UNIVERSITI PUTRA MALAYSIA

EFFECTS OF CLIMATIC STRESS ON THE SEVERITYOF PNEUMONIA AND REPRODUCTIVE FUNCTIONS OF LOCAL CROSSBRED DOES INFECTED BY Mannheimia haemolytica

ARSALAN MAQBOOL

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By

ARSALAN MAQBOOL

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

June 2020

DEDICATION

I dedicate this to my parents: thank you for the absolute support with my life, I am honoured to have you as my parents, thank you for your prayers, thank you for giving me a chance to prove and improve myself through all my walk of life. May ALLAH continue to reward and protect you, AMEEN.

To my beloved wife and daughters, whose unconditional encouragement and support made it possible for me to commence PhD. thank you for believing in me, thank you for your prayers, understanding, patience and perseverance throughout the course of my PhD. I love you all. Most of all I pledge allegiance to the Lord Almighty for the strength and encouragement He has given me. May ALLAH continue to reward and protect you, AMEEN.

To my brothers and sister: Hoping that with this research I have proven to you that there is no mountain higher as long as Allah is on our side. Hoping that, you will walk again and be able to fulfil your dreams. May ALLAH continue to reward and protect you, AMEEN.

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I would like to conclude by again expressing my deepest gratitude and love to all for their care, love, great source of motivation, inspiration, encouragement and endless support.

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

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June 2020

Chairman : Professor Faez Firdaus Jesse bin Abdullah, PhD
Institute : Tropical Agriculture and Food Security

Pneumonic mannheimiosis is a respiratory disease which has been considered a major constraint to the development of small ruminant production. This disease is characterized by acute febrile course with severe fibrinopurulent bronchopneumonia and septicaemia occurring with a higher prevalence in goats. The main causative agent is *Mannheimia haemolytica* serotype A2, which is the most frequent isolate from pneumonic lungs. It is a commensal of the nasopharynx and is an opportunist organism that gains access to the lungs when the host is immunocompromised. To the best of our knowledge, the effects of climatic stress on the severity of pneumonia and changes in female reproductive physiology due to *M. haemolytica* A2 infection have not yet been reported. Therefore, this research has been designed to evaluate the effects of climatic stress on the severity of pneumonia and reproductive physiology in experimental does challenged with *M. haemolytica* serotype A2 in the rainy and hot seasons.

A total of twenty-four female goats were divided equally for the rainy and hot season over the period of 60 days each. For each season, 12 goats were divided into three treatment groups i.e. negative control (group 1), non-vaccinated (group 2), and vaccinated (group 3). All goats were acclimatized and synchronized before experimental trials. At week 1, group 3 were immunized with a commercially available vaccine, while group 2 and group 1 were given phosphate buffer saline (PBS). Groups 2 and group 3 were intranasally challenged with *M. haemolytica* A2 with 10^5 cfu/ml 14 days post-vaccination, whereas goats in group 1 were inoculated intranasally with PBS. Experimental animals were observed for clinical responses throughout the study period. Blood samples were collected weekly for the determination of immune responses (haptoglobin, serum amyloid A, interleukin-1β, interleukin-6, immunoglobulins-M, immunoglobulins-G, cortisol and heat shock protein-70), and reproductive hormones (progesterone, estrogen, follicle-stimulating

hormone, luteinizing hormone). At the end of the study period, all animals were euthanized for post mortem and histopathological examination. Environmental temperature and humidity were also recorded throughout the study.

The present study revealed that the environmental temperature showed non-significant ($p>0.05$) difference between the rainy and hot season, while its relative humidity was significantly ($p<0.05$) higher during the rainy season compared the hot season. The findings of the present study demonstrated that the does inoculated with *M. haemolytica* A2 had significantly ($p<0.05$) increased rectal temperature, heart and respiratory rate after twenty-four hours post-challenge in group 2 compared to group 1 and group 3 in both seasons. The mean weekly lung auscultation scores of group 2 goats were significantly higher ($p<0.05$) in the rainy season compared to those in the hot season. A significant ($p<0.05$) decline in the body condition score was observed in group 2 goats in the rainy season compared to those in the hot season.

