An investigation of the barriers to infectious disease interventions in Indigenous Australian communities

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Statement of the Contribution of Others

Nature of Assistance	Contribution	Names, Titles and Affiliations of Co-Contributors
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Co-investigator and co-author	Assisted in publications including data analysis	Professor Jenni Judd, Central Queensland University
Co-investigator and co-author	Led and assisted in publications	Professor David Durrheim, NSW Ministry of Health and University of Newcastle
Co-investigator and co-author	Led and assisted in publications	Professor Sherry Saggers, Curtin University
Co-author	Led and assisted in publications	Professor Michael Evans, University of British Columbia
Led and assisted in publications	Led and assisted in publications including data analysis	Professor Peter Doherty, University of Melbourne
Led and assisted in publications	Led and assisted in publications including data analysis	Professor Katherine Kedzierska, University of Melbourne
Led and assisted in publications	Led and assisted in publications including data analysis	Associate Professor Steven Tong, University of Melbourne
Led and assisted in publications	Led and assisted in publications	Associate Professor Peter Massey, NSW Ministry of Health and University of Newcastle
Co-author	Led and assisted in publications	Dr Keith Eastwood, NSW Ministry of Health
Co-author	Assisted in publications, data collection and analysis and the coordination of the influenza study	Dr Jenny Kelly, University of Queensland
Co-investigator and co-author	Assisted in publications and community and health service engagement	Dr Carmel Nelson, Institute of Urban Indigenous Health

Research Officer (WA)	Assisted in data collection, data analysis and community and health service engagement	Ms Jean Roberts, Kimberley Aboriginal Medical Service Council
Research Officer (NSW)	Assisted in data collection, data analysis and community and health service engagement. Co-contributor to publications	Ms Kylie Taylor, NSW Ministry of Health
Research Officer (NSW)	Assisted in data collection, data analysis and community and health service engagement. Co-contributor to publications	Mr Glenn Pearce, NSW Ministry of Health
Research Officer (Strongyloides study)	Assisted in data collection, data analysis and co-author to publications	Professor Michelle Smith, University of Alberta
Research Officer (Strongyloides study)	Assisted in data collection, community engagement and co-author to a publication	Ms Melody Muscat, University of the Sunshine Coast
Research Assistant (Palm Island)	Assisted in data collection, community engagement and co-author to a publication	Mrs Magdalena Blackley, Palm Island Community
Research Assistant (Torres Straits)	Assisted in data collection and community engagement	Ms Susan Reilly, James Cook University
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Research Assistant (QLD)		Assisted in data collection, data analysis, community engagement, and co-author	Ms Jennifer Broome, Mamu Aboriginal Medical Service Inc
Co-author		Led and assisted in publications	Dr Wendy Page, Miwatj Health Corporation
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Abstract

This research uses qualitative methods to investigate barriers to infectious diseases in Indigenous Australian communities using two infectious diseases as examplars; strongyloidiasis (ICD B78.9) and swine influenza, H1N1 (ICD J10.1) that caused a pandemic in 2009. An infection with *Strongyloides stercoralis*, a parasitic intestinal worm causing a disease- strongyloidiasis, is not a notifiable disease in Australia. Alternatively, the influenza A strain known as H1N9p2009 is a notifiable disease within the Australian health care system.

The purpose of using these diseases as exemplars is to provide a better understanding of barriers to effective interventions for infectious diseases in selected Indigenous Australian communities in two studies – Strongyloides and Influenza H1N1. This thesis focuses on addressing three research questions. These are:

1. What are, and have been, the barriers that have prevented effective of control and treatment of Strongyloides and H1N1 swine influenza in Indigenous Australian communities?
2. How are these barriers understood and articulated by Aboriginal communities/people, health staff and researchers? and
3. How does the outcome of this research inform Indigenous communities, researchers and public health policy makers about the barriers of controlling infectious diseases in Indigenous communities?

Two studies based on the exemplars were undertaken for this research is and presented in publications as book chapters and peer reviewed journals to form the structure of the thesis. There are 3 book chapters and 11 peer reviewed journal articles; 11 publications are core to this thesis and 3 articles are extensions to the influenza part of this study. The purpose of including the extension research is to highlight the biological and immunological barriers within Indigenous peoples for influenza prevention and treatment.

The Strongyloides study and related articles used qualitative methods to investigate the views and perspectives of Indigenous community members, health professionals and researchers to the barriers of controlling and treating Strongyloides in Indigenous Australian communities. Interviews were undertaken using purposive sampling, qualitative data was recorded and verified with participants and thematically analysed. The findings were categorised into major and sub themes.

The influenza H1N1 study applied a PAR framework to better understand community members' perceptions and risks of pandemic influenza. The outcome of using a qualitative PAR framework was an effective way to gain depth of knowledge and understandings from participants. Aboriginal and Torres Strait Islander community controlled organisations and health services were involved in the implementation, interpretation and monitoring of the project. As a result, novel features of PAR with Aboriginal and Torres Strait Islander communities and organisations emerged. These novel features included the importance of working in a multi-disciplinary team with Aboriginal and Torres Strait Islander researchers; the complexities and importance of obtaining multi-site human research ethics approval processes; the importance and value of building the research capacity of both experienced and novice researchers in PAR; the need to use localised sampling protocols; and the process of undertaking a collective research process and enacting action research and feedback. The most effective responses of this project are in pre-existing relationships that had been established over a long period between Aboriginal medical services and investigators while research relationships established specifically for the purposes of the project, were less successful.

Key messages were drawn from publications in this thesis and five principles were developed to improve ways to address the barriers for infectious disease intervention in Indigenous communities. These are:

1. Increase knowledge and information about the diagnosis and treatment of the disease and share this information with communities.
2. Collaboratively work with local leadership to support a community-driven model that has genuine and respectful partnerships between local Indigenous people, health professionals and government agencies.
3. Develop and adopt effective communication strategies to share knowledge and information about infectious diseases to different stakeholders in order to respond effectively.
4. Plan, develop and implement public policy about infectious disease interventions that addresses institutionalised racism and incorporates local Indigenous knowledge.
5. Indigenous engagement strategies must identify and use pre-existing relationships and incorporates Indigenous people's values.

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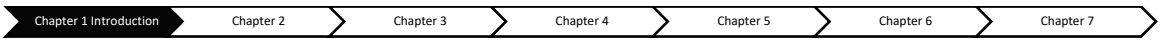
Chapter. 1 Introduction



1.1 Chapter Brief

In order to gain an appropriate perspective of this thesis, it's important that I provide the context of this research from my perspective as an Indigenous researcher. This chapter aims to provide this context by detailing my research journey based on my background and family history. An overview of the structure of the thesis is included to show the sequence of chapters with published papers as well as details on my contribution and co-authors. Also included is information about how this research was funded, ethics approvals, the location of research sites and other outputs from the research. The conclusion to the chapter provides further context to my research journey and features the key messages that have been the primary outcome of this research.

1.2 Context

I am Jirrbal from North Queensland and I follow my grandfather Jutungy's (John Thomas Grant), cultural lineage, and my grandmother, Bubbumurry (Chloe Grant) who was Girramay. My mother Billimba (Irene Miller) always told us who we were and where we came from. It is from this lineage I am able to provide context to this thesis and from my perspective as an Aboriginal person undertaking qualitative research. My father, Clarence Miller, was from New Zealand and a veteran of two tours of military service for the New Zealand Army Corps and the New Zealand Air Force during World War II. He immigrated to Australia in the 1950's, married mum and they had six children together. He left us in 1975 when I was five years old to live mostly alone, in the bush as a miner, for the remainder of his life.

Photo (Right to Left) – My father Clarence (decd. 2011) holding my eldest brother Ken (decd. 2019), Irene (Bilimba decd. 2013), Aunty Bonnie holding my cousin Stanley (Mum's sister-in-law), cousins Glenda and Edna (Mugunarn decd.), Aunty Emily (Mum's cousin) and my Grandmother Chloe (Bubbumurry decd. 1974)

My mother and grandmother are the most inspirational figures in my life having both lived through Queensland Protectionist era – Copies of my grandparent's Exemption Certificates from the *Aboriginals Protection and Restriction of the Sale of Opium Act 1897* issued by the Protector of Aborigines are a reminder of the inhumane law and policies forced upon my family (see Attachment 1). Despite facing incredible social and economic challenges, my mother believed in the power of books and with her understanding of knowledge brings change, she ensured we had access to a set of encyclopaedias during our schooling. My mother's want of a better future for us kids, sparked my desire to learn. I distinctly remember when I was fifteen, I took myself off to the local council library and began my first library search to see if there was any information about my people. I came upon a section of books about Aboriginal people and started sifting through the titles on the spine of the books. A book titled "Searching for Aboriginal Languages – Memoirs of a Field Worker" by Bob Dixon (Dixon, 1984) stood out. Bob Dixon's name sounded familiar and I recollected from conversations I overheard between my mother and my Uncle - Ernie Grant - that he had something to do with our family. I opened the first few pages and I was immediately struck in disbelief as a photograph of my grandmother and Aunty Mamie Grant - who was married to my eldest Uncle Edgar Grant (Mugu decd.) - stared up at me. A rush of emotion came over me, my eyes welled up and I became overwhelmed – a moment I won't forget - as I couldn't believe that my family was featured in a book.

Photo - Aunty Mamie Grant (decd.) and my Grandmother, Chloe Grant (Source: Dixon 1984)

A book I didn't know existed and I immediately thought, did anyone else in my family know? I rushed to the librarian to share my excitement about my discovery and asked to take the book out. As this was my first time in a library, she helped me arrange a borrowing card and explained all that was needed to know about borrowing and returning books.

"Searching for Aboriginal Languages – Memoirs of a Field Worker" evolved through the work of Bob Dixon's study of Aboriginal languages in Australia. He arrived in 1963 and spent the next fourteen years documenting and studying Aboriginal languages and dialects of the rainforest region of North Queensland.

It was through grandmother Bubbumurry's (Chloe) understanding of the changing complexities of her family's future language survival and her vision to document the Jirrbal and Girramay dialects, she endorsed Bob Dixon's work in recording all of our Dyirbal language. Bob Dixon and Grandmother Bubbumurry's work is a legacy for my family and all Jirrbal people. Before completely retiring, Professor Bob Dixon along with Uncle Ernie, generously gave of their time to review my PhD proposal with particular reference to my planned methodology chapter and the use of specific Dyirbal words – Jirrbal means people and Dyirbal refers to language. Both scholars confirmed this was in context with language and culture.

The context and motivation for this research centres around my deep commitment to addressing health inequalities between Indigenous and non-Indigenous Australians. I began my research journey late in my career as I was propelled into senior leadership roles as a junior academic. Having survived these roles early in my career, I spent almost ten years building my teaching capacity in mainstream higher education and quickly reached a level of proficiency. I was awarded two national teaching awards through the Australasian College of Educators, 2008 and 2010 respectively.

During this time however, constant racialised criticism by some students enrolled in my subjects, compelled me to build a level of resilience towards the misconceptions and misunderstandings about my teaching and place in academia. Despite this weighing heavily on me, I was successful in being awarded teaching research grants

and felt this was my way forward in academia. I approached my academic supervisor at the time and asked how I should progress into a stronger research trajectory.

In 2006 I was invited to become a member of a team of Indigenous scholars on a NHMRC research capacity building grant entitled "*Building Indigenous Research Capacity in Indigenous Australians and community controlled health services*". The grant was led by chief investigators who had a strong interest in developing research capacity in both immerging Indigenous researchers and community controlled organisations.

Photo - Building Indigenous Research Capacity Scholars, Chief Investigators, mentors and family

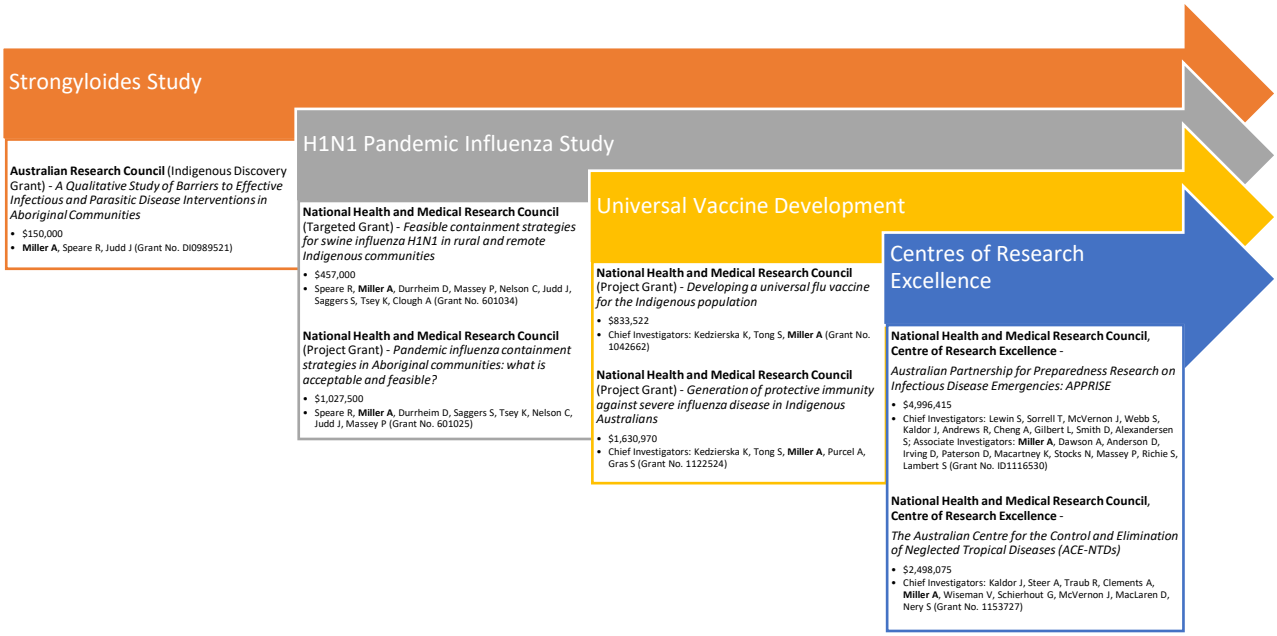
This experience had a profound impact on my career which led me to my first grant awarded by the Australian Research Council, and Indigenous Discovery grant (Grant No. 0989521) and in 2009. This success continued after being granted two National Health and Medical Research Council grants (Grant No. 601034 and 601025) - all three grants have supported this PhD research. I have been very fortunate to be successful in a series of collaborative grants which has helped me to secure senior positions in universities. As a result, I have collaboratively published in a range of research fields beyond this thesis.

I currently hold the position of Pro Vice-Chancellor Indigenous Engagement and BHP Chair in Indigenous Engagement at Central Queensland University. My most recent appointment was Pro Vice-Chancellor Indigenous Leadership at Charles Darwin University. Other positions I've held include Academic Director of Indigenous Education and Research and Professor of Indigenous Research at Griffith University, Professor and Head of School at Southern Cross University, Founding Head of the Department of Indigenous Studies at Macquarie University and Deputy Head of School at James Cook University. During the past twenty three years in higher education, I have had experience in senior and executive management and leadership, academic program development, teaching and research. My research track record in competitive grants totals around twenty million dollars.

This thesis is the impetus of an ongoing program of research (See Figure 1.1) that began in 2008 in which I took the major lead in design, implementation, analysis and writing. In the thesis I have personally analysed the sum of the work with a critical perspective providing innovative perspectives on Indigenous research (See Table 1.4). The original research concept of investigating barriers to controlling infectious diseases in Indigenous communities was supported by three successful grants. Some of the research papers resulting from these grants are included in this thesis. The impact from this body of work in the Influenza H1N1 study, is demonstrated through it informing changes to the Australian Health Management for Pandemic Planning and the Queensland Health Influenza and Pandemic Plan for Indigenous communities.

Although not part of this research nor what I am presenting as my PhD thesis, health departments recorded a disproportionate amount of morbidity and mortality between Indigenous and non-Indigenous people during 2009H1N1 pandemic. As a result, I was invited to collaborate on further research with University of Melbourne's Doherty Institute. This collaboration resulted in another two successful NHMRC project grants (Grants No's 1042662 and 1122524). Three papers from these grants are included as an extension in this thesis (See Table 1.1) to demonstrate how immunological factors contribute to adverse outcomes for Indigenous people infected with H1N1 Influenza and the need for improved vaccination effectiveness and for a different approach to research. My roles on these grants were to provide leadership, guidance and advice on Indigenous research ethics, protocols and cultural engagement for research translation. As a consequence of co-leading these grants, I've had the incredible opportunity to publish with Nobel Prize winner, Professor Peter Doherty.

Figure 1.1. Program of Research



The latest addition to the program of research are two successful NHMRC Centre's of Research Excellence (Grant No's: 1116530 and 1153727). The research pillars of these Centre's include Strongyloides and Influenza as areas for further research. My role on both grants is to continue to provide leadership, guidance and advice on research design, Indigenous research ethics, protocols and cultural engagement for research translation.

1.3 Research Questions

My PhD research uses qualitative research methods that forms the basis of this research to focus on two infectious diseases strongyloidiasis and swine influenza, H1N1 that caused a pandemic in 2009. An infection with *Strongyloides stercoralis*, a parasitic worm causing a disease called strongyloidiasis, is not a notifiable disease in Australia, whereas, influenza (H1N9p2009) is within the Australian health care system. This research aimed to use these two diseases, one endemic and chronic, the other, acute, to provide an understanding of barriers to effective interventions for infectious and parasitic diseases in selected Indigenous Australian communities.

This thesis focuses on addressing three research questions.

1. What are, and have been, the barriers that have prevented effective of control and treatment of Strongyloides and H1N1 swine influenza in Indigenous Australian communities?
2. How are these barriers understood and articulated by Aboriginal communities/people, health staff and researchers?
3. How does the outcome of this research inform Indigenous communities, researchers and public health policy makers about the barriers of controlling infectious diseases in Indigenous communities?

Two studies based on the exemplars were undertaken for this research and is presented in publications as book chapters and peer reviewed journals to form the structure of the thesis. I have used a chapter diagram located at the top of the first page of each chapter to help guide the reader.

1.4 Thesis Chapter Structure

This thesis as displayed in Table 1.1, is structured around 14 publications, 11 core articles and 3 illustrative extension outputs of the original research. There are 3 book chapters, and 11 peer reviewed journal articles published in Australia and internationally. There are also 17 conference presentations listed at the end of this chapter to highlight how I have disseminated this research. Also, community presentations, community reports and media coverage of this research added to the significant outcomes of this research. The chapter order is to provide an overview of the health status of Aboriginal and Torres Strait Islander people, in-depth detail on the two infectious diseases as exemplars for the research, the methodology that was used to study these diseases and the results and findings chapters. Finally, a conclusion chapter to highlight key messages resulting from the research and from the approach and critical analysis I have used as an Indigenous person, a community leader and an experienced researcher.

Table 1.1 Thesis structure

Chapter and Title	Publications	Details
1. Introduction	Context Research Questions Thesis Structure Publication Contribution Funding and Ethics Approvals	This chapter provides an overview of my role and outlines the research questions, describes the structure of the thesis, how each chapter is presented, and provides detail on the research questions, funding for the research, ethics approvals, research sites and other research outputs results from this research.
2. Background	2.1 **Miller A** & Speare R. Health Care for Indigenous Australians, Ch12 in Willis, E. & Reynolds, L. Eds *Understanding the Australian Health Care System Second Edition*. Elsevier: Australia, 2012.	This chapter provides an overview of the main health conditions that play a significant role in the overall health status of Indigenous peoples. This chapter also demonstrates the public policies that impacted Indigenous health status, including infectious diseases, despite the accessibility to effective treatment. The published book chapter presented in this thesis provides the general context of the health of Indigenous Australians. The book chapter presented is the second edition following major restructure of the

3. The Exemplars: Strongyloides and H1N1 Influenza

Strongyloides

3.1 Page W, Shield J, O'Donahoo F, **Miller A**, Judd J, Speare R. Strongyloidiasis in Oceania. Chapter 3 in Ed. A. Loukas. *Neglected Tropical Diseases - Oceania*. Springer, SPi Global. 69-99, 2016.

3.2 **Miller A**, Smith ML, Judd JA, Speare R. *Strongyloides stercoralis*: Systematic Review of Barriers to Controlling Strongyloidiasis for Australian Indigenous Communities. *PLoS Neg. Trop. Dis.* 8(9) e3141, 2014.

3.3 Speare R, **Miller A**, Page W. Strongyloidiasis: a case for notification in Australia? *The Medical Journal of Australia,* 202 (10)523-524, 2015.

H1N1 Influenza

a. **Miller A** & Durrheim D. Aboriginal and Torres Strait Islander communities forgotten in new Australian Pandemic

first publication published in 2009 in which I led the writing.

The research for this thesis centres around two infectious diseases, one caused by a parasitic infection of Strongyloides and the other a virus, a pandemic influenza strain known as swine flu H1N1. The papers in this chapter provide details on the nature of these diseases, public policy issues and the social and cultural context surrounding the barriers to treatment and controlling them in Indigenous communities in Australia.

Action Plan: ‘Ask us, listen to us, share with us’. *The Medical Journal of Australia*, 193 (6)316-317, 2010.

3.5 Massey PD, **Miller A**, Durrheim DN, Speare R, Saggers S, Eastwood K. Pandemic influenza containment and the cultural and social context of Indigenous communities. *Rural and Remote Health* 9 (online), 1179, 2009.

Extension on Research

3.6 Qui Quinones-Parra S, Grant EJ, Loh L, Nguyen THO, Campbell K, Tong S, Miller A, Doherty PC, Vijaykrishna D, Rossjohn J, Gras S, Kedzierska K. Pre-existing CD8+ T cell immunity to the novel H7N9 influenza A virus varies across ethnicities. *PNAS*, Vol. 111, (3)1049-1054, 2014.

There is an additional paper (3.6) that shows an extension of the original research into a complementary study examining bio-medical barriers to protection from new strands of pandemic influenza and its impact on Indigenous populations in Australia, New Zealand and Alaska. This paper is included to show the relevance of the work, the influence my research approach has already had on imagining understandings of and responses to infectious diseases in Indigenous communities by proposing to improve vaccination effectiveness specifically for

			Indigenous populations, and hence the contribution of my work to global health.
4.	Methodology and Methods	4.1 Evans M, **Miller A**, Hutchinson P & Dingwall C. "De-Colonizing Research Practice: Indigenous Methodologies, Aboriginal Methods, and Knowledge/Knowing", in *Oxford Handbook of Qualitative Research*. Patricia Leavy (ed.) New York: NY, Oxford University Press, 179-191, June 2014. 4.2 **Miller A**, Massey PD, Judd JA, Kelly J, Durrheim DN, Clough AR, Speare R, Sagger S. A methodology for listening to Aboriginal and Torres Strait Islander people in Australia about Pandemic Influenza. *Rural and Remote Health,* (15) 2923, 2015.	This chapter details the methodology used in this research and published in an international textbook on qualitative research methods, and a peer reviewed journal article.

5.	Findings: Strongyloides	5.1 **Miller A**, Smith ML Judd JA, Speare R. Policy implications for controlling communicable diseases in Indigenous Communities: Case of Strongyloidiasis in Australia. *Aboriginal Policy Studies*, 7(1) 148-179, 2018. 5.2 **Miller A,** Young EL, Tye V, Cody R, Muscat M, Sanders V, Smith ML, Judd JA, Speare R. A community-directed integrated *Strongyloides* control program in Queensland, Australia. Control of Communicable Diseases in Human and Animal Populations: 70th Anniversary Year of the Birth of Professor Rick Speare (2 August 1947 – 5 June 2016). *Trop. Med. Infect. Dis.* 3(2) 48, 2018.	This chapter specifically details two Strongyloides papers that address research questions 1 and 2.

6.	Findings: Influenza H1N1	6.1 Massey PD, **Miller A**, Saggers S, Durrheim DN, Speare R, Taylor K, Pearce G, Odo T, Broome J, Judd J, Kelly J, Blackley M, Clough A. Australian Aboriginal and Torres Strait Islander communities and the development of pandemic influenza containment strategies: Community voices and community control. *Health Policy*, (103) 184–190, 2011.	This chapter details two H1N1 influenza papers that address research questions 1 and 2.
		Extension on Research 6.2 Valkenburg SA, Josephs TM, Clemens EB, Grant EJ, Wang GC, Price DA, **Miller A**, Tong S, Thomas PG, Doherty PC, Rossjohn J, Gras S, Kedzierska K. Molecular basis for universal HLA-A*0201 $CD8^+$ T Cell immunity against influenza viruses. *PNAS*, April 19, 113 (16) 4440-4445, 2016. 6.3 Clemens EB, Grant EJ, Wang Z, Gras S, Peta Tipping P, Rossjohn J, **Miller A**, Steven Y. C. Tong SYC and Kedzierska K. Towards identification of immune and genetic correlates of severe influenza	These additional papers (6.2 and 6.3) , based on a previous study (Qui Quinones-Parra et al., 2014), showed that Indigenous populations, including Indigenous Australians and Alaskans, are at greater risk from severe influenza disease caused by newly emerging influenza viruses. Thus, prolonged and more severe influenza infection in the Indigenous population might reflect differences in CD8+ T-cell immunity associated with specific HLA profiles expressed. Molecular sequencing of Indigenous donors identified two new human leukocyte antigen (HLA) (gene complex) alleles that are unique to Indigenous

		disease in Indigenous Australians. *Immunology and Cell Biology,* (94) 367-377, 2016.	Australians. This discovery provides new information on how to develop a new and targeted broad-spectrum universal vaccine for emerging influenza strains. Again, these papers are included to show the relevance of the work, the influence my research approach has already had on imagining understandings of and responses to infectious diseases in Indigenous communities by developing improved vaccination effectiveness specifically for Indigenous populations, and hence the contribution of my work to global health.
7.	Key Messages and Conclusion	Significance Benefit Limitations Key Messages Principles to address barriers for infectious disease interventions in Indigenous communities Conclusion	This chapter details the significance, and the benefits and limitations of the research. Additionally, the chapter provides key messages for communities, researchers and government. These messages form the basis of principles to address barriers for infectious disease interventions in Indigenous communities.

1.5 Publication Contribution

My contributions to the core publications of this thesis are detailed in Table 1.2.

Table 1.2 Publication Contribution

Publication	My Contribution
2.1 **Miller A** & Speare R. Health Care for Indigenous Australians, Ch12 in Willis, E. & Reynolds, L. Eds *Understanding the Australian Health Care System Second Edition*. Elsevier: Australia, 2012.	AM conceived and presented the idea. AM undertook literature reviews and searches and contributed to the majority of writing. RS contributed to the writing and editing to the final version of the paper.
3.1 Page W, Shield J, O'Donahoo F, **Miller A**, Judd J, Speare R. Strongyloidiasis in Oceania. Chapter 3 in Ed. A. Loukas. *Neglected Tropical Diseases - Oceania.* Springer, SPi Global. 69-99, 2016.	WP, JS and RS conceived and presented the idea and led the writing of the paper. AM undertook literature reviews and searches and contributed to the writing. AM and JJ contributed to the writing and editing to the final version of the paper. FO was posthumously included in authorship.
3.2 **Miller A**, Smith ML, Judd JA, Speare R. *Strongyloides stercoralis*: Systematic Review of Barriers to Controlling Strongyloidiasis for Australian Indigenous Communities. *PLoS Neg. Trop. Dis.* 8(9) e3141, 2014.	AM undertook literature reviews, searches and analysis and led the majority of writing. MS contributed to the literature reviews and searches, writing and editing of the paper. JJ and RS contributed to the final version of the paper.
3.3 Speare R, **Miller A**, Page W. Strongyloidiasis: a case for notification in Australia? *The Medical Journal of Australia,* 202 (10)523-524, 2015.	RS conceived and presented the idea. AM and PW contributed to writing and editing final version of the paper.

3.4 **Miller A** & Durrheim D. Aboriginal and Torres Strait Islander communities forgotten in new Australian Pandemic Action Plan: 'Ask us, listen to us, share with us'. *The Medical Journal of Australia*, 193 (6)316-317, 2010.	DD conceived and presented the idea. DD and AM contributed to writing and editing final version of the paper.
3.5 Massey PD, **Miller A**, Durrheim DN, Speare R, Saggers S, Eastwood K. Pandemic influenza containment and the cultural and social context of Indigenous communities. *Rural and Remote Health* 9 (online), 1179, 2009.	PDM conceived and presented the idea. PDM, AM, DD, RS, SS and KE contributed to writing and editing final version of the paper.
4.1 Evans M, **Miller A**, Hutchinson P & Dingwall C. "De-Colonizing Research Practice: Indigenous Methodologies, Aboriginal Methods, and Knowledge/Knowing", in *Oxford Handbook of Qualitative Research*. Patricia Leavy (ed.) New York: NY, Oxford University Press, 179-191, June 2014.	ME conceived and presented the idea. ME, AM, PH and CD contributed to specific sections of the chapter and overall editing the final version.
4.2 **Miller A**, Massey PD, Judd JA, Kelly J, Durrheim DN, Clough AR, Speare R, Sagger S. A methodology for listening to Aboriginal and Torres Strait Islander people in Australia about Pandemic Influenza. *Rural and Remote Health,* (15) 2923, 2015.	AM conceived and presented the idea. AM developed the theoretical position, conceptual framework and undertook the majority of the writing and editing of the paper. PDM, JJ, JK, DD CL, RS and SS contributed to writing and editing final version of the paper.
5.1 **Miller A**, Smith ML Judd JA, Speare R. Policy implications for controlling communicable diseases in Indigenous Communities: Case of Strongyloidiasis	AM undertook literature reviews, searches and data analysis and contributed to the majority of writing. MS contributed to the literature reviews and searches, writing and editing of the

in Australia. *Aboriginal Policy Studies*, 7(1) 148-179, 2018.	paper. JJ and RS contributed to the final version of the paper.
5.2 **Miller A,** Young EL, Tye V, Cody R, Muscat M, Sanders V, Smith ML, Judd JA, Speare R. A community-directed integrated *Strongyloides* control program in Queensland, Australia. Control of Communicable Diseases in Human and Animal Populations: 70th Anniversary Year of the Birth of Professor Rick Speare (2 August 1947 – 5 June 2016). *Trop. Med. Infect. Dis.* 3(2) 48, 2018.	AM and RS conceived and presented the idea and undertook literature reviews, searches, data analysis and contributed to the majority of writing. EY, VT and RC are health practitioners and help conceptually developed the paper. MM, JJ and MS contributed to the literature reviews, writing and editing of the paper. VS and RS undertook quantitative data analysis.
6.1 Massey PD, **Miller A**, Saggers S, Durrheim DN, Speare R, Taylor K, Pearce G, Odo T, Broome J, Judd J, Kelly J, Blackley M, Clough A. Australian Aboriginal and Torres Strait Islander communities and the development of pandemic influenza containment strategies: Community voices and community control. *Health Policy*, (103) 184–190, 2011.	PDM conceived and presented the idea and undertook literature reviews, searches, data analysis and led the writing of the paper. AM, SS, KT, GP, TO, JB, JK, JJ and MB undertook data collection and collectively undertook group data analysis. SS, DD, RS and AC contributed to the final version of the paper.

1.6 Funding

The two studies that form the basis of this thesis was funded by three grants. Funding to undertake the Strongyloides research was granted by the Australian Research Council (ARC) Grant No. 0989521 and the H1N1 influenza grants (Grant No. 601034 and 601025) by the National Health and Medical Research Council (NHMRC). Table 1.3 details the funding agency, title of the project and the grant approval number and Chief investigators.

Table 1.3 Funding

Funding Agency	**Research Grant Title**	**Grant Number & Chief Investigators**
Australian Research Council (ARC) Discovery Indigenous Research Grant	A Qualitative Study of Barriers to Effective Infectious and Parasitic Disease Interventions in Aboriginal Communities	Grant No. 0989521 **Miller A**, Supervisors: Speare R, Judd J
National Health and Medical Research Council (NHMRC) Targeted Grant	Feasible containment strategies for swine influenza H1N1 in rural and remote Indigenous communities	Grant No. 601034 Speare R, **Miller A,** Durrheim D, Massey P, Nelson C, Judd J, Saggers S, Tsey K, Clough A
National Health and Medical Research Council (NHMRC) Project Grant	Pandemic influenza containment strategies in Aboriginal communities: what is acceptable and feasible?	Grant No. 601025 Speare R, **Miller A** Durrheim D, Saggers S, Tsey K, Nelson C, Judd J, Massey P

1.7 Ethics Approval

Human Research Ethics Committee (HREC) approvals were granted from universities and state authorities. For the three research grants, there were five Human Ethics Committee's that provided ethics approval. The two influenza grants were merged into one study as both projects had very similar objectives. Table 1.4 details ethics approvals by authorising body and approval number. The National Influenza Studies required four human research ethics committee approvals as this was a multi-site study in three Australian states. The Strongyloides study only

required one approval application to undertake the study as this was a qualitative study interviewing key participants. There was a project undertaken before this research that required ethics approval. I have gained permission from senior Indigenous Woorabinda health staff and the health service to publish the outcomes of this project and to include it as part of my overall research. Chapter five has ethics approval for a study that was conducted in Central Queensland in the Aboriginal community of Woorabinda. The context of this study is described in the paper presented including human research ethics processed and approvals.

Table 1.4 Human ethics approvals

Human Research Ethics Committees (HREC)	**Approval Number**
Griffith University: QLD	OTH/07/12/HREC (1)
QLD James Cook University: QLD	H3546
Aboriginal Health and Medical Research Council: NSW	746/10
Hunter New England HREC: NSW	09/09/16/4.01
Aboriginal Health Ethics Committee: WA	291 06/10
Rockhampton Health Service District: QLD	04.06 (2)

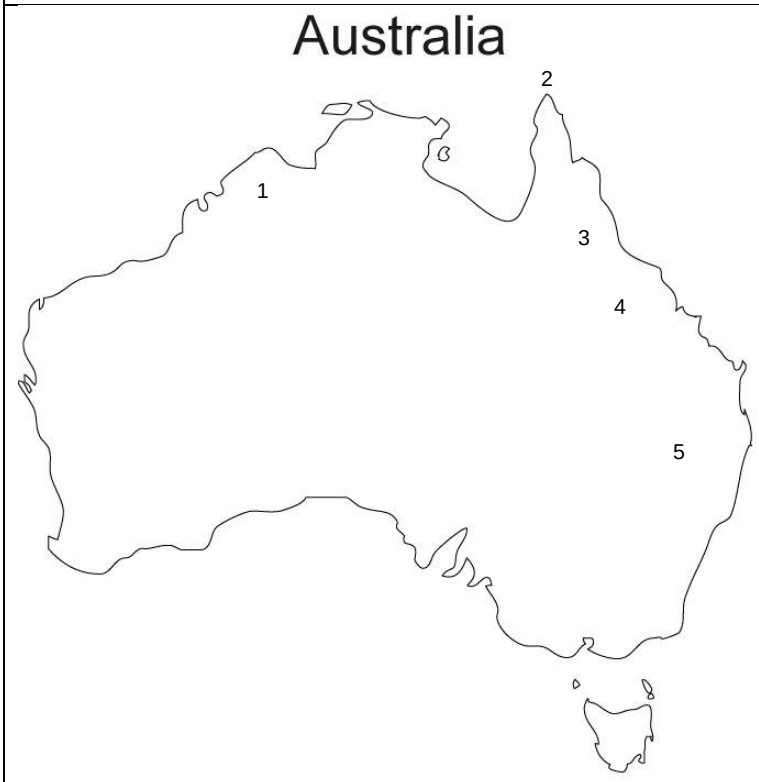
(1) This ethics approval was for Strongyloides research.

(2) The ethics approval for the Woorabinda paper discussed in Chapter 5 of this thesis under a 'Woorabinda Strongyloides Eradication Project', funded under the Aboriginal and Torres Strait Islander Commission (ATSIC).

1.8 Research Sites

This research was conducted in some Aboriginal and Torres Strait Islander communities across Australia – see below Figure 1.2. We trained local Indigenous researchers and employed them to guide the research aligned with local community protocols. Telephone interviews were conducted in various locations across Australia but not listed below.

Figure 1.2 Research sites

Location	Key
	1 Western Australia: the Kimberly region 2 Queensland: Torres Strait Islands 3 Far North Queensland region 4 Central Queensland 5 New South Wales: Hunter New England region

1.9 Nomenclature

In this thesis, the term Indigenous refers respectfully to Aboriginal and Torres Strait Islander people. In some of the chapters and publications of the thesis, Indigenous populations refers to Maori people of New Zealand and First Nations people of Alaska.

1.10 Acknowledgement to Country

I would like to acknowledge all Aboriginal and Torres Strait Islander peoples and their land on which this research was conducted and to pay respect to Elders past, present and emerging. This research drew on the knowledge and experience held by Aboriginal and Torres Strait Islander people from many parts of this country.

1.11 Presentations and dissemination

There has been signifant outcomes from the grants, Box 1.1 is a list of conference presentations, posters, invited speaker and keynote addresses. Presentations were also delivered to Indigenous community boards and local government representatives.

1.11 Conclusion

This thesis has been undertaken over an extended period of time from 2008 to 2018. There have been significant disruptions in the course of this research due to personal challenges –including changing positions in universities, health issues and the tragic death of my principal supervisor; who was a close friend and mentor. As detailed earlier in this chapter, this extended time has allowed me to develop a program of research that started with this body of work and extended to additional research projects culminating into my role in two centres of research excellence (See Figure 1.1).

Generic and specific key messages that are a primary outcome of this research are described in my Dyirbal language. The words *djilbay* (knowing how to do something) and *wiyamay* (knowing what to and how to do it), are the two conceptual ways I have categorised the key messages from this research. The two categories of key messages are generic key messages (*djilbay*) and specific key messages (*wiraway*). The d*jilbay* generic key messages are embedded in publications throughout this thesis include models of capacity building, community engagement, applying Indigenous ethical standards and Indigenous organisational engagement that aims to inform and influence other research policy development about infectious diseases in Indigenous communities.

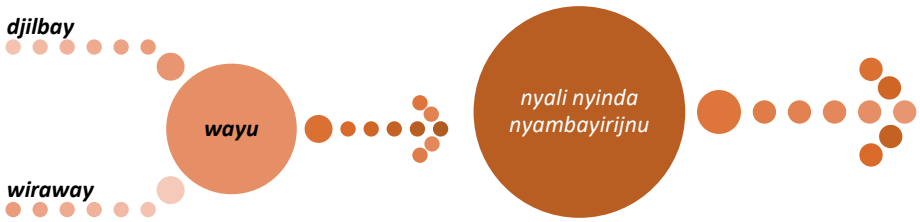
The *wiraway* generic key messages can broadly be applied to other infectious diseases impacting on Indigenous communities. The *wiraway* specific key messages are synthesised from the research and the publications in this thesis. These *wiraway* specific key messages are sorted according into the two exemplars and themed into three areas: key messages for communities, researchers and health professionals and government. These key messages are distilled further to compile research and engagement principles – a process translated in Dyirbal as *wayu*. I have synthesised, *wayu,* these *wiraway* specific key messages into 5 principles to address

barriers for infectious disease interventions in Indigenous communities. These principles are:

1. Increase knowledge and information about the diagnosis and treatment of the disease and share this information with communities.
2. Collaboratively work with local leadership to support a community-driven model that has genuine and respectful partnerships between local Indigenous people, health professionals and government agencies.
3. Develop and adopt effective communication strategies to share knowledge and information about infectious diseases to different stakeholders to respond effectively.
4. Plan, develop and implement public policy about infectious diseases interventions that addresses institutionalised racism and incorporates local Indigenous knowledge.
5. Indigenous engagement strategies must identify and use pre-existing relationships that incorporates Indigenous people's values.

To apply these principles, I have provided another Dyirbal concept as my research framework standpoint - *nyali nyinda nyambayirijnu***,** which means collaboratively thinking of solutions to complex problems (published as *ŋali ŋinda ŋambayiriŋu* in Chapter 4). A diagrammatical representation of the development of these principles, in light of my research framework standpoint is shown in Figure 1.3. I'm introducing my research position to show how my research journey begins and in my final chapter, share how to enact this standpoint. The arrows represent the conceptual movement towards collaborative solutions between Indigenous and non-Indigenous peoples.

Figure. 1.3 Research Framework Standpoint



The next chapter details a book chapter that was the start of my journey into a research career. The reason to include this book chapter was to highlight the historical policies that have, and continue to have, detrimental impact on the health of Indigenous Australians.

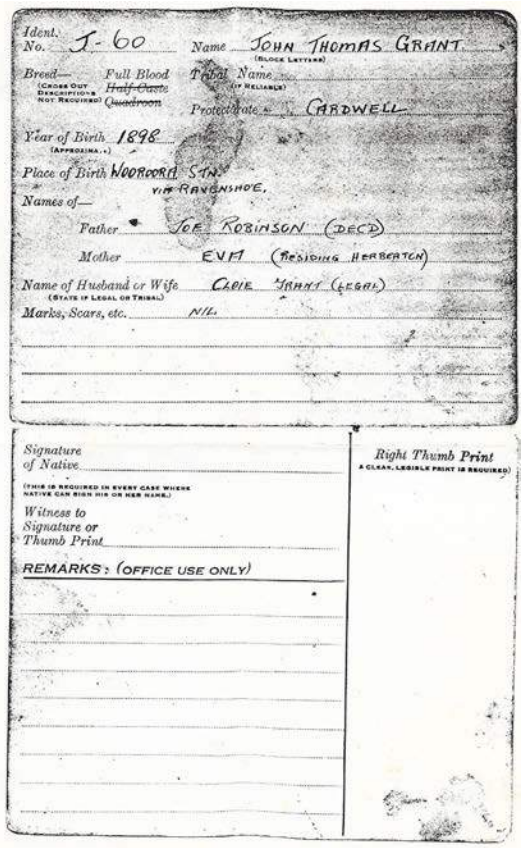
Box 1.1 Presentations and Dissemination

- **Miller A**. Strongyloidiasis in Aboriginal Communities. Invited Speaker, *"Intersection between Chronic and Infectious Disease"*, Australasian Tropical Health Conference, Brisbane, 23 Sept 2016.
- Page W, Shield J, Bradbury R, **Miller A**, Judd J, Sheorey H, Ross K, Garrard T, Robertson G. Strongyloidiasis in Australia: Challenges in a developed country, National Strongyloides Working Group, a special interest group of the Australasian College of Tropical Medicine. Poster Presentation, XVII International Congress for Tropical Medicine and Malaria, Brisbane, 18-22 Sept 2016.
- **Miller A**, Judd J, Speare R. Strongyloidiasis in Aboriginal Communities. Invited Speaker, XVII International Congress for Tropical Medicine and Malaria, Brisbane, 18-22 Sept 2016.
- Young ME, **Miller A**, Muscat M. A community-directed integrated *Strongyloides* control program in Queensland, Australia. Guest Speaker, International Workshop on Strongyloidiasis Incorporating the 11th National Workshop on Strongyloidiasis (Australia), Brisbane, 17 September 2016.
- **Miller A**, Smith ML, Judd JA, Speare R. *Review of the Barriers to controlling Strongyloides in Indigenous Australian Communities*. Invited Speaker. ASM & ACTM Annual National Parasitology and Tropical Medicine Master Class, Perth WA 6-7 March 2015.
- **Miller A**, Smith M, Judd JA & Speare R. *Review of the Barriers to controlling Strongyloides in Indigenous Australian Communities*. In: Proceedings for 8th National Workshop on Strongyloidiasis: Expanding the Horizon on Strongyloidiasis, Canberra, ACT, 23-24 Mar 2013.
- Judd J, **Miller A,** on behalf of the Influenza Studies Group: Communities influence government policy: A case study of listening to Indigenous voices about Pandemic Influenza, Oral Paper, Population Health Congress Adelaide, 9-10 September 2012.
- Judd J, **Miller A** and Speare R, *Strongyloides and Health Promotion: a neglected area of Health Promotion Action*, Poster, Population Health Congress Adelaide, 9-12 September 2012

- Judd J, **Miller A** and Speare R, *Strongyloides and Health Promotion: a neglected area of Health Promotion Action*, 7thNational Strongyloides Workshop, Fremantle, WA March 20-21, 2012
- **Miller A**, Saggers S, Judd JA, Kelly J, Durrheim DN, Massey PD & Speare R. *Ask U, Listen to Us, Share with Us: Participatory Action Research in Indigenous Influenza Studies***.** Invited Speaker In Proceedings for Australian Society for Medical Research National Scientific Conference – Indigenous Health Action on Prevention, Cairns, QLD, 13-16 Nov 2011.
- **Miller A**, Saggers S, Judd J, Kelly J, Durrheim DN, Massey PD, Speare R *Aboriginal and Torres Strait Islander communities developing pandemic influenza containment strategies***.** Keynote Speaker In Proceedings for Listen to Indigenous People about Pandemic Influenza: Ask Us, Listen to Us, and Share with Us, Cairns, QLD, 22-23 Sept 2011.
- **Miller A**, Saggers S, Judd J, Kelly J, Durrheim DN, Massey PD, Speare R. *Aboriginal and Torres Strait Islander communities developing pandemic influenza containment strategies***.** In: Proceedings for Communicable Disease Control Conference, Canberra, ACT, 4-6 Apr 2011.
- Massey PD, **Miller A**, Speare R, Saggers S, Judd J, Kelly J, Blackley M, Pearce G, Taylor KA, Odo T, Broome J, Purcell C, Clough A, Durrheim DN. *Influenza Studies with Indigenous Communities*. Ministry of Health & Health Research Council H1N1 Workshop, Auckland, NZ, 16 June 2010.
- **Miller A**, Massey PD, Pearce G, Taylor KA, Speare R, Saggers S, Blackley M, Broome J, Odo T, Purcell C, Judd JA, Kelly J, Clough A, Durrheim DN. *Taking the next steps*. NSW Health (Hunter New England) Introduction to Indigenous Research Workshop, 7-9 Jun 2010, Newcastle & Tamworth, NSW.
- **Miller A**, Pearce G, Taylor KA, Broome J, Odo T, Blackley M, Speare R, Durrheim DN, Saggers S, Tsey K, Massey PD, Judd JA, Nelson C, Clough A, Thompson M, Kelly J, Roberts J. *Engaging Indigenous Services in Influenza Research.* James Cook University Tropical Lecture Series, Townsville, QLD, 13 May 2010.
- **Miller A**, Speare R, Durrheim D, Saggers S, Tsey K, Judd J, Nelson C, Clough A, Thompson M, Kelly J. *Feasible containment strategies for pandemic H1N1 in Indigenous communities*. NHMRC H1N1 Workshop, Canberra, ACT, 10-11 Dec 2009.
- **Miller A.** *A Qualitative Study of Barriers to Effective Infectious and Parasitic Disease Interventions in Aboriginal Communities*. In: Proceedings for 5th National

Workshop on Strongyloidiasis: Closing the Gap on Strongyloidiasis, Centre for Remote Health, Alice Springs, NT, 17 Sept 2009.

Attachment 1. My grandparent's Exemption Certificate



Ident. No. J-60 Name JOHN THOMAS GRANT (BLOCK LETTERS)

Breed— (CROSS OUT DESCRIPTIONS NOT REQUIRED) Full Blood Half-Caste Quadroon Tribal Name (IF NECESSARY)

Protectorate CARDWELL

Year of Birth 1898 (APPROXIMATE)

Place of Birth WOORROORA STN. VIA RAVENSHOE.

Names of—

Father JOE ROBINSON (DECD)

Mother EVA (RESIDING HERBERTON)

Name of Husband or Wife (STATE IF LEGAL OR TRIBAL) CADIE GRANT (LEGAL)

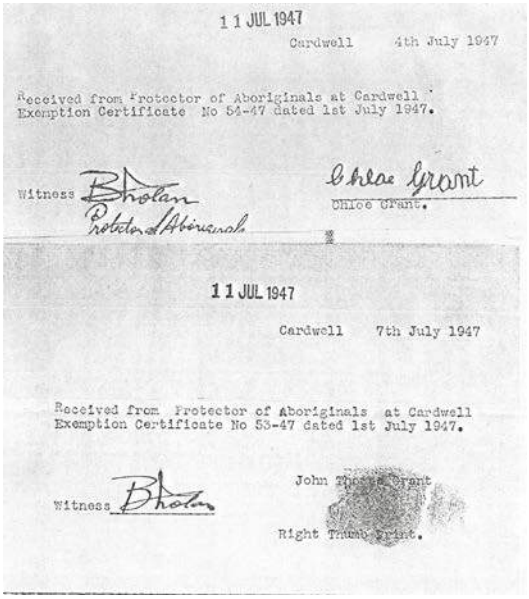
Marks, Scars, etc. NIL.

Signature of Native (THIS IS REQUIRED IN EVERY CASE WHERE NATIVE CAN SIGN HIS OR HER NAME.)

Witness to Signature or Thumb Print

Right Thumb Print (A CLEAR, LEGIBLE PRINT IS REQUIRED)

REMARKS: (OFFICE USE ONLY)



11 JUL 1947

Cardwell 4th July 1947

Received from Protector of Aboriginals at Cardwell Exemption Certificate No 54-47 dated 1st July 1947.

Witness B Nolan Protector of Aboriginals

Chloe Grant

Chloe Grant.

11 JUL 1947

Cardwell 7th July 1947

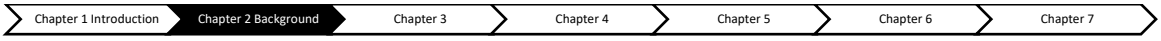
Received from Protector of Aboriginals at Cardwell Exemption Certificate No 53-47 dated 1st July 1947.

Witness B Nolan

John Thomas Grant

Right Thumb Print.

Chapter. 2 Background



2.1 Chapter Brief

The aims of this chapter are to describe the context and health status of Aboriginal and Torres Strait Islander people, provide a brief overview of the impact of infectious diseases on Indigenous people and highlight the need for this research in the context of infectious diseases affecting Aboriginal and Torres Strait Islander communities. The paper presented as a published book chapter is to highlight the historical policies that have, and continue to have, detrimental impact on the health of Indigenous Australians.

2.2 Overview

The paper presented for this chapter provides an introduction to the health of Indigenous Australians. The paper is a published chapter that provides an overview of the history and development of the Aboriginal Medical Services (AMS) movement, details funding arrangements for Indigenous health, explores the epidemiology of health and illness of Indigenous Australians and compares this data with international Indigenous populations. The chapter also examines Indigenous Australian participation in the health workforce and the current public health policies affecting the health of Indigenous Australians.

In 2014, the estimated population of Indigenous Australians was 713,600, and New South Wales had the highest number of people 220,902 or 31% of the total Indigenous population. The Northern Territory had the highest proportion of Indigenous Australians, which was 30% of the total NT population Australian Indigenous (HealthInfoNet 2015).

Indigenous Australians are more disadvantaged than all other Australians on all social, economic, educational and health indicators (SCRGSP 2014). There has been some marginal improvement to some health indicators like life expectancy and infant mortality, however, health outcomes remain largely unchanged (SCRGSP 2014). In terms of health, the leading 5 primary causes of deaths constituting 78.7%

of all deaths for Indigenous Australians are: diseases of the circulatory system (I00-I99; 621 deaths or 25.2%); neoplasms (C00-D48; 524 deaths or 21.2%); external causes of mortality (V01-Y98; 380 deaths or 15.4%); endocrine, nutritional and metabolic diseases (E00-E90; 225 deaths or 9.1%) and diseases of the respiratory system (J00-J99; 194 deaths or 7.9%) (ABS 2014 B).

From historical accounts, infectious diseases have drastically affected Indigenous peoples from around the world. Aboriginal and Torres Strait Islander people have also, experienced this when Europeans came to Australia (Anderson 2007). Indigenous peoples generally enjoyed better health in 1788 than most people living in Europe.

> They did not suffer from smallpox, measles, influenza, tuberculosis, scarlet fever, venereal syphilis and gonorrhoea, diseases that were common in 18th century Europe. Indigenous people probably suffered from hepatitis B, some bacterial infections (including a non-venereal form of syphilis and yaws) and some intestinal parasites
>
> (Australian Indigenous Health*InfoNet 2015)*.

Since the beginning of the twentieth century, Australia has experienced a significant drop in deaths caused by infectious diseases (ABS 1997). Advances in public health, medical interventions and increased socio-economic status have largely been responsible for this decline (AIHW 2014).

In Australia, death rates from infectious diseases decreased from 185 to 6 per 100,000 between 1921 and 1995 (Figure 2). During this time infectious diseases were the main cause of death from diseases such as diphtheria, polio, tetanus, malaria and tuberculosis (ABS 1997). However, infectious diseases currently contribute significantly to morbidity and mortality of Indigenous Australians compared to the non-Indigenous population and is particularly important in rural and remote communities (ABS 2012). There are effective interventions for the control of many of these diseases however the implementation of these control strategies in rural Indigenous communities is frequently sub-optimal (Miller et al. 2014). Barriers at multiple levels appear to impact on effective interventions for infectious disease in Indigenous communities.

The major infectious diseases effecting Indigenous Australians include tuberculosis, hepatitis (A, B, and C), sexually transmissible infections, HIV/AIDS, *Haemophilus*

influenza type b, pneumococcal disease, meningococcal disease and skin infections (Burns et al. 2003). Infectious diseases are caused by bacterial, viral, prion, fungal and parasitic infections (Department of Health and Aging 2014; Centre for Rural and Remote Health 2014). The type of infectious disease usually determines the methods to address the risk factors (Burns et al. 2003). Addressing these risk factors have included improving infrastructure in sanitation, and increased access to vaccination and medication (antibiotics and antivirals) and consequently have decreased the severity of infectious diseases (AIHW 2014).

The National Notifiable Disease Surveillance System (NNDSS) provides information about specific infectious diseases that comes from individual studies or state and territory notifiable disease collections (NNDSS 2015). Data from state and territory collections are collected and published by the NNDSS. However, Indigenous status is often not reported for large proportions of notifications (HealthInfoNet 2015). Influenza and pneumonia (J09-J18) is ranked the 13th leading cause of death nationally for Indigenous Australians (ABS 2012). The standardised death rates for Indigenous Australians in NSW, Qld, SA, WA, and the NT for certain infectious and parasitic diseases (A00-B99) is 25.0 compared to 9.1 for Non-Indigenous people which is almost 3 times higher (ABS 2010).

2.3 Summary

In summary, the purpose of this chapter was to gain an understanding of the health status of Aboriginal and Torres Strait Islander people, provide a brief overview of the impact of infectious diseases on Indigenous people and the need to understand how multiple causal pathways causes by oppressive public policies have impacted on the health status of Indigenous Australians. Historical responses by Indigenous Australians to oppressive public policies have led to the establishment of Aboriginal medical services in order to gain access to better healthcare. Despite such developments, addressing Indigenous health require increases in funding to better understand the social determinants of health, improve workforce developments, improve health service delivery and support research to provide evidence-based health care for Indigenous Australians.

The next chapter will provide an in-depth examination of two infectious disease exemplars used in this research – strongyloides and influenza H1N1. Notwithstanding the major causes of poor health are chronic conditions, infectious

diseases caused by strongyloides and influenza play a significant role in the poor health status of Indigenous Australians. By understanding the barriers to effective interventions of these two diseases, may improve ways to understand address other health conditions, particularly from the perspective of Indigenous Australians.

2.4 Paper Presented

Miller A & Speare R Health Care for Indigenous Australians, Ch12 in Willis, E. & Reynolds, L. Eds *Understanding the Australian Health Care System Second Edition*: p.149-160, Elsevier: Australia, 2012.

2.5 References

Anderson W. The colonial medicine of settler states: comparing histories of Indigenous health. *Health and History*, 2007, 9(2): 144-154.

ABS (Australian Bureau of Statistics). Australian Social Trends 1997. (ABS Catalogue no 4102.0) Canberra: Australian Bureau of Statistics, 1997.

ABS (Australian Bureau of Statistics). Census of population and housing: characteristics of Aboriginal and Torres Strait Islander Australians, 2011. (ABS Catalogue no 2076.0) Canberra: Australian Bureau of Statistics, 2012 A.

ABS (Australian Bureau of Statistics). Estimates and projections, Aboriginal and Torres Strait Islander Australians, 2001 to 2026. (ABS Catalogue no.3238.0) Canberra: Australian Bureau of Statistics, 2014 A.

ABS (Australian Bureau of Statistics). Causes of death, Australia, 2012: Deaths of Aboriginal and Torres Strait Islander Australians, 2014 B. Last Retrieved 8 June 2015 from http://www.abs.gov.au/ausstats/abs@.nsf/Lookup/by%20Subject/3303.0~2012~Main%20Features~Leading%20Causes%20of%20Aboriginal%20and%20Torres%20Strait%20Islander%20Deaths~10015

AIHW (Australian Institute of Health and Welfare). Australia's health 2014: the 14th biennial health report of the Australian Institute of Health and Welfare. Canberra: Australian Institute of Health and Welfare, 2014.

Australian Indigenous Health*InfoNet*. *Overview of Australian Indigenous Health status, 2014*. 2015, Last Retrieved 8 June 2015 from http://www.healthinfonet.ecu.au/health-facts/overviews.

Burns J, Burrow S, Genovese E, Pumphrey M, Sims E, Thomson N. Other communicable diseases. In: Thomson N, ed. *The health of Indigenous Australians*. South Melbourne: Oxford University Press: 397-441, 2003.

Miller A, Smith ML, Judd JA, Speare R. *Strongyloides stercoralis*: Systematic Review of Barriers to Controlling Strongyloidiasis for Australian Indigenous Communities. *PLoS Neglected Tropical Diseases*, 8(9): e3141, 2014.

National Notifiable Disease Surveillance System (NNDSS). Introduction to the National Notifiable Diseases Surveillance System, Department of Health: Australian Government http://www.health.gov.au/internet/main/publishing.nsf/Content/cda-surveil-nndss-nndssintro.htm Last accessed 15 June 2015.

SCRGSP (Steering Committee for the Review of Government Service Provision), *Overcoming Indigenous Disadvantage: Key Indicators 2014*. Productivity Commission: Canberra, 2014.

2.5.1 Miller & Speare Health care for Indigenous Australians

Chapter 12

Health Care for Indigenous Australians

Adrian Miller, Rick Speare

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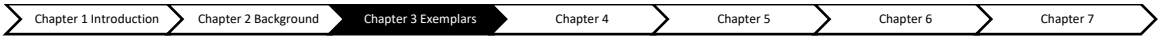
Chapter. 3 The Exemplars – Strongyloides and H1N1 Influenza



3.1 Chapter Brief

This chapter aims to describe two exemplars used in this thesis to provide a better understanding of the barriers to controlling infectious diseases in Indigenous communities. The first exemplar is a neglected tropical disease caused by an intestinal parasite called Strongyloides. The second exemplar is the human swine flu H1N1 that caused a pandemic in 2009. This chapter describes the impact that these two diseases have had on the health of Indigenous Australians.

3.2 Overview

3.2.1 Exemplar 1 - Strongyloides

There are over 50 species of *Strongyloides,* and only two infects humans; *S. stercoralis* and *S. fuelleborni* (Speare 1989). These two species contain two sub-species, *S. fuelleborni* in Africa and *S. kellyi* in Papua New Guinea (PNG) (Viney et al. 1991). *S. stercoralis* is widespread throughout Indigenous communities and causes serious disease while *S. kellyi* is localised to PNG and has only been reported to cause serious disease in infants (Page et al. 2016). *S. stercoralis* is a neglected tropical disease and strategies are being developed internationally to control this parasite (Olsen et al. 2009). Strongyloides infection is caused by infective larvae penetrating the skin and undergoes a blood-lung migration. Adults end up living in the tunnels of the mucosal lining of the gastrointestinal tract. The parasitic stage of Strongyloides is female only and reproduces by parthenogenesis or asexual reproduction (Speare 1989).

Strongyloides is transmitted by contact with contaminated soil (or water) containing infective larvae (Sheorey et al. 2000). These infective larvae have developed from faeces which has deposited indiscriminately. The uniqueness of *S. stercoralis* is that it can become autoinfectious, with small infective larvae formed in the gut and re-entering the tissues by penetrating the wall of the lower bowel. The practical result of

this is that a single infection can last many years and probably for life. Also, if the immune response of the host is suppressed, the rate of successful colonisation by autoinfective larvae increases, numbers of adult worms in the gut rises, and a serious and potentially fatal disease (the hyperinfective syndrome) develops (Shield and Page 2008).

