GASTROINTESTINAL ILLNESSES CAUSED BY MICROBES IN SYDNEY, AUSTRALIA

Stephanie M. Fletcher

Doctor of Philosophy (Science)

2013

CERTIFICATE OF ORIGINAL AUTHORSHIP

I certify that the work in this thesis has not previ	ously been submitted for a degree nor
has it been submitted as part of requirements for	a degree except as fully acknowledged
within the text.	
I also certify that the thesis has been written by r	me. Any help that I have received in my
research work and the preparation of the thesis its	self has been acknowledged. In addition,
I certify that all information sources and literature	used are indicated in the thesis.
Signature of Student	Data

Acknowledgements

I want to firstly acknowledge my Heavenly Father, Almighty God, for the wisdom, knowledge and understanding he has granted me to accomplish this task. As such, I dedicate this thesis to the countless children who die from diarrhoea; and hope that its findings, conclusions and recommendations will help to reduce the burden illness amongst the poor and disadvantaged.

I would like to express sincere gratitude to all persons who contributed in one way or another to the completion of this work. Special thanks to the following persons and institutions:

PhD-Supervisors

Professor John Ellis- UTS: Science; Principal Supervisor; Dr. Damien Stark- St. Vincent's Hospital, Sydney; Co- Supervisor; Professor David Sibbritt- UTS: Health; Co- supervisor.

External Partners and Institutions

ⁱProfessor John Harkness, the Microbiology Department and Medical Records Department, St. Vincent's Hospital, Sydney;

iiA/Professor Sebastian Van Hal and Liverpool Hospital Medical Records Department;

iiiDr. David Andresen, and the Microbiology Department, Children Hospital Westmead

Professor William Rawlinson and Mr Juan Meriff; SEALS and staff of the Medical Records

Department, Prince of Wales Hospital.

^{iv}Professor Mary-Louise McLaws, School of Public Health & Community Medicine, The University of New South Wales.

Wider community and friends

Karen Gayle, Jeniffer Harn for assistance with proof reading.

Lastly, but by no means least: Heartfelt gratitude to my Family members around the world, who have encouraged, supported and prayed for me as I made the journey from Jamaica to Australia; and continued their support over the duration of this study.

ⁱ Provided clinical guidance and interpretation of clinical data.

ii Internal Ethics approval; assistance with laboratory databases, clinical guidance and interpretation of clinical and microbiology data.

iii Assisted with internal Ethics approval; laboratory databases, clinical guidance and interpretation of clinical and microbiology data.

iv Advisor on epidemiology, biostatistics, data analysis.

Peer Reviewed Publications arising from this Thesis-

Journal Articles

- 1. **Fletcher SM**, Stark D, Ellis J. Prevalence of Gastrointestinal pathogens in Sub-Saharan Africa; Systematic Review and Meta-analysis. 2011. J Pub Health Africa. 2(e30):127-37. Epub 2011 September 05.
- 2. **Fletcher SM**, Stark D, Harkness J, Ellis J. Enteric Protozoa in the Developed World: a Public Health Perspective. 2012. Clin Microbiol Rev. 25 (3):420-49.
- 3. **Fletcher SM**, Van Hal S, Andresen D, McLaws M-L, Stark D, Harkness J, Ellis J. Gastrointestinal pathogen distribution in symptomatic children in Sydney, Australia. 2013. J Epidemiol Global Health. 3(1);10.1016/j.jegh.2012.11.004.
- 4. Fletcher SM, McLaws M-L, Ellis J.(2013) Systematic review of the prevalence of gastrointestinal pathogens worldwide; Journal of Public Health Research, *IN PRESS* (accepted 14 May 2013).