The present study revealed a significant ($p<0.05$) increased concentrations of immune parameters in group 2 compared to group 1 and 3 in both seasons. The magnitude of interleukin-1β, cortisol and heat shock protein-70 were significantly ($p<0.05$) increased in group 2 in the rainy compared to that in the hot season. While, the acute phase proteins and interleukin-6 responses were similar within each group in both seasons. The IgM response significantly ($p<0.05$) increased post-vaccination in group 3, which further increased significantly ($p<0.05$) post-challenge and remained higher until week 5, followed by significant ($p<0.05$) increase in IgG levels and remained increased throughout the study in both seasons.

The present study revealed a significant ($p<0.05$) increase in progesterone concentrations of group 2 post-challenge. Besides, estrogen, follicle-stimulating hormone and luteinizing hormone concentrations significantly ($p<0.05$) decreased in group 2 compared to group 1 and group 3 in both seasons. The significant ($p<0.05$) histopathological changes were observed in group 2 compared to group 1 and 3 in both seasons; these changes were characterized by congestion, degeneration, and necrosis of epithelial cells with moderate to severe inflammatory cell infiltration in lungs, sub-mandibular lymph nodes, reproductive organs (ovaries, uterus, cervix), anterior pituitary glands, mammary glands and supra-mammary lymph nodes. In conclusion, climatic stress has an effect on the severity of pneumonia; the intensity of infection due to *M. haemolytica* A2 is higher in the rainy season compared to the hot season. *M. haemolytica* A2 infection has an association with the reproductive physiology of does under tropical conditions. Furthermore, it is observed that vaccination provided defensive shelter against mannheimiosis.

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

KESAN TEKANAN IKLIM TERHADAP KETERUKAN PNEUMONIA DAN FUNGSI REPRODUKTIF BAKA KACUKAN TEMPATAN BERIKUTAN JANGKITAN *Mannheimia haemolytica*

Oleh

ARSALAN MAQBOOL

Jun 2020

Pengerusi : Profesor Faez Firdaus Jesse bin Abdullah, PhD
Institut : Pertanian Tropika dan Sekuriti Makanan

Mannheimiosis pneumonik adalah penyakit respiratori yang dianggap penghalang utama perkembangan pengeluaran ruminan kecil. Penyakit ini ditandai dengan demam akut berterusan berserta bronkopneumonia fibrinopurulen (fibrinopurulent bronchopneumonia) dan septisemia yang teruk yang lebih kerap berlaku pada kambing. Agen penyebab utama adalah *Mannheimia haemolytica* serotip A2, yang paling sering terasing daripada paru-paru pneumonik. Ia adalah komensal kepada nasofarinks dan merupakan organisma oportunis yang memasuki paru-paru ketika perumah mengalami kurang daya tahan (immunokompromi). Mengikut pengetahuan kami, kesan tekanan iklim terhadap keterukan pneumonia dan perubahan fisiologi pembiakan haiwan betina akibat jangkitan *M. haemolytica* A2 belum lagi dilaporkan. Oleh itu kajian ini direka bentuk bagi menilai kesan tekanan iklim terhadap keterukan pneumonia dan fisiologi pembiakan yang diuji dengan *M. haemolytica* serotaip A2 dalam musim hujan dan panas.

Sejumlah dua puluh empat ekor kambing betina dibahagikan sama rata setiap satu kumpulan untuk musim hujan dan musim panas bagi tempoh 60 hari. Untuk setiap musim, 12 ekor kambing dibahagikan kepada tiga kumpulan rawatan iaitu kawalan negatif (Kumpulan 1), tidak diberi vaksin (Kumpulan 2) dan diberi vaksin (Kumpulan 3). Kesemua kambing telah disuaiiklim dan diselaras sebelum uji kaji percubaan dijalankan. Pada minggu 1, kumpulan 3 diimunisasi dengan vaksin yang sedia diperolehi secara komersial, sementara kumpulan 2 dan kumpulan 1 diberi garam tampan fosfat (phosphate buffer saline/PBS). Kumpulan 2 dan kumpulan 3 diuji secara intranasal dengan *M. haemolytica* A2 dengan 10^5 cfu / ml 14 hari selepas pemvaksinan, manakala kambing dalam kumpulan 1 diinokulasi secara intranasal dengan PBS.