S. stercoralis is listed as a gastrointestinal helminth, and autoinfective larvae can invade any organ of the body. Strongyloidiasis can manifest with a variety of signs and symptoms on the skin, as gastrointestinal and respiratory symptoms or infection in other organs (Page et al. 2016). There are challenges of diagnosing strongyloidiasis because clinical manifestations are usually non-specific and intermittent (Page et al. 2016). Strongyloidiasis has been classified into acute strongyloidiasis, chronic strongyloidiasis and hyperinfection, however, the categories are not precisely defined (Page et al. 2016).

The significance of strongyloidiasis in Aboriginal communities is that the parasite is hyperendemic with high rates, typically much greater the 5% (Johnson et al. 2005). However, since strongyloidiasis is not a notifiable disease, data on incidence is inadequate (Speare, Miller & Page 2015). Some of the highest prevalence's in the world have been recorded in northern Australia with prevalence's of 35% in some groups (Shield et al. 2015). In most societies, the prevalence is under 5%, even in communities with severe poverty (Powloweski 1988). Unfortunately, researchers and many clinicians in Australia have largely ignored strongyloidiasis, and the impact of the parasite on these communities has not been documented. Apart from occasional case reports of serious disease as demonstrated by a systematic review conducted as part of my PhD research, there has been limited research into incidence, prevalence and the impact Strongyloides on Indigenous communities (Miller et al. 2014).

3.2.1.1 Papers Presented for Strongyloides

Page W, Shield J, O'Donahoo F, **Miller A**, Judd J, Speare R. Strongyloidiasis in Oceania. Chapter 3 in Ed. A. Loukas. *Neglected Tropical Diseases - Oceania*. Springer, SPi Global. 69-99, 2016.

Miller A, Smith ML, Judd JA, Speare R. *Strongyloides stercoralis*: Systematic Review of Barriers to Controlling Strongyloidiasis for Australian Indigenous Communities. *PLoS Neglected Tropical Diseases*, 8(9) e3141, 2014.

Speare R, **Miller A**, Page W. Strongyloidiasis: a case for notification in Australia? *The Medical Journal of Australia,* 202 (10) 523-524, 2015.

3.2.2 Exemplar 2 - H1N1 Influenza

Human swine influenza (influenza A H1N109) has symptoms similar to seasonal influenza and include fever, cough, fatigue, myalgia, pharyngitis, chills, dyspnoea, coryza and headache (WHO 2009). Complications from this infection can result in pneumonia and severe cases cause death (WHO 2009). The influenza virus transmitted via respiratory droplets from a symptomatic individual. Unless individuals are vaccinated, it is necessary to control transmission by adopting appropriate hygiene practices, social distancing or isolation and limit social activities.

In early 2009 in Mexico, a novel influenza virus was first reported in large numbers of young adults presenting with serious respiratory condition. Within a short period the new influenza A H1N1 virus was identified in the USA state of California and was linked to the cases in Mexico (CDC 2009). The World Health Organization (WHO) reported in April 2009 more than 882 cases in Mexico and seven cases in the USA, including 62 deaths caused by the H1N1 influenza virus. However, by June, 30,000 confirmed cases have been reported in 74 countries. The situation was defined as 'a public health emergency of international concern' (WHO 2009). Approximately 1.5 million people were believed to have been infected in 214 countries, with over 25,000 confirmed deaths in 2011 (Gable et al. 2011). Although the range of illness varied with the majority of cases mild, more serious illness was noted within particular groups (Flint 2009).

Influenza infection was substantially higher in Indigenous population and the risk of hospitalisation and morbidity and similar to the 1919 pandemic influenza outbreak, where 10-20% of Indigenous Australians died compared to <1% of non-Indigenous Australians (Briscoe 1996). During the 2009 H1N1 influenza pandemic, Aboriginal and Torres Strait Islander people comprised of 2.5% of the total Australian population but accounted for 16% of hospitalisations and 9.7% admissions to ICU (Flint et al. 2009). Aboriginal and Torres Strait Islander people from the Northern Territory, Queensland and Western Australia were 3-12 times more likely to be hospitalised than non-Indigenous Australians. The H1N1 influenza pandemic affected Indigenous

populations more than non-Indigenous populations in Oceania and the Americas. Indigenous communities with a higher prevalence of comorbidities that includes diabetes, obesity, asthma, and chronic obstructive pulmonary disease, as well as pregnancy appear to have contributed to the higher risks and complications of the disease (La Ruche et al 2009, Kumar et al 2009, Miller et al 2015). Social disparity, institutionalised racism within health services and differences in access to culturally safe health services have also been reported as contributing to disadvantage and delayed treatment (Miller et al. 2015). Given these factors and the subsequent impact they had on Indigenous communities, this part of the research project set out to ensure that the Australian national, state and territory pandemic plans adequately reflected the risk status of Indigenous peoples and promoted meaningful engagement to mitigate this risk (Miller et al. 2015).

The publications for this chapter are two published letters designed to raise the awareness and importance of pandemic influenza and the impact this disease has had on the morbidity and mortality in Indigenous people. Secondly, to highlight the inadequacies of the Australian Pandemic Plan in protecting and supporting Indigenous communities in a pandemic influenza outbreak. It is important to note that investigating and subsequent funding of this research was initiated and driven by Indigenous communities and their organisations.

3.2.2.1 Papers Presented for Influenza H1N1

Miller A & Durrheim D. Aboriginal and Torres Strait Islander communities forgotten in new Australian Pandemic Action Plan: 'Ask us, listen to us, share with us'. *The Medical Journal of Australia*, 193 (6): 316-317, 2010

Massey PD, **Miller A**, Durrheim DN, Speare R, Saggers S, Eastwood K. Pandemic influenza containment and the cultural and social context of Indigenous communities. *Rural and Remote Health* 9 (online), 1179, 2009.

3.3 Summary

In summary, the strongyloides papers provides in-depth clinical information and makes a case for including strongyloidiasis as a notifiable disease in Australia. The systematic review revealed that there is limited published research on the barriers to effective intervention for strongyloides. More importantly, the review did identify five points of intervention: (1) develop reporting protocols between health care system and communities; (2) test all Indigenous Australian patients, immunocompromised

patients and those exposed to areas with *S. stercoralis*; (3) health professionals require detailed information on strongyloidiasis and potential for exposure to Indigenous Australian people; (4) to establish testing and treatment initiatives within communities; and (5) to measure and report prevalence rates specific to communities and to act with initiatives based on these results. By defining barriers to control of strongyloidiasis in Australian Indigenous people, improved outcomes of prevention, treatment of strongyloidiasis and increased health overall are attainable.

The influenza H1N1 paper identified that decisions on appropriate pandemic containment measures need to be made in genuine partnership with communities, recognizing that some cultural practices may amplify or reduce infection risk. Also, public health experts must work with communities in genuine and respectful partnership to define what pandemic containment measures are culturally appropriate and acceptable.

There is a fundamental need for governments to acknowledge and respond effectively to the specific requirements of Aboriginal and Torres Strait Islander people in public policy development. Prevention and preparedness must include government support of planning in respectful partnership with Aboriginal and Torres Strait Islander communities, health organisations and representative bodies. Mandating this support and partnership at all levels of government will allow a greater understanding of infection risk and identification of cultural, social, economic and health service factors that may contribute to poor health outcomes, and ensure culturally safe and effective prevention and mitigation strategies.

A strong theme emerging from this work is the message to government: “Ask us, listen to us, share with us”. Solutions to limit the burden on Aboriginal and Torres Strait Islander populations exist, but respectful partnership is necessary to unearth them. The partnership must not be a token one, but one developed through engagement with communities, and with the flexibility to be localised to meet the specific needs of diverse urban, rural and remote Aboriginal and Torres Strait Islander communities in all states and territories. Health information delivered with a local flavour is a key message from the project. “Ask us, listen to us, share with us” is a strong message that governments must heed if the impact of pandemic influenza on Aboriginal and Torres Strait Islander communities is to be limited.

Finally, the extension research in influenza showed Australian Indigenous people may be particularly vulnerable to the H7N9 influenza disease.The next chapter delves into the methodology I used for the two studies, my research standpoint and

why I chose it and the application of a participatory action research within an Indigenous knowledge framework.

3.3.1 Extension of the Research Publication

I've included in this chapter an update on the influenza research with Indigenous populations. This research is an extension of the original research question on the barriers for controlling infectious diseases in Indigenous communities. This new research aims to identify immunologic barriers for not only Australian Aboriginal people but also Indigenous populations of New Zealand and North America. The findings show these Indigenous populations would be particularly vulnerable to new strands of influenza like H7N9.

Quiñones-Parra S, Grant EJ, Loh L, Nguyen THO, Campbell K, Tong S, **Miller A**, Doherty PC, Vijaykrishna D, Rossjohn J, Gras S, Kedzierska K. Pre-existing $CD8^+$ T cell immunity to the novel H7N9 influenza A virus varies across ethnicities. *PNAS*, 2014, Vol. 111, (3), 1049–1054.

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Centre for Disease Control and Prevention (CDC). Swine influenza A (H1N1) Infection in two children – Southern California, Mar–Apr 2009, *Morbidity Mortality Weekly Report.*2009, vol. 58 (15):400-402.

Flint SM, Davis JS, Su JY, Oliver-Landry EP, Rogers BA, Goldstein A. Disproportionate impact of pandemic (H1N1) 2009 influenza on Indigenous people in the Top End of Australia's Northern Territory. *Med J Aust*, 2010, 193 (10): 617-622.

Gable L, Courtney B, Gatter R & Kinney ED, *Global Public Health Legal Responses to H1N1. The Journal of Law, Medicine and Ethics,* 2011, *vol 39: 46–50.*

Kumar A, Zarychanski R, Pinto R, Cook DJ, Marshall J, Lacroix J, et al. Critically ill patients with 2009 influenza A (H1N1) infection in Canada. *Jama*, 2009, 302 (17): 1872-1879.

La Ruche G, Tarantola A, Barboza P, Vailant L, Gueguen J, Gastellu-Etchegorry M et al. The 2009 pandemic H1N1 influenza and indigenous population in Americas and the Pacific. Euro-Surveill 2009, 2014, 14 (42).

Miller A, Smith ML, Judd JA, Speare R. *Strongyloides stercoralis*: Systematic Review of Barriers to Controlling Strongyloidiasis for Australian Indigenous Communities. *PLoS Neglected Tropical Diseases*, 2014, 8(9): e3141.

World Health Organization (WHO). World now at the start of 2009 influenza pandemic. Media centre. 2009. At: www.who.int/mediacentre/news/statements/2009/h1n1_pandemic_phase6_20090611/en/ [Last accessed 18 August 2017].

3.5 Strongyloides Papers

3.5.1 Page, Shield, O'Donahoo, Miller, Judd, & Speare Strongyloidiasis in Oceania.

Strongyloidiasis in Oceania

3

Wendy Page, Jennifer Shield, Francis O'Donahoo,
Adrian Miller, Jenni Judd, and Rick Speare

Abstract

Strongyloidiasis is a potentially fatal disease caused by species of *Strongyloides* (Nematoda). In Oceania, two species infect humans: *S. stercoralis* and *S. kellyi*. *S. stercoralis* is widespread throughout Oceania and causes serious disease in any age group. *S. kellyi* is localised to Papua New Guinea and causes serious disease in infants. Infective larvae enter the body through the skin and migrate through the tissues. Adult females live in the mucosa of the proximal small intestine. The life cycle of *S. stercoralis* includes autoinfection, unusual in parasitic worms, whereby some of the offspring of the parasitic adults become infective in the lower intestine and complete the life cycle in the same person. This ensures that the infection per-

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A. Loukas (ed.), *Neglected Tropical Diseases - Oceania*, Neglected Tropical Diseases, DOI 10.1007/978-3-319-43148-2_3

sists, and the population of the worms can increase out of control, usually when the person is immunodeficient or immunosuppressed. The worms can be eliminated by oral ivermectin, and the person is probably cured if their serology is negative 6 months after treatment. This chapter contains details of the life cycles, transmission, clinical manifestations, diagnostic tests and how to interpret them, most effective treatment options, how to ensure that treatment has been effective and what to consider when developing effective prevention and control strategies.

Keywords
Strongyloidiasis • Strongyloides • Strongyloides stercoralis, • Strongyloides kellyi • Stongyloides fuelleborni • Neglected tropical diseases, • NTD • Soil trandmitted helminths • STH • Oceania

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3.5.2 Miller, Smith, Judd, & Speare. Strongyloides stercoralis: Systematic review of barriers to controlling Strongyloidiasis for Australian Indigenous communities

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PLOS | NEGLECTED TROPICAL DISEASES

Strongyloides stercoralis: Systematic Review of Barriers to Controlling Strongyloidiasis for Australian Indigenous Communities

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Abstract

Background: *Strongyloides stercoralis* infects human hosts mainly through skin contact with contaminated soil. The result is strongyloidiasis, a parasitic disease, with a unique cycle of auto-infection causing a variety of symptoms and signs, with possible fatality from hyper-infection. Australian Indigenous community members, often living in rural and remote settings, are exposed to and infected with *S. stercoralis*. The aim of this review is to determine barriers to control of strongyloidiasis. The purpose is to contribute to the development of initiatives for prevention, early detection and effective treatment of strongyloidiasis.

Methodology/Principle Findings: Systematic search reviewing research published 2012 and earlier was conducted. Research articles discussing aspects of strongyloidiasis, context of infection and overall health in Indigenous Australians were reviewed. Based on the PRISMA statement, the systematic search of health databases, Academic Search Premier, Informit, Medline, PubMed, AMED, CINAHL, Health Source Nursing and Academic was conducted. Key search terms included strongyloidiasis, Indigenous, Australia, health, and community. 340 articles were retrieved with 16 original research articles published between 1969 and 2006 meeting criteria. Review found barriers to control defined across three key themes, (1) health status, (2) socioeconomic status, and (3) health care literacy and procedures.

Conclusions/Significance: This study identifies five points of intervention: (1) develop reporting protocols between health care system and communities; (2) test all Indigenous Australian patients, immunocompromised patients and those exposed to areas with *S. stercoralis*; (3) health professionals require detailed information on strongyloidiasis and potential for exposure to Indigenous Australian people; (4) to establish testing and treatment initiatives within communities; and (5) to measure and report prevalence rates specific to communities and to act with initiatives based on these results. By defining barriers to control of strongyloidiasis in Australian Indigenous people, improved outcomes of prevention, treatment of strongyloidiasis and increased health overall are attainable.

Citation: Miller A, Smith ML, Judd JA, Speare R (2014) *Strongyloides stercoralis?*: Systematic Review of Barriers to Controlling Strongyloidiasis for Australian Indigenous Communities. PLoS Negl Trop Dis 8(9): e3141. doi:10.1371/journal.pntd.0003141

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Introduction

Strongyloidies stercoralis, a nematode parasite, is well documented as a potentially fatal soil transmitted helminth, described as a unique and complex human parasite in Speare [1]. *S. stercoralis* is a cosmopolitan parasite, but is more prevalent in tropical regions of the world, including tropical Australia. Rural and remote regions of Australia, in particular, Queensland, Northern Territory, Western Australia, north of South Australia and northern areas of New South Wales, endemic rates [1-5]. Australia's Indigenous communities have high prevalence of strongyloidiasis (disease resulting from *S. stercoralis*) as do immigrants from other endemic countries, travellers to these countries and military personnel who have spent time in endemic regions [6,7]. Soulsby, Hewagama and Brady [8] report four cases of strongyloidiasis in non-Indigenous people resulting from work-related exposure presenting at Alice Springs Hospital and by implication acquired indirectly from Indigenous populations. Those infected included a teacher at an Indigenous school, a child care worker, an ex-nurse and a paediatrician. Very high prevalence rates are reported for Australian Indigenous communities [3,4,6,7,9,10]. Johnston, Morris, Speare, et al. [7] describe strongyloidiasis as a clinically important condition in Australia. Kline, McCarthy, Pearson, et al. [11] discuss major neglected tropical diseases in Oceania and emphasize strongyloidiasis as an important infection despite the lack of data on overall prevalence rates and clinical impact.

Strongyloidiasis in a community is evidence that individual(s) in that community has been exposed to *S. stercoralis* from soil contaminated by human faeces [6]. Infected individuals pass first

Author Summary

Strongyloides stercoralis, a nematode parasite, has a well-documented history of infecting human hosts in tropic and subtropic regions mainly through skin contact with inhabited soil. The result is strongyloidiasis, a human parasitic disease, with a unique cycle of auto-infection contributing to a variety of symptoms, of which, hyper-infection causing fatality may occur. In Australia, Indigenous community members often located in rural and remote settings, are exposed to and infected with strongyloides. Previous researchers report strongyloidiasis as a recurrent health issue for Indigenous Australians. This is a systematic review to determine the barriers to control for this pernicious pathogen. Barriers to control can be defined across three key themes: (1) health status, (2) socioeconomic status, and (3) health care literacy and procedure. By conceptualizing these barriers and addressing steps to control as outlined in this study, there is potential for improvement in prevention and treatment outcomes of strongyloidiasis and subsequently, overall health for Australian Indigenous people. This study contributes to furthering prevention and treatment of strongyloidiasis, increasing exposure to the issue of strongyloidiasis in Australian Indigenous people. It is the intent of this paper to express the need to have continued research and further health policy directed specifically to eradicate strongyloidiasis in Australian Indigenous communities.

stage larvae in the faeces; these develop on the soil to infective larvae which penetrate the skin of the next host. After a blood-lung migration, parasitic adult females (there is no parasitic male) molt and develop into adult female worms in tunnels in the small intestinal mucosa [12]. Eggs are then laid in the tunnels, hatch, and produce first stage larvae in the intestinal lumen. Most of these pass out in the feces. A small number, however, change to infective larvae in the gut. These autoinfective larvae penetrate the wall of the large intestine and re-enter the body. Hence, *S. stercoralis* is a very unusual nematode, producing infective larvae not only externally in the soil, but also internally [12].

The occurrence of the autoinfective larvae is the main reason strongyloidiasis is such a serious disease [12,13]. Infection is life-long since adult worms are replaced by young worms and the infection does not end when the original crop of adults die. Worm numbers can rise incrementally to produce severe disease, known as the hyperinfection syndrome. Autoinfective larvae, migrating from the lumen of the large intestine, can carry enteric bacteria into the body, resulting in sepsis in any organ. Of patients with the hyperinfection syndrome, 50% present with a septic event (pneumonia, septicaemia, meningitis, peritonitis) usually caused by an enteric bacteria or polymicrobial suite of enteric bacterial [14]. Complicating this is that *S. stercoralis* has an immunosuppressive effect [15,16]. Hyperinfection occurs mainly, but not exclusively, in the people who are immunocompromised or immunodeficient with a high case fatality rate of hyperinfection, at least 60% [6,7,9,10,13,17,18].

Strongyloidiasis is usually symptomatic [14] but most signs and symptoms are non-specific. The exception is with larva currens, a rapidly moving urticarial linear rash that marks the passage of an autoinfective larvae through the skin [14,19]. This is pathognomonic of strongyloidiasis. The other non-specific signs and symptoms can include gastrointestinal (e.g., abdominal pain, nausea, diarrhea, weight loss), respiratory (e.g., cough (productive and non-productive), haemoptysis, cutaneous (e.g., urticara) and general malaise [7,10,14,20]. Hyperinfective strongyloidiasis, in addition to the spectrum of acute-infection symptoms, can also clinically present as paralytic ileus, pulmonary haemorrhage, pneumonia, meningitis, septicaemia or other bacterial infections [6,10,14,16,18,20 22].

Diagnostic testing includes serology and faecal examination. Once diagnosed, strongyloidiasis can be eradicated with specific anthelmintics, ivermectin being the drug of choice [6,7,12,17]. The recommended treatment for strongyloidiasis has changed with the development of more effective anthelmintic drugs. Thiabendazole was the first moderately effective anthelmintic introduced in the mid-1970s [23,24]. Albendazole, a benzimidazole like thiabendazole, was recommended as the treatment of choice for strongyloidiasis about the mid-1990s [25]. It was replaced by ivermectin as first line recommended anthelmintic in the early 2000s [10].

In Australia, ivermectin is not licensed for children <5 years or for use in pregnancy [26,27], although there is no evidence of harm in these groups [10]. Albendazole is used for > 6 months and <10 kg to adults, not licensed for use during pregnancy [26 28]. Fatality from strongyloidiasis most often results from missed or late diagnosis, inadequate treatment and/or the use of immunosuppressant drug therapy in high risk groups [6,10,17]. Co-infection of strongyloidiasis with HTLV-1 is associated with more serious strongyloidiasis and potential resistance to treatment [10,15]. In addition, HTLV-1 carriers are more likely to develop T-cell leukaemia when infected with *S. stercoralis* [29 32].

There are questions about the limited information available about the prevalence, clinical picture, diagnosis and public health approaches to manage strongyloidiasis in rural and remote Indigenous communities in tropical regions of Australia [5,33]. Programs based on the treatment of stool positive individuals have also been associated with decreases in prevalence [7]. Researchers suggest that little published evidence of public health approaches to control strongyloidiasis exists [7,34] and there is a need to consider mass drug administration in Indigenous Australian communities with high prevalence of strongyloidiasis [10,11].

This systematic review attempts to answer the questions, what is the epidemiology of strongyloidiasis in Australian Indigenous people, and, what, if any, are the mentioned barriers to control? The aim of this review is to identify research focused on strongyloidiasis in this specific population and to collect and analyse available data specific to symptoms, diagnosis and treatment to determine barriers to control of strongyloidiasis. For the purpose of this paper, we respectively use the term Indigenous to represent Australian Aboriginal people and Torres Strait Islanders.

Methods

The outline and focus of this paper is framed on the concept of a translational research framework described by Thomson [35] within the Australian Indigenous HealthInfoNet. This systematic review was designed as a narrative review of the evidence as a way to summarise, explain and interpret evidence with thematic analysis [36].

This systematic review was based on the PRISMA statement, a tool to summarize accurate, reliable, quality evidence by way of transparent reporting (Checklist S1) [37,38]. A systematic search of health databases, Academic Search Premier, Informit, Medline, PubMed, AMED, CINAHL, Health Source Nursing and Academic was performed to search for all articles published 2012 and prior were included in the search. Articles were searched through the online academic search site, Google Scholar and

Table 1. Search strategy.

Number	Keywords
1	Strongyloidiasis or strongyloides
2	Strongyloidiasis or strongyloides and Australia
3	Strongyloidiasis or strongyloides and Australia and Aboriginal or Indigenous
4	Strongyloid* and Australia
5	Strongyloid* and Indigenous
6	Strongyloid* and Indig*
7	Strongyloid* and Aborig* or Abor*
8	parasite infe* and Australia and Abor*
9	para* infe* and Australia and Abor*
10	para* infe* and Australia and Indig*
11	strongyloid* and community
12	strongyloid* and health
13	parasite and infe* and Australia and indig*
14	gastro* infe* and Australia and abor*
15	pedia* and Australia and abor*
16	infectious disease and Australia and abor*
17	11 and 4 or 5 or 6 or 7
18	12 and 4 or 5 or 6 or 7
19	10 and 16 and 5 or 6 or 7
20	1 and 16
21	5 or 6 and 15
22	10 and 11
23	10 and 12

*asterisks added to root word to find all forms of word during library search.
doi:10.1371/journal.pntd.0003141.t001

internet searches for websites containing information about strongyloidiasis. Key search terms included strongyloidiasis, Indigenous, Australia, health, and community with search strategy developed to access the broadest range of articles about strongyloidiasis are presented in Table 1. Reference lists of original articles, review articles, grey literature and websites were searched for potential articles to review for inclusion. Language restrictions were not imposed.

To meet inclusion criteria, original qualitative or quantitative research articles contained content addressing one or more of the following: symptoms, diagnosis, treatment, and barriers to control of strongyloidiasis. The location of the studies had to be Australia and include Australian Indigenous people. Exclusion criteria included, review articles and non-peer reviewed literature, original research articles with animal only studies, pharmaceutical therapy only studies and studies not differentiating *S. stercoralis* or strongyloidiasis from amongst other parasites or parasitic infections.

Based on these selection criteria, articles were reviewed in two stages. First stage, article titles and abstracts were screened to meet the requirements of strongyloidiasis as topic, Australian location and inclusion of Indigenous Australians. Second stage, articles were read as full text. Articles meeting final criteria were included in the study. Figure 1 represents the overall article search outcome.

From the original research questions, (1) what is the epidemiology of strongyloidiasis in Australian Indigenous people? and (2) what, if any, are the mentioned barriers to control? Description of studies was collected and a thematic analysis conducted [36]. Key data extracted were: purpose of study, study design, participant description, symptoms, diagnosis, treatment, barriers to control, and author's conclusions. Articles were presented in a database with publisher details and summarized key data. The categories of symptoms, diagnosis, treatment and barriers to control were further assessed and coded using thematic analysis to determine recurring items in each. Symptoms were defined as manifestations of strongyloidiasis and included symptoms and signs due to strongyloidiasis and other existing concurrent conditions. Diagnosis was defined medical diagnoses including health status, tests performed and results.

Assessment of treatment of strongyloidiasis was based on the recommended therapy at the time of publication and defined as details on therapy provided and the comments on outcomes. Barriers to control were defined as a medical context, symptom and/or condition, or social determinant (derived from categories of symptoms, diagnosis, treatment and each authors' summary and conclusions) that inhibited overall health and/or recovery from strongyloidiasis of the individual(s). Once the barriers to control items were documented, they were then coded into barrier themes and health level. Detailing each barrier and the associating theme and level supports the translational knowledge concept by assisting to identify the relevant stakeholders [39].

Results

Figure 1 provides an overview of the literature search results. 340 articles were retrieved with a total of 16 articles, published

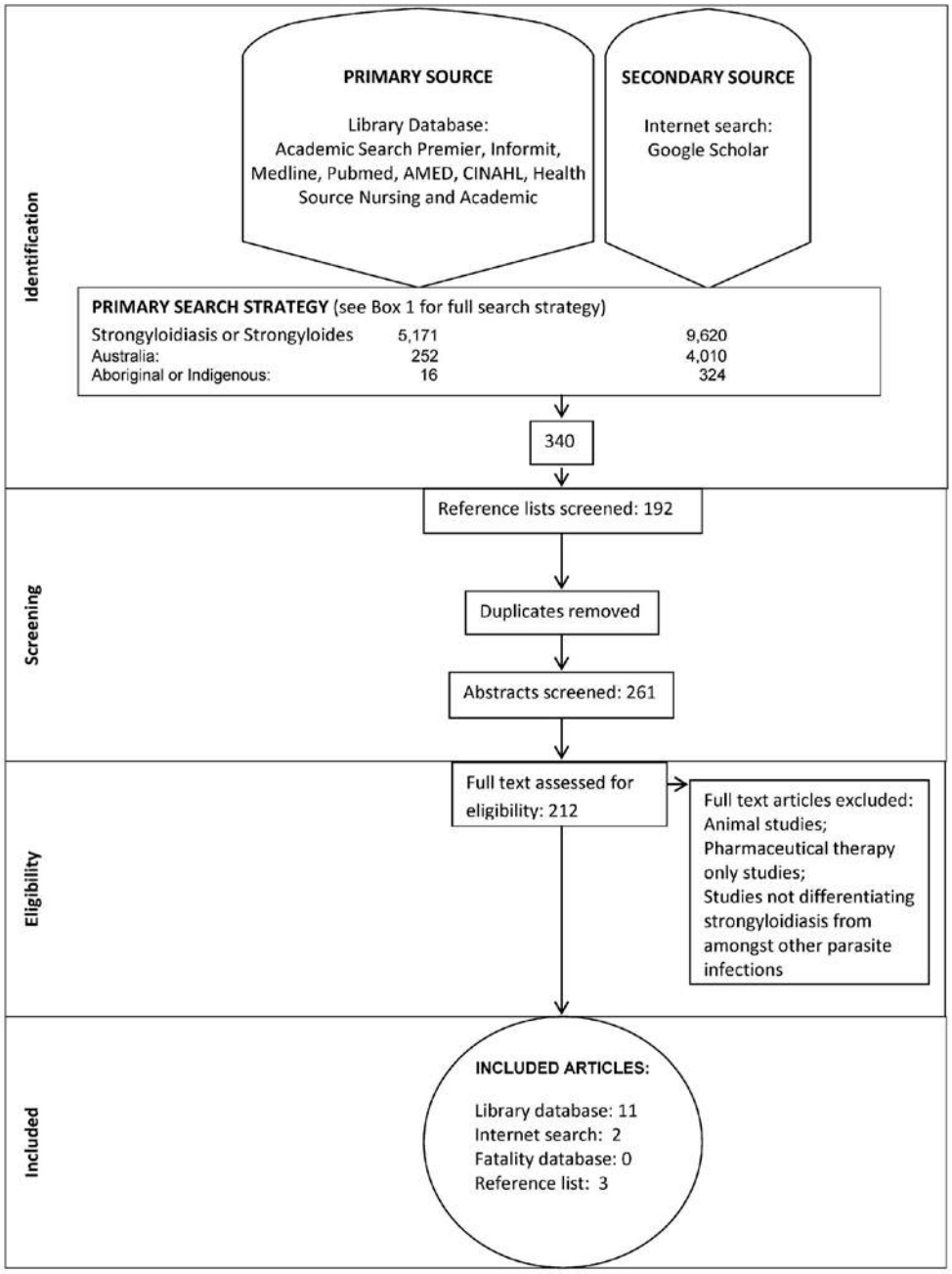

Figure 1. Flow diagram represents systematic review search based on the PRISMA statement reporting guidelines for systematic reviews and meta-analyses [38].
doi:10.1371/journal.pntd.0003141.g001

between 1969 and 2006, eligible for the systematic review and are summarized in Table 2. Eleven eligible articles were from electronic library databases. Google Scholar revealed two additional eligible articles. The reference lists reviewed from published articles, grey literature and internet websites reporting on strongyloidiasis infections of Indigenous people of Australia

Table 2. Summary of publications with original research on strongyloidiasis in Australian Indigenous people*.

Study	Purpose of Study	Study Location	participants+	Study Design
[4]	To investigate the biomedical consequences of lifestyle changes among communities in order to help people understand changes and to cope with them.	Arhhem Land, Northern Territory	403 Iac	Cross-sectional and longitudinal
[5]	To report prevalence and distribution of infections with *S. stercoralis* in communities.	Remote communities, Queensland	122 Ic	Retrospective
[21]	To present the case of one adult with 10 episodes of meningitis due to strongyloidiasis.	Fitzroy Crossing, Western Australia	1 Ia	Retrospective case
[22]	To report a case study of a child that demonstrates how clinically unsuspected strongyloidiasis progresses to hyperinfection after increase in immunosuppression medication.	Adelaide Childrens Hospital	1 Ic	Case
[16]	To describe a case of hyperinfection.	Royal Darwin Hospital	1 Ia	Case
[28]	To explore the utility of antibody tests for confirming cure of strongyldoidiasis in endemic population.	Arnhem land, Northern Territory	508 Iac	Case control
[15]	To determine whether complicated strongyloidiasis occurs in association with HTLV-1 infection.	Alice Springs Hospital	18 Iac	Retrospective case
[41]	To compare infection-related mortality rates and pathogens associated for Indigenous and non-Indigenous adults.	Alice Springs Hospital	351 Ia; 162 Na	Retrospective comparison
[40]	To compare bloodstream infection rates, pathogens and mortality among Indigenous and non-Indigenous adults.	Alice Springs Hospital	614 Ia; 69 Na	Retrospective comparison
[42]	To report biopsy findings using histological assessment and examination under dissecting microscope in intestinal mucosal biopsies from children.	Royal Alexandra Hospital for children	30 Ic	Prospective comparison
[43]	To indicate the extent or severity of diarrheal disease in children in communities.	Kimberley region, Northern Territory	100 Ic	Prospective
[44]	To show that the severity of diarrheal disease in children as a consequence of underlying small intestinal mucosal damage.	Royal Darwin Hospital, Northern Territory	339 Ic; 36 Nc	Prospective comparison
[45]	To describe clinical presentation, diagnosis and management of strongyloidiasis and to identify predisposing factors.	Townsville General Hospital	9 Iac; 5 Nac	Retrospective
[46]	To describe strongyloidiasis in children.	Darwin Hospital	8 Ic	Case
[50]	To describe clinical and laboratory features of strongyloidiasis.	Royal Darwin Hospital	64 Iac; 4 Nac	Retrospective
[51]	To present the case of an infant with meningitis and who subsequently developed complete small-intestinal obstruction.	Royal Alexandra Hospital for Children	1 Ic	Case

+a = Adult(s); c = child(ren), ac = adult(s) and child(ren), I = Indigenous; N = non-Indigenous;
*For the purpose of this paper, we respectively use the term Indigenous to represent Australian Aboriginal people and Torres Strait Islanders.
doi:10.1371/journal.pntd.0003141.t002

revealed three eligible articles. Study design included case studies, retrospective and prospective comparison and non-comparison studies. Participant numbers ranged from 1 to 683. Indigenous Australian children were reported in 12/16 studies, of those 8/12 reported children only. Indigenous Australian adults were reported in 7/16 studies, of which 4/7 reported adult only. Thirteen studies were conducted in hospital and four in Indigenous communities. Eleven studies examined strongyloidiasis only with the remaining discussing the parasitic infection in the context of other infections [40,41] or while examining gastrointestinal issues [42 44].The 16 papers included 2537 Indigenous participants and 272 non-Indigenous participants.

Eleven papers described manifestations of strongyloidiasis, including symptoms and signs due to strongyloidiasis as well as other concurrent conditions (Table 3). Studies noted strongyloidiasis symptoms such as diarrhoea, malnutrition and anorexia, abdominal pain, abdominal distension, anemia, septicaemia, and fever. Other concurrent conditions including Type 2 Diabetes, Lupus, Chronic Liver Disease and Chronic Lung Disease, Alcoholism, Pneumonia, Bronchitis, COPD, Acute Rheumatic Fever, Acute Renal Failure and/or general gastrointestinal, cardiac and respiratory problems were reported. Gunzburg, Gracey, Burke, et al. [43] reported only diarrheal symptoms as this was the scope of the study. Page, Dempsey, and McCarthy [28] and Prociv & Luke [5], although studying strongyloidiasis specifically, did not focus on symptomology. Four studies [4,15,40,42] did not discuss symptomology due to the aim of the study.

All sixteen studies provided data on diagnosis of strongyloidiasis determined by one or more tests (Table 4). Nine studies performed purposeful testing [4,5,21,28,40 43]. Five studies reported *strongyloidiasis* had been diagnosed when not suspected [15,22,42,45,46].

Articles were reviewed for the adequacy of treatment noting that recommended therapy has changed with time (Table 5). Eight

Table 3. Manifestations of strongyloidiasis in Indigenous Australian patients*.

Study	Participant details +	Other condition	Symptoms/signs due to strongyloidiasis
[4]	403: 10 yr and older	hepatitis B	not listed
[5]	122: under 15 yr	not listed	not listed
[15]	513: 351 Ind; 162 Non	not listed	not listed
[16]	1 female 18 yr	Grade-IV lupus glomerulonephritis (LG) with nephrotic syndrome, hypertension, febrile neutropenia, chronic gastric erosions, non-insulin dependent diabetes, poor cardiovascular and respiratory function	diarrhea, abdominal pain, anorexia
[21]	1 male adult	recurring meningitis, alcoholism	*E. coli* septicaemia
[22]	1 female 12 yr	Systemic lupus erythematosus, paralytic ileus, candidiasis, pneumonia	anemia, headache, back pain, fever, confusion, bacterial septicaemia
[28]	508: 13 yr and older	not listed	not listed
[40]	614 Ind; 69 Non: under 15 yr	not listed	not listed
[41]	18 Case series (C) (4 detailed): C1 female 39 yr; C2 male 29 yr; C3 male 32 yr; C4 male 41 yr	C1 chronic liver disease, alcoholism, shoulder pain, epigastric pain, cachectic; C2 peripheral neuropathy, chronic liver disease, alcoholism, HTLV-1, hepatitis B, pleuritic chest pain, productive cough, dyspnea; C3 chronic liver disease, alcoholism, bilateral crackles, wheeze, dyspnea, hypotensive; C4 Type 2 diabetes, chronic liver disease, alcoholism, hypotensive, crackles, wheeze, acute renal failure, intravascular coagulopathy	C1 abdominal pain, severe pruritus, diarrhea, faecel incontinence; C2 abdominal pain, diarrhoea; vomiting, septic shock; C3 abdominal pain, pruritus, diarrhea; C4 Fever, diarrhea, abdominal pain
[42]	3: 1–5 yr	not listed	partial villous atrophy of third degree
[43]	100: 0–5 yr	not listed	Diarrhea
[44]	338 Ind; 37 Non: children	hypokalemia; cryptosporidium	diarrhoea; malnutrition
[45]	9 Case series: C1 17mos;C2 42 yr; C3 49 yr; C4 11yr; C5 7mo; C6 17 yr; C7 30 yr; C8 1 yr; C9 26 yr	C1 croup; C2 alcoholism, COPD, trichuriasis; C3 no details; C4 nil; C5 bronchitis, cryptosporidiosis; C6 alcoholism, trichuriasis; C7 systemic lupus erythematosus, alcoholism, giardiasis; C8 Giardiasis; C9 Alcoholism, trichuriasis, toxic epidermal necrolysis, allergies	C1 diarrhoea, rash; C2 abdominal pain; C3 no details; C4 diarrhoea; C5 diarrhoea; C6 abdominal pain, diarrhea, nausea, vomiting/C7 pruritus, death; C8 diarrhoea, vomiting, rash; C9 diarrhoea, septicaemia, recurrent infections
[46]	3 Case series: C1 1 yr; C2 2 yr; C3 4 yr	C1 anaemia; C2 bronchitis, otitis media; C3 acute rheumatic fever	C1 diarrhoea, failure to thrive, hypokalemia, hypernatremia, partial intestinal obstruction; C2 gastroenteritis, hypokalemia, partial intestinal obstruction; C3 gastroenteritis, intestinal obstruction
[50]	68: 64 Ind; 3 Non	Alcoholism, scabies (and "other" parasites), pulmonary disease, congestive cardiac failure	anaemia, diarrhea, gastrointestinal symptoms, malnutrition
[51]	1 female 6mo	Pneumonia, *H. influenza*, meningitis	Intestinal obstruction with granulomata around larvae, vomiting, abdominal distention
Total	**2537 Ind; 272 Non**		

+Participant details: Indigenous Australian unless otherwise specified, Ind = Indigenous, Non = non Indigenous.
*For the purpose of this paper, we respectively use the term Indigenous to represent Australian Aboriginal people and Torres Strait Islanders.
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articles discussed the use of one or a combination of albendazole, thiabendazole and ivermectin. Three articles described a subgroup of patients receiving no therapy [28,42,45] and one article mentioned the use of pyrantel only for strongyloidiasis [5]. Pyrantel is ineffective against *S. stercoralis* [47]. In two articles, prednisolone or prednisone, a treatment which suppresses the immune system and as a result can increase the severity of strongyloidiasis, was administered to patients. Walker-Smith [42] discussed diagnoses of giardiasis and strongyloidiasis in children and provided no data on treatment. Einsiedel & Fernandes [15] detailed treatment therapies across four case studies, of which, only one case received correct strongyloidiasis treatment with ivermectin. Overall, adequate treatment was documented in publications in only 5.2% of cases.

Barriers to control of strongyloidiasis were summarized in terms of item, theme and health access level (Table 6). Three barriers themes emerged as items contributing to adequate management of strongyloidiasis: (1) health status; (2) socioeconomic status; (3) health care literacy and procedures. Theme 1, health status was defined patients' health prior to and at the time of diagnosis of strongyloidiasis. This included concurrent infections (e.g., meningitis, pneumonia), concurrent chronic health conditions (e.g., Lupus, Chronic Liver Disease, Chronic Lung Disease, Acute Rheumatic Fever, HTLV-1, Hepatitis B, alcoholism, immunocompromised, immunosuppressed) and the phenomenon of strongyloidiasis (e.g., re-infection, hyperinfection, at times asymptomatic, chronic diarrhoea, septicaemia). Theme 2, socioeconomic status included living conditions, racial disparities, communication (e.g., interaction between community, patients, health professionals/institutions).Theme 3, health care literacy and procedures involved barriers that influence the diagnosis and treatment outcomes (e.g., delayed diagnosis, difficult to detect, failure to recognize symptoms, inadequate knowledge/treatment/treatment dose, serology test cut off, lack of communication, lack of screening, lack of follow-up, treatment non-compliance).

Table 4. Tests performed to diagnosis patients' condition not necessarily specifically related to strongyloidiasis diagnosis.

Study	Tests Performed
[4]	Blood; Stool
[5]	Stool
[15]	Abdominal scan; Chest x-ray; Serology; Stool
[16]	Abdominal scan; Brain scan; Chest x-ray; Blood; Stool
[21]	Cerebral spinal fluid protein level/neutrophil count; CT scan; Blood; Stool
[22]	Cytology; Gastric aspirate; Lung biopsy
[28]	Serology
[40]	Blood
[41]	Serology
[42]	Intestinal biopsy
[43]	Stool
[44]	Blood; Stool
[45]	Stool
[46]	Abdominal x-ray; Chest x-ray; Gastric aspirate
[50]	Stool
[51]	Abdominal x-ray; Abdominal x-ray/barium enema; Gastric aspirate; Laparotomy; Lumbar puncture; Stool

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Einsiedel & Fernandes [15] had the largest number of symptoms and signs and other conditions associated with barriers to control of strongyloidiasis. The top four barriers listed most often (determined by the most barriers per article, total of 4) were delayed diagnosis, inadequate treatment, living conditions and malnutrition. Barriers to control are located across all four health access levels: (1) Individual; (2) Public/Community; (3) Organization; and (4) Healthcare system.

Discussion

This study reviewed original articles on strongyloidiasis in Indigenous Australian people. Articles were analyzed for symptoms, diagnosis and treatment and barriers to control of Strongyloidiasis. Overall outcomes are presented as *symptomology, diagnosis and treatment protocols, community research and action and addressing barriers to control.*

Symptomology

The broad spectrum of symptoms, as represented in manifestations of strongyloidiasis in Table 3, illustrates the complex nature of Strongyloidiasis that is so often misdiagnosed. Many of these manifestations, such as diarrhoea, stomach pain, malnutrition, dehydration and vomiting are common to many illnesses and diseases. As described by researchers [6,15,16,20,43,45,46], strongyloidiasis can present many varying symptoms or be asymptomatic [43,46]. It is important to recognize that strongyloidiasis can potentially exist for years presenting often with non-specific symptoms and signs (e.g., diarrhoea) as well as at times with periods without symptoms.

Hyperinfection. Einsiedel and Fernandes [15], Byard, Bourne, Matthews et al., [22] and Potter, Stephens and De Keulenaer [16] report specific cases of hyperinfection. Of these 4 specific cases fatality occurred in two of these studies [15,22]. Results support previous research indicating that cases of hyperinfection and fatality may be prevented the earlier strongyloidiasis is diagnosed as undetected strongyloidiasis over longer periods lead to this outcome. Adams, Page and Speare [6] and Speare and Durrheim [12] report attention must be paid to those who are immunocompromised and, in all cases, steroid medication should not be administered until a diagnosis of strongyloidiasis is confirmed or ruled out. Early diagnosis increases probability of recovery. The possibility of hyperinfection or disseminated strongyloidiasis in immunocompromised patients, particularly in endemic areas, needs consideration [48]. The current protocol in place is to give the first dose of ivermectin when strongyloidiasis is suspected (i.e., when blood or faeces is taken) and then to give follow-up doses when test are positive. For those from a high prevalence area taking an immunosuppressive treatment (and until finished) are to continue with follow up strongyloidiais treatment every three months [26,27,49].

Diagnosis and treatment protocols

Delayed diagnosis, inadequate knowledge/treatment/treatment dose, lack of communication and lack of follow up by health professionals were described as particular issues in the majority of studies [5,15,16,22,29,40,44,45,50,51]. Infection should be suspected in every person with unexplained abdominal pain, diarrhoea, cutaneous symptoms or eosinophilia and the laboratory alerted of a provisional diagnosis [45]. Testing for strongyloidiasis is particularly important for patients from populations in *S. stercoralis* endemic areas. Rural and remote Indigenous communities (more specifically northern Australia) and including immunocompromised patients are at particular risk for hyperinfecion before administering immunosuppressive medication [22]. Protocol including clinical screening index, stool microscopy and culture, full blood count, immunoglobulin levels, and serological testing is recommended [22].

Majority of studies reported Indigenous Australian children with strongyloidiasis suggesting a diagnosis of strongyloidiasis should be considered when Indigenous children presenting with even non-suspecting general gastro-intestinal symptoms. Mucosal damage in Indigenous Australian children is possibly a result of damage produced by repeated episodes of gastroenteritis and/or parasitic infection, including strongyloidiasis [42]. Reduction in

Table 5. Assessment of whether cases reported in papers were adequately treated according to the recommended anthelmintic for that time.

Study	Anthelmintic used	Comment	Total	Evidence*	%
[4]	No comment on treatment	Total 411 (positive: 60% serology; 41% faeces)	246	0	0
[5]	Pyrantel used as a routine de-wormer in Queensland Aboriginal health program – does not treat strongyloidiasis; thiabendazole given for strongyloidiasis (sometimes) but usually for 2 days not 3; so arguably none received adequate treatment	Multiple cases in children (<16yr) – 1971–1991: thiabendazole used, but probably not for most cases; comment made that children often refused drug due to unpleasant side effects	632	0	0
[15]	Albendazole = 1 (single dose); Ivermectin = 3; No treatment = 14	In 18 patients treatment was inadequate since 14 no treatment; 1 single dose albendazole; 3 single dose of ivermectin. (15/18 patients died)	18	0	0
[16]	Albendazole and ivermectin (sequence)	Treatment successful	1	1	100
[21]	No comment on therapy	1 adult male	1	0	0
[22]	No comment	Indigenous female child with hyperinfection	1	0	0
[28]	Albendazole single = 10 (inadequate); Albendazole multiple = 10 (adequate); Ivermectin single =19 (inadequate); Ivermectin multiple = 42 (adequate)	Was a critical paper in that demonstrated albendazole was less effective than ivermectin; hence, both albendazole and ivermectin considered adequate	79	52	66
[40]	No comment	Study on blood stream infection	73	0	0
[41]	No comment	Study on deaths in hospitalized patients	2	0	0
[42]	None described	Not stated how many children had *S. stercoralis*			
[43]	No comment on treatment	12 children with *S. stercoralis* in faeces	12	0	0
[44]	No comment	Study on diarrhoea in children admitted to Royal Darwin Hospital	23	0	0
[45]	Thiabendazole	Of 6 adults, 4 adequately treated; Of 3 children, 2 adequately treated	9	6	67
[46]	Thiabendazole	Case 1: 1 course of unstated length; eosinophilia on discharge; Case 2: No details; eosinophilia on discharge; Case 3: No details	3	0	0
[50]	Thiabendazole	Details for Indigenous patients not given; comment made that 57% of all (not just Indigenous) patients received adequate treatment	64		57 (54–61)
[51]	Thiabendazole multiple doses and courses	No larvae found at end and eosinophil count normal	1	1	100
Total			**1165**	**60**	**5.2**

*Evidence of adequate treatment.

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the frequency of gastroenteritis and parasitic infection in Indigenous children should greatly reduce incidence of small intestinal mucosal damage [42]. Working to eradicate or reduce strongyloidiasis infection in children with early detection and immediate treatment could decrease strongyloidiasis and mucosal damage. Given the challenges of diagnosing infection, standardizing treatment in communities for an extended period could potentially decrease infections rates [5].

Lack of follow-up. There was a repeated lack of follow-up within and across cases of strongyloidiasis [15,45,50]. It is quite possible that patients treated for stronygloidiasis may continue to carry the infection as has been presented in cases with people suffering from strongyloidiasis infection for years after initial exposure [16,21]. This is problematic for a number of reasons. There is increased health risk to the patient as a result of continued infection including hyperinfection and fatality. The lack of awareness of continued infection in patient leads to increased risk for infection in the patients' community and decreases awareness by health professionals and community for need to eradicate the infestation within community and finally. This leads to inadequate reporting of strongyloidiasis in communities and under-representation of strongyloidiasis prevalence rates. Diagnosis and treatment of strongyloidiasis is challenging and requires specific knowledge. This knowledge must be acquired and maintained by health professionals in Australia and in particular, when assisting Indigenous Australian community members [6]. Assistance begins not only at the point of care in the hospital but also at the community level.

Treatment. The low rate of adequate treatment documented in the cases reported in the literature is of concern (Table 5). Einsiedel and Fernandes [15] highlighted that many (14/18) Indigenous patients in Central Australia received no treatment. Our reassessment of the four patients that did receive treatment in their series showed that all regimes were inadequate. Serological diagnosis means that confirmation of strongyloidiasis is usually delayed and for patients in remote areas of Australia this delay may have extended to several weeks [12]. As a result some clinicians used the approach that if a sample was collected for *S. stercoralis* serology the patient should receive the first dose of ivermectin [48]. Subsequent management would then depend on the serological result.

Community research and action

Parasitic diseases have significant health risk and morbidity for Australian Indigenous people [11,20]. Rural and remote communities are the most affected [3,18]; mainly in children; and those

Table 6. Barriers to control of strongyloidiasis.

Item described in one or more studies	Barrier Theme[+]	Level[*]	[4]	[5]	[15]	[16]	[21]	[22]	[28]	[40]	[41]	[42]	[43]	[44]	[45]	[46]	[50]	[51]
Antibiotic prior treatment	(1)(3)	(1)(2)(3)(4)								Y								
Chronic Diarrhoea	(1)(3)	(1)														Y		
Concurrent Chronic Infections	(1)(2)(3)	(1)(2)(4)					Y	Y										
Concurrent Health Conditions/Disease	(1)(3)	(1)(2)(3)			Y	Y	Y									Y		
HTLV-1	(1)(2)	(1)(2)(3)(4)			Y													
Immunocompromised	(1)(3)	(1)(3)						Y										
Immunosuppression	(1)(3)	(1)(3)			Y	Y												
Sepsis	(1)(3)	(1)(3)			Y		Y											
Malignancy	(1)	(1)			Y													
Malnutrition	(1)(2)	(1)(2)(4)			Y									Y		Y		
Hypokalemia	(1)	(1)(3)												Y				
Hyperinfection	(1)(3)	(1)(3)(4)			Y	Y	Y	Y										
Re-infection	(1)(2)(3)	(1)(2)(3)(4)					Y		Y	Y								
Asymptomatic	(1)(3)	(1)											Y			Y		
Delayed Diagnosis	(2)(3)	(3)(4)			Y	Y		Y							Y			
Difficult to detect	(1)(2)(3)	(3)(4)						Y										
Failure to Recognize Symptoms	(3)	(3)(4)			Y		Y											
Inadequate Knowledge	(3)	(3)(4)		Y	Y		Y					Y						
Inadequate Treatment	(3)	(3)(4)			Y	Y						Y				Y	Y	Y
Inadequate treatment dose	(3)	(3)(4)		Y														Y
Serology test cut off	(3)	(3)(4)							Y									
Lack of Communication	(2)(3)	(2)(3)(4)			Y													
Lack of screening	(3)	(2)(3)(4)																Y
Lack of/Inadequate Follow-up	(2)(3)	(1)(2)(3)(4)			Y										Y		Y	
Treatment Non-compliance	(1)(2)(3)	(1)(2)(3)(4)		Y			Y								Y			
Racial Disparities	(2)(3)	(1)(2)(3)(4)									Y							
Lower SES	(1)(2)(3)	(1)(2)(4)	Y				Y			Y								
Living conditions	(1)(2)	(1)(2)(4)	Y				Y			Y	Y			Y				

Y = at least one incident of symptom or condition or determinant reported in one or more patients.
+(1) Prior/current health status; (2) Overall SES status; (3) Health care knowledge and procedures.
*(1) Individual; (2) Public/Community; (3) Organization; (4) Healthcare system.
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immunocompromised with a number of cases of fatality reported [15,22,40,41]. Studies in 2002 and 2005 report there are limited published examples of community interventions in Australia to control strongyloidiasis [7,52]. Johnston, Morris, Speare, et al. [7] found no evidence of studies examining roles of environmental interventions and expressed the need to do so. The need for initiatives for housing and sanitation are imperative [15]. Issues of environmental health must be addressed concurrently with health service initiatives to develop long term and sustainable improvements in control of infectious parasitic and non-parasitic diseases in rural and remote Indigenous communities in Australia [10,11,20]. There may be increased risks associated with a casual approach to management and may be significantly higher for Indigenous Australian people living in HTLV-1 endemic Central Australia [10,40]. Einsiedel and Woodman [40] further state the risk of strongyloidiasis in Indigenous communities and HTLV-1 infection may further predispose people to complicated strongyloidiasis.

Addressing barriers to control

Steps to address the barriers to control should include: (1) development of *S. stercoralis* and strongyloidiasis reporting protocols across health care system and communities (e.g., consistent case study reporting methods, documentation of current infection sites) [6,40]; (2) testing all Indigenous Australian patients, immunocompromised patients and those exposed to or living in areas of strongyloidiasis (e.g., rural/remote communities) presenting with gastrointestinal or respiratory symptoms (take particular notice of individuals from these groups with repeated visits to hospital) [7,15,16,48]; (3) requirement of health professionals to have detailed information and education regarding strongyloidiasis and the potential for exposure in Indigenous Australian communities (e.g., understanding of the expanse of symptoms and potential for asymptomology, difficulty in diagnosis, need for variety of tests and retesting, accurate follow-up to confirm patient cleared of infection) [5,15,21,42]; (4) establishment of testing and treatment initiatives in the community (e.g., over extended periods and periodically and treat symptomatic and asymptomatic strongyloidiasis carriers) [6,10,12,15,45]; (5) measure and report prevalence specific to Indigenous Australian communities and to act with initiatives based on these results [6,12,40].

Limitations. Studies analyzed for this review had an overall lack of detailed information on prevalence rates, diagnosis and treatment outcomes. Repeated lack of follow-up made it difficult to determine outcomes for those reported infected with strongyloidiasis in studies. In addition, a number of articles [5,15,50] conducted retrospective studies of hospital records with reported missing data, missing records and inconsistent reports. Case studies did not have a consistent reporting protocol to facilitate analysis within and across cases. It was unfortunate that a number of studies had to be excluded from this review as they had gathered overall parasite infection data in Indigenous Australian communities but had not further represented data by parasite (e.g., hookworm, *S. stercoralis*). This data would have been potentially valuable for increasing both the evidence and support to further define strongyloidiasis a problem for Indigenous Australians.

Conclusions. If barriers are managed, current research and the health care system can report accurately and provide the data required to support initiatives to eradicate strongyloidiasis in Indigenous Australian communities. Addressing these barriers would support conclusions of researchers that health education and public health interventions and guidelines for mass treatment with follow-up for effective treatment are essential [6,10,11]. As Einsiedel and Woodman [40] state sustainable improvements require a coordinated approach based on dialogue, cultural understanding and development of locally specific solutions by Indigenous people themselves. This comprehensive focus with Indigenous Australian people and their communities on strongyloidiasis is imperative. Community initiatives to eradicate endemic parasite infection such as hookworm have had success and there is potential to do the same with *S. stercoralis* [10].

Supporting Information

Checklist S1 PRISMA 2009 checklist [38] utilized in systematic review with referring page numbers, tables and figures represented in manuscript.
(DOC)

Author Contributions

Analyzed the data: AM MLS JAJ RS. Wrote the paper: AM MLS JAJ RS.

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3.5.3 Speare R, Miller A, Page W. Strongyloidiasis: a case for notification in Australia?

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Strongyloidiasis: a case for notification in Australia?

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3.6 H1N1 Influenza Papers

3.6.1 Miller & Durrheim. Aboriginal and Torres Strait Islander communities forgotten in new Australian Pandemic Action Plan: 'Ask us, listen to us, share with us'.

Aboriginal and Torres Strait Islander communities forgotten in new Australian National Action Plan for Human Influenza Pandemic: "Ask us, listen to us, share with us"

Adrian Miller and David N Durrheim on behalf of the Aboriginal and Torres Strait Islander Community Influenza Study Group

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3.6.2 Massey, Miller, Durrheim, Speare, Saggers, & Eastwood. Pandemic influenza containment and the cultural and social context of Indigenous communities.

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LETTER TO THE EDITOR

Pandemic influenza containment and the cultural and social context of Indigenous communities

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Dear Editor

The World Health Organization has directed nations to prepare for a future influenza pandemic. While many countries have developed comprehensive plans, the needs of marginalized communities have often been neglected. In recognition of these weaknesses in current planning practice we strongly support the call that 'the time is now' for genuine and respectful partnerships to redress yet another omission for Indigenous people[1,2].

Pandemic plans emphasise non-pharmaceutical containment measures, including early recognition and isolation of suspected cases, quarantining of contacts, and social distancing. Although the Australian plan recognizes the increased risk for Indigenous people, it does not acknowledge that Indigenous Australians must inform containment strategies if these are to be appropriate and effective for all Australians[3]. A review of 37 national pandemic plans found that plans, including the Australian plan, inadequately addressed the needs of socially and economically disadvantaged communities in their disease containment policies[4].

Indigenous Australians, particularly in rural and remote areas, experience profound social disparity, including overcrowding, excess co-morbidity, poor access to health care, communication difficulties with health professionals, reduced access to pharmaceuticals, and institutionalized racism[5]. History clearly demonstrates the devastating toll of previous influenza pandemics on Indigenous Australians. During the 1918–1919 pandemic, mortality rates approaching 50% were reported in some Australian

Indigenous communities, compared with the national rate of 0.3%[6]. The leprosy control program used in Aboriginal communities in the past included isolation, incarceration and other punitive measures that caused much fear. The fear drove people into hiding and increased the disease risk for families and communities[7].

In order to avoid further marginalization, stigmatization and inequality, we must ensure that the call to 'close the gap' does not become another shallow slogan[1]. Decisions on appropriate pandemic containment measures need to be made in genuine partnership with communities, recognizing that some cultural practices may amplify or reduce infection risk[8].

During a recent focus group discussion with Indigenous people from Aboriginal medical services and Aboriginal health services in a rural area of Australia, concerns were raised about the currently recommended pandemic social distancing and other infection control strategies. Many of these concerns were associated with individual and group memories of intrusive government surveillance and control of Indigenous people in the past. These memories impacted on people's responses to contemporary government policy. Planned policies to control and contain outbreaks may meet with the same passive and active resistance that past government policies provoked[9].

Public health experts must work with communities in genuine and respectful partnership to define what pandemic containment measures are culturally appropriate and acceptable. The basis of genuine and respectful partnerships is captured in the human rights approach, which demands that individuals and communities are adequately involved in the decisions that affect their wellbeing. These are essential first steps[10]. History has shown that Indigenous Australians must be involved in decision-making processes that impact on their health in order to link genuine and respectful partnerships to aspirations for self-determination of Indigenous communities and organisations. The consequences of inflexibly enforcing a non-Indigenous model of containment will be dire.

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3.7 Extension on the Research

3.7.1 Quiñones-Parra, Grant, Loh, Nguyen, Campbell, Tong, Miller, Doherty, Vijaykrishna, Rossjohn, Gras, & Kedzierska. Pre-existing CD8$^+$ T cell immunity to the novel H7N9 influenza A virus varies across ethnicities

Preexisting CD8$^+$ T-cell immunity to the H7N9 influenza A virus varies across ethnicities

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Contributed by Peter C. Doherty, December 4, 2013 (sent for review November 8, 2013)

The absence of preexisting neutralizing antibodies specific for the novel A (H7N9) influenza virus indicates a lack of prior human exposure. As influenza A virus–specific CD8$^+$ T lymphocytes (CTLs) can be broadly cross-reactive, we tested whether immunogenic peptides derived from H7N9 might be recognized by memory CTLs established following infection with other influenza strains. Probing across multiple ethnicities, we identified 32 conserved epitopes derived from the nucleoprotein (NP) and matrix-1 (M1) proteins. These NP and M1 peptides are presented by HLAs prevalent in 16–57% of individuals. Remarkably, some HLA alleles (A*0201, A*0301, B*5701, B*1801, and B*0801) elicit robust CTL responses against any human influenza A virus, including H7N9, whereas ethnicities where HLA-A*0101, A*6801, B*1501, and A*2402 are prominent, show limited CTL response profiles. By this criterion, some groups, especially the Alaskan and Australian Indigenous peoples, would be particularly vulnerable to H7N9 infection. This dissection of CTL-mediated immunity to H7N9 thus suggests strategies for both vaccine delivery and development.

CD8 T cells | HLA types

Emerging unexpectedly in February 2013, the H7N9 influenza A virus (IAV) has thus far caused 137 human infections with 45 deaths (1). Clinical manifestations include major respiratory compromise, multiorgan failure, and exceedingly high serum cytokine and chemokine levels (2). Although May through September saw only five such cases, two more were recorded in October (1), indicating that H7N9 may return during the northern winter. Furthermore, the presence of a natural avian reservoir and the severity of the disease emphasized the need to focus on protective immunity. Most patients had contact with poultry within a week before clinical onset (2), suggesting that domestic birds are the source (2, 3). Even so, the potential for person-to-person spread is highlighted by ferret experiments (4) and instances of infection via close family contact (3). A very real concern is that further mutations may facilitate human-to-human transmission (5).

Evidence from animal (6) and human studies (7–9) suggests that, in the absence of neutralizing antibodies (NAbs), preexisting memory CD8$^+$ T lymphocytes (CTLs) directed at conserved and/or cross-reactive IAV peptide + class I HLA (pHLA1) epitopes can diminish disease severity. The recall of IAV-specific CTLs promotes recovery manifested by milder symptoms, diminished virus shedding and transmission (6, 7). A comprehensive analysis of the 2009 pandemic H1N1 IAV (H1N1pdm-2009) indicated that CTL memory provided some protection for the antibody naïve (9). Thus, cross-reactive CTL memory generated after a prior encounter with seasonal or pandemic IAVs, or by a CTL-directed vaccine, could potentially limit the severity of an H7N9 pandemic.

The present analysis probes the extent of preexisting CTL immunity in populations that have not been exposed to the H7N9 virus. This potential for CTL recall is defined for HLA1s that are differentially prominent in various ethnicities. Using an evolutionary and immunological approach, we show substantial levels of immunogenic peptide conservation for nucleoprotein (NP) and matrix-1 (M1), with estimated coverage according to known HLA1 presentation profiles ranging between 16% and 57% of the global population. Overall, the findings support the view that it is important to consider developing vaccines with a T cell–based component that has the potential to protect against severe novel IAV infections. Furthermore, given that some ethnicities, including Australia's Indigenous and Alaskan people, show evidence of a diminished HLA1-related response capacity, it is essential that health policy development and planning gives such groups priority in IAV vaccination campaigns. The 2009 H1N1 pandemic caused higher attack rates and morbidity among Indigenous populations in the Americas, New Zealand, and Australia (10).

Results

Conservation of CTL Antigenic Regions in the Novel H7N9 Virus. The first step was to establish which known immunogenic IAV

Significance

The severity of the novel H7N9 influenza A virus (IAV) and the lack of neutralizing antibodies raise real pandemic concerns. In this scenario, CD8$^+$ T lymphocytes (CTLs) may provide a layer of protection against the H7N9 virus. Our study dissects the extent of preexisting CTL immunity with the potential to respond to H7N9. We identified conserved immunogenic peptides with the capacity to elicit robust CTL responses against any human IAV, including the H7N9 virus, as well as the mutations that abolish CTL recognition. The human leukocyte antigen class I molecules that present these peptides vary in prevalence depending on the ethnicity. Such analyses found that the Alaskan and Australian Indigenous people may be particularly vulnerable to the H7N9 influenza disease.

Author contributions: S.Q.-P., E.G., L.L., P.C.D., S.G., and K.K. designed research; S.Q.-P., E.G., L.L., T.H.O.N., K.-A.C., D.V., and S.G. performed research; S.Q.-P., E.G., L.L., D.V., S.G., and K.K. analyzed data; and S.Q.-P., S.Y.C.T., A.M., P.C.D., D.V., J.R., S.G., and K.K. wrote the paper.

The authors declare no conflict of interest.

Data deposition: The atomic coordinates and structure factors have been deposited in the Protein Data Bank, www.pdb.org (PDB ID code 4NQV for NP44-A1 and 4NQX for NP44-S7N).

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peptides are conserved within H7N9, using IAVs that caused major human pandemics or epidemics as a reference (Table S1). Included were the pandemic H1N1-1918 A/Brevig Mission/1, H2N2-1957 A/Japan/305, H3N2-1968 A/Hong Kong/16 and H1N1-2009 A/Auckland/viruses, and seasonal H1N1 IAVs from 1933, 1983, and 2006. Our focus was on peptides from the prominent NP and M1 (11, 12) proteins, as identified in the Immune Epitope Database (www.immuneepitope.org). We found a substantial level of conservation within NP (Fig. 1*A*) and M1 (Fig. 1*B*) with respect to H7N9-derived pHLA1 epitopes (Fig. 1). Analysis of 76 NP peptides established that 12 were conserved (Table S2), whereas 18 were unique to H7N9 and had not been found previously (Table S3). The remaining 46 were classified as variable (Fig. 1*A*), meaning that they are shared by at least one IAV isolated before the advent of H7N9-2013 (Table S4). Evidence of such conservation was even higher for M1 (Fig. 1*B*). Of 39 peptides, 20 were conserved, 9 were unique to H7N9, and 10 variable (Tables S5–S7). Remarkably, all 14 immunogenic peptides within $M1_{47\ 88}$ have been conserved over the last century, suggesting that this M1 region could be a target for a universal CTL vaccine.

Mapping Conserved NP and M1 Peptides Across All IAV Lineages. To confirm the conservation of the NP and M1 peptides across all human IAVs, including H1N1 (1918–1957, 1977–2009, and 2009–2013), H2N2 (1957–1968), and H3N2 (1968–2013), we identified the established, nonsynonymous amino acid (aa) changes (Fig. 2, gray bars). Then, immunogenic CTL peptides were deposited onto this map, according to the conserved, unique, and variable nomenclature (Tables S2–S7). The epitopes within NP and M1 that do not fall on the variable bars show regions that have not evolved in human IAVs over the last century, indicating that they are functionally important for virus survival. Interestingly, this confirms that the conserved epitopes, identified in Fig. 1, have not changed in other human viruses (except for NP_{259}; in green). Conversely, the variable (red) and unique (blue) epitopes are found predominantly in the variable-gray regions (Fig. 2). Phylogenetic analysis highlights the avian origins of the H7N9 NP and M1 genes (Fig. S1). Interestingly for M1, H7N9 is closely related to the H1N1pdm-2009 IAVs that are well established in humans (Fig. S1*B*), indicating a higher prevalence of shared peptides than for NP. The close phylogenetic relationship to avian IAVs further suggests that CTL epitope–based vaccines designed for H7N9 might confer protection against other avian IAVs (H5N1 and H9N2) that occasionally infect humans.

Recall Potential of Memory CTLs Specific for Conserved H7N9 Peptides. Based on the conservation analysis (Figs. 1 and 2), we dissected human CTL immunity toward the H7N9 IAV by probing reactivity to conserved, unique, and selected variable immunogenic peptides. We first characterized the recall potential of preexisting memory pools specific for conserved H7N9 peptides. The analysis focused predominantly on NP, the major target for immunodominant CTL responses (11) and the highly conserved, immunodominant A*0201-restricted $M1_{58\ 66}$. The conserved NP epitopes included A*0301-$NP_{265\ 273}$, B*2705-$NP_{383\ 391}$, B*5701-$NP_{199\ 207}$, B*1801-$NP_{219\ 228}$, B*0801-$NP_{225\ 233}$, B*0702-$NP_{172\ 181}$, and A*2402-$NP_{39\ 47}$ (Fig. 3). We classified the WT form of the $NP_{383\ 391}$ peptide (found in H7N9) that binds B*2705 as conserved, although an escape mutant is prominent in H3N2 strains (13). To unravel the recall potential of preexisting CTL memory to the H7N9 virus, peripheral blood mononuclear cells (PBMCs) obtained from healthy adults expressing a spectrum of HLAs were stimulated with the relevant conserved antigenic peptides for 10 d. The presence and frequencies of peptide-specific CTLs across multiple donors were then determined by an IFN-γ/TNF-α production (Fig. 3).

Our data show CTL responses to six of eight conserved epitopes: A*0301-NP_{265}^{+}, A*0201-$M1_{58}^{+}$, B*2705-NP_{383}^{+}, B*5701-NP_{199}^{+}, B*1801-NP_{219}^{+}, and B*0801-NP_{225}^{+} (Fig. 3 *A*–*F*). For these immunogenic peptides, all donors (n = 42) displayed specific CTL responses. In contrast, we did not detect any CTLs specific for B*0702-NP_{172} or A*2402-NP_{39} (Fig. 3 *G* and *H*), both classified as conserved. This suggests that, although the peptides may be conserved, these are weak epitopes that do not elicit CTL reactivation. At least for B*0702, this could reflect preferential presentation of immunodominant (but highly variable) variants of NP_{418} (14) (see below). As a consequence, B*0702^{+}NP_{172} may be subdominant and unlikely to play a major role in IAV-specific CTL immunity.

Most of these memory CTL responses to the conserved pHLA1s, A*0301^{+}NP_{265}, A*0201^{+}$M1_{58}$, B*2705^{+}NP_{383}, B*5701^{+}NP_{199}, B*1801^{+}NP_{219}, and B*0801^{+}NP_{225} (Fig. 3) displayed a robust functional potential and were detected at frequencies comparable to those found for the prominent A*0201^{+}$M1_{58\ 66}$ CTL epitope (Fig. 3*B*). This indicates that a substantial proportion (16–57%; Table 1) of the human population should have preexisting CD8^{+} CTLs that can respond to the H7N9 IAV. With ethnic differences in mind, we estimated population coverage based on the HLA types that present known, conserved immunogenic H7N9 NP and M1 peptides. Clearly, the extent of such CTL immunity to H7N9 varies considerably across ethnicities (African, 37%; Caucasoid, 57%; Oriental, 37%; Amerindian, 36%; Indigenous Alaskans and Indigenous Australian, 16%). This suggests that both the potential to recruit established CTL immunity and disease severity could show a clear ethnic bias in the face of an H7N9 pandemic.

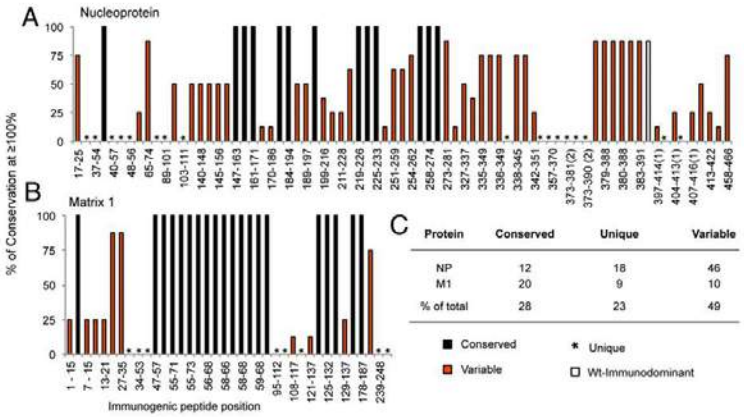

Fig. 1. High level of conservation for H7N9 CTL peptides. CTL antigenic peptides within (*A*) NP and (*B*) M1 were obtained from the Immune Epitope Database (IEDB, www.iedb.org; April 2013) and analyzed using the IEDB's Epitope Conservancy Analysis tool (http://tools.immuneepitope.org/tools/conservancy/iedb_input). (*C*) Summary of numbers and percentages of conserved, unique and variable epitopes within NP and M1. Conservation at 100% match was determined by comparing the corresponding CTL peptides in H7N9 to those of representative strains that have circulated in the human population (Table S1). Black, CTL peptides conserved over the last century; red, variable epitopes; *, unique CTL peptides for the H7N9 IAV; white, conserved H7N9-NP_{383} peptide that binds to HLA-B*2705 (escape mutants were identified in H3N2 strains for NP_{383}).

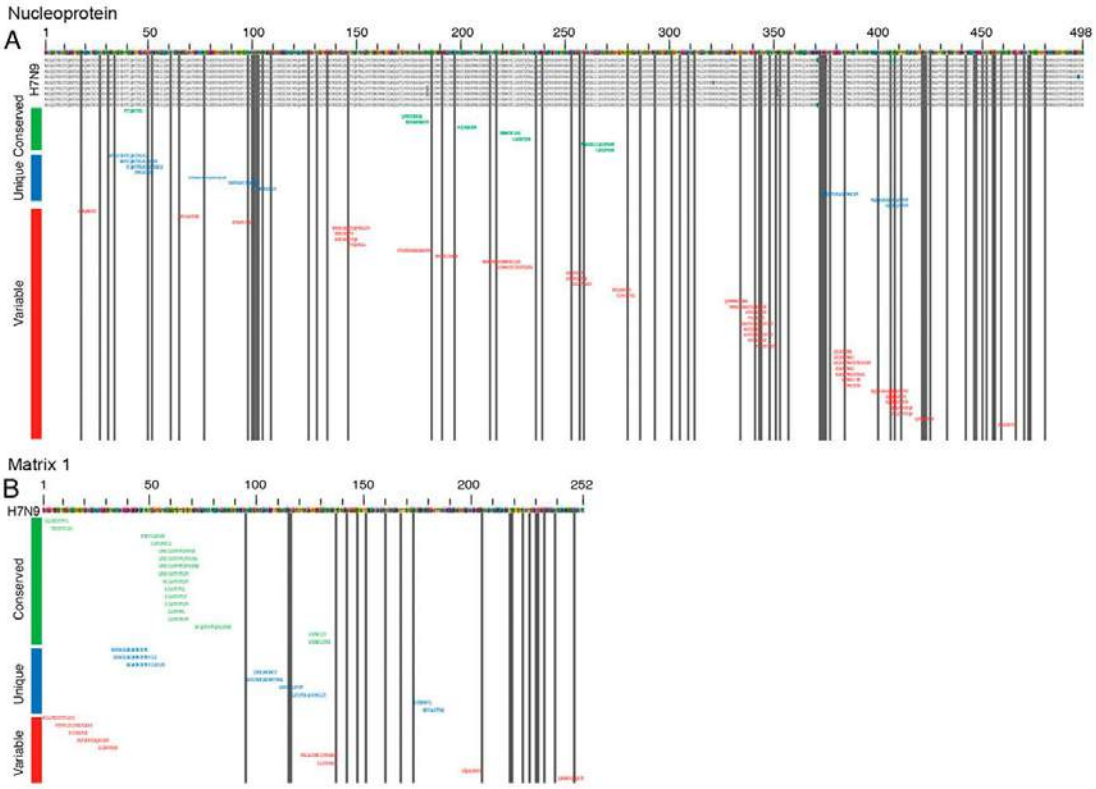

Fig. 2. CTL peptide map for NP and M1 across all human IAV lineages. The analyses spanned the full protein-coding region of the NP and M1 proteins to deduce changes in the conserved, unique and variable epitopes (Tables S2–S7). Green, blue, and red bars on the left of the peptides refer to conserved, unique, and variable CTL peptides, respectively. The horizontal gray bars throughout the alignments highlight the nonsynonymous substitutions established in H1N1, H2N2, and H3N2 viruses through their evolutionary history in human population. CTL peptides within (*A*) NP and (*B*) M1, which do not fall on the gray bars, show regions that have not changed in human influenza A viruses (the exception being NP_{258}), indicating lesser selection pressure on those sites.

Lack of Established CTL Responses to Unique H7N9 Peptides. We then examined CTL responses to the antigenic peptides unique to the H7N9 virus (Table S3). Although human populations that have not previously encountered H7N9 would likely see these pHLA1s as novel, there is also the possibility that there could be some "plasticity" in the cross-recognition of antigenic variants (15, 16). We thus screened unexposed individuals for responses to unique H7N9 epitopes, A*0101-$NP_{44\ 52}$ (Fig. 4 *A* and *B*), A*6801-$NP_{89\ 101}$ (Fig. 4*G*), and the $NP_{37\ 54}$, $NP_{373\ 390}$, and $NP_{397\ 414}$ presented by B*1501 (Fig. S2). PBMCs expressing a spectrum of HLAs were cultured with either the H7N9 peptide(s) or peptides from other human IAVs. Analysis of the normally immunodominant

Table 1. Estimation of the population coverage according to the HLA restriction of conserved epitopes in H7N9

		Population coverage across ethnicities						
Peptide(s)	Restriction	Caucasoid*	North American natives†	Oriental*	African*	Amerindian*	Alaskan Yupik‡	Australian Aboriginals§
$M1_{58-66}$	HLA-A2	25	21.66	27.17	15.76	24.78	2.3	12.7
$NP_{265-273}$	HLA-A3	11.9	6.6	3.26	6.48	3.98	0.1	1.4
$NP_{383-391}$	HLA-B27	3.71	8.5	3.62	1.46	4.98	13.28	0.1
$NP_{199-207}$	HLA-B57	2.91	3	1.33	3.96	0.68	0	0.5
$NP_{219-228}$	HLA-B18	6.31	2	0.92	4.62	0.5	0.6	0.2
$NP_{225-233}$	HLA-B8	7.41	3.7	1.4	4.83	1.1	0.4	1.2
	Total	57.24	45.46	37.7	37.11	36.02	16.7	16.1

Percentages based on HLA coverage for the relevant HLA supertype.
*From ref. 31.
†From ref. 9.
‡From ref. 7.
§From ref. 32.

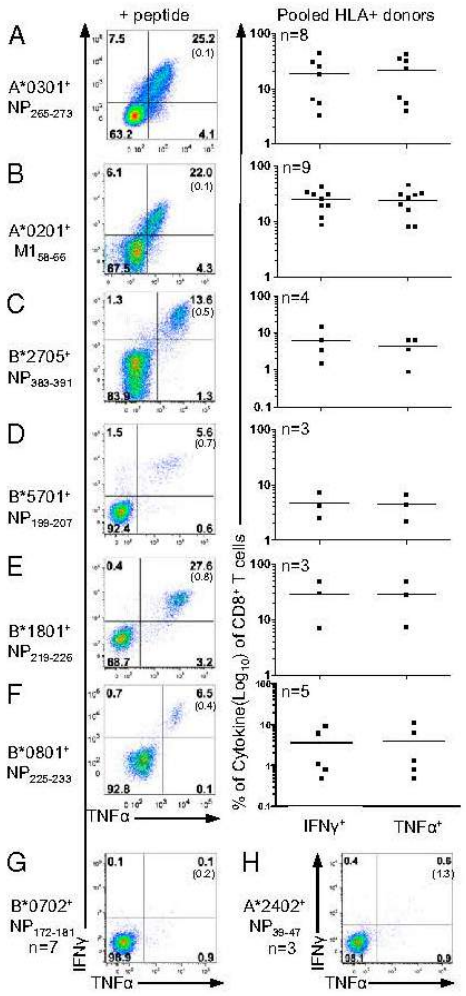

Fig. 3. CTL responses to conserved immunodominant H7N9 peptides. PBMCs from healthy donors were peptide-stimulated and cultured for 10 d. CTL responses were determined by an IFNγ/TNFα intracellular cytokine staining (ICS). Representative FACS plots for (*A*) A*0301$^+$NP$_{265}$, (*B*) A*0201$^+$M1$_{58}$, (*C*) B*2705$^+$NP$_{383}$, (*D*) B*5701$^+$NP$_{199}$, (*E*) B*1801$^+$NP$_{219}$, (*F*) B*0801$^+$NP$_{225}$, (*G*) B*0702$^+$NP$_{172}$, and (*H*) A*2402$^+$NP$_{39}$ are shown. Values for no peptide are in brackets. Graphs show pooled data from multiple donors. Background (no peptide controls) was subtracted.

A*0101-NP$_{44\ 52}$ showed that the H7N9-specific substitution at p9 (Y9N) was not recognized by CTLs that respond to either H1N1pdm-2009 NP$_{44}$ or to the seasonal NP$_{44}$-S7N variant (Fig. 4 *A* and *B*). Furthermore, preestablished HLA-A*0101$^+$NP$_{44}$ specific memory CTLs do not recognize the Y9H variant of H3N2, indicating that that any mutation at p9 leads to immune escape.

To understand the molecular basis of the cross-reactivity (with WT) of H7N9-NP$_{44}$-S7N vs. evasion by the H7N9-NP$_{44}$-Y9N and H7N9-NP$_{44}$-Y9H variants, we analyzed thermal stability and crystal structures for HLA*A0101 in complex with NP$_{44}$ variants (Fig. 4 *C*–*F*). The NP$_{44\ 52}$ (WT) and NP$_{44}$-S7N are comparable in their capacity to stabilize the HLA-A*0101 molecule, with a thermal melt point of 58.2 °C and 59.5 °C (Fig. 4*C*). However, the p9 mutations reduced the stability of the pHLA1 by 10 °C (Fig. 4*C*), most likely as a result of the large, aromatic Tyr being replaced with a smaller Asn or a charged His. In addition, the refold yield of HLA-A*0101 in the presence of NP$_{44}$-Y9H and NP$_{44}$-Y9N was decreased by 50×, thereby precluding structural studies. Thus, the reduced thermal stability of the NP$_{44}$-Y9N (H7N9) and NP$_{44}$-Y9H (H3N2) complexes likely results in reduced peptide presentation and immunogenicity. Further determination of HLA*A0101 crystal structures allowed precise definition of the cross-reactivity between the NP$_{44}$-WT and the seasonal NP$_{44}$-S7N. Structural analysis (Table S8) of NP$_{44}$-WT and NP$_{44}$-S7N bound to HLA-A*0101 (resolution of 2.4 and 2.0 Å) show that NP$_{44}$-WT adopts a classical extended conformation in the antigen-cleft of HLA-A*0101 (Fig. 4*D*) (17). The P2-Thr and P9-Tyr are buried, acting as anchor residues along with the P6-Leu. The P3-Glu is partially buried in the D pocket and forms a salt bridge with the Arg156. The P4-Leu, P5-Lys, and P8-Asp are solvent exposed and represent potential contact points for the T cell receptor (TCR) (Fig. 4*D*). The substitution at p7 Ser→Asn did not affect the conformation of the peptide within the antigen-binding cleft (Fig. 4*E*). Overall, analyzing stability and structure for the NP$_{44}$ variants shows that, although NP$_{44}$-S7N does not change either parameter when bound to HLA-A*0101, the variations at p9 within NP$_{44}$-Y9N-H7N9 or NP$_{44}$-Y9H-H3N2 drastically decrease the stability of the pHLA1 complex, with a consequent loss of T-cell recognition.

To understand whether CTLs can recognize any of the other, unique H7N9 peptides, we analyzed those with the capacity to bind A*6801 and B*1501. It seems that, although CTLs are induced by a spectrum of IAV NP$_{89}$ variants, the A*6801-NP$_{89}$-H7N9 is not recognized by these memory sets (Fig. 4*G*). Thus, H7N9-NP$_{89}$ is an escape variant in the 1–9% of the population that expresses HLA-A*6801. Similarly, the NP$_{37}$, NP$_{373}$, and NP$_{397}$ presented by HLA-B*1501 did not induce any responses (Fig. S2), although IAV-specific CTLs directed at other immunodominant epitopes, HLA-A*0301-NP$_{265}$ (Fig. S2; D15-1 and D15-2) and HLA-A*0201 M1$_{58}$ (Fig. S2; D15-3), were readily detected.

Overall, our analysis of the potentially immunogenic NP and M1 peptide variants unique to H7N9 indicates that individuals expressing HLA-A*0101, HLA-A*6801, and HLA-B*1501 will lack preexisting memory CTLs capable of recognizing epitopes defined by those HLA1 types. The H7N9-NP$_{44}$-Y9N variant is within an immunodominant epitope in HLA-A*0101$^+$ individuals, with this immunoevasion affecting the 1–14% of individuals with that HLA type, depending on ethnicity. In contrast, the nonantigenic A*6801-NP$_{89}$ H7N9 variant would affect 1–9% of the population expressing A*6801. We found no CTL responses to any of the B*1501 variants tested (Fig. S2).

CTL Cross-Reactivity for the Variable B*3501- and B*0702-NP$_{418}$ Epitope. Having assessed preexisting CTL immunity to conserved and unique (to H7N9) epitopes, we then analyzed the peptides that can be shared with H7N9 and are variably expressed in different IAVs (Table S4). The extent of any such cross-reactivity would depend on the influenza infection history. Interestingly, the variable peptides within H7N9 most closely resemble those of the pandemic H1N1-1918 virus (Table S4). This is evident from the minimal aa differences in key peptides from the H7N9 and H1N1-1918 strains (Fig. S3). Indeed, the H7N9 variant of the immunodominant NP$_{418}$ peptides presented by the large B7 family (15, 16) was identical to that within the 1918-H1N1 virus and closely resembled that from H1N1pdm-2009 (Table S4). In agreement with our previous data (16), this H7N9-NP$_{418}$ variant is not recognized by memory CTL specific for the various seasonal influenza types from the last decades (Fig. S4*B*). Tetrameric complexes of HLA-B*0702 and HLA-B*3501 with different NP$_{418}$ peptides were used to stain PBMCs stimulated in vitro with a pool of 12 NP$_{418}$ variants. The H7N9 variant of the B*3501-NP$_{418}$ tetramer showed none to minimal cross-reactivity for CTLs stimulated with the NP$_{418}$ peptides expressed by recently circulating IAVs (Fig. S4). Prior exposure to the pandemic H1N1pdm-2009 may, however, give some protection to B*0702$^+$ individuals (Fig. S4*A*).

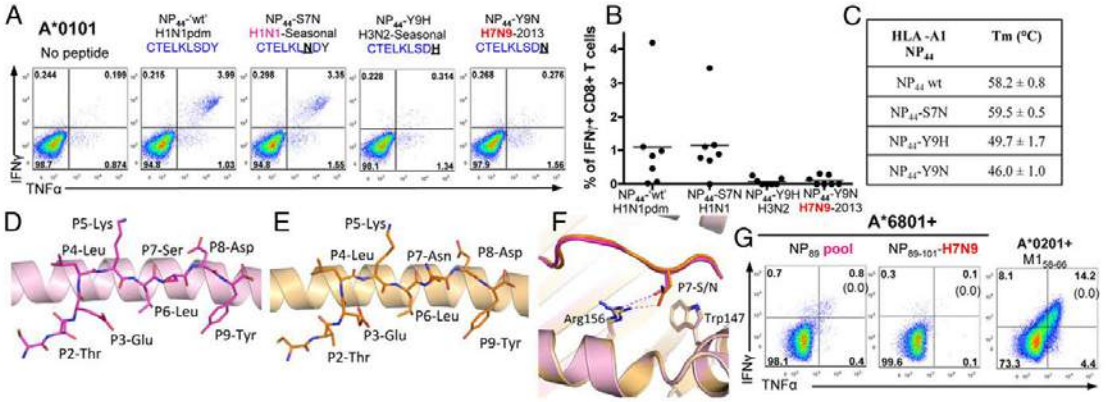

Fig. 4. H7N9 escape mutants for A*0101-NP_{44} and A*6801-NP_{89}. (*A–F*) The Y9N mutation in the immunodominant H7N9 NP_{44} peptide abrogates CTL recognition by reducing thermal stability. (*A*) Representative FACS plots for CTL responses to different A*0101-NP_{44} variants. (*B*) CTL responses (IFNγ ICS, $n = 7$) against four NP_{44} variants. (*C*) Thermal stability for the A*0101-NP_{44} variants. (*D* and *E*) Crystal structures of HLA-A*0101 (cartoon) bound to the NP_{44}-WT peptide (pink) and to the NP_{44}-S7N peptide (orange), respectively. Only the α1-helix of the HLA is shown for clarity. (*F*) Superposition of the HLA-A*0101 binding cleft to NP_{44}-WT (pink) and NP_{44}-S7N (orange), with the Arg156 and Trp147 of the HLA represented in stick; the H bond shown as dashed lines. (*G*) An ICS response to a unique H7N9 peptide NP_{89} restricted by HLA-A*6801, following stimulation with the NP_{89}-H7N9 variant or a pool of NP_{89} seasonal and pandemic variants (Table S4). Confirmation of prior IAV exposure was determined by assessing the reactivity to A*0201-$M1_{58}$.

Thus, our data suggest that there is the potential for a rapidly spreading H7N9 IAV to recall robust, immunodominant, $CD8^+$ CTL memory in substantial numbers of people (average of 35% across multiple ethnicities, range 16–57%; Table 1). Even so, although that may ameliorate influenza disease and reduce viral spread for some individuals and groups, it is also the case that such cross-reactivity is not found for certain HLA types that are prevalent in what may be extremely vulnerable populations.

Discussion

Although human cases of the newly emerged H7N9 virus are thought to have resulted primarily from contact with infected birds, the genetic characteristics of this virus raise real concerns that a mutant could readily emerge to cause efficient human-to-human spread. As we have no prior history with this pathogen, individuals of all ages would be susceptible. In the absence of protective NAbs, evidence from both human studies and animal experiments suggests that IAV-specific $CD8^+$ CTL immunity promotes more rapid recovery and milder disease (6–9). Hence, cross-reactive CTL memory pools generated by previous infection with seasonal or pandemic IAVs could potentially provide some protection against an H7N9 pandemic. The present analysis focuses on the capacity of $CD8^+$ T cells primed by infection with currently circulating and past H1N1 and H3N2 IAVs to respond to peptides that are shared with, or unique to, the H7N9 virus. Our sequence, phylogenetic, and immunologic analyses show that 28% of the CTL peptides within the immunogenic NP and M1 proteins are conserved between the IAVs of interest, 49% are found variably in that spectrum, and 23% are unique to H7N9. Studies are underway to understand whether the stability of certain regions within the viral NP and M1 results from ineffective $CD8^+$ T-cell immunity or the functional necessity for the influenza virus.

Perhaps of greater significance is the recognition that some HLA1 alleles present conserved IAV peptides. Strong representation of HLA A*0201, A*0301, B*5701, B*1801, and B*0801 in any ethnic group is predictive of preexisting CTL memory, and thus protection, following challenge with a novel IAV. Conversely, individuals with HLA-A*0101, A*6801, B*1501, and A*2402 may have little, if any, evidence of established CTL immunity to, for example, the H7N9 virus. Interestingly, HLA1 has been the one parameter repeatedly associated with HIV control, with B57 and B27 being the most protective, whereas the converse is true for B*35 and B*53 (18). Although we have tested preexisting $CD8^+$ T-cell immunity to H7N9 in a vast number ($n = 59$) of samples ($n = 42$ for Fig. 3; $n = 10$ for Fig. 4; $n = 7$ for Figs. S1–S4), the donors displayed a number of HLAs, which made the sample size for each HLA smaller. Further studies need to dissect influenza-specific CTLs in a larger number of donors corresponding to specific HLAs across different ethnicities.

The present analysis thus adds to other insights indicating that the impact of established IAV CTL immunity should be analyzed across different ethnicities (19). Thus far, H7N9 infection has been limited to the ethnic Chinese population. The overall conservation of CTL antigenic peptides within H7N9 is 35%, ranging between 57% (Caucasoid), 38% (Oriental), 37% (African), 16% (Australian Aboriginals), and 16% (Alaskan Natives), making the latter two groups most vulnerable to H7N9 challenge. This is consistent with the high adult mortalities (up to 100%) for isolated Alaskan villages in the 1918–1919 pandemic (20). Similarly, the Indigenous Australians were highly susceptible to the A/H1N1 pandemic viruses in 1918 (21) and 2009 (10). As many as 10–20% died in 1919 (21) vs. <1% of other (predominantly Caucasian) Australians. Hospitalization and morbidity rates for the Indigenous were also greatly increased in the recent 2009 A/H1N1 pandemic (22, 23), with 16% of hospitalized patients being from those communities. Although this may reflect a combination of factors, including household crowding, a high prevalence of comorbidities, and difficulties in accessing healthcare, the relative lack of HLAIs that present conserved IAV peptides may also be a contributing factor.

Close to 50% of the immunogenic H7N9 NP peptides are found with variable prevalence in other IAVs known to have established CTL memory in human populations. With both the H1N1pdm-2009 virus and H7N9, it is intriguing that the variable CTL peptides more closely resemble those from the pandemic H1N1-1918 than from recently circulating H1N1 (before 2009) and H3N2 influenza strains. Sequence analysis of the "resurrected" H1N1-1918 influenza virus indicates that this pathogen was, indeed, avian derived. It also seems that the 1918 NP survived and remained stable in the swine influenza reservoir, to emerge again in the H1N1pdm-2009 virus. Similarly, evolutionary analysis of H7N9 shows that all gene segments are of avian origin (24).

From our analysis, it seems that memory CTLs specific for prominent variable peptides (like NP_{418}) from recently circulating

seasonal strains would not recognize a large proportion of the variable H7N9-derived peptides in any pandemic situation. A major variant that does not stimulate preexisting CTLs is the H7N9-Y9N substitution of HLA-A*0101-NP_{44}. This mutation to an anchor residue at peptide P9 greatly destabilizes the pHLA complex, compromises CTL binding/accessibility, and can lead to viral escape, similar to what occurs in a mouse model (25).

Overall, the level of CTL peptide conservation within the H7N9 NP and M1 proteins appears to be lower than the 70–80% found previously for the swine-derived H1N1pdm-2009 (26). Lower CTL epitope conservation may partly explain the relative severity of H7N9 influenza in ethnic Chinese, with 37% population coverage of cross-reactive HLA types. Infection outcomes in known H7N9 cases were far from uniform. Some recovered within a few days, whereas others required steroid treatment, intensive care unit admission (75%), and mechanical ventilation (86%) (27). In all, 34% of hospitalized patients ultimately died. It is highly possible that some of the difference in outcomes was influenced by the extent of cross-reactive CTL memory.

Materials and Methods

Donors and PBMC Isolation. PBMCs were obtained from 52 donors: HLA-A*0101$^+$ (n = 7 donors), A*0201$^+$ (n = 9 donors), A*0301$^+$ (n = 8 donors), B*2705$^+$ (n = 4 donors), B*0702 (n = 7 donors), B*5701 (n = 3 donors), B*1801 (n = 3 donors), B*0801 (n = 5 donors), A*6801 (n = 3 donors), B*2402 (n = 3 donors), and B*15:01 (n = 3 donors) healthy individuals, after informed consent was obtained. HLA genotyping was done at the Victorian Transplant and Immunogenetics Service (West Melbourne, Australia). The experiments were conducted according to the Australian National Health and Medical Research Council Code of Practice and approved by the University of Melbourne Human Ethics Committee.

Epitope Conservation Analysis. H7N9 NP and M1 proteins sequences from the Global Initiative on Sharing All Influenza Data (GISAID, www.gisaid.org) and the epitope data from the Immune Epitope Database (www.immuneepitope.org, accessed July 2013) were used to map antigenic CTL regions within the immunogenic internal influenza proteins NP (76 epitopes) and M1 (39 epitopes), as described in *SI Materials and Methods*.

T-Cell Restimulation, Intracellular Cytokine Assay, and Tetramer Staining. PBMCs were stimulated with NP- and M1-derived peptides for 10 d, followed by the analysis of influenza-specific CTLs by a 5-h ICS or tetramer staining, as described in *SI Materials and Methods*. Based on the conservation sequence analysis (Tables S2–S7), CTL reactivity to H7N9 was assessed to a total of 39 NP and 1 M1 immunogenic peptides: the conserved $M1_{58}$, 8 conserved NP peptides, 7 H7N9 unique, and 26 variable NP peptides.

Protein Expression, Purification, Crystallization, and Thermal Stability. HLA-A*0101–soluble HLA1 heterodimers containing NP_{44} peptides were prepared, crystallized, and structures solved as described in *SI Materials and Methods*. The coordinates have been submitted to the Protein Data Bank (PDB) (ID codes 4NQV for NP44-A1 and 4NQX for NP44-S7N. Molecular graphics representations were created using PyMol (28). To assess the effect of peptide mutations, we tested the stability of each pHLA complex (29) using a thermal shift assay (*SI Materials and Methods*).

Phylogenetic Analysis and Deduction of Ancestral Nonsynonymous Substitutions. Maximum likelihood analysis was performed for the full protein coding genes of the NP and M1 using the general time reversible substitution model with the γ-shaped rate variation in RaXML v7.7 (30). Ancestral nonsynonymous substitutions along the branches of the NP and M1 protein gene trees were deduced using the baseml program in PAML.

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Chapter. 4 Methodology and Methods

4.1 Chapter Brief

This chapter aims to provide details about the methodology applied and developed in this research, the funding sources and ethics approvals. There are two published papers presented about the methodological approaches applied and explored in this research. Both papers discuss the application of participatory action research (PAR) approach to addressing the research questions stated in Chapter 1 of this thesis. The papers have been published in a peer reviewed journal article and in an international textbook on qualitative research methods. Paper 1 is a journal article that directly relates to the influenza exemplar and paper 2 is a book chapter that promotes the incorporation of Indigenist research principles into PAR.

4.2 Overview

The methodology and my worldview standpoint are presented in this chapter. My worldview is set from philosophical assumptions that guide my actions throughout my research (Creswell 2012). My worldview for this research begins with this song by Jimmy Murray written in 1967. Jimmy Murray, my granduncle, wrote and sung this song about “a bad cold”, which he believes he caught from non-Indigenous people, so he addresses this Jangala song to them – a love-song style with strong emotions. His throat is dry, and he can scarcely sing, but he works clay under water with his hands and applies it to his throat as a poultice to treat his sore throat (Dixon & Duwell 1990). Jimmy Murray was my grandmother’s brother who are from the Girramay people from Far North Queensland. Jimmy Murray describes, in song, his illness, how he feels and how he treats his cold and how this cold has impeded him as a member of his community. This cold my granduncle had must have affected him so badly that he wrote a song about this experience. The common cold, an infectious disease and to many people today is a normal part of life. But imagine the common cold was something you or your family had rarely experienced before or had limited knowledge of, and you know it wasn’t around before you had encountered a new

group of people. Also, your knowledge of treating the symptoms of a cold was based on your experience with other common causes.

Dry Throat by Jimmy Murray

(Girramay Dialect)	**(English Translation)**
Ngay ngayba jida	*My throat is dry*
Jangala jinbala	*Too sore sing Jangala*
Ngayi jirajira	*A thick, dry throat*
Gilngaragu maya	*A bad cold grips me*
Gudangu garrindu	*The cold blocks my throat*
Gudangu garrindu	*The cold blocks my throat*
Marrimarrigubi	*Such a heavy cold*
Banggu nyurranginyju	*Caught from you people*
Banggu nyurranginyju	*Caught from you people*
Gudan gilngaragu	*The cold impedes me*
Marrimarrigubi	*Such a heavy cold*
Malanggumbangurru	*With my hands, under water*
Malanggumbangurru	*With my hands, under water*
Marrany mangurrubi	*I work the clay, for a poultice*
Banggu nyurranginyju	*Caught from you people*
Gilngaragu gudan	*The cold impedes me*
Gudan gilngaragu	*The cold impedes me*
Marrimarrigubi	*Such a heavy cold*
Ngayi jirajira	*I think, dry throat*
Jinbalambangubi	*And I cannot sing properly*

(Source: Dixon & Duwell 1990)

My research draws from people's experiences of how infectious diseases are understood, interpreted and investigated and why treatments have not been as effective in Indigenous communities. I have chosen two disease examplars,

strongyloidiasis caused by the inflection of an intestinal worm *Strongyloides sterceralis* and pandemic influenza (pH1N1).

I am Aboriginal, and I am from the Jirrbal people of North Queensland - ***garbawuɽu*** section of my community and my totem is ***guridjala*** - *eagle hawk*. My grandmother, Chloe Grant (Bubbumurry), had a vision in the late 1960's to preserve our language and culture by giving consent to Robert Dixon, a linguist, to research and record in detail, Dyrribal (Mamu, Girramay / Jirrbal dialects) language and culture (Dixon 1972, Dixon 1984). I also draw inspiration from my grandmother's actions to value the power of research and the benefits it can have for Indigenous people.

There has been a long history of research that has had little or no benefit for Australian Indigenous people. The history of research and Indigenous people:

- Has not generally been to the advantage or benefit of Indigenous peoples and that it has been considered 'seriously damaging and harmful' and 'insensitive, intrusive and exploitative' (Manderson et al. 1998); and
- Is designed to serve the academic, political or professional needs of researchers (NAHS 1989).

The following quotes further document the history and sentiment of research on Indigenous peoples.

> In whichever discipline researchers have worked - history, sociology, anthropology, psychiatry - most have failed to perceive the insiders' view - how black people themselves perceive and understand their condition (Langton 1981, p16).

> Indigenous perceptions of Australian research practice have emphasized their subject status, in which academics have been seen to descend on a community, gain peremptory permission to conduct their work, collect their data (biological or social) and leave, with little or no feedback to the community and no lasting benefits to it. (Manderson et al. 1998, p223).

My worldview for research is centred on the following presented in my language:

ŋaɖa ŋambayiriɲu - I think

ŋali ŋinda ŋambayiriɲu - You and I are thinking

I undertake my research through the understanding that I am an Aboriginal person with the ability to deeply think about complex issues - ŋaɖa ŋambayiriɲu. Historically, there has been a view that Indigenous peoples were incapable of thinking through complex issues. Early colonial constructions described Indigenous people as lacking the ability to use their minds, their intellect or to invent, build, cultivate land, produce items of value and participate in the arts of civilisation (Smith 2005). It is important for me as an Aboriginal person and a researcher to critically reflect on the past constructions of Indigenous people to find answers where both Indigenous and non-Indigenous voices are equally valued and heard - ŋali ŋinda ŋambayiriɲu.

My worldview for my research relates to the critical reflection of Aboriginalism and Indigenist Research Principles (Evans et al. 2014; Attwood 1992; Rigney 1997). Aboriginalism is imbedded with the assumption about the nature of power and knowledge that is drawn from the work of Edward Said, Orientialism and originally by Michele Foucault (Said 1979; Faubion 1994). However, Said and Foucault's work originates in what Flyvbjerg describes as the Aristotelian concept of phronesis, translated as prudence or practical wisdom, or "true state, reasoned, and capable of action about things that are good or bad for man" (Flyvbjerg 2001:2). Phronesis goes beyond both analytical (episteme) and technical (techne) knowledge to consider the role of values and power in judgements and decisions made by a social or political actor (Flyvbjerg 2001).

Therefore, regarding phronesis or phonetic social science, Aboriginalism is the intellectual development and constructions of authoritative and essentialist truths of "Aborigines"; which is characterised by the relationship between power and knowledge (Attwood 1992). Aboriginalism exists on three levels: the first as Aboriginal Studies through the teaching and scholarly pursuit of knowledge about Aborigines by non-Aboriginal intellectuals who claim Aborigines cannot represent themselves and therefore must be represented by experts who know more about them than they know about themselves (Said 1979; Attwood 1992). The second level from a style of thought that emphasizes the imagined distinction between Aborigines and Europeans to construct Aborigines as the "Other" and to form a "Them" and "Us" relationship (Attwood 1992). The third level is described as corporate and government institutions exercising authority over Aborigines claiming rights, laws and information about them (Said 1979; Attwood 1992). In line with Foucault "discourse analysis", it is at this point Attwood unable to document a fourth

level, which is the role of that Aboriginal people play in developing, controlling and determining their own intellectual authoritative and essentialist truth (Foucault 2000).

My worldview for this thesis combines my the deep connection to my Aboriginal identity – language, culture, family (relationships) and land (place), Indigenous research principles and the adoption of other philosophical positions (Figure 4.1).

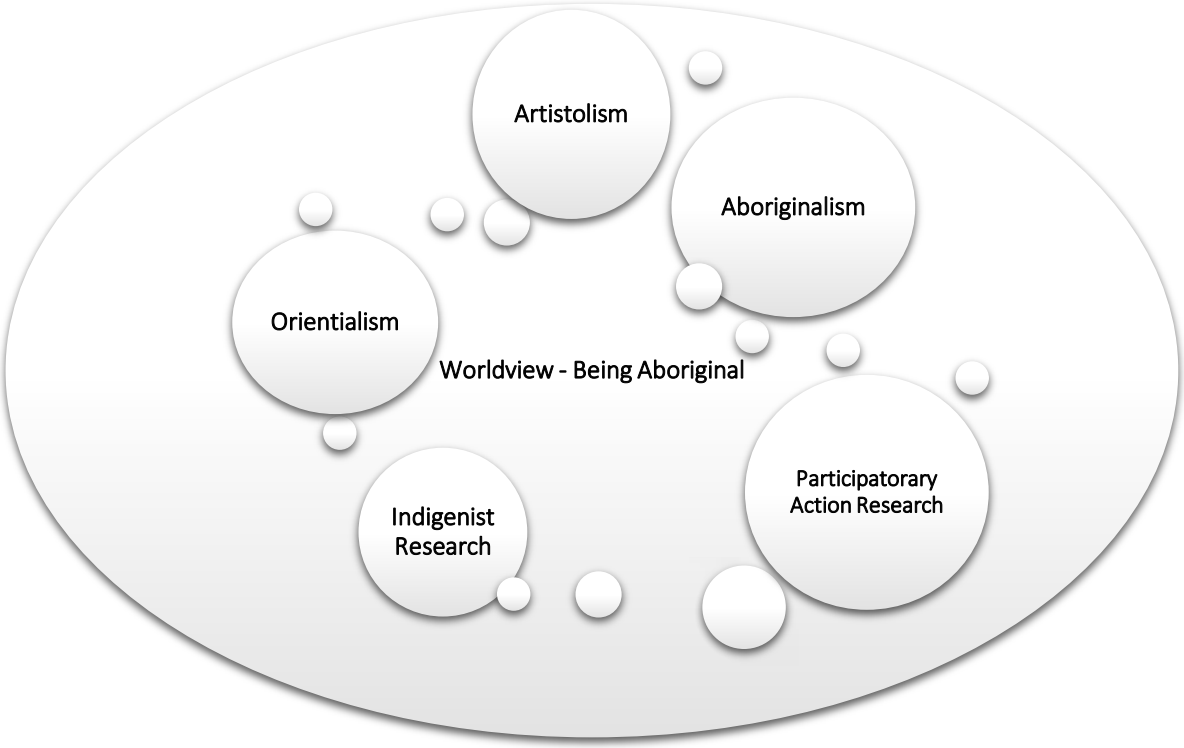

Figure 4.1 My Worldview for research

4.3 Papers Presented

Miller A, Massey PD, Judd JA, Kelly J, Durrheim DN, Clough AR, Speare R, Sagger S. A methodology for listening to Aboriginal and Torres Strait Islander people in Australia about Pandemic Influenza. *Rural and Remote Health*, 2015, Vol 15, Issue 3/4.

Evans M, **Miller A**, Hutchinson P & Dingwall C. “De-Colonizing Research Practice: Indigenous Methodologies, Aboriginal Methods, and Knowledge/Knowing”, in *Oxford*

Handbook of Qualitative Research. Patricia Leavy (ed.) New York: NY, Oxford University Press, 2014: 179-191.

The first paper presented in this chapter describes the use of a Participatory Action Research (PAR) approach in two National Health and Medical Research Council (NHMRC) research grants - grant number 601025 and 601034.

Before undertaking these projects, a pilot study in New South Wales Hunter New England region with six Aboriginal communities exploring people's concern about pandemic influenza was conducted. The pilot study identified five (5) themes from Aboriginal people (1) local resource person; (2) clear communication; (3) access to health services; (4) households and funerals; (5) social and community support issues. According to international indigenous experiences, influenza pandemics are a serious threat to the health and social functioning of communities (Massey et al. 2009:1-2). Therefore, risk reduction measures for influenza in Indigenous Australian communities must be developed in collaboration with Indigenous communities to maximise their acceptance (Massey et al. 2009). The pilot study team instigated further conversations with other researchers from Queensland and Western Australia. This lead to the formation of a larger research team that comprised researchers with expertise in infectious diseases, qualitative research, health promotion, public health, primary health care and Indigenous health research. The newly formed team than applied for two NHMRC grants which were both successful.

The paper presented for this study describes the use and effectiveness of the PAR framework to better understand community members' perception and risks of pandemic influenza. A qualitative PAR framework was effective in gaining deep understandings from participants. Aboriginal and Torres Strait Islander community controlled organisations and health services were involved in the implementation, interpretation and monitoring of the project. As a result, novel features of PAR with Aboriginal and Torres Strait Islander communities and organisations emerged. These novel features included the importance of working in a multi-disciplinary team with Aboriginal and Torres Strait Islander researchers; the complexities and importance of obtaining multi-site human research ethics approval processes; the importance and value of building the research capacity of both experienced and novice researchers in PAR; the need to use localised sampling protocols; and the process of undertaking a collective research process and enacting action research

and feedback (Miller et al 2015). The most effective responses of this project are in pre-existing relationships that had been established over a long period between Aboriginal medical services and investigators while research relationships established specifically for the project, were less successful (Miller et al. 2015).

The second paper was used to guide me through the research process as a conceptual checklist for the Strongyloides exemplar. This paper focuses on developing of an Indigenist Participatory Approach to research, which is fundamentally engrained in the traditions and knowledge systems of Indigenous peoples. The paper is published as a book chapter to describe Indigenous methodologies and methods that have become both systems for generating knowledge, and ways of responding to the processes of colonisation.

My fellow co-authors from Canada and I have developed specific Indigenous research methods that have emerged from language, culture, and worldview. These creative and new approaches draws deeply from our communities', and thus express and enacts traditional knowledge systems in contemporary terms. The result is more pertinent research, better take up and dissemination of research results, and a general improvement in the situations of Indigenous communities and peoples (Evans et al. 2014).

My specific contribution to this chapter details a research approach that incorporates Indigenist research principles, Participatory Action Research (PAR) framed within my Indigenous cosmological worldview and language - Jirrbal. I use the main features of a tropical cyclone as an analogy – the cyclone itself, the wind of the cyclone and the eye of the cyclone. *ŋala gumbarra* is the cyclone that captures the cyclical stages of both Indigenist research principles (*ŋala gumbarra gayga*) and PAR (*ŋala gumbarra gulubu)*. The methods image provides a framework for data collection and analysis that underpins the methodological Cyclone Analogy (Figure 4.2).

Cyclone Analogy **Methods**

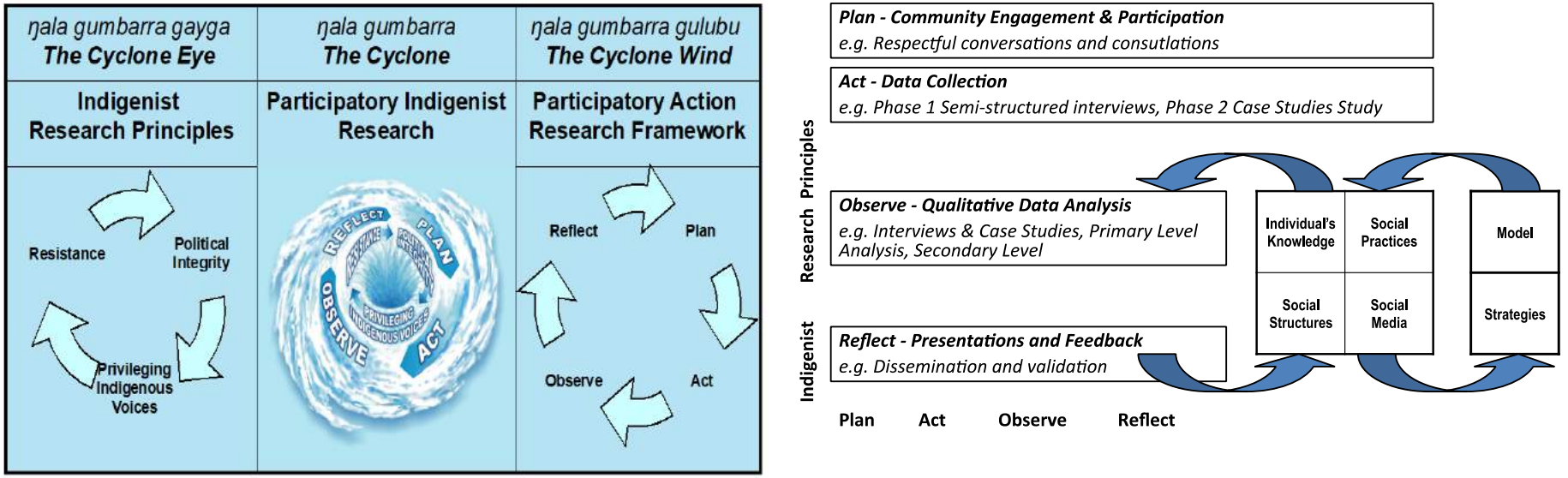

Figure 4.2 Cyclone Analogy

4.4 Summary

The methodological approach for both papers applied a PAR framework. Both papers explored deeper research matters, like Indigenous world views, that impact on research processes when working with Aboriginal and Torres Strait Islander peoples. I shared my research standpoint and worldview, how I formed them and how I applied them within the two studies. In a practical sense, a PAR approach is appropriate in research projects with and for Indigenous people, but there are factors like relationships, ethic approval complexities and the value of establishing a multi-disciplinary team that should be taken into consideration. These papers will stimulate further discussion on developing new and innovative ways to undertake research that positively impacts and benefits the research needs of Aboriginal and Torres Strait Islander people, their communities and organisations. The next chapter examines the findings of the strongyloides study with two peer reviewed journal publications. The first is a qualitative paper exploring the knowledge and experiences of health staff and researchers. The second highlights the perspectives of Aboriginal people of a successful community-driven intervention to control strongyloides.

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ORIGINAL RESEARCH

Using a participatory action research framework to listen to Aboriginal and Torres Strait Islander people in Australia about pandemic influenza

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ABSTRACT

Introduction: This article describes the use and effectiveness of the participatory action research (PAR) framework to better understand community members' perceptions and risks of pandemic influenza. In 2009, the H1N1 influenza pandemic affected Indigenous populations more than non-Indigenous populations in Oceania and the Americas. Higher prevalence of comorbidities (diabetes, obesity, asthma and chronic obstructive pulmonary disease) as well as pregnancy in Indigenous communities may have contributed to the higher risks of severe disease. Social disparity, institutionalised racism within health services and differences in access to culturally safe health services have also been reported as contributors to disadvantage and delayed appropriate treatment.
Methods: Given these factors and the subsequent impact they had on Australian Aboriginal and Torres Strait Islander communities, the authors set out to ensure that the Australian national, state and territory pandemic plans adequately reflected the risk status of Aboriginal and Torres Strait Islander peoples and promoted meaningful engagement with communities to mitigate this risk. A national study explored the views of Aboriginal and Torres Strait Islander people and their experiences with H1N1 and used a qualitative PAR framework that was effective in gaining deep understandings from participants. Aboriginal and Torres Strait

Islander community-controlled organisations and health services were involved in the implementation, interpretation and monitoring of this project.

Results: As a result, important features of the implementation of this PAR framework with Aboriginal and Torres Strait Islander communities and organisations emerged. These features included the importance of working in a multidisciplinary team with Aboriginal and Torres Strait Islander researchers; the complexities and importance of obtaining multi-site human research ethics approval processes; the importance and value of building the research capacity of both experienced and novice researchers in PAR; the need to use localised sampling protocols; and the process of undertaking a collective research process and enacting action research and feedback.

Conclusions: The most effective responses of this project were embedded in pre-existing relationships with individuals within organisations that had been established over a long period of time between Aboriginal medical services and investigators; however, research relationships established specifically for the purposes of the project were less successful because of changes in personnel and organisational support. The participatory approach used in this study has the potential to be applied to vulnerable populations in other countries.

Key words: community engagement, Indigenous health, methodology, pandemic influenza, participatory action research, research capacity.

Introduction

A study using participatory action research to explore Indigenous Australians' perspectives of H1N1

This study's multidisciplinary team of researchers set out to influence change in the Australian national pandemic plans. A national study was conducted to explore the views of Aboriginal and Torres Strait Islander people about their experiences with H1N1 using a qualitative participatory action research (PAR) framework[1]. Aboriginal and Torres Strait Islander community-controlled organisations and health services were involved in the implementation, interpretation and monitoring of the project. The research team designed the study to have PAR framework across multiple sites in Australia. The study used qualitative research methods to collect and analyse information from Aboriginal and Torres Strait Islander participants who had experienced the 2009 H1N1 pandemic (H1N109). Community-based researchers were selected from all participating communities and trained in qualitative research methods. The overarching principles were to develop and maintain strong relationships with communities and organisations, to engage in genuine and open dialogue about the research and to align with national ethical standards. The aims of the study were to:

- identify barriers to the implementation of current containment strategies for H1N109 in rural and remote Aboriginal and Torres Strait Islander communities
- develop culturally appropriate and effective containment strategies for H1N109 and future pandemics in these communities, modified where possible by the experience of the pandemic.

The H1N109 influenza pandemic resulted in higher incidence in New Zealand Maori and Pacific Islanders and greater morbidity in Indigenous populations in the Americas, New Zealand and Australia[2]. Hospitalisations and deaths from H1N109 were three to six times more common in Indigenous peoples than non-Indigenous peoples living in the same regions[3-7]. A higher prevalence of diabetes, obesity, asthma, chronic obstructive pulmonary disease and pregnancy in Indigenous communities may have contributed to the higher risks of severe disease. Social disparity, institutionalised racism and differences in access to culturally safe health

services also contributed to delayed appropriate treatment[3,8]. However, a new study has identified a possible biological explanation for greater susceptibility in Australian Aboriginal people to various strains of influenza[9].

During the 2009 H1N1 pandemic, the national pandemic influenza plans frequently masked or neglected the lives, needs and interests of disadvantaged groups within the population[10,11]. The result of this neglect was to further disadvantage the people most likely to require protection from a pandemic[12].

Health researchers have long advocated better understanding of important social aspects of the prevention and response to infectious disease outbreaks, including influenza. However, published research and understanding in this field falls significantly behind that of non-communicable diseases[13]. Social aspects of communities such as cultural values, importance of norms, strong family ties and social networks may impede or facilitate pandemic risk reduction efforts[14]. Understanding these values and planning from the perspective of the at-risk population is important, but for this to be effective it is essential that the planning is done with respectful engagement of vulnerable communities[15].

Choice of methodology

PAR is recognised as a method of research that may be more acceptable to Australian Aboriginal and Torres Strait Islander people, and was supported by the community research partners involved in this project[15–17]. PAR differs from other research methods in that it seeks to bring about positive change, not simply investigate or describe an issue. In addition, the research process is based on equal and collaborative involvement of the community and participants affected by the issue[18–21].

Historically, research on Aboriginal and Torres Strait Islander peoples, and Indigenous people in other countries, has been deemed inappropriate as researchers sought to collect and describe the data without providing benefits to the people or communities researched[22]. The Aboriginal researchers employed on this project were acutely aware of the practice of researchers taking information from community members without giving anything back[19].

PAR offers a way to make the research meaningful for a community[18], being based on an action cycle that assists in improving processes for addressing issues from the communities' perspectives[22,24]. The research team applied a PAR approach that was collaborative, participatory and based on equal partnerships between Aboriginal and Torres Strait Islander community members, organisations, research assistants and researchers. It was driven and owned jointly by the community and the researchers, and involved a two-way respectful conversation that fed into both the process and the outcome of the research. Rather than a linear model of researcher-led data retrieval and analysis, PAR is a cyclical process of planning, acting, observing and reflecting (Fig1). This design enabled each new collection of data in the H1N109 project to be grounded in reflections formed on the previous data.

Historically, research has not been a positive experience for Indigenous communities[25]. Researchers have a responsibility to cause no harm, but traditional forms of research have been a source of distress for Indigenous peoples due to inappropriate methods and practices[23,26]. PAR offers a way to make the research meaningful for the community and enables an action research cycle that assists in improving processes for addressing issues, such as pandemic influenza, from the communities' perspectives.

PAR is increasingly recognised as useful for health research in marginalised groups like Indigenous populations[27]. It has potential to reduce the negative effects that conventional research has had on Indigenous peoples[28,29] by recognising the community knowledge power base.

> *The recognition that power is directly related to knowledge lies at the very heart of the collaborative participatory research project. For public health researchers who are committed to reducing the health inequalities that are associated with social disadvantage, this approach offers a strategy that embraces self-determination, encourages and even demands ongoing consultation and negotiation, and*

provides opportunities for capacity-building and empowerment in the communities involved in the research[30].

Importantly, when communities seek control of the research agenda, and actively engage in the research, they are establishing themselves as more powerful agents[27]. With the increasing use of PAR approaches to address public health issues, there is potential for bridging the gap between research and practice in addressing social issues and creating conditions that facilitate people's control over the determinants of their health[31]. A key strength of PAR is the partnership between participants' real world knowledge and researchers' methodological expertise[31]. Partnerships that are formed with marginalised and vulnerable populations need to ensure that concepts of cultural humility and cultural safety are integrated, and maintain mutual respect and trust[31]. PAR stages included engagement with community groups, organisations, individual and group interviews, yarning (talking) circles and community reports. Strong community engagement at different sites meant that the engagement processes, although based on standard principles of research, was adapted to the differing local contexts and stakeholders.

Methods and results

During this study, the research team identified important and novel aspects of the methods.

Multidisciplinary team and Aboriginal and Torres Strait Islander researchers

The research team comprised senior and early-career researchers, Aboriginal and Torres Strait Islander and non-Aboriginal and Torres Strait Islander people. Members came from a wide variety of disciplines including medicine, veterinary science, epidemiology, public health, anthropology, health promotion, nursing and education. In common was a commitment to, and a long history of working on, applied research prioritised with Aboriginal and Torres Strait Islander communities. Members also shared a value of social justice for Aboriginal and Torres Strait Islander people. All researchers had established relationships with at least one other person on the team and some had long histories of working together. There was an assumed complementarity of knowledge and skills in the team, an assumption that was tested and confirmed as the research progressed.

Aboriginal and Torres Strait Islander researchers were recruited from their local communities across Australia: three were employed in community-controlled health services; two were government health employees, and four were community members with diverse employment histories. Researchers of both genders were employed at each research site and included senior community members and young people. These researchers had different knowledge and skill sets and different educational backgrounds[17]. Training workshops were held in various locations to train Aboriginal and Torres Strait Islander researchers in qualitative research methods. These workshops were led by very experienced qualitative researchers who had worked in remote Aboriginal communities for many years. The Aboriginal and Torres Strait Islander researchers collected qualitative data, advised on cultural and community protocols, and the research team collectively analysed this data.

Ethics

Human Research Ethics Committee (HREC) approvals were granted from universities and state authorities. HRECs included James Cook University (H3546) in Queensland, the Aboriginal Health and Medical Research Council (746/10) and the Hunter New England HREC (09/09/16/4.01) in New South Wales, and the *Western Australian Aboriginal Health Ethics Committee* (291 06/10). Under ethical research principles involving Aboriginal and Torres Strait Islander participants the additional ethics criteria required can be methodologically challenging in a number of ways. Gaining documented approvals and support from community-controlled organisations, local government and other agencies was required for this study. Additional ethical challenges included ensuring that local community protocols for consultations were followed and that data had local ownership[32]. This meant that in 2009 multisite approval processes across jurisdictions and universities were necessary. Additionally, all ethics applications had to document how the project adhered to specific ethical principles centered on spirit and integrity and included responsibility, respect, reciprocity, equality and survival and protection[32].

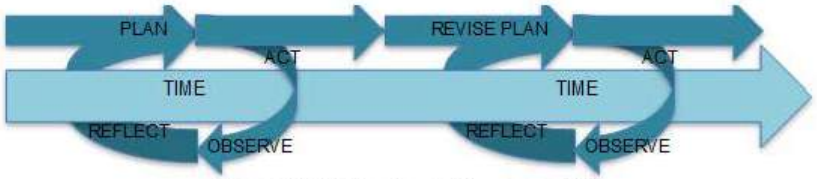

Figure 1: Participatory action research[23].

Capacity building

An important foundation for the research strategy was the capacity building of all team members involved in PAR. A series of training workshops that focused on qualitative research methods, data collection and data analysis were conducted in three of the research sites in Australia. These workshops were conducted at key points of the research journey, just in time for it to be relevant and meaningful to the researchers[33]. The training workshops were attended by chief and associate investigators, and research assistants, at various locations. This collaborative process highlighted another two-way learning approach to the research which placed equal value on respecting the values of Indigenous and non-Indigenous members' cultures, knowledge, processes and worldviews[34].

The multidisciplinary nature of the research team and the various stages of their research careers necessitated different levels of support, mentoring and capacity development. The research team members benefited from their learning from the Aboriginal and Torres Strait Islander researchers by challenging their own assumptions and approaches to research. At the same time, community researchers gained a better understanding of the formal research process and the opportunities available from the higher education system. Support, guidance and mentoring provided the community researchers with opportunities to help them plan their future careers and education pathways.

Sampling

As is appropriate for this type of qualitative research, the Aboriginal and Torres Strait Islander researchers operated within existing social and work networks to identify study participants. This approach enabled participants from across the communities to be involved. A purposive sampling technique was used in the selection of participants, which included Aboriginal community-controlled health services staff and Aboriginal and Torres Strait Islander community members of mixed ages and genders.

Collective research process

The PAR cycles included engagement with community groups, organisations, individual and group interviews, yarning circles and feedback presentations for community reports. The sampling framework and data collection questions were developed by the research team as part of the training workshops. A collective and collaborative process was used involving all researchers at all stages of data collection, data coding, data analysis and reporting. Using a thematic analysis process at each site the data were coded inductively with a thematic coding scheme. Then a collective and collaborative process was used where the researchers identified and defined themes across all the data. As the combined themes and concepts emerged, further data reduction and interpretation occurred. This culminated in a novel, systematic and innovative group analysis and writing process. The PAR framework allowed Aboriginal and Torres Strait Islander researchers to become equal and valued members of the research team. Despite numeracy and literacy levels, the Aboriginal and Torres Strait Islander researchers were well supported in their capacity development. Two major challenges occurred, one during data collection and the other during analysis. During interviews, community-based researchers initially did not probe participants for further

information on areas of common understanding. During analysis the other challenge was deciding on how to document community-based strategies that were deemed ineffective (on the basis of evidence) in reducing transmission of influenza but were perceived effective by the community.

Research action and feedback

The participants spoke of the need to enter into a respectful dialogue with Aboriginal and Torres Strait Islander communities, to discover what communities wanted to know before authorities told them their views. It was considered important that researchers, government agencies and health services listen deeply to what is really meant, and then share the information that is needed by the communities.

An interim report was developed and presented to participants and organisations involved in the study to closely consider and comment on what was found as an essential activity of the PAR framework[34]. The data gathering process and the dissemination of the interim report provided many opportunities for the PAR process to flow from the research. New or modified ways to reduce risk from H1N109 were adopted by families, health services, community groups and government departments involved in the research. Examples included families increasing hand washing and reducing direct social contact when sick, a childcare centre ensuring that sick children did not attend the centre, health services planning for outreach services and a state health department engaging more closely with the Aboriginal community-controlled health sector. Self-determination and empowerment are key values that the research action and feedback was able to support. These values are integral in the development of Indigenous health. The major themes and subthemes from the study (Table 1) were confirmed throughout the PAR framework.

Discussion

Vulnerable or neglected groups and populations often become more disadvantaged during epidemics and other emergencies[35]. Typically their special needs are ignored because health system responses are designed to maximise efficiency and produce the best outcomes for the majority of the population[36]. The research framework that was adopted allowed the voices of vulnerable groups to be heard, listened to and appropriate action taken in respectful, collaborative partnerships. The most effective responses in this study were seen in relationships that had been established over decades between Aboriginal medical services and investigators, while research relationships established specifically for the purposes of the project were less successful because of changes in personnel.

A number of strengths of the research framework used became clear throughout the project. The perspectives of Aboriginal and Torres Strait Islander people were paramount to the research process. Respect of and for Aboriginal and Torres Strait Islander cultures underpinned the project. PAR is an approach that may work towards de-colonising research[27,28,37] and bringing about sustainable change. Further strengths of PAR included having people working together with different capabilities and skills but complementary experiences and directions, research training, mentoring and capacity building of the whole team, and actions to reduce the risk of H1N109 being implemented as the research progressed.

In this study, the PAR framework enabled a collaborative partnership between Aboriginal and Torres Strait Islander community members, organisations, and novice and experienced researchers. The collection and analysis of this data formed an interim report that captured the main findings so that health services and organisations could use this to improve their responses to pandemic influenza. Throughout the entire project, Aboriginal and Torres Strait Islander community research assistants were actively involved in research capacity training, data collection, group analysis of the data, and writing up of the research findings. The important role they played in the research project has been described previously[17]. The findings from this research were used as an advocacy tool with government to include Aboriginal and Torres Strait Islander peoples in the National Pandemic Plan. This is a good example of how knowledge translation could look in practice.

Table 1: Major study themes and subthemes

Major theme	Subthemes
Importance of family and ways of life	Keeping families safe Our families, our ways
Realities of living	Big families, small houses Realities of inadequate infrastructure
Key messages for government and health services	Knowledge is power Ask us, listen to us, share with us Partnerships and collaborations are vital More responsive health services are needed Acceptable strategies

Making the implicit explicit was both a strength and a challenge for the research team. At times, the Aboriginal and Torres Strait Islander researchers were placed at some risk when they explored issues that most often go unsaid in communities. As a result, when working with the data, the community researchers were able to provide a more complete translation of the concepts raised by the research.
If the project was to be repeated, the research team would be expanded to include a person allocated to coordinate community engagement at each site. Further, to enable deeper understandings to emerge and acceptance of new measures developed, all participants and groups would need to be fully engaged in the research process. Community organisations operate in dynamic and changing environments, therefore flexible engagement strategies are necessary. Developing strong mutually agreed frameworks for engagement may assist in this challenging process.

The initial results of this research have been published elsewhere and include a number of recommendations and strategies for government, health services and families[1]. An important focus of this article is the translational research framework[28]. Translational research contributes to informing practice and policy in Indigenous health[28]. Translational research is associated with the concept of knowledge translation developed in Canada and mandated by the Canadian Institutes of Health Research (CIHR)[28,29]. Within CIHR's 'knowledge to action process' model, a representation of knowledge translation, this article can be defined as the 'identify problem/identify, review and select knowledge' step[39,40].

Actions to reduce the risk of pandemic influenza transmission in the community need to be driven by the understandings emerging from this research. The importance of family and community ways was a strong and recurring message for governments. The reality of life in Aboriginal and Torres Strait Islander communities differs from that of many non-Indigenous communities, and pandemic influenza strategies need to take account of these differences. The key messages to government and health services stemming from the research were that community engagement and partnership is vital, and health services need to be more responsive. In 2013, this study's research team was given the opportunity to provide feedback on the revised Australian Health Management Plan for Pandemic Influenza. The results of this research are being incorporated into the latest revisions of this plan.

The social aspects of communities, such as cultural values, importance of norms, strong family ties, and social networks, need to be integral in research methods for addressing issues in vulnerable populations. The model of research described here could provide a useful starting point for researchers who are working in these environments and with these populations, and argues for respectful engagement with communities as a cornerstone for this type of research.

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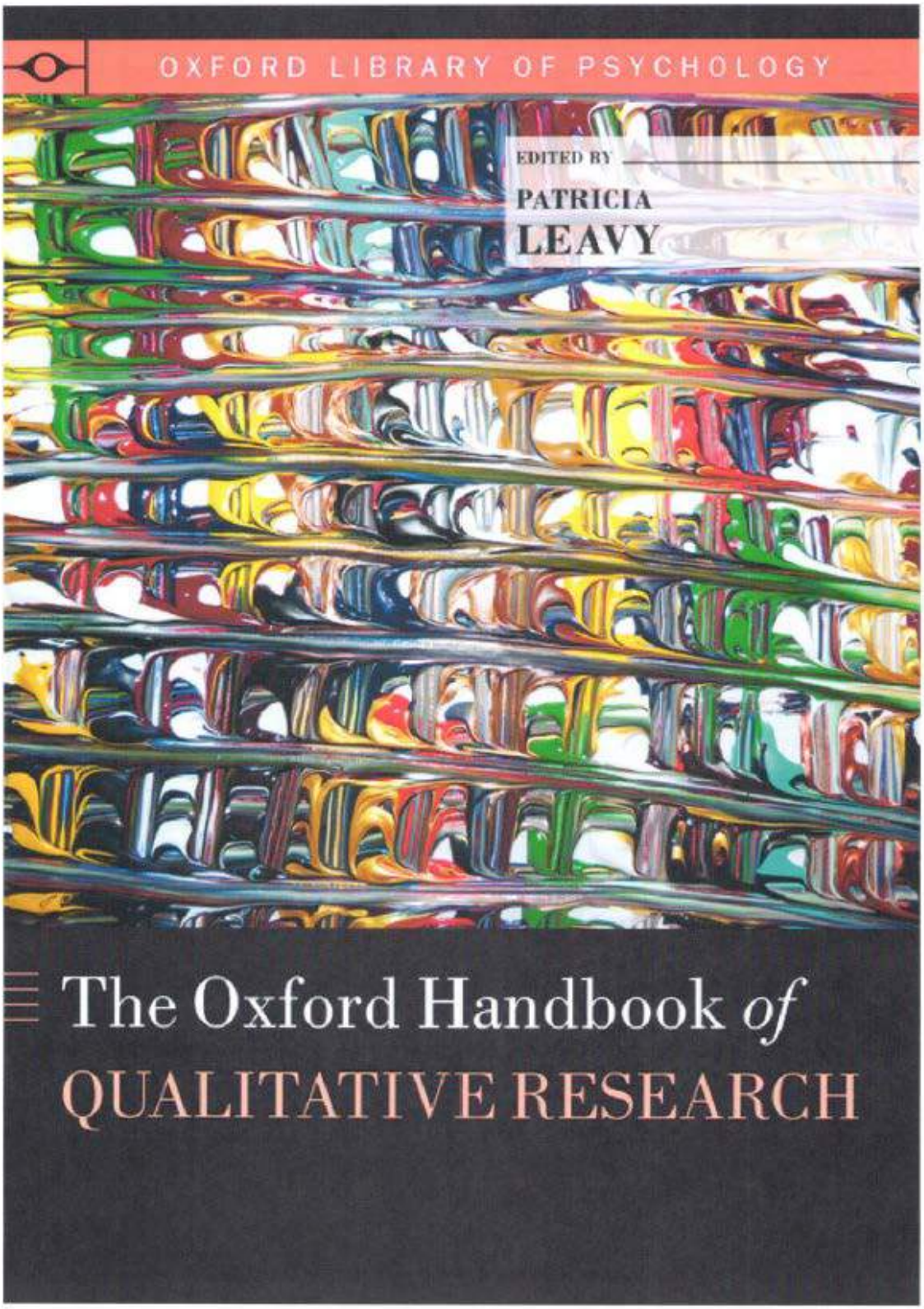
4.7 Evans, Miller, Hutchinson & Dingwall. De-colonizing research practice: Indigenous methodologies, Aboriginal methods, and knowledge/knowing



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CHAPTER

10 Decolonizing Research Practice: Indigenous Methodologies, Aboriginal Methods, and Knowledge/Knowing

Mike Evans, Adrian Miller, Peter Hutchinson, *and* Carlene Dingwall

Abstract

Indigenous approaches to research are fundamentally rooted in the traditions and knowledge systems of Indigenous peoples themselves, although Indigenous methodologies and methods have become both systems for generating knowledge and ways of responding to the processes of colonization. Very specific Indigenous methods emerge from language, culture, and worldview. This chapter describes two such Indigenous research approaches drawn from the work of two Indigenous scholars with their communities in Australia and Canada. Although creative and new, these approaches draw deeply from their communities and thus express and enact traditional knowledge systems in contemporary terms. This approach may result in more pertinent research, better take-up and dissemination of research results, and a general improvement in the situations of Indigenous communities and peoples.

Key Words: Indigenous methodologies, decolonization, participatory action research

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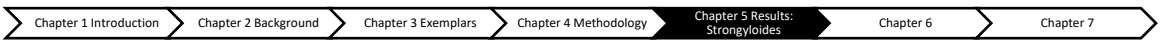
Chapter. 5 Findings: Strongyloides



5.1 Chapter Brief

This chapter aims to present findings from two studies that investigated the impact of Strongyloides on Indigenous communities and present both qualitative and quantitative study findings and results that provide deep insights into the barriers controlling and treating Strongyloides. Also, evidence presented here aims to better inform public health policy and provide insight into community engagement to mobilise local Indigenous leadership in mass drug administration.

5.2 Overview

This chapter presents two papers from two different studies, and both investigate the impact of Strongyloides on Indigenous communities. Both studies provide deep insights into the barriers controlling and treating Strongyloides in Indigenous communities.

5.3 Papers Presented

Miller A, Smith ML Judd JA, Speare R. Policy implications for controlling communicable diseases in Indigenous Communities: Case of Strongyloidiasis in Australia. *Aboriginal Policy Studies*, 7(1) 148-179, 2018.

Miller A, Young EL, Tye V, Cody R, Muscat M, Sanders V, Smith ML, Judd JA, Speare R. A community-directed integrated *Strongyloides* control program in Queensland, Australia. Control of Communicable Diseases in Human and Animal Populations: 70th Anniversary Year of the Birth of Professor Rick Speare (2 August 1947 – 5 June 2016). *Trop. Med. Infect. Dis.* 3(2) 48, 2018.

The first paper is a qualitative study to investigate the views and perspectives of health professionals and researchers to the barriers of controlling and treating Strongyloides in Indigenous Australian communities. Interviews where undertaken with health professionals and researchers, using purposive sampling, qualitative data

was recorded and verified with participants and thematically analysed (Ethics approval number OTH/07/12/HREC). The results were thematically organised into major and sub themes.

The outcome from this study is that Australian Indigenous communities will continue to suffer effects of increased morbidity and mortality associated with and due to lack of control and prevention of *Strongyloides stercoralis*. Issues such as institutional racism, improvements to health promotion, education, socioeconomic determinants and health care systems policy and procedures need to be addressed.

This study identifies direct implications for controlling and preventing of *Strongyloides stercoralis*. These implications include increasing knowledge and understanding of the risks to health for Indigenous community members and highlighting the need for prevention policy development for neglected tropical diseases in Indigenous communities. Additionally, increasing knowledge and understanding about *Strongyloides stercoralis* treatment, diagnosis and healthcare access so that health professionals and policymakers who work within Indigenous health are better informed. More importantly, raising awareness of systematic institutional racism in the control and prevention of neglected tropical diseases in Indigenous communities and a health promotion framework can provide the basis for multiple level of interventions to control and prevent Strongyloides in Indigenous communities and to make effective and sustainable changes.

The second paper is largely quantitative but has added information of local Indigenous health promotion strategies that enhanced the success of the trial. This study occured in the remote Aboriginal community of Woorabinda in central Queensland, Australia in 2004. There were 944 residents with a high prevalence of strongyloidiasis resulting in morbidity and at least one death. In 2004-2005 the community initiated and implemented a Strongyloides control program, treating all residents with oral ivermectin, repeating dosage for those with positive Strongyloides serology, running their health promotion campaign using locally made resources and addressing relevant environmental health problems.

Ninety-two percent of the community residents participated in the program and prevalence of strongyloidiasis at the time of the ‘test and treat’ intervention was 16.6% [95% confidence interval 14.2-19.3]. Cure rate after two doses of ivermectin was 79.8%, and transmission was stopped. The local leadership and governance for this program resulted in a high level of community involvement. The commitment

required of these leaders was demanding and involved intense work over a period of several months but was considered worth the outcome. Apart from controlling strongyloidiasis, the community took pride in the fact that they had developed and run the program. This Woorabinda study appears to be the first community-directed Strongyloides control program in Australia and possibly globally and is a significant study that demonstrates that Indigenous leadership and participation is essential in undertaking a community wide mass drug administration.

My role in this study was to re-engage the community, develop and write a manuscript, gain permission to publish the results of the study and to contextualise the role the Indigenous community and health staff played in the mass drug administration trial to test and treat for Strongyloides. Previous attempts to re-engage the health service and community failed for some reasons which occurred over long period - sensitive matters which cannot be discussed in this thesis). I used research funds (ARC Grant No. 0989521) to appoint an Indigenous researcher who had cultural connections with the community to undertake consultations. With ethics, approval (OTH/07/12/HREC) consultations recommenced, and additional information about the context of the study was revealed, recorded and added to the manuscript. Permission to write and published the study was approved, and this was co-presented by health staff and researchers at the 2016 International Strongyloides Workshop (see reference in list of presentations).

5.3.1 Miller, Smith, Judd, & Speare. Policy implications for controlling communicable diseases in Indigenous communities: Case of Strongyloidiasis in Australia.

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Article

Policy Implications for Controlling Communicable Diseases in Indigenous Communities: Case of Strongyloidiasis in Australia

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Policy Implications for Controlling Communicable Diseases in Indigenous Communities: Case of Strongyloidiasis in Australia

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Abstract: *The objective of this paper is to document the knowledge and experiences of healthcare professionals and researchers in Australia about the barriers to controlling Strongyloides stercoralis in Australian Indigenous communities. Qualitative research methods were used to conduct in-depth semi-structured interviews, which were digitally recorded, transcribed, and participant-checked. Data were thematically analysed to identify significant themes. Five major themes were identified:*

1. *Barriers to health/treatment;*
2. *Access to healthcare;*
3. *Policy;*
4. *Learning opportunity; and*
5. *Ideas for intervention.*

The findings suggest that Australian Indigenous communities will continue to suffer increased morbidity and mortality due to a lack of control or prevention of Strongyloides stercoralis. Issues such as institutional racism, improvements to health promotion, education, socioeconomic determinants, and health care system policy and procedures need to be addressed. This study identifies several direct implications for Indigenous health:

- *The need for increased knowledge and understanding of the risks to health for Indigenous community members;*
- *The need for prevention policy development for neglected tropical diseases in Indigenous communities;*
- *The need for increased knowledge and understanding of the treatment, diagnosis, and healthcare access concerning Strongyloides stercoralis for health professionals and policymakers who work within Indigenous health;*
- *The need to raise awareness of systematic institutional racism in the control and prevention of neglected tropical diseases in Indigenous communities; and*

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- *The need for a health promotion framework that can provide the basis for multiple-level interventions to control and prevent Strongyloides in Indigenous communities.*

Introduction

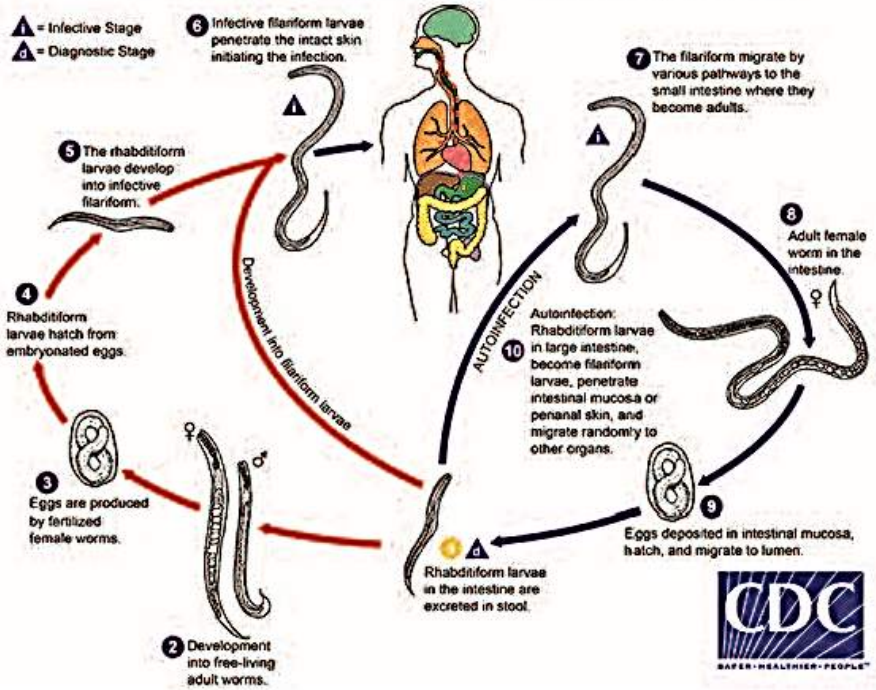
Infectious diseases contribute significantly to the morbidity and mortality of Indigenous Australians, particularly in rural and remote communities, at a much higher rate than in the mainstream Australian community (AIHW 2015; Holt, McCarthy and Carapetis 2010; Flannery and White 1993). There are many highly effective interventions for the control of these diseases. However, implementation of these interventions in rural Indigenous communities is frequently suboptimal. Barriers at multiple levels appear to impact on effective interventions in Indigenous communities.

Strongyloides stercoralis is an intestinal nematode transmitted by contact with damp soil containing infective larvae (Speare 1989; Sheory, Walker and Biggs 2000). These infective larvae are developed from faeces indiscriminately deposited on the ground. The larvae penetrate the skin and travel to the lungs, where they penetrate the alveolar spaces and are carried through the bronchial tree to the pharynx (Sheory, Walker and Biggs 2000). They are then swallowed and reach the intestines where they develop into adults that live in tunnels in the small intestinal mucosa (Sheory, Walker and Biggs 2000). The uniqueness of *S. stercoralis* is that it can become autoinfectious, with small infective larvae formed in the gut and re-entering the tissues by penetrating the wall of the lower bowel. The practical result of this is that a single infection can last many years and probably for life; the longest recorded infection is 65 years (Leighton and MacSween 1990). Also, if the immune response of the host is suppressed, the rate of successful colonisation by autoinfective larvae increases, the number of adult worms in the gut rises, and a serious and potentially fatal disease (the hyperinfective syndrome) develops.

The significance of strongyloidiasis in rural and remote Indigenous communities is that it is a highly infectious parasite, a disease with a unique life-cycle of autoinfection that causes a variety of symptoms, including fatality from hyper-infection and lifelong infection if left untreated (Johnson et al. 2005). Australian Indigenous people living in rural and remote settings are exposed to and are infected with *S. stercoralis*. Some of the highest prevalence levels in the world have been recorded in northern Australia, with a prevalence of 40% not uncommon in some groups (Adams, Page and Speare 2003). In most societies, the prevalence is under 5%, even in communities with severe poverty. The impact of the parasite on communities has been documented, including case reports of serious disease (Walker, Blake and Downing 1976; Yiannakou et al. 1992; Mak 1993). One case series (Kukuruzovic et al. 2002) showed that Indigenous children with acute strongyloidiasis and diarrhoea were more likely to have hypokalaemia (low blood potassium) than were similar children with diarrhoea due to other causes. Work has been done in remote Australian Indigenous communities with mass drug administration (MDA) programs such as those conducted by Kearns et al. (2009) administering ivermectin across communities to attempt

an eradication of scabies and strongyloidiasis. Recently, Kearns et al. (2017) focused on administering ivermectin for the treatment of strongyloidiasis across two remote Australian Indigenous communities. Both studies have presented research supporting that MDA programs incorporating routine treatment with community engagement and education can decrease and potentially eradicate strongyloidiasis (Kearns et al. 2009; Kearns et al. 2017).

FIGURE 1. The life cycle of *Strongyloides stercoralis* (CDC 2015)



Diagnostic tests suitable for use in Australian Indigenous communities are available. Speare and Durrheim (2004) estimated that detecting and curing a positive case of strongyloidiasis in these hyperendemic northern communities are relatively inexpensive, costing $590 per case if community-wide screening were implemented. In Caucasian groups, chronic strongyloidiasis produces significant symptomatology in 67% of infected individuals (Grove 1980). There is no reason to believe this is not the case in Indigenous Australians. The diagnosis of strongyloidiasis in mainstream Australians with no risk factors, particularly related to travel history, is so rare that there are few to no published case reports.

A systematic review of the peer-reviewed literature published between 1969 and 2010 has presented the status of strongyloidiasis for Australian Indigenous community members and summarized the barriers to its control (Miller et al. 2014). The main barriers to management are health status, socioeconomic status, healthcare literacy, and procedures. Concurrent health conditions and infections, living conditions and racial disparities, the

difficulty of detection, and inadequate knowledge/treatment (e.g., medication dosage) are, but a few of the main barriers presented (Miller et al. 2014).

The barriers to controlling infectious diseases for health improvement at the personal level in rural and remote Indigenous communities include

1. communication difficulties between health staff and Indigenous patients based on the lack of a shared understanding of disease causation and the simple fact that English is not the first language for many people in remote locations (Trudgeon 2000; McConnel 2003; Cheng, Blum and Spain 2004);
2. fear of disclosure of culturally sensitive illnesses (Newman et al. 2007)
3. fear of discrimination (Lowe et al. 1995; Trudgeon 2000; Newman et al. 2007);
4. remoteness from essential specialised health services (Gruen, Weeramanthri and Bailie 2002; McGrath 2006);
5. lack of the funds needed to purchase medication and equipment (Couzos and Davis 2005; Couzos 2005);
6. the need for education in maternal and child health (Molyneux 2006);
7. the need for involvement from other government sectors and agencies (Molyneux 2006);
8. the need for the establishment of surveillance, diagnosis, monitoring, and evaluation systems (Molyneux 2006); and
9. at the population and governmental levels, the potential influence of racist attitudes negatively impacting health expectations and services (Lowe, Kerridge and Mitchell 1995; Trudgeon 2000; Aldrich, Zwi and Short 2007).

Although many barriers have been explored from the intervention perspective, no research has qualitatively explored the barriers from the Indigenous community's perspective—the health service staff working in Indigenous communities—or have documented the experiences of leading experts in the field outside of their clinical intervention or professional role.

Strongyloidiasis is not considered a notifiable disease in the Australian public health system (Speare, Miller and Page 2015). The purpose of this study is to describe the barriers for the prevention, treatment, and control *S. stercoralis* from the perspective of experienced researchers and healthcare workers in Australia. *S. stercoralis* infects humans mainly through skin contact with contaminated soil. In discussing the control of communicable diseases such as strongyloidiasis, the term "control" implies prevention. In this study, the authors want to make it explicit that prevention must be considered from a public health and Indigenous community perspective. The perspectives of researchers and community members affected by *S. stercoralis* or other infectious diseases have a better chance of influencing policy. Policy development about control and prevention must deal with and address institutional racism for successful implementation (including the key messages to government, researchers, and community members). For the purposes of this paper, the authors focus on these policy implications and therefore do not specifically explore the eradication of *S. stercoralis*.

In a systematic review of the barriers to the control of strongyloidiasis, Miller et al. (2014) described the need for a detailed, clinical picture in order to manage *S. stercoralis* in Australia, including prevalence rates, evidence, and community-based public health approaches to control strongyloidiasis. This study explores the barriers to the implementation of infectious disease interventions for diagnosing, treating, and preventing strongyloidiasis from the perspective of experienced healthcare professionals with extensive medical knowledge and experience in the field of researching and/or diagnosing and treating strongyloidiasis. The aim of this paper is to document the knowledge and experiences of these experienced healthcare professionals concerning strongyloidiasis in Indigenous Australian communities and to use their knowledge and experience to better understand the policy implications for controlling and preventing strongyloidiasis.

Methods

The study was conducted in Australia and focused on barriers to the treatment, control, and prevention of strongyloidiasis in Indigenous communities. The authors used a descriptive qualitative study to explore the perspectives of healthcare professionals as key informants for strongyloidiasis in the context of Indigenous communities, environmental health, and health care systems (Pope and Mays 2006; Pope, Reibland and Mays 2006). Purposive sampling was used to recruit health professionals and researchers with long-term experience with *S. stercoralis* participants. The participants in this study are described as health professionals who work within laboratories, research institutions, and primary health care services in rural and remote and urban settings from around Australia. Participants were eligible to be included in the study if they worked in Indigenous communities in Australia and/or had experience diagnosing and treating strongyloidiasis. Participant recruitment was undertaken by selecting nationally known health professionals and researchers working on the diagnosis and treatment of strongyloidiasis.

Telephone interviews were conducted with participants based on a semi-structured interview guide. Participants were provided with open-ended interview questions prior to scheduled telephone interviews. These open-ended questions focused on their experiences with the barriers to controlling *S. stercoralis*, including health care system/policy, drug treatment, the Australian public policy context, and the Indigenous community context. Probes were used to help participants elaborate on their experiences in the field. All interviews were audio recorded and transcribed verbatim. Participants were provided with a copy of their transcript to confirm and approve the accuracy of the transcription. No revisions were requested by any of the participants. Thematic analysis using constant comparison was applied to the transcribed interviews (Creswell 2012). Two members of the research team individually coded each transcription, and then the larger research team met to discuss the codes and develop the coding framework.

Research ethics approval was granted by the Human Research Ethics Committee of Griffith University, Brisbane, Australia. All participants signed an informed consent to participate in

their interview and to allow information and possible quotes to be published. Their anonymity and confidentiality were included in the consent process. However, some participants were not concerned about being recognized through the information they shared.

Results

This study identified five major themes and sub-themes as major barriers to controlling strongyloidiasis in Indigenous Australian communities: barriers to health/treatment, access to health care, policy, learning opportunities, and ideas for intervention (see Table 1).

TABLE 1: Themes and sub-themes

Major Theme	Sub-theme
1. Barriers to Health/Treatment	1.1 Perspectives of Racism • Infrastructure/Environment • Diagnosis/Treatment • Normalisation 1.2 Diagnosis/Clinical Knowledge • Diagnosis • Clinical Knowledge 1. 3 Community in Context • Trust • Environment
2. Access to Health Care	2.1 Treatment/Medication
3. Policy	3.1 Government Funding 3.2 Institutional Racism
4. Learning Opportunity	4.1 Community Perspective 4.2 Ethical Research
5. Ideas for Intervention	5.1 Cost Effective 5.2 Knowledge Translation 5.3 Community Partnership • Identification • Health Promotion and Prevention Programs/Strategies • Registration/Prevalence

Barriers to Health/Treatment

Perspectives of racism

Racism is perceived at both individual and institutional levels, particularly in controls over accessing data and knowledge of the disease.

Infrastructure/Environment

The environment itself exposes a community to *S. stercoralis* infestation, an environment related to housing and infrastructure resulting from influences of racism that impede people from decreasing their exposure:

> Some issues in the housing, in internal housing areas, but also the external housing area, in particular like compromised infrastructure, like overflow in septic tanks, leaking taps … hardware. So we had a look at some behaviours, the activities of daily living in some of the houses, and where these wet areas or damp areas were persisting, and in particular the kids, basically, the external housing environments harboured the nematode.
>
> *Participant 1*

Diagnosis/Treatment

A lack of education and knowledge among health professionals about *S. stercoralis*, including on infection rates, symptoms, and asymptomatic behaviour, can lead to misdiagnosis and ineffective treatment. The individual and institutional level of control of this necessary information perpetuates the issues described by health professionals in the field working with *S. stercoralis* infections:

> Lot of challenges around diagnosis but diagnosis is important because if you get to a point where you fixed up the sanitation, and you've done your treatments, or all you do is a selective treatment program, or people come in, there are issues with diagnosis…the first issue of diagnosis is lack of education amongst clinicians that Strongyloides is a significant
>
> *Participant 4*

.....

> People have got multiple parasites, wouldn't it be good to treat them with ivermectin and do some follow-up? I don't get it; I honestly don't get why they only look at bloody treating bits and pieces and not looking at the whole raft of issues.
>
> *Participant 1*

> The only way people can actually get the medication is if they've had a blood test and it comes up positive so you're actually getting the appropriate drugs, and for adults it's relatively simple because they'd normally be taking blood anyway to check out for chronic diseases, and then they send it off for Strongyloides as well, but for children they hardly ever take blood from children unless they think it's absolutely, absolutely essential, so they never get tested and so they never get treated.
>
> *Participant 2*

Normalisation

The assumption that people in the community are always ill and allowing it to continue as a "normal state" is a form of racism, as is the perspective among the people themselves that feeling ill is normal for everyone:

> The process, it's called normalisation, so not feeling well becomes normal in the person's mind, and so if you're not unwell for a long period of time and somebody says how are you today, and you'll say I'm okay because you haven't been more sick, I suppose recently. They don't actually recognise that they've got the symptoms. They think it's normal to have diarrhoea all the time and belly aches and things like that…that process is normalisation.
>
> *Participant 2*

.....

> The terrible quotes that were around, it's only the sick who die. I've just found strange comments coming from medical profession and then a concept you could treat individuals, but somehow you couldn't treat the individuals in an endemic area just because it was endemic.
>
> *Participant 9*

.....

> There is a degree where even people who are very, very good people just see so much morbidity all the time that from that you just get habituated to seeing it. You become immune to it which is not, I don't think it's necessarily racism, it's not an acceptance that it's right, but it's just so often that you see these things…certainly you can get habituated to seeing people coming in with disastrous health problems and I think some people they just lose sight of the fact…I believe in the principle just because it's a remote Indigenous community, health care should basically be as good as somebody who lives in the city essentially, and except for distance and things like that, there's no reason you shouldn't aim for the same baseline. Poor sanitation is not acceptable in the middle of [Australia] so it shouldn't be acceptable in indigenous communities.
>
> *Participant 4*

.....

> Normalisation with regards to the disease actually comes from speaking to health care workers, community workers, people, other researchers who have actually gone into the communities to look at the issue as well…I think it's a growing issue.
>
> *Participant 7*

Diagnosis/Clinical Knowledge

S. stercoralis infection is diagnosed via blood or stool sample, and both have diagnosis limitations/issues. Without diagnosis and subsequent treatment, the infection can lead to a suppressed immune system, life-threatening complications, and death.

Diagnosis

Stool testing is not ideal, as larvae are intermittent and are less likely to be observed in stool in chronic strongyloidiasis:

> The fact that you can have chronic strongyloidiasis and you can treat it, but your subsequent source specimens will be negative and then like maybe seven weeks later one will turn up positive again. That's just the nature of the worm, that's just the nature of the beast. And the limitations with regard to finding the organism in the stool which requires live larvae to be present. There are issues in terms of specimen transportation with regard to that in Australia.
>
> *Participant 4*

.....

> Currently, the gold standard is faecal culture, and faecal culture has a lot of practical issues. We rely on fresh stool samples to have an effective specimen for culture. By the time a faecal sample, if submitted, reaches the lab it can be three or four days old and by that time the parasite's dead so we can't get culture, a positive culture, so it does concern me that we're issuing reports saying that the culture is negative and giving false negative reports…that's a practical issue.
>
> *Participant 5*

Obtaining samples is often impeded by non-compliance. For example, non-compliance associated with obtaining blood from children or stool samples are barriers to diagnosis and treatment:

> They're much more willing to give stool samples from little children than from older children. I think there's also the shame aspect of things too as well, but yeah it is harder to get stool samples.
>
> *Participant 2*

Strongyloides infection can be either symptomatic or asymptomatic. The longer a person suffers from infection, the higher the risk of hyperinfection potentially leading to death:

> Every test has its limitations, and part of the thing about clinician education is not just to be aware of strongyloidiasis but to be wary when all your tests are negative as well. Because they can be negative, but someone might still have strongyloidiasis. They probably won't on the basis of probabilities, but it comes down to a situation like hyperinfection, you can't be too careful.
>
> *Participant 4*

.....

> Under a microscope, you've got the situation of being able to diagnose it, but because it's in chronic strongyloidiasis, it's not necessarily showing in the faeces. It seems that phases you can diagnose it in the faeces are in the acute phase when someone's probably got diarrhoea, and it is their first episode or certainly when disseminated. When [larvae] is in its millions and in both those cases, the Strongyloides in serology is not as reliable. The body might not have developed its own immune response, and in disseminated strongyloidiasis, the immune system may be so low that it can't mount an immune response…in the primary care setting, we're really looking for identifying those that have chronic strongyloidiasis and then looking to treat that before they're actually running into the complications…people die from septicaemia. If you get to the disseminated phase which is when [larvae] multiplies into its millions having a drug that's going to kill something that's in its millions is very hard, and that's why disseminated strongyloidiasis has a high fatality rate.
>
> *Participant 9*

Clinical Knowledge

The lack of clinical understanding of *S. stercoralis* leads to inadequate clinical practice, reduced health, and increased risk for people exposed. Health professionals armed with detailed information on *S. Stercoralis,* prevalence, diagnosis, and treatment would radically influence the infection rates amongst individuals and decrease the symptoms and concurrent health problems resulting from strongyloidiasis:

> From a clinical perspective, I think working with the remote clinics, most of them don't know about Strongyloides, they wouldn't have a clue about it.
>
> *Participant 1*

> From the point of view of the clinician, I think probably an awareness of ivermectin and its role in eradicating Strongyloides.
>
> *Participant 6*

Strongyloides can be symptomatic, asymptomatic, or both; it can mimic many other illnesses. If health professionals were more aware of this issue, they could have increased opportunities to make accurate diagnoses:

> The fact that we don't really know how many of the ordinary everyday symptoms of ill health are caused by Strongyloides being inside the body as against other factors. And because some of the symptoms of Strongyloides infection can be nausea, vomiting, diarrhoea, rashes, not sleeping well, not eating well, all of those sort of common run of the mill symptoms of feeling crook, and we don't go that extra step of testing to see whether they've got Strongyloides or not but it could well be that in many instances that's the cause of the problem.
>
> *Participant 6*

Failure to understand the complexity of the auto-infective cycle and incorrect diagnoses can lead to disseminated strongyloidiasis and to extreme decreased health, and potentially death:

> You've got a health profession that are trained in Australia that are ignorant of Strongyloides, It's understanding about the auto-infective cycle and the fact that if you don't think of it, you're not going to diagnose it and the evidence is that those who die from strongyloidiasis, there's probably been warnings signs beforehand, but medical professionals have not been alert or aware of it to consider it, and my experience has been that when people do die they're actually preventable deaths.
>
> *Participant 9*

Community in Context

Disease and infection can be described in the context of community. Lack of knowledge of the disease (including exposure and transmission processes), community experience with health professionals, and the community's environment and location all influence how strongyloidiasis is understood and how that understanding, in turn, influences barriers and outcomes.

Trust

Barriers within the community can include mistrust of the health professionals:

> The sort of barriers that [non-community member(s)] encountered was a lot of mistrust, why are they taking my blood, are they going to take it and sell it to someone else and make a profit out of it, those sorts of thoughts…And there were some people who refused to cooperate and so they just moved onto another person.
>
> *Participant 5*

Environment

A community's environmental health (or lack thereof) influences exposure and infection rates. Transmission rates increase along with reductions in environmental health:

> Environmental health [government department] can say look you've got a problem; we're going to advocate, that sewerage system's broken down, go and get it fixed. The environmental health don't actually fix it, they have advocacy role to see that it's done and then you have the infrastructure that's managed by councils, managed by housing authorities, it's managed in a different section but they usually have responsibility for building appropriate housing.
>
> *Participant 9*

Community awareness of ways to prevent transmission could decrease the exposure and transmission of *S. Stercoralis*:

> It's actually poor sanitation, whether that's educational to some degree with the kids avoiding, say if the septic tank is broken avoid running around the outflow from the septic tank or whether it's just the infrastructure side of things and the good disposal of sewerage.
>
> *Participant 4*

Diagnosing at the community level is challenging:

> They say you need three stool samples, either consecutively or three stool samples over a week because the Strongyloides larva output is so irregular. And certainly, we only ever did it by a single sample. For us in community, it is quite difficult to get that one sample, let alone trying to get three…to get to the laboratory from a community, we're never going to see Strongyloides. What we have found is most of the kids have often got….bugs in their tummy. Then they're actually treated for Giardia when it actual fact it could have been the Strongyloides underlying it. We will never know. So they would have got the three-dose of albendazole in the community as a sort of protocol. By the time they get the poo sample back, I think we found that 50% or more of the kids had Giardia and Trichuris.
>
> *Participant 8*

Access to Healthcare

Treatment/Medication

The inability to treat Strongyloides effectively and the difficulty of accessing health care influence the community's ability to prevent and treat it. By engaging a full-faceted approach

to prevention, a program should focus on improving the environment to decrease exposure to and infection of *S. Stercoralis*:

> We concentrate on engaging those people in the house in regards to the cleanliness of the house, internal environment, but also the hygiene factor in the house
>
> *Participant 1*

The difficulty of diagnosing Strongyloides contributed to a lack of treatment:

> The other problem with ivermectin is basically the protocols…that unless the person has got a positive diagnosis for Strongyloides, they're not given ivermectin. If they're suspected of having it, but they haven't got a positive diagnosis, they will give albendazole, and they'll offer three doses, but they usually only watch one of them being swallowed, and we know that even three doses of albendazole on three different days isn't effective.
>
> *Participant 2*

Disseminated Strongyloides leading to hyperinfection requires long-term treatment:

> Go by the evidence ivermectin is superior to albendazole based on trials. So single dose ivermectin is superior to three doses of albendazole in terms of elimination and then getting a second dose of ivermectin two weeks later is marginally better than just giving a single dose of ivermectin. That's for chronic infection, if somebody's got hyperinfection it's a completely different story. You need to keep treating them until they get better and then after that even give them a bit more…in terms of the Australian setting, I can't think of any reason why you wouldn't give the people ivermectin provided they don't have a particular [no side effects taken with other medications].
>
> *Participant 4*

The gastrointestinal condition of the person with Strongyloides influences the absorption rate of medication at the individual level. Ivermectin is safe and, with the correct therapeutic dose, will decrease infection rates:

> Both ivermectin and albendazole are not that well absorbed through the gut, so we don't know what therapeutic blood levels are reached in individuals. You're going to get individual variation and variation due to the diet they take and the condition of their gut at the time of medication. Given that the medication is relatively safe it's probably still easier to overmedicate someone than to miss the Strongyloides infection.
>
> *Participant 5*

Policy

The policy theme includes narratives around government funding and institutional racism. Control, normalization, and cost influence what illness or disease is declared important to public health, which in turn determines funding allocation for control, prevention, and drug treatment strategies and initiatives.

Government Funding

Recognizing outbreaks and having the staff to manage them is an issue:

> Certainly, in the [location], we have the Centre for Disease Control, public health nurses and doctors that can provide guidance. But often when a community is having a big outbreak or a raised prevalence, they say at the Public Health Unit, can you [multidiscipline team] come and help us? With the high staff turnover in community, certainly not with the health workers, but with the…staff, people unless they've been around for a long time, they're nervous about shutting up shop for a week, and running around and screening and treating everybody.
>
> *Participant 8*

Institutional Racism

Avoidance, denial, and normalisation of strongyloidiasis in communities have been described as institutional racism by public health and public policy:

> Public policy arena there might be some endemic racism, there's still institutionalised racism…I know that the doctors and nurses generally don't exhibit that. What other reason can you come up with for as to why there is such disparity?
>
> *Participant 4*

Institutional racism is expressed as a lack of focus on the health of Indigenous people:

> I don't know it's one of those things where no one has gone to the trouble of doing anything about it for Indigenous people. I suppose it's one of those institutional racism things that health departments can be pretty guilty of.
>
> *Participant 6*

The government's normalization and lack of urgency concerning illness affect communities with grandparents raising children orphaned by parents succumbing to disease (most often considered preventable):

> When I first started working in the Department of Health it really annoyed me when people would say oh that's for remote; they can wait as if it wasn't very important that something should happen quickly. I think across the board everyone tends to forget that out there is people who are sick, who are very inconvenienced by whatever illness it is that they've got, and are dying at a very early age which means that you've got heaps of kids out there without any mothers or fathers. There's grandmothers and aunties who are looking after too many kids for what they deserve because they're looking after all the kids of the ones who've died. I don't know how you do it, but there's definitely this view held by a number of people in the bureaucracy that feel that because it's out bush there's no real hurry.
>
> *Participant 6*

Further perspectives confirm that there is a lack of urgency concerning to need to supply medications to remote areas:

> I suppose in pharmacy is where I first came across [institutional racism]and I'll never forget the first day that I was working in the pharmacy, and a heap of scripts came in which is about 500 kilometres away and if you were in a suburban pharmacy anywhere and a heap of scripts came in the size of the heap that came in that day you'd almost shit yourself. I won't get these done today. And when I said to the girl "wow when do they want these", she said, "oh it's all right, there's no hurry, a couple of weeks will do". That was the first impact that I had of this view that people out bush can wait. If a doctor's seen a patient and want them to have a drug, we make sure they get it as quickly as they can in the suburbs but if they live out bush there's nowhere near the same sense of immediacy, and because of that, people are not thinking that their medicines are very important.
>
> *Participant 6*

It is reported that Australia's Indigenous communities are lacking basic needs and health care:

> It's a disease considered of a third world country, so it's not considered a mainstream issue, and because the decision makers live in probably first world conditions and just doesn't affect the decision-makers I think that's the reason that nothing's done or things that can be done aren't actually addressed, and I think particularly for remote Indigenous communities, out of sight is out of mind and that applies to other things.
>
> *Participant 9*

The status of Indigenous communities appears to continue to be deemed lower than that of other communities, leading to a lack of urgency in healthcare provision:

> The bureaucracy don't see it that way but if you see it as institutional racism because if it were white people in their own suburbs in mainstream set up, they'd be thinking.. better do something about getting rid of it, I suppose the bottom line is when something affects you, you're more likely to want to see something done about it…the people that aren't in influential positions are less likely to have their issues addressed than the ones who are in influential positions.
>
> *Participant 9*

Learning Opportunity

Combining clinical and community perspectives has the potential to improve health in communities, including the eradication and treatment of strongyloidiasis and ongoing ethical research.

Community Perspective

Community involvement and engagement in all aspects of research are imperative:

> We set an engagement process with community…I think it's best practice, so it shows people, researchers or whoever's coming in to do this type of work or research work, know how to actually engage in a community…we tested the engagement process pretty rigorously, and we used it on multiple sites, and we never, ever, ever had an issue with engagement on a community with it.
>
> *Participant 1*

Non-Indigenous health professionals need exposure and learning opportunities within the community for greater awareness and understanding of what is needed:

> Because we had non-Indigenous clinicians with us, they just grew from this experience; they were just overawed with it. So it was about learning, and also it was about them learning of how we operate as well, and what benefits they can get from our way of learning and implementing these things, but also incorporating their views. Their views were valued too; incorporating their views into our stuff, and how we can fit in with that and they can fit in with us.
>
> *Participant 1*

.....

> The next step it is really important for us to link with communities and with patients and hope that they are willing to let us in.
>
> *Participant 3*

Indigenous community Elders play an integral role in the community and need to be included:

> Aboriginal Elders participating in the discussion and ways of educating community leaders…I think their involvement in spreading the information is vital in terms of getting control programs going. I think to any success has got to come from them and be supported by them.
>
> *Participant 5*

There must be ongoing community training within the community to foster a better understanding of and engagement with health issues in more acceptable ways:

> I've found for certain drugs and certain conditions; we don't always need health workers, nurses, doctors, to do stuff. But if we do want to focus on a particular disease or illness, then we actually can train people up with enough information to actually

> be able to go out and do work in the community - it's often a lot more acceptable for the community workers to go and sit in a home and have a chat about what's going on than to try and drag people to the clinic or for the clinic staff to go out.
>
> *Participant 8*

Ethical Research

Research needs to be conducted with the community, not on the community, along with appropriate feedback to the community so that appropriate actions can be implemented to address the issues:

> Our research with community, I got a letter of acknowledgement for the research [from] all the traditional owners on that site and from that area, and when the research was finished we went around to all those traditional owners and sat there and explained what we needed to explain properly,...and they signed the acknowledgement that we'd consulted and everything in regards to the completion of the research. Now I've never, ever seen that data on any research paper that I've read, I've never, ever seen it done…We need to get that message out that people need to explain research and what are the benefits of the research for the people who are going to be part of the research.
>
> *Participant 1*

In working with the community, Indigenous viewpoints must be included in research:

> [An] ethics approval process [must] allow for an Aboriginal viewpoint in regards to who we can talk to, who we can't talk to, who we're supposed to be talking to, who holds data, who's responsible for data, and who ultimately owns the data.
>
> *Participant 1*

Ideas for Intervention

Cost Effective

Cost-effective health care in the long term is essential. Appropriate policies for treating and preventing Strongyloides must be established, including finding appropriate drug producers from other companies/countries if necessary. Ivermectin is safe and cost-effective and is the best evidence-based treatment:

> [Ivermectin] is not expensive in terms of, in comparison with some other drugs.
>
> *Participant 2*

.....

> I completely believe in that holistic thing. And, if you can combine a couple of things like scabies and Strongyloides, you know how they come together because it was a one drug, and you certainly see that with lots of MDAs [Mass Drug Administration].
>
> *Participant 8*

.....

> You'd probably, in the long run, save a fair bit of money by reducing morbidity for other diseases too in terms of lifting people out of the impoverished sort of living circumstances.
>
> *Participant 4*

Knowledge Translation

There must be a shift from dated clinical perspectives and medical models to a multidisciplinary, multifaceted innovation. Knowledge translation as described by the Canadian Institutes of Health Research encompasses an integrated approach and sharing of knowledge between researchers and knowledge users (e.g., government, public health, and community; CIHR 2016). In this circumstance, knowledge of *S. stercoralis* (the parasite) and strongyloidiasis (the disease) must be shared with all affected communities:

> Information [must] get out to the remote communities [to increase] their level of knowledge and understanding of this infection.
>
> *Participant 5*

.....

> I think in a first world country like Australia; we should be able to expect that a condition that is an infectious chronic disease that's transmissible through poor sanitation should be something that is notifiable and then you have appropriate public health strategies to address it.
>
> *Participant 9*

Knowledge translation among health professionals and communities increases education about *S. stercoralis*, which is crucial for treating and preventing strongyloidiasis:

> You need education for GPs, the health professionals. You need education for the community, and then the next group will be that environmental health group that are monitoring what's happening in the environment.
>
> *Participant 9*

Community Partnerships

Community-based partnerships along with community acknowledgement and respect for community/traditional owners are essential components of any intervention.

Identification

Intervention begins at the identification of each community:

> Identifying the communities that are affected…my thinking has been that the ones that are most neglected are the ones that are then going to be identified.
>
> *Participant 9*

We need to acknowledge that the community's need of a particular level of health service is as important as the needs of urban areas:

> In the infrastructure of the way primary health care is delivered to people, you've got to make sure that your systems are in place to ensure that people out bush get as close as possible to the same level of service as people in the suburbs in mainstream.
>
> *Participant 6*

We need to move away from treating on an individual case-by-case basis toward a community-level approach and intervention:

> I think it requires a massive undertaking from community members as well as from the treating health centres to actually make that happen. Policy-wise, for Strongyloides, I'm still a little bit out on that. At the moment we treat individuals. And I haven't done enough analysis yet to see how much of that is household clustering. At the moment, policy-wise for Strongyloides, we just treat the person. We don't even screen the rest of the household.
>
> *Participant 8*

Working with the community to identify their specific circumstances and needs in order to plan strategies and outcomes is important:

> Each community is unique, as you know, and each community gazes in different ways, and we've got to work out and do the homework on how which engagement process will work to get the maximum benefit. You're looking at a multifaceted approach in regards to the engagement process.
>
> *Participant 1*

Health promotion and prevention programs/strategies

Health education and promotion are ways to involve the community in eradicating strongyloidiasis. Engaging children about the benefits to their health and well-being of understanding the parasite is a key message:

Kids were integral to that little project and yeah, frigging fantastic. We followed up on it too, with health education and health promotion, and we integrated the regular worming cycles and that with the child health checks. Everyone's happy there, no one's got worms, they're going to school, the houses are clean.

Participant 1

Community engagement activities need to include adults and children:

Would be good if you got the adults educating the kids, so you teach the adults and the community health workers or whatever or other adults. Then the parents would know that too to be more careful of it because you're teaching the kids so it would stick in their mind a bit more too.

Participant 4

With support, community representation can enhance diagnosis and treatment strategies:

There has been some attempt in educating people in remote communities in regards to this infection, and once they are convinced of this worm and the presence of this worm, usually they're quite supportive in the program. Whether or not the government authorities will support and fund the diagnosis and treatment of this infection. I think it varies. The more community voices that speak up in regards to removing Strongyloides from their communities the more effective it would be.

Participant 5

Strategies need to focus on concurrent infections and conditions:

Mass treatment's the go because you're not only looking at treating for Strongyloides if you give someone ivermectin you're looking at all the other parasites and things you can kill as well. And these people should be thinking outside of the square because most of the people on the community and the kids are, they're polyparasitised, so they've got multiple parasitic infections, not just Strongyloides. If we're going to treat, we're going to knock on the head all these other things that are impacting on people's lives as well.

Participant 1

Kids should be mass-treated for all worms:

You've got the potential to [do] the de-worming for all the kids, to be able to have kids de-wormed. We don't test the kids because we don't do blood on kids but the kids could be de-wormed with ivermectin and albendazole and then the adults at the time you're doing the blood…and then you follow them up if they've got a positive result and then you've got the education

Participant 6

Treatment programs must include the people and their environment. Public health approaches with standard guidelines continue to be required, but innovative strategies must be incorporated to be flexible and fluid at the community level in order to treat and decrease Strongyloides:

> Existing policies and guidelines, however, if you're looking at it from a clinical perspective it's very narrow, like the CARPA manual (CARPA 2014), it's quite anal, we look at it and think, "Oh yeah, just chuck a pill down someone's head, and that's all." Well, that's not how it's going to work. By having those policies and procedures, they need to be innovative and open enough to be able to do innovative work and not rigid.
>
> *Participant 1*

A main element of any treatment protocol must be the environment:

> It's very simple; it comes down to nineteen-century public health measures. If you can bring in the nineteenth-century public health measures…you do a bit of treatment, whether it's selective mass treatment or mass treatment or just individuals when they come in sick, and that's enough awareness of it to consider strongyloidiasis, it doesn't really matter. But it just comes down to basic sort of bread and butter sanitation issues I reckon.
>
> *Participant 4*

.....

> The issue is whether or not you do a mass treatment program and I think that if you do a mass treatment program without having improved sanitation you're actually wasting your time to a degree. That said, you can't write these things off, but the sanitation is what keeps it going.
>
> *Participant 4*

Eradication via routine drug administration could be an accepted protocol in community treatment programs:

> For Strongyloides control…a once-yearly mass drug administration can drop the prevalence of Strongyloides very quickly.
>
> *Participant 8*

The routine screening and treatment of many people increase the accuracy of prevalence rate measurement:

> It would be good if done as a routine and would also give you more of an idea of the prevalence. But obviously there's a selection bias because it's only people presenting with diarrhoea, but it's a start. It's also a marker for programs designed…in terms of eradication so if you were going to do selective mass treatment you need to have some sort of marker as to an outcome or improve sanitation.
>
> *Participant 4*

Developing innovative technologies may increase testing success:

> Unfortunately, we don't have any point of care test which would be useful. I think what is needed is some testing system that can be done with low technology so that we don't rely on collecting the specimen and sending it into a major centre for testing, [so] it can be done out in a field laboratory type environment.

Participant 5

Registration/Prevalence

Gaining a better understanding of Strongyloides and of the full extent of the prevalence of the parasite requires that a national registry be created. Monitoring *S. Stercoralis* is necessary for an effective and long-term intervention. Our understanding of infection, transmission, and prevalence can be improved through registration similar to that used for other diseases like scabies:

> There have been suggested approaches to having a Strongyloides register so that we can tell which individuals are infected or have been infected and it remains on their record so that if further down the track treatment has been effective then the Dr. can re-treat that individual. In terms of spread of this infection if you have a register, you can see or track where it's likely to, spread, to occur.

Participant 5

By monitoring the details of infection, protocols can be developed to address the particular circumstances/situations associated with infection:

> The first thing I'd do is make strongyloidiasis notifiable, so you could actually gather your data for who was positive and then do some mapping…a register to gather all of that information to answer some of the questions for a disease that hasn't had much research go into it, and then you've got the general practice primary health care setting, and that can have a protocol for people coming through.

Participant 9

.....

> The information and the access to data and the clarification of data coming out… doesn't acknowledge the incidence of Strongyloides.

Participant 1

Discussion

This study presents perspectives from experienced health professionals and researchers working directly with Australian Indigenous communities who treat and diagnose infec-

tious diseases, specifically strongyloidiasis. The overall themes presented were barriers to health/treatment, prevention, access to health care, policy implications, learning opportunities, and ideas for intervention.

Barriers to Health and Treatment

The key themes for *S. stercoralis* infection and subsequent acute and chronic disease included racism, diagnosis/clinical knowledge, and community in context. As shown in Miller et al. (2014), racial disparