red cells), moderate (30-59%) or severe (>60%) and microhaematocrit centrifugation was used to determine PCV. Sodium chloride floatation was used for detection of GIP followed by McMaster faecal egg count (FEC) to classify infection severity as mild (50-799), moderate (800-1200) or severe (>1200). Laboratory mice (n=24) were inoculated with mild (1-29%), moderate (30-59%) and severe (>60%) doses of *M. ovis* and observed for weekly changes in PCV and parasitaemia. Serum samples obtained after euthanasia were used for quantitative ELISA assay of inflammatory and reproductive markers while organ samples were processed by routine H&E staining. Examination of blood smears revealed an overall *M. ovis* prevalence of 50.7% with a higher risk among breeds, pregnant and lactating animals. Faecal analysis revealed 82.2% incidence of GIP, especially *Strongyle/Coccidia* (50.9%) co-infection with different patterns of EPG and OPG in among small ruminants. There was a higher incidence of mild GIP infections and *M. ovis*/Mixed GIP (24.9%) was associated with a lower mean PCV. A higher mean parasitaemia was observed in the co-infections of *M. ovis*/Mixed GIP (29.72±2.02) and a lower mean

PCV coincided with severe *M. ovis* or nematode infection (25.23±0.741). Mean PCV correlated negatively with EPG output (r = -0.214, p=0.002) and parasitaemia (p= 0.0009, r=-0.18). *M. ovis* cells appeared in the blood films within one-week and reached a dose-dependent peak parasitaemia in the 4th-week pi with a significant and dose-dependent drop in PCV at weeks 2 & 3 post infection (pi). The serum concentration of haptoglobin (Hp) decreased significantly ($p<0.05$) by 48.7% in GP-severe (3.92±0.95 µg/ml) compared to the GP-control (7.6±0.9µg/ml), while serum amyloid A (SAA) increased significantly ($p<0.05$) by 89% in the severe infection group (16.8±1.2µg/ml) compared to the GP-control (8.9±2.4µg/ml). Serum progesterone increased significantly ($p<0.05$) by 166% in GP-severe (27.4±1.0ng/ml) and 96% in GP-moderate (20.2±2.4ng/ml) while oestrogen levels decreased significantly ($p<0.05$) by 52.9% in the GP-severe (10.38±2.3ng/ml) than the GP-control (22.1±0.6ng/ml). The ovary in GP-severe showed mild leucocytic infiltration, vacuolation and hypertrophy of lutein cells. In the spleen, there were extensive haemorrhage, hypercellularity, infiltration of neutrophils and macrophages in the red pulp. In the lymph node, there was congestion with diffused cellular hyperplasia while the liver showed increased size and number of Kupffer cells, congestion of sinusoid, diffused necrosis of hepatocytes and leucocytic infiltration. The kidneys showed a severe proliferative lesion in the glomerulus, leucocytic infiltration and congestion of the renal veins. Haemotropic *M. ovis* and gastrointestinal parasites were common in the study area and the risk of *M. ovis* infection depends on the breed and physiological status of small ruminants. Dysregulated secretions of female reproductive hormones, changes in acute phase proteins, and the cellular changes in the ovary are novel aspects of this study which shades light on the pathogenic mechanisms of haemoplasma infection.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Doktor Falsafah

EPIDEMIOLOGI JANGKITAN HAEMOTROPIC *Mycoplasma ovis* DI LADANG RUMINAN KECIL TERPILIH DAN RESPON SEL PERUMAH DALAM MENCIT DIJANGKITI JANGKITAN *M.ovis*

Oleh

BURA PAUL THLAMA

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Hemotropik *Mycoplasma ovis* adalah bakteria parasit epierythrositik zoonosis yang menyebabkan anemia hemolitik, pengurangan hasil pengeluaran, dan kematian pada biri-biri dan kambing. Kes klinikal terpencil bagi penyakit hemotropik mycoplasma telah direkodkan dalam ruminan kecil di Malaysia sejak era 1990an dan tinjauan terbaru bagi kawanan terpilih di Selangor juga melaporkan hubungan diantara *M. ovis* dan beban jangkitan cacing nematoda yang sangat teruk dalam kambing. Walaupun ujian protein fasa-akut dan *cytokines* menawarkan alternatif yang lebih murah dan sensitif sebagai penunjuk jangkitan awal, peranan kedua-dua ujian dalam diagnosis haemoplasma tidak diketahui. Kajian ini dijalankan bertujuan untuk menyiasat epidemiologi *M. ovis* dalam kawanan ruminan kecil terpilih dan mengetahui respon klinikal bagi *cytokines*, protein fasa-akut dan hormone reproduktif betina dalam model tikus. Sampel dan data telah dikumpulkan melalui tinjauan rentas bagi lima kawanan ruminan kecil di Negeri Sembilan, Malaysia. Smear darah yang telah diwarnakan menggunakan Giemsa telah diperiksa untuk mengesan *M. ovis* dan jangkitan diklasifikasikan sebagai ringan (1-29% sel merah dijangkiti), sederhana (30-59%) atau berat (>60%) dan teknik emparan mikrohaematokrit telah digunakan untuk menentukan PCV. Teknik apungan sodium klorida telah digunakan untuk mengesan GIP diikuti teknik McMaster *faecal egg count* (FEC) untuk mengklasifikasikan jangkitan sebagai ringan (50-799), sederhana (800-1200) atau berat (>1200). *M. ovis* telah disuntik dalam tikus makmal (n=24) mengikut dos ringan (1-29%), sederhana (30-59%) dan berat (>60%) dan perubahan dalam PCV serta parasitemia telah dipantau secara mingguan. Sampel serum yang diperolehi selepas euthanasia telah digunakan untuk ujian ELISA kuantitatif bagi mengukur penanda inflamatori dan reproduktif manakala sampel organ telah diproses menggunakan rutin pewarnaan H&E. Secara keseluruhan, pemeriksaan smear darah mendedahkan jangkitan *M. ovis* sebanyak 50.7% dengan risiko yang lebih tinggi dalam kalangan haiwan yang bunting dan menyusu. Analisis najis/tinja menunjukan jumlah jangkitan GIP adalah 82.2%,

terutamanya dalam jangkitan bersama *Strongyle/Coccidia* (50.9%) dengan corak EPG dan OPG berbeza dalam beberapa kategori ruminan kecil. Terdapat kelaziman jangkitan GIP ringan dan *M. ovis*/campuran GIP (24.9%) yang tinggi yang menunjukkan min PCV yang rendah. Min parasitemia yang tinggi telah ditunjukkan bagi jangkitan bersama *M. ovis*/campuran GIP (29.72±2.02) dan min PCV yang rendah bertepatan dengan jangkitan *M. ovis* atau nematoda yang teruk (25.23±0.741). Min PCV berhubung kait secara negatif dengan pengeluaran EPG ($r = -0.214$, $p=0.002$) dan parasitaemia ($p= 0.0009$, $r=-0.18$). Sel *M. ovis* telah dijumpai pada filem darah dalam masa seminggu dan mencapai kemuncak dos-bergantung parasitamia pada minggu keempat selepas jangkitan (pi) dengan penurunan bergantung pada dos PCV yang signifikan pada minggu ke-2 dan ke-3 pi. Kepekatan serum haptoglobin (Hp) menurun secara signifikan ($p<0.05$) sebanyak 48.7% dalam GP-berat (3.92±0.95 µg/ml) berbanding GP-kawalan (7.6±0.9µg/ml), manakala serum amyloid A (SAA) meningkat secara signifikan ($p<0.05$) sebanyak 89% dalam kumpulan jangkitan berat (16.8±1.2µg/ml) berbanding GP-kawalan (8.9±2.4µg/ml). Serum progesterone meningkat secara signifikan ($p<0.05$) sebanyak 166% dalam GP-berat (27.4±1.0ng/ml) dan 96% dalam GP-sederhana (20.2±2.4ng/ml), manakala tahap estrogen telah menurun secara signifikan ($p<0.05$) sebanyak 52.9% dalam GP-berat (10.38±2.3ng/ml) berbanding GP-kawalan (22.1±0.6ng/ml). Ovari bagi GP-berat menunjukkan infiltrasi leukosit yang ringan, vakulasi dan hipertrofi sel lutein. Selain itu, terdapat pendarahan yang besar pada limpa, hiperselulariti, infiltrasi neutrophil dan makrofaj di bahagian pulpa merah limpa. Seterusnya, terdapat kemampatan hyperplasia sel yang meluas pada nod limfa manakala terdapat peningkatan saiz dan bilangan sel Kupffer, kemampatan sinusoid, nekrosis hepatokrit yang menyeluruh dan infiltrasi leukosit pada organ hati. Histologi ginjal menunjukkan luka proliferative yang teruk di dalam glomerus, infiltrasi leukosit dan kesesakan salur darah ginjal. Hemotropik *M. ovis* dan parasite gastrointestin adalah lazim di kawasan kajian dan risiko jangkitan *M. ovis* bergantung kepada baka dan status fisiologi ruminan kecil. Rembesan hormon reproduktif betina yang tidak terkawal, perubahan protein fasa-akut, dan perubahan sel pada ovari adalah aspek baru dalam kajian ini yang memberi sinar kepada mekanisma patogenik bagi jangkitan haemoplasma.

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This thesis was submitted to the Senate of the Universiti Putra Malaysia and has been accepted as fulfilment of the requirement for the degree of Doctor of Philosophy. The members of the Supervisory Committee were as follows:

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Date: 08 July 2021

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ACTH	Adrenocorticotrophic hormone
ALP	Alanine aminotransferase
ANOVA	Analysis of Variance
AOR	Adjusted odds ratio
APP	Acute Phase Proteins
APR	Acute phase reaction
AST	Aspartate Aminotransferase
BCS	Body Condition Scores
BUN	Blood urea nitrogen
Ca.	*Candidatus*
CFT	Complement fixation test
CI	95% confidence intervals
CK	Creatinine kinase
CL	Corpus luteum
CLA	Caseous lymphadenitis
CNS	Central nervous system
CO_2	Carbon dioxide
COF	Cystic ovarian follicle
CRP	C-reactive protein
CV	Coefficient of variation
CV	Coefficient of variation
DNA	Deoxyribonucleic acid
DPX	Xylene dibutyl phthalate
DVS	Department of Veterinary Services
E2	Oestrogen

EDTA	Ethylenediamine tetracaetic acid
ELISA	Enzyme-linked immunosorbent assay
EPG	Egg per gram
EXP	Expected prevalence
FAMACHA	Faffa Malan chart
FAT	Fluorescent antibody test
FEC	Faecal egg count
FOC	Faecal oocyst count
FSH	Follicle stimulating hormone
GDP	Gross domestic products
GGT	Gamma glutamyl transferase
GIP	Gastrointestinal parasites
GnRH	Gonadotropin releasing hormone
GPS	Global positioning
GPS	Global positioning
H&E	Haematoxylin-eosin
Hb	Haemoglobin
HIV	Human immunodeficiency virus
Hp	Haptoglobin
HRP	Horseradish peroxidase
HS	Haemorrhagic septicaemia
HSD	Honest significant difference
IACUC	Institutional Animal Care and Use Committee
IBM	International Business Machines
ICR	Institute of Cancer Research
IFAT	Indirect immunofluorescent antibody test

IFN-γ	Interferon gamma
IL-1	Interleukin 1
IL-6	Interleukin 6
LH	Luteinizing hormone
M. ovis	*Mycoplasma ovis*
Mcc	*Mycoplasma capricola* subsp. *capricolum*
MCH	Mean corpuscular haemoglobin
MCHC	Mean corpuscular haemoglobin concentration
MCV	Mean corpuscular volume
Mmc	*Mycoplasma mycoides* subsp. *capri*
MT	Metric ton
NaCl	Sodium chloride
OD	Optical density
OIE	Office of International Epizootics
OmpA	Outer membrane protein A
OPG	Ova per gram
OR	Odds ratio
OT	Oxytocin
p	Statistical significance
P4	Progesterone
PBS	Phosphate-buffered saline
PCR	Polymerase chain reaction
PCV	Packed cell volume
PGE	Parasitic gastroenteritis
PGE2	Prostaglandin E2
PGF2α	Prostaglandin F2α

pi	Post-infection
PR-IH	Prolactin inhibitory hormone
PRL	Prolactin
PR-RH	Prolactin releasing hormone
qPCR	Quantitative PCR
RBC	Red blood cell
RBP	Retinol-binding protein
RFLP	Restriction fragment length polymorphism
RPM	Revolutions per minute
rRNA	Ribosomal ribonucleic acid
SAA	Serum amyloid A
SD	Standard deviation
SE	Standard error
SPSS	Statistical Package for Social Sciences
SSL	Self-sufficiency level
TNF-α	Tumour necrosis factor-alpha
TTR	Transthyretin
UPM	Universiti Putra Malaysia
WBC	White blood cell
$\chi 2$	Chi-square

CHAPTER 1

GENERAL INTRODUCTION

1.1 Background of the study

In Malaysia, small ruminant production is a critical enterprise which contributes to the agricultural economy through job creation and the provision of animal protein (Loh, 2002). However, disease outbreaks and the cost of diseasise prevention and control are major challenges hampering the rapid development of the industry (Chandrawathani et al., 1999; Jesse et al., 2013). The prevention and control of parasitic disease was the primary strategy adopted by the Department of Veterinary Services (DVS) Malaysia to boost the existing small ruminant population (Ann Zainalabidin et al., 2015). However, the DVS program mainly recognised helminths, haemoprotozoa and coccidia as the leading causes of morbidity and mortality in small ruminants without paying attention to haemotropic *Mycoplasma ovis*, which recently emerged as a leading cause of anaemia and morbidity in small ruminants. Generally, parasitism is a global phenomenon that is limiting the productivity of small ruminant due to its negative impact on their health and welfare (Urquhart et al., 1996; Bhat et al., 2012). Diseases caused by helminths, coccidia and haemoparasites are common causes of illness and economic losses in small ruminant production in the tropics (Ann Zainalabidin et al., 2015). For instance, emerging haemotropic *M. ovis* infection (Hornok et al., 2009; Wang et al., 2017) and parasitic gastroenteritis (PGE) complex (Mpofu et al., 2020) represent severe threats to small ruminant health and productivity worldwide.

Mycoplasma ovis is the agent of haemotropic mycoplasmosis in sheep and goats (Hornok et al., 2009; Jesse et al., 2015; Stuen, 2016; Machado et al., 2017; Wang et al., 2017). Infection of *M. ovis* may produce either mild, moderate, or severe outcomes in small ruminants depending on several factors (Gulland et al., 1987b). The age, physiological status (e.g., pregnancy and lactation), immunity, nutrition and concurrent blood or parasitic gastrointestinal infections (Hornok et al., 2009; Sykes et al., 2010; Jesse et al., 2015). Disease outbreak triggers anaemia and high mortality in kids and lambs (Hornok et al., 2009; Martínez-Hernández et al., 2019), but the clinical disease may contrast between an overt life- threatening haemolytic anaemia, and mild chronic anaemia, ill- thrift, and infertility (Burroughs, 1988; Messick, 2004; Wang et al., 2017). The clinically affected sheep and goats have fever, anorexia, pale mucous membranes, lymphadenopathy, haemoglobinuria, and decreased milk production (Faraj & Kamal, 2017). Specific economic losses due to *M. ovis* infection in small ruminants is due to decreased production of milk, extended duration of fattening, abortion, morbidity, mortality, and high cost of antibiotic treatment (Sutton & Jolly, 1973; Tagawa et al., 2012a; Wang et al., 2017; Urie et al., 2019).

Sheep and goats are highly susceptible to infection by a range of gastrointestinal parasites, including trematodes, cestodes, nematodes and protozoa (Paul et al., 2016). Among gastrointestinal parasites, *Strongyle* nematodes are by far the most pathogenic and economically important species in small ruminants (Gibbons & Khalil, 1982; Soulsby, 1982; Urquhart et al., 1996). *Haemonchus contortus* is the most significant cause of parasitic gastroenteritis (PGE) in sheep and goats in tropical and subtropical areas (Chandrawathani et al., 1999). The age, gender, physiological status (pregnancy and lactation), nutrition, and immunological status of small ruminants determines the outcome of PGE (Nisbet et al., 2016). Most commonly, PGE is a subclinical infection in healthy animals, but prolonged poor nutrition, weak immunity and concurrent haemoparasitic or bacterial infections exacerbate disease and precipitate acute outbreaks leading to mortality (Besier et al., 2016). Clinically affected sheep and goats show signs of diarrhoea, anaemia, decreased weight gain, weakness, oedema of dependent parts, reduced productivity and occasionally mortality (Soulsby, 1982). The negative impact of PGE in small ruminants is due to morbidity, mortality and cost of treatment and control measures (Regassa et al., 2006; Nwosu et al., 2007; Owhoeli et al., 2014).

1.2 Statement of the problem

In Malaysia, earlier studies have detected *Mycoplasma ovis* and related "*Candidatus*" M. wenyonii" in blood smears taken from selected small ruminant and cattle farms in the Klang valley (Jesse et al., 2015; Mohd Hasan et al., 2017). Also, severe clinical cases of *M. ovis* infection with concurrent high nematode worm burden in small ruminants is a common clinical scenario in Malaysia (Fatimah et al., 1998; Jesse et al., 2013; 2017a). Moreover, *Haemonchus contortus* is the second leading cause of mortality in smallholder sheep and goat flocks in Malaysia (Nor-Azlina et al., 2011). However, the relationships between PGE and haemotropic *M. ovis* co-infections in small ruminants under field conditions is unknown. Furthermore, chronic infections of haemoplasmas cause anoestrus or delayed oestrus, early embryonic deaths, and abortions in swine while *M. wenyonii* causes swellings of the udder, decreased milk production and reproductive inefficiency in dairy cows (Smith et al., 1990; Messick, 2004). Recent molecular studies also described the transplacental transmission of bovine haemoplasmas (Hornok et al., 2011). These studies provided further evidence pointing that the infection of reproductive tissues is an essential aspect of hemoplasma infections requiring further investigations. It is, therefore, necessary to conduct comprehensive field surveys to elucidate prevalence, risk factors, co-infections, and severity of haemotropic *Mycoplasma ovis* among small ruminants and plan experimental study using mice model to explore the host cell response which involve the reproductive physiology when the host is infected with different severity of *M. ovis* infection.

1.3 Justification of the study

According to the National Agro-food Policy 2011-2020, the local demand for mutton and goat milk is expected to increase from 1.4 million metric ton (MT) in 2010 to 1.8 million MT in 2020 due to rapid population and economic growth (Mohammad Nor & Rosali, 2015). Thus, small ruminant production is becoming an attractive enterprise which could likely augment the agricultural gross domestic products (GDP) and livelihoods of farmers in Malaysia (Melissa et al., 2016). Notwithstanding the economic potentials of sheep and goat production, many challenges, including morbidity and mortality due to disease outbreaks, and the high cost of disease prevention and control measures are significant factors that hamper the rapid development of small ruminant industry in Malaysia (Fatima et al., 2007; Shanmugavelu, 2014). Despite the high prevalence and economic concerns due to mortality, morbidity, decreased production and reproductive inefficiency in the small ruminant industry, there is no current published information on the clinical epidemiology of haemotropic *Mycoplasma ovis* among small ruminants under field conditions in Malaysia. Also, irrespective of the evidence of poor reproductive performance seen during haemoplasma infections in cattle and swine, there is no current information on the host cell and reproductive responses of small ruminants to different severity of experimental or field infection of haemotropic *Mycoplasma ovis.* We employed microscopic examination of blood smear and faecal floatation techniques to investigate *M. ovis* and gastrointestinal parasites in this study because it is the earliest and universally accepted method for obtaining the first impression in laboratory investigation of gastrointestinal and haemoparasites (Gulland et al., 1987a, 1987b; Soulsby, 1982; Urquhart et al., 1996). So far, microscopy is the most commonly accessible, fast and inexpensive method for direct detection of anaplasmosis, babesiosis, theileriosis and haemotropic mycoplasmosis in small ruminants (Ait Lbacha et al., 2015; Hampel et al., 2014; Paul et al., 2020). In addition, microscopic examination is still applied in the current laboratory diagnosis of parasites because it also allows both qualitative and quantitative assessment of infection to be carried out simultaneously (Gulland et al., 1987a; Urquhart et al., 1996; Hampel et al., 2014). These advantages informed our choice of microscopy as a reliable method for achieving the objectives outlined in this study. This survey is also the first large-scale epidemiological study of haemotropic *Mycoplasma ovis* in our local setting and the first study to investigate the responses of cytokines, acute phase proteins and reproductive hormones under different severities of *M. ovis* infection. The results from this study will elucidate the prevalence, risk factors, co-infections, and different severities of *M. ovis* and gastrointestinal parasites in small ruminants and present further insights into pathogenic mechanisms of *M. ovis*. The ultimate long-term goal of the present study is to translate results into suitable interventions to mitigate *M. ovis* and GIP infections and their economic impacts on the small ruminant industry in Malaysia.

1.4 Hypotheses

This study was designed to investigate the following hypotheses.

1. The prevalence of haemotropic *Mycoplasma ovis* among small ruminants is not associated with epidemiological factors.

2. The occurrence of gastrointestinal parasites among small ruminants is not associated with epidemiological factors.

3. Co-infection with gastrointestinal and haemoparasites increase the severity of haemotropic mycoplasmosis among small ruminants.

4. Experimental infection with different severity of *M. ovis* in mice model would produce significant alterations in the cytokine, acute-phase protein, and reproductive hormone profiles according to the severity of the infection.

1.5 Objectives

This study was designed with the following objectives:

1. Investigate the prevalence and risk factors, and severity of haemotropic *Mycoplasma ovis* infection among small ruminants from Negeri Sembilan, Malaysia.

2. Describe the occurrence and associated factors of gastrointestinal parasites among small ruminants from Negeri Sembilan, Malaysia.

3. Describe the effects of different severity of *M. ovis*, GIP and co-infections of parasites on the clinical parameters of small ruminants from Negeri Sembilan, Malaysia.

4. Investigate the cytokine, acute phase protein and female reproductive hormone responses in experimental with different severity of *M. ovis* infection using mice model.

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