Haiwan uji kaji ini diperhatikan untuk tindak balas klinikal sepanjang tempoh kajian. Sampel darah dikumpulkan setiap minggu untuk penentuan tindak balas imun (haptoglobin, serum amiloid A, interleukin-1β, interleukin-6, imunoglobulin-M, imunoglobulin-G, kortisol dan protein kejutan haba-70), dan hormon pembiakan (progesteron, estrogen, hormon perangsang folikel, hormon peluteinan). Pada akhir tempoh penyelidikan, semua haiwan telah dimatikan untuk bedah siasat dan pemeriksaan histopatologi. Suhu dan kelembapan persekitaran juga dicatatkan sepanjang kajian.

Kajian ini mendedahkan bahawa suhu persekitaran menunjukkan perbezaan yang tidak signifikan ($p > 0.05$) antara musim hujan dan musim panas, dan kelembapan relatif lebih tinggi ($p < 0.05$) semasa musim hujan berbanding musim panas. Penemuan kajian ini juga menunjukkan bahawa haiwan yang diinokulasi dengan *M. haemolytica* A2 telah menunjukkan peningkatan secara signifikan ($p < 0.05$) suhu rektum, jantung dan kadar pernafasan selepas dua puluh empat jam pasca ujian bagi kumpulan 2 berbanding kumpulan 1 dan kumpulan 3 dalam kedua-dua musim. Skor min auskultasi paru-paru mingguan kambing kumpulan 2 secara signifikan lebih tinggi ($p < 0.05$) pada musim hujan berbanding dengan musim panas. Penurunan ($p < 0.05$) skor keadaan badan yang ketara diperhatikan pada kambing kumpulan 2 semasa musim hujan berbanding dengan musim panas.

Kajian ini menunjukkan peningkatan kepekatan parameter imun ($p < 0.05$) yang signifikan pada kumpulan 2 berbanding kumpulan 1 dan 3 pada kedua-dua musim. Magnitud interleukin-1β, kortisol dan protein kejutan haba-70 meningkat secara signifikan ($p < 0.05$) pada kumpulan 2 semasa musim hujan berbanding musim panas. Sementara itu, fasa protein akut dan tindak balas interleukin-6 adalah serupa dalam setiap kumpulan pada kedua-dua musim. Tindak balas IgM secara signifikan ($p < 0.05$) meningkat pada pasca vaksinasi kumpulan 3, dan terus meningkat dengan ketara ($p < 0.05$) dalam pasca ujian dan kekal lebih tinggi hingga minggu ke-5, diikuti dengan peningkatan secara signifikan ($p < 0.05$) bagi tahap IgG dan kekal meningkat sepanjang kajian dalam kedua-dua musim.

Kajian ini juga menunjukkan secara signifikan ($p < 0.05$) peningkatan kepekatan progesteron kumpulan 2 dalam pasca ujian. Selain itu, estrogen, hormon perangsang folikel dan kepekatan hormon peluteinan menurun secara signifikan ($p < 0.05$) pada kumpulan 2 berbanding kumpulan 1 dan kumpulan 3 dalam kedua-dua musim. Perubahan histopatologi yang ketara ($p < 0.05$) diperhatikan pada kumpulan 2 berbanding kumpulan 1 dan 3 pada kedua-dua musim. Perubahan ini ditandai dengan kesesakan, degenerasi dan nekrosis sel epitelial dengan tahap sederhana hingga teruk penyusupan keradangan sel ke dalam paru-paru, kelenjar limfa submandibular, organ pembiakan (ovari, uterus, serviks), kelenjar pituitari anterior, kelenjar mamari dan kelenjar limfa supra-mamari. Kesimpulannya, tekanan iklim mempunyai kesan terhadap keterukan pneumonia; intensiti jangkitan disebabkan *M. haemolytica* A2 lebih tinggi pada musim hujan berbanding musim panas. Jangkitan *M. haemolytica* A2 mempunyai kaitan dengan fisiologi pembiakan dalam keadaan tropika. Tambahan pula, vaksinasi memberikan perlindungan pertahanan terhadap mannheimiosis.

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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:

Faez Firdaus Jesse bin Abdullah, PhD
Professor
Faculty of Veterinary Medicine
Universiti Putra Malaysia
(Chairman)

Abd Wahid bin Haron, PhD
Professor
Faculty of Veterinary Medicine
Universiti Putra Malaysia
(Member)

Mohd Azmi bin Mohd Lila, PhD
Professor
Faculty of Veterinary Medicine
Universiti Putra Malaysia
(Member)

Eric Lim Teik Chung, PhD
Senior Lecturer
Faculty of Agriculture
Universiti Putra Malaysia
(Member)

Annas bin Salleh, PhD
Senior Lecturer
Faculty of Veterinary Medicine
Universiti Putra Malaysia
(Member)

ZALILAH MOHD SHARIFF, PhD
Professor and Dean
School of Graduate Studies
Universiti Putra Malaysia

Date: 11 August 2022

Declaration by Members of Supervisory Committee

This is to confirm that:

- the research conducted and the writing of this thesis was under our supervision;
- supervision responsibilities as stated in the Universiti Putra Malaysia (Graduate Studies) Rules 2003 (Revision 2012-2013) were adhered to.

Signature: _____
Name of Chairman of Supervisory Committee: Professor Dr. Faez Firdaus Jesse bin Abdullah

Signature: _____
Name of Member of Supervisory Committee: Professor Dr. Abd Wahid bin Haron

Signature: _____
Name of Member of Supervisory Committee: Professor Dr. Mohd Azmi bin Mohd Lila

Signature: _____
Name of member of Supervisory Committee: Dr. Eric Lim Teik Chung

Signature: _____
Name of Member of Supervisory Committee: Dr. Annas binSalleh

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PBS	Phosphate Buffer Saline
LPS	Lipopolysaccharide
OMP	Outer membrane protein
Hp	Haptoglobin
SAA	Serum amyloid A
IgM	Immunoglobulin M
IgG	Immunoglobulin G
IL-1β	Interleukin-1β
IL-6	Interleukin-6
HSP-70	Heat Shock Protein-70
PM	Post mortem lesion
APP	Acute phase protein
Ab	Antibody
P4	Progesterone
E2	Estrogen
FSH	Follicle-stimulating hormone
LH	Luteinizing hormone

CHAPTER 1

INTRODUCTION

1.1 Introduction

Pneumonia recognized as a disease in the early 20th century (Jones, 1921; Hepburn, 1925). The disease commonly prevails worldwide, especially in goats and has a disastrous economic impact (Oremeyi et al., 2013; Abdullah et al., 2015). Economic losses caused by pneumonia were reported worldwide at a colossal $3 billion annually (Watts and Sweeney, 2010). The incidence rate of pneumonia in ruminants differs from 10 to 40%, whereas mortality exceeds 20%; these percentages are higher in young ruminants (Rico et al., 2017). Furthermore, this disease is endemic, and it is responsible for 39% of the mortalities in the small ruminant industry in Malaysia (Chung et al., 2015).

Among the etiological agent's bacteria are the most important, frequently associated with respiratory diseases in ruminants are *Mannheimia haemolytica*, *Pasteurella multocida*, *Mycoplasma bovis* and *Histophilus somni* (Taylor et al., 2010; Griffin et al., 2010; Klima et al., 2014). *M. haemolytica* is the major cause of the respiratory problem in small ruminant globally (Rahal et al., 2014; Abdullah et al., 2015). This microorganism resembles *Pasteurella haemolytica* biogroup 1 which was renamed in 1999 as *Mannheimia*, in acknowledgement to German microbiologist Walter Mannheim, who studied the taxonomy of the family Pasteurellaceae (Angen et al., 1999). In Malaysia, the leading causative agent for respiratory problem among small ruminants is *M. haemolytica* serotype A2 (Jasni et al., 1991; Zamri-Saad, 1991; Salisi et al., 2012). The bovines are the most particular carriers of *M. haemolytica* where molecular evidence shows that there is a certain quantity of horizontal transmission from animal to animal during a pneumonia epidemic (Timsit et al., 2013). *M. haemolytica* is a weak haemolytic, gram-negative, non-motile and coccobacillus-shaped bacterium. *M. haemolytica* belongs to superkingdom bacteria; phylum Proteobacteria; class Gamma Proteobacteria; order Pasteurellales; family Pasteurellaceae and genus Mannheimia (Zecchinon et al., 2005; Subramaniam et al., 2011; Shanthalingam et al., 2014). **Institut** The accurate diagnosis of *M. haemolytica* depends on bacteriological examinations, biochemistry, biotyping, and isolate serotyping (Kumar et al., 2015).

Mannheimia and Pasteurella species (previously called *P. haemolytica*) are commensal residents of the upper respiratory tract of ruminants (Hailu et al., 2017); however, several researchers still consider that *P. multocida* is involved as well (Radostits et al., 2000; Sisay & Zerihun, 2003). The status of virulence factors in the pathogenicity of *M. haemolytica* has been reported by Marru et al., (2013), where the virulence factors are unswervingly involved in the alteration of the organism from commensal into a pathogenic entity, usually responsible for promoting adhesion, colonization, and proliferation of the organism in animal tissues (Wehausen et al.,

2011). At least six components of *M. haemolytica*, have been identified as virulence factors. These include the capsule, outer membrane proteins, adhesins, neuraminidase, endotoxin lipopolysaccharide (LPS), and exotoxic leukotoxin (LktA); of these, Lkt is pivotal in the induction of pneumonia (Zamri-Saad & Mera, 2001; Finlay & McFadden, 2006). Lkt-mediated infiltration and destruction of neutrophils and other leukocytes impairs bacterial clearance and contributes to the development of fibrinous pneumonia (Dassanayake et al., 2007). LPS may act synergistically with Lkt, enhancing its effects and producing endotoxic activity (Jesse et al., 2019).

Researchers demonstrated that *M. haemolytica* plays a significant role as a secondary pathogen in the final progression of severe pleuropneumonias and cannot act alone in the lack of a precise influencing factor (Zecchinon et al., 2005; Kawamoto et al., 2007; Hodgson et al., 2012). Its pathogenesis involves many predisposing agents such as viruses, bacteria, climate stress, weaning, dehorning and transportation, whereby it causes immunosuppression and contributing to the growth of pneumonic mannheimiosis in sheep and goats (Zecchinon et al., 2005; Taylor et al., 2010; Abdullah et al., 2015). These factors would ultimately damage the pulmonary protection capability mechanisms by initiating hazardous effects on the ciliated cells and mucous coating of the trachea, bronchi, and bronchioles (Kumar et al., 2015). *M. haemolytica* from the nasopharynx will then reach the ventral bronchi, bronchioles, and alveoli by gravitational drainage along the tracheal floor thereby penetrating into the lung tissue (Adamu, 2007), allowing *M. haemolytica* to colonize it, leading to broncho-alveolar pneumonia, acknowledged as febrile respiratory disease with fibrinopurulent bronchopneumonia, septicemia and pleurisy (Abdelsalam 2008; Alemneh & Tewodros, 2016). Young animals may die within few days after clinical manifestations of disease, and survivors may become persistently infected (Emikpe et al., 2010). In adult ruminants the distress usually appears within 10 to 14 days after exposure to stressful conditions; typically, onset has been reported earlier than that (Walkey et al., 2012). This infection is monitored by increased morbidity and mortality rate (Ackermann and Brogden, 2000; Shiferaw et al., 2006).

Among the indicators to measure the severity of pneumonia, cortisol (Abdelsalam, 2008) and HSP70 (Boehmer et al., 2011) has been reported as reputable; besides acute phase proteins, cytokines, antibodies titre has been described as essential indicators. However, there is no data on these parameters as well as reproductive hormones after infection of *M. haemolytica* serotype A2 via an intranasal route of inoculations in the real host goat. The hypothalamus plays a vital role to control the secretion of gonadotropins (Hafez & Hafez, 2013). For the first time Jesse et al., (2017) exposed the association between adenohypophyseal lesions, decreased hypothalamic production of GnRH, luteinizing hormone, follicle-stimulating hormone, estrogen and progesterone in buffalo heifers experimentally inoculated with *P. multocida* type B:2. No data/ study is available in female goats in terms of host cell responses and changes in reproductive physiology due to *M. haemolytica* infection.

Literature regarding the severity of pneumonia during different seasons is scarce; so far, two studies have reported discrepant results, where, Jasni et al., (1990) highlighted an increasing number of pneumonia cases during the rainy seasons. On the other hand, Albasha et al., (2018) reported a higher number of cases in goats during the dry seasons. However, it has been unclear that regardless of number of cases, which season increases the severity of pneumonia in goats.

Therefore, this study has been proposed to address this research gap.

1.2 Problem Statement

Studies involving mannheimiosis in small ruminants have reported valuable information on the clinical signs, gross lesions and histopathological changes focusing on the respiratory system. However, knowledge of this disease regarding pathophysiological changes in the reproductive system are yet to be exposed. There is enormously low information related to the effects of *M. haemolytica* on the reproductive physiology of small ruminants during or at post-infection. Information on these will play a significant role in getting a better understanding and knowledge of the pathogenesis and severity of *M. haemolytica* infection in the study area. There is a dearth of information regarding the effects of climatic change on the severity of pneumonia in goats. The possible association with reproductive losses in goats due to *M. haemolytica* infection are lack; therefore, a proper understanding is imperative.

1.3 Hypotheses

It is hypothesized that after experimental infection with *M. haemolytica* serotype A2, there will be a host cell response in goats via the intranasal route.

The climatic stress has an association with the severity of clinical responses in female goats experimentally infected with *M. haemolytica* A2.

Climatic stress has an association with Acute Phase Protein (Hp, SAA), Antibodies (IgM, IgG), cytokines (IL-1β and IL-6), Serum cortisol and Heat Shock Protein-70 concentrations in pneumonic female goats.

Climatic stress has an association with the changes in the concentration of female reproductive hormones (FSH, LH, estrogen, progesterone) in does experimentally infected with *M. haemolytica* A2.

Climatic stress has an association with microscopic changes in reproductive tissues of does experimentally infected with *M. haemolytica* A2.

1.4 Objectives

The primary aims of this research are determining the effects of climatic stress (rainy and hot season) regarding the severity of pneumonia infection in female goats; together with the host cell responses and changes in female reproductive physiology via experimental infection *of M. haemolytica* serotype A2.

1- To evaluate the association of severity of clinical responses due to the effects of climatic stress (rainy and hot season) in female goats (vaccinated and non-vaccinated) via experimental infection of *M. haemolytica* serotype A2.

2- To determine the effect of climatic stress (rainy and hot season) on Acute Phase Protein (Hp and SAA), Antibodies (IgM and IgG), pro-inflammatory cytokines (IL-1β and IL-6), Cortisol, and Heat Shock Protein-70 concentrations in experimentally inoculated female goats (vaccinated and non-vaccinated) with *M. haemolytica* serotype A2.

3- To determine female reproductive hormones (FSH, LH, estrogen, progesterone) in pneumonic female goats (vaccinated and non-vaccinated) due to effects of climatic stress (rainy and hot season) via experimental infection of *M. haemolytica* serotype A2.

4- To study the tissue changes (microscopically) in pneumonic female goats (vaccinated and non-vaccinated) due to the effects of climatic stress (rainy and hot season) via experimental infection of *M. haemolytica* serotype A2.

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