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Abstract

Although a decreasing trend of human notifications was observed from 2001 to 2014 (Chapter 1), the incidence of human leptospirosis in New Zealand continues to be higher than in other high-income countries and affecting predominately people occupationally exposed to livestock (i.e. abattoir workers and farmers). Additionally, evidence suggests that leptospirosis may have a higher detrimental effect on production in deer compared with beef cattle or sheep. It was also observed that vaccination against \textit{Leptospira} of not previously infected animals reduce the risk of urinary shedding of leptospires after challenge, and that there is limited evidence supporting or disproving that maternally derived antibodies interfere with the effect of vaccination when animals are vaccinated at a young age.

When sero-positivity was defined as a serum microscopic agglutination test (MAT) titre of \(\geq 48\), 6.6% of farmers (Chapter 2) and 5.1% of veterinarians (Chapter 3) were sero-positive to at least one of five \textit{Leptospira} serovars (Hardjo-bovis, Pomona, Copenhageni, Ballum, Tarassovi). Veterinarians had a higher risk of being sero-positive when they slaughtered cattle or pigs at home or worked in a mixed animal practice. Assisting calving of cattle or deer, farming deer alone or in combination with cattle and/or sheep, flat terrain on farm, and abundance of wild deer on farm, increased \textit{Leptospira} sero-positivity of farmers. Apart from vaccinating farmed livestock, increased awareness of such risk factors and the use of protective equipment may reduce the human leptospirosis incidence in these occupational groups.

Similar to earlier observations in abattoir workers, \textit{Leptospira} sero-prevalence of farmers and veterinarians was associated with the recall of influenza-like illness of sampled individuals. Using the estimated incidence of influenza-like illness attributable to \textit{Leptospira} infection (population attributable risk) of veterinarians (0.05%), farmers (1.3%) and abattoir workers (2.7%), we quantified the burden of human leptospirosis in terms of disability-adjusted life years (DALYs) and economic
cost of infection; the latter including the cost of vaccination, which is primarily used in dairy cattle (Chapter 4). Annual DALYs were estimated to be 0.43 per 100,000 people in New Zealand, and 16.76 per 100,000 people when only considering the occupationally-exposed population (abattoir workers, farmers, veterinarians). This ranks leptospirosis in New Zealand’s high-risk population similar to worldwide estimates of DALYs for rabies and dengue. The total annual cost of leptospirosis due to human disease (i.e. treatment and absence from work); production loss in deer, beef cattle, and sheep; and the cost for vaccinating them was estimated to be NZ$25.36 million. One third of this total was attributed to vaccination of dairy cattle. The annual cost of human treatment and workplace absence due to severe and mild leptospirosis was NZ$4.49 million. Total lost production cost was NZ$11.31 million, half of which was attributable to reproductive and growth reduction in deer. No estimates are currently available from any other country for the public health burden and the overall economic loss including farmed livestock for this disease.

Since vaccination of livestock is currently regarded as the most effective means of preventing human exposure, the literature on the efficacy of Leptospira vaccines for preventing urinary shedding was systematically reviewed (Chapter 5). The meta-analysis of vaccination trial results, using articles with sufficiently detailed data, resulted in a pooled vaccine efficacy estimate of 82% when shedding was assessed by culture.

The findings of this thesis contribute towards a better understanding of the public health burden, economic cost, infection sources for humans, and the efficacy of vaccination for reducing the risk of Leptospira urinary shedding in domestic livestock.
Acknowledgement

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My time living in New Zealand has been one of the greatest in my life and I want to thank all the people that made me feel at home. In these years I have crossed paths with so many beautiful friends, from so many different places and backgrounds, who have enriched my own life so much and made me realise how lucky I am for living these experiences. I would name them all in these lines if I were confident of not leaving anyone behind. So many good friends have gone overseas over the years, leaving always a bitter sweet taste because of their departure but with the comfort of knowing that pieces of friendship are now all over the world. Life, of course, would not be the same without Football (and Frisbee lately) and charcoal BBQs (ok, and gas as well). Thanks to all friends that participated in these uncountable magnificent events for bringing so much happiness.

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Declaration

This thesis was formatted as five independent research chapters suitable for journal publication. Therefore, concepts and/or methodology described in a chapter may be repeated in another chapter. My input as main author of this research was to plan and coordinate sampling of veterinarians and farmers, develop questionnaires to record relevant information, process samples in the laboratory and test them for antibodies against \textit{Leptospira}, conduct systematic literature search, select studies for meta-analysis, analyse data, and draft manuscripts reporting findings. People that contributed substantially to the research were made co-authors as listed at the beginning of each chapter.
List of abbreviations

MUHEC: Massey University Human Ethics Committee
MAT: Microscopic Agglutination Test
OR: Odds Ratio
RR: Relative Risk
PR: Prevalence Ratio
CI: Confidence Interval
PI: Probability Interval
PAR: Population Attributable Risk
PAF: Population Attributable Fraction
LRT: Likelihood Ratio Test
REML: Restricted Maximum Likelihood
MCMC: Markov Chain Monte Carlo
DALYs: Disability-Adjusted Life Years
YLL: Years of Life Lost
YLD: Years Lost due to Disability
MDA: Maternally Derived Antibodies
IgM: Immune Globulin of class M
IgG: Immune Globulin of class G
PBMC: Proliferation of peripheral Blood Mononuclear Cells
PCR: Polymerase Chain Reaction
FA: Fluorescent Antibody
DFM: Dark Field Microscopy
ACC: Accident Compensation Corporation
List of publications


List of conference presentations


Contents

Abstract

Acknowledgement

Declaration

List of abbreviations

List of publications

List of conference presentations

List of figures

List of tables

Introduction

1 Literature review

1.1 Summary ........................................... 2
1.2 Introduction ....................................... 4
1.3 Materials and Methods ............................ 5
1.4 Human leptospirosis ............................... 5
1.5 *Leptospira* in domestic animals and wildlife .......... 8
1.6 Production effects .................................. 14
  1.6.1 Cattle ......................................... 14
  1.6.2 Sheep .......................................... 15
  1.6.3 Deer ........................................... 16
1.7 Registered vaccines ................................ 17
1.8 Vaccine coverage ................................... 17
1.9 Immunity against *Leptospira* ...................... 24
1.9.1 Humoral immune response ........................................... 24
1.9.2 Cell-mediated immunity ............................................ 26
1.10 Maternally derived antibodies (MDA) and vaccination ............ 27
1.11 Vaccine efficacy ................................................... 29
  1.11.1 Cattle ......................................................... 30
  1.11.2 Deer and sheep ............................................... 31
1.12 Multivalent and monovalent vaccines ............................... 33
1.13 Long term vaccine efficacy ........................................ 34
1.14 Conclusion ...................................................... 36
1.15 Acknowledgement .................................................. 38

References ........................................................................ 39

2 *Leptospira* sero-positivity in farmers .............................. 51
  2.1 Summary .................................................................. 52
  2.2 Introduction .......................................................... 53
  2.3 Material and Methods ............................................... 55
    2.3.1 Sampling frame .................................................. 55
    2.3.2 Sample collection ............................................... 55
    2.3.3 Serological testing .............................................. 55
    2.3.4 Questionnaire ................................................... 56
    2.3.5 Data description .................................................. 56
    2.3.6 Sero-prevalence in farmers and animals .................... 56
    2.3.7 Multivariable model building ................................. 57
    2.3.8 Multivariable model specification and convergence diagnostics 57
    2.3.9 Leptospirosis in farmers pre-sampling ...................... 57
    2.3.10 Influenza-like illness ......................................... 58
    2.3.11 Statistical software ............................................ 58
    2.3.12 Human ethics application ..................................... 58
  2.4 Results .................................................................... 59
    2.4.1 Serology in farmers .............................................. 59
    2.4.2 Animal contact, vaccination and previous animal serological status .................................................................................................................................................................................. 61
    2.4.3 Association between previous animal sero-prevalence and farmer sero-status ...................................................... 61
    2.4.4 Risk factors for *Leptospira* sero-positivity in farmers .... 63
CONTENTS

2.4.5 Previous leptospirosis ....................................... 64
2.4.6 Association between serology and influenza-like illness .... 65
2.5 Discussion ....................................................... 67
2.6 Conclusion ...................................................... 72
2.7 Acknowledgement ............................................... 73

References .......................................................... 75

3 Leptospira sero-positivity in veterinarians ....................... 81
3.1 Summary ......................................................... 82
3.2 Introduction ....................................................... 83
3.3 Materials and Methods ......................................... 85
  3.3.1 Study Design ............................................... 85
  3.3.2 Recording of risk factors .................................. 85
  3.3.3 Statistical analysis ......................................... 86
  3.3.4 Human ethics application .................................. 87
3.4 Results .......................................................... 88
  3.4.1 Titre distribution ........................................... 88
  3.4.2 Sero-prevalence ............................................. 88
  3.4.3 Age and gender .............................................. 89
  3.4.4 Occupational exposure to animals ......................... 89
  3.4.5 History of previous leptospirosis episodes ............... 90
  3.4.6 Influenza-like illness in the last 18 months ............ 91
  3.4.7 Unadjusted associations .................................. 91
  3.4.8 Multivariable analysis .................................... 92
3.5 Discussion ....................................................... 94
3.6 Conclusion ...................................................... 98
3.7 Acknowledgement ............................................... 99

References .......................................................... 101

4 Burden of leptospirosis in New Zealand ........................... 105
4.1 Summary ......................................................... 106
4.2 Introduction ....................................................... 107
4.3 Materials and Methods ......................................... 109
  4.3.1 Simulation model ........................................... 109
  4.3.2 Burden of leptospirosis .................................... 109
4.3.3 Cost of leptospirosis .................................. 112
4.4 Results .............................................. 118
  4.4.1 Annual number of human leptospirosis cases ........ 118
  4.4.2 DALYs .......................................... 118
  4.4.3 Human and animal cost of leptospirosis ............. 119
4.5 Discussion .......................................... 123
4.6 Conclusion .......................................... 128
4.7 Acknowledgement ..................................... 129

References ............................................. 131

5 Meta-analysis of vaccine efficacy ..................... 137
  5.1 Summary ........................................... 138
  5.2 Introduction ..................................... 140
  5.3 Materials and Methods .............................. 143
    5.3.1 Research question ........................... 143
    5.3.2 Literature search strategy .................... 143
    5.3.3 Screening of records ......................... 143
    5.3.4 Eligibility criteria .......................... 144
    5.3.5 Data extraction ................................ 144
    5.3.6 Bias assessment for individual studies ........ 144
    5.3.7 Methods for measuring shedding of leptospires in urine . 145
    5.3.8 Meta-analysis .................................. 145
    5.3.9 Software ....................................... 146
  5.4 Results ........................................... 147
    5.4.1 Selection of articles .......................... 147
    5.4.2 Data extraction and bias assessment ............ 148
    5.4.3 Meta-analysis exclusions ....................... 148
    5.4.4 Articles included in meta-analyses ............. 150
    5.4.5 Meta-analysis of vaccine efficacy assessed by culture . 150
    5.4.6 Meta-analysis of vaccine efficacy assessed by PCR .......... 152
    5.4.7 Meta-analysis of vaccine efficacy assessed by FA .......... 153
    5.4.8 Urinary shedding assessed by DFM ................ 154
  5.5 Discussion .......................................... 155
  5.6 Conclusion .......................................... 160
  5.7 Acknowledgement ..................................... 161
References

6 General discussion

6.1 Introduction .............................................. 172
6.2 Under-ascertainment of human leptospirosis ...................... 172
6.3 Occupational exposure ...................................... 174
6.4 Leptospira sero-positivity and influenza-like illness .......... 176
6.5 Burden of leptospirosis in New Zealand ......................... 177
6.6 Control of leptospirosis ...................................... 178
6.7 Methodology critiques ...................................... 181
   6.7.1 Microscopic agglutination test .......................... 181
   6.7.2 Antibody titre duration .................................. 181
   6.7.3 Recalling influenza-like illness ......................... 182
6.8 Future research ............................................ 183
   6.8.1 Leptospirosis in dairy cattle ............................ 183
   6.8.2 Leptospirosis in wildlife .................................. 183
   6.8.3 Sero-prevalence to serovars other than Hardjo-bovis and Pomona in livestock ........................................... 184
   6.8.4 Spatial analysis of animal’s serology data ............... 184
   6.8.5 Post-acute leptospirosis sequelae ......................... 185
   6.8.6 Serological surveys in other at risk occupations .......... 185
   6.8.7 Analysis of human notified cases ....................... 185

References

Appendices

.1 Appendix I: Farmer questionnaire ............................ 196
.2 Appendix II: Prevalence model .................................. 208
.3 Appendix III: Prevalence model clustering ...................... 209
.4 Appendix IV: Multivariable model ............................. 210
.5 Appendix V: Veterinarian questionnaire ......................... 215
.6 Appendix VI: Burden and cost Code ............................ 222
.7 Appendix VII: Burden and cost assumptions .................... 240
.8 Appendix VIII: Summary of trials for meta-analysis ........... 245
# List of figures

1.1 Number of notified cases 2001-2014 ........................................ 7  
1.2 Number of notified cases by serovar 2001-2014 .......................... 8  
1.3 Percentage of notified cases by occupation 2001-2014 ............... 9  
2.1 Spatial distribution of farms .................................................. 59  
2.2 MAT titre distribution ......................................................... 60  
3.1 MAT titre distribution by serovar .......................................... 88  
3.2 Percentage of time spent in contact with different animal species ... 90  
4.1 Density distribution of annual cost per 100,000 people by species ... 121  
5.1 Systematic selection of studies ............................................... 147  
5.2 Forest plot culture .............................................................. 151  
5.3 Funnel plot culture .............................................................. 152  
5.4 Forest plot PCR .............................................................. 153  
5.5 Forest plot FA .............................................................. 154
## List of tables

<table>
<thead>
<tr>
<th>Table</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1</td>
<td>Sero-prevalence in beef cattle, sheep, and deer</td>
<td>11</td>
</tr>
<tr>
<td>1.2</td>
<td>Registered vaccines</td>
<td>19</td>
</tr>
<tr>
<td>2.1</td>
<td><em>Leptospira</em> sero-prevalence</td>
<td>60</td>
</tr>
<tr>
<td>2.2</td>
<td><em>Leptospira</em> animal sero-prevalence</td>
<td>62</td>
</tr>
<tr>
<td>2.3</td>
<td>Unconditional associations</td>
<td>63</td>
</tr>
<tr>
<td>2.4</td>
<td>Multivariable model</td>
<td>65</td>
</tr>
<tr>
<td>2.5</td>
<td><em>Leptospira</em> sero-status and influenza-like illness</td>
<td>66</td>
</tr>
<tr>
<td>3.1</td>
<td>Sero-prevalence in veterinarians</td>
<td>89</td>
</tr>
<tr>
<td>3.2</td>
<td><em>Leptospira</em> sero-positivity and influenza-like illness</td>
<td>91</td>
</tr>
<tr>
<td>3.3</td>
<td>Unadjusted associations</td>
<td>92</td>
</tr>
<tr>
<td>3.4</td>
<td>Multivariable model</td>
<td>93</td>
</tr>
<tr>
<td>4.1</td>
<td>Expected annual incidence</td>
<td>118</td>
</tr>
<tr>
<td>4.2</td>
<td>DALYs</td>
<td>119</td>
</tr>
<tr>
<td>4.3</td>
<td>Cost of leptospirosis</td>
<td>120</td>
</tr>
<tr>
<td>5.1</td>
<td>Systematic bias assessment</td>
<td>149</td>
</tr>
</tbody>
</table>
xxiv

LIST OF TABLES