Conference Abstracts and Presentations

- 1. **Fletcher SM**, Stark D, Ellis J. 2010. Enteric Pathogens in Sub-Saharan Africa: Environmental Health Implications: Systematic Review 2nd IFEH Africa Group All Africa Environmental Health Congress 2010; May 24-27, 2010; Cross Roads Hotel, Lilongwe, Malawi. (Oral)
- 2. **Fletcher SM**, Stark D, Ellis J, Harkness J. 2010. Gastrointestinal Illness caused by Microbes. A study of Hospitalised patients in Sydney, Australia. 74th Annual Educational Conference (AEC) & Exhibition 2010 June 6-9, 2010; June 6-9, 2010; Albuquerque, New Mexico, USA.: National Environmental Health Association, 720 S Colorado Blvd., Suite 1000-N, Denver, CO 80246-1926. (Oral)
- 3. **Fletcher SM**, Stark D, Ellis J, Harkness J. 2010. Etiology of Gastrointestinal Illness in patients in Sydney. 74th Annual Educational Conference (AEC) & Exhibition 2010 June 6-9, 2010; 2010 June 6-9, 2010; Albuquerque, New Mexico, USA.: National Environmental Health Association, 720 S Colorado Blvd., Suite 1000-N, Denver, CO 80246-1926. (Oral)
- 4. **Fletcher SM**, Stark D, Ellis J, Harkness J. 2010. Gastrointestinal Illness caused by Microbes. A study of Hospitalised patients in Sydney, Australia. The 26th RNSH-UTS-USyd-Kolling's Scientific Research Meeting; 9-10 November 2010; Kolling Institute, St. Leonards, Australia: RNSH-UTS-USyd-Kolling's Scientific Research Meeting. (Poster)
- 5. **Fletcher SM**, Li Y, Stark D, Ellis J. 2011. Infectious Gastrointestinal Pathogens in Developed and Developing Countries: a Meta-Analysis. Communicable Disease Control Conference Canberra, ACT; 4 -6 April 2011: Public Health Association of Australia. p. 71. (Poster)
- 6. **Fletcher SM**, Li Y, McLaws M-L, Stark D, Ellis J. 2011. Infectious Gastrointestinal Pathogens in Developed and Developing Countries: a Meta-Analysis. 2nd International

- Scientific Conference; 2-4 November 2011; Port Dickson, Malaysia: Masterskill University College of Health Sciences. (Poster)
- 7. **Fletcher SM**, Stark D, Harkness J, Ellis J. 2011. Food and water-borne protozoa: current considerations for public health. 2nd International Scientific Conference; 2-4 November 2011; Port Dickson, Malaysia: Masterskill University College of Health Sciences. (Oral)
- 8. **Fletcher SM**, Li Y, Stark D, McLaws M-L, Ellis J. 2011. Infectious Gastrointestinal Pathogens in Developed and Developing Countries Worldwide: a Meta-Analysis 7th World Congress of the World Society of Pediatric Infectious Diseases; 16-19 November 2011; Melbourne, Victoria, Australia: World Society of Pediatric Infectious Diseases. p. 9. (Oral)
- 9. **Fletcher SM**, Stark D, Li Y, McLaws M-L, Ellis J. 2011. Prevalence of Gastrointestinal Pathogens in Developed and Developing Countries: a Meta-Analysis 7th World Congress of the World Society for Pediatric Infectious Diseases WSPID 2011; 16-19 November, 2011; Melbourne, Australia: World Society for Pediatric Infectious Diseases. (Poster)
- 10. **Fletcher SM**, Van Hal S, Andresen D, McLaws M-L, Stark D, Harkness J, Ellis J. 2012. Childhood Diarrhoea in Sydney, Post Implementation of Universal Rotavirus Vaccination 2012 ASID Annual Scientific Meeting; 21-25 March 2012; Fremantle, Western Australia: The Australasian Society for Infectious Diseases (ASID). (Poster)
- 11. **Fletcher SM**, Stark D, Harkness J, Ellis J. 2012. Water and Foodborne Enteric Protozoa: Current Considerations for Environmental Health. 76th Annual Educational Conference (AEC) & Exhibition 2012 June 28-30, 2012; San Diego, California: National Environmental Health Association, USA. (Oral)
- 12. **Fletcher SM**, Van Hal S, Andresen D, McLaws M-L, Stark D, Harkness J, Ellis J. 2012. Childhood Diarrhoea in Sydney, Post Implementation of Universal Rotavirus Vaccination 76th Annual Educational Conference (AEC) & Exhibition 28-30 June 2012; San Diego, California: National Environmental Health Association, USA. (Poster)
- 13. **Fletcher SM**, Li Y, Stark D, Ellis J. 2012. Infectious Gastrointestinal Pathogens in Developed and Developing Countries: a Meta-Analysis 76th Annual Educational Conference (AEC) & Exhibition 2012 June 28-30, 2012; San Diego, California: National Environmental Health Association, USA. (Poster)
- 14. **Fletcher S,** Caprarelli G, Meriff J, Andresen D, Van Hal S, Stark D. & Ellis JT. 2013, 'Geographical Distribution and Epidemiology of Enteric Protozoan Infections in Sydney: A multicentre Study.', paper presented to the Communicable Disease Conference, Canberra, ACT. (Poster)
- 15. **Fletcher S**, Andresen D, Van Hal S, Meriff J, Harkness J, Stark D. & Ellis, J. 2013, 'Comparison of Algorithms Used to Diagnose Enteric Protozoan Infections: Towards Determination of a Gold Standard.', paper presented to the Communicable Disease Conference, Canberra, ACT. (Poster)
- 16. **Fletcher S**, Van Hal S, Andresen D, McLaws M-L, Stark D, Harkness J. & Ellis J. 2013, 'Childhood Diarrhoea in Sydney, Post Implementation of Universal Rotavirus Vaccination', paper presented to the Communicable Disease Conference, Canberra, ACT, 21-25 March 2012. (Oral and poster)

Table of Contents

Τā	able of	Con	tents	٧
Li	st of Ta	bles		viii
Li	st of Fig	gure	S	ix
Li	st of Bo	xes		ix
E>	ecutive	e Su	mmary	×
1	Gen	eral	Introduction	1
	1.1	Ove	rview of the Health Status and Health Care System in Australia	1
	1.2	Hea	Ith seeking behaviour in Australia	3
	1.3	Gas	trointestinal Illnesses Surveillance in New South Wales State	4
	1.4 Estimating Disease Burden		mating Disease Burden	6
	1.5	Ove	rview of the study	7
	1.5.	1	Why hospitalised patients?	7
	1.5.	2	Study sites	
	1.5.	3	Research Ethics	9
			line of the Thesis	
2	•		tic Review of the Prevalence of Gastrointestinal Pathogens Worldwide	
	2.1		tract	
	2.2		oduction	
	2.3		rview of Gastrointestinal Illness	
	2.4		nition of 'gastrointestinal illness'	
	2.5		ease transmission and risk factors	
	2.6	Met	hods	
	2.6.		Search strategy	
	2.6.	2	Eligibility and study selection criteria	
	2.6.	3	Data abstraction and analysis	
	2.6.		Analysis and synthesis of results	
			mating the prevalence of gastrointestinal pathogens	
	2.7.	1	Description of studies	
	2.7.	2	Overall detection of pathogens	
	2.7.		Regional Distribution of Enteric Pathogens	
			ussion	
			Conclusions and Policy implications	
3	-		ology and Clinical Profile of Gastrointestinal Illnesses in Sydney	
	3.2		tract	
	3.3		oduction	
	3.4		hods	
	3.4.		Study sites	
	3.4.		Laboratory methods (to add Methods from Revised chapter 2 and 4)	
	3.4.		Patient data collection and analysis	
	3.4.		Statistical analysis:	
	3.5		ults	
	3.5.	1	Demographic and clinical characteristics	49

	3.5.	2	Pathogens associated with diarrhoea	
	3.5.	3	Relationship between pathogens and disease risk factors	59
3	3.6	Disc	ussion	64
	3.6.	_	Conclusion	
4	Gas	troir	itestinal pathogen distribution in symptomatic children in Sydney, Austra	ilia70
4	.1	Abst	tract	71
4	.2	Intro	oduction	73
4	.3	Met	hods	75
	4.3.	1	Study setting	75
	4.3.	2	Microbiology methods	76
	4.3.	3	Medical record review	77
	4.3.	4	Statistical methods	78
4	.4	Resu	ults	80
	4.4.	1	Demographics	80
	4.4.	2	Clinical profile	80
	4.4.	3	Pathogen distribution	82
	Sea	sona	l distributionl	90
	4.4.	4	Management and Treatment of Diarrhoea	90
4	.5	Disc	ussion	92
	4.5.	1	Limitations	95
	4.5.	2	Conclusion	96
5	Con	npari	ison of algorithms used to diagnose enteric protozoan infections: toward	S
det	ermir	natio	n of a gold standard	97
5	5.1	Abst	tract	98
5	5.2	Intro	oduction	. 100
Ν	/lethc	ods		. 102
	5.2.	1	Setting and Study Sites	. 102
	5.2.	2	Microbiology methods	. 102
	5.2.	3	Data extraction and analysis	. 105
5	5.3	Resu	ults	. 106
	5.3.	1	Enteric Parasites Summary	. 106
	5.3.	2	Comparison of Results based on Testing Algorithms	. 112
5	5.4	Disc	ussion	. 118
	5.4.	1	Conclusions	. 124
6	Geo	grap	phical distribution and epidemiology of enteric protozoan infections in	
Syd	ney:	Αmι	ulticentre study	. 126
6	5.1	Abst	tract	. 127
6	5.2	Intro	oduction	. 129
6	5.3		hods	
	6.3.		Microbiological methods	
	6.3.		Data description and analysis	
6	5.4		ults	
	6.4.		Clinical and epidemiological profile	
			Spatial distribution	

6.5	Discussion.	. 151
6.5	5.1 Conclusion	. 155
7 Su	mmary and Recommendations	. 156
7.1	Children	. 158
7.2	Older children/adults	. 159
7.3	Pathogens and Risk factors	. 160
7.4	Limitations	. 163
7.5	Conclusion	. 164
8 Re	ferences	. 165
9 Ap	pendices and Supplementary Tables	. 192
9.1	Appendix 1: SURVEY QUESTIONNAIRE	. 208
9.2	Appendix 2: LABORATORY SURVEY	. 213

List of Tables

Table 1-1: Australia National hospital separations for ICD-10-AM categories (A00–B99),
2008/09 and 2009/10 6
Table 2-1: Age specific and source related regional estimate of overall pathogen detection
25
Table 2-2: Weighted average prevalence of enteric pathogens from children 0-12 years in
developing regions and OECD countries27
Table 2-3: Weighted average prevalence of enteric pathogens from older children/adults
>12 years in developing regions and OECD countries
Table 3-1: Distribution of diarrhoeal cases based on specimen tested and sample
reviewed¶ in the four study sites
Table 3-2: Distribution of cases from the four hospitals based on age and gender 50
Table 3-3: Age distribution of diarrhoea cases based on gender, clinical profile and
pathogens detected 51
Table 3-4: Distribution of bacterial and viral pathogens based on clinical and risk factors in
diarrhoea cases in Sydney, 2007-2010 57
Table 3-5: Association between selected pathogens, demographic, clinical and other risk
factors
Table 4-1: Total cases tested for enteric pathogen in 0-5 years old children in two hospitals
2007-2010, Sydney
Table 4-2: Summary of clinical findings associated with diarrhoea in 0-5 years old children.
81
Table 4-3: Comparison of rate of enteric pathogens isolated from 0-5 years old children in
two hospitals83
Table 4-4: Prevalence of (A) single enteric pathogens and (B) multiple enteric pathogens in
children 0-5 years in Sydney 2007-2010
Table 4-5: Adjusted Odds Ratio of the association between enteric pathogen and age
group in children
Table 4-6: Relationship between enteric pathogen, clinical signs and symptoms in
hospitalised children, 2007-2010
Table 5-1: Overall prevalence of enteric protozoa from Cyst, Ova and Parasite test,
Hospital A, 2007-2010
Table 5-2: Overall prevalence of enteric protozoa from Cyst, Ova and Parasite test,
Hospital B 2007-2010 109
Table 5-3: Overall prevalence of enteric protozoa from Cyst, Ova and Parasite test,
Hospital C for 20008-2010 110
Table 5-4: Overall prevalence of enteric protozoa from Cyst, Ova and Parasite test,
Hospital D for 2007-2010 111
Table 5-5: Prevalence of enteric protozoa based on microbiology test in four hospitals in
Sydney
Table 5-6: Mean difference in protozoa detection rates amongst four Sydney Hospitals 117
Table 6-1: Distribution of cases and specimen tested in the four study sites
Table 6-2: Demographic and clinical characteristics of diarrhoeal cases by Hospitals 140

Table 6-3: Age specific distribution of cases based on demographic, clinical signs and protozoa detected
Supplementary Table 9-3: Summary of Enteric protozoa, Laboratory Tests, and frequency with which tests are conducted in four Sydney Hospitals
List of Figures
Figure 3-1: Age-distribution of patients with enteric bacteria and viruses diagnosed in diarrhoeal cases in Sydney
Figure 3-2: Seasonal distribution of (A) Bacterial pathogens and (B) Viral pathogens associated with diarrhoea
Figure 4-1: Age distribution of viral pathogens associated with childhood diarrhoea in Sydney, 2007-2010
Figure 4-2: Monthly distribution of viral pathogens associated with childhood diarrhoea in Sydney, 2007-2010
Figure 5-1: Prevalence of Cryptosporidium spp., Giardia intestinalis, Blastocystis, and Dientamoeba fragilis based on Microbiology tests conducted at Four Sydney Hospitals 2007-2010
Figure 6-1: Flow diagram showing the distribution of cases based on gender, age and protozoa detected
Figure 6-2: Distribution of protozoa cases based on age and gender (A), age groups (B), and gender and protozoa detected (C)
Figure 6-3: Map of NSW showing distribution of number of cases affected by the five enteric protozoa: Blastocystis (A), Giardia (B), Cryptosporidium (C), Dientamoeba (D), and Cyclospora (E). Note the change of scale in (F) zooming in on Cyclospora cases in Sydney
CBD. Colours represent number of cases
List of Boxes
Box 1: Definition of 'gastrointestinal illness'

Executive Summary

Gastrointestinal illness (GIT) is a leading cause of preventable illness and death worldwide. Only a few studies provide estimates of the prevalence of pathogens associated with GIT illnesses in developed countries. In Australia, there are an estimated 17.2 million cases of GIT occur annually, however, the disease surveillance system only captures a few GIT illnesses, and the majority of pathogens causing illness are unknown. This study therefore seeks to fill this gap in knowledge by providing an overview of the epidemiology and prevalence of specific pathogens, clinical characteristics and risk factor for disease among hospitalised patients in Sydney, Australia.

Chapter One is a general overview which seeks to provide background and context for this study. The chapter sets the study in the Australian context in terms of the health system, infectious disease surveillance, health seeking behaviour and related determinants and also provides some perspective on why a hospital based study was conducted. An overview of the study sites is also provided.

In order to set the broad context for the topic, a systematic review of the literature is presented in Chapter Two. It provides age- and region-specific random-effect estimates of the detection rates of diarrhoeal pathogens in developed and developing settings. The review outlines that developing regions have significantly more pathogens detected than the OECD countries, and individual pathogen prevalence differs between developed and developing settings.

Chapter Three outlines a retrospective cross-sectional survey of laboratory and clinical records for patients seen at four major public hospitals in Sydney, from January 2007 to December 2010. The aim was to describe the clinical and epidemiological characteristics of GIT illnesses, in symptomatic patients presenting to hospital in Sydney. The chapter describes and discusses the prevalence of several viral, bacterial and protozoan pathogens that cause GIT illnesses in older children/adults and children, and associated risk factors.

In Chapter Four, a similar approach is used to describe the distribution of gastrointestinal pathogens in symptomatic children 0-5 years old in Sydney. It presents the clinical features and prevalence of pathogens associated with gastrointestinal illnesses for children 0-5 years old, presenting to two major public hospitals in Sydney with diarrhoea, for the period January 2007-December 2010.

An in-depth analysis of enteric protozoa was undertaken in Chapters Five and Six since enteric protozoa were frequently implicated in diarrhoeal illness and there is limited information about their epidemiology in Australia. Chapter Five evaluates the prevalence of enteric protozoa based on testing algorithms used to diagnose enteric protozoan infections in four hospitals, and suggest that a gold standard approach is needed. Chapter Six then incorporates spatial analysis to describe the epidemiology and geographical distribution of enteric protozoa in the state of New South Wales (NSW). Chapter Seven concludes with a discussion of the implications of the main findings and proposes recommendations to address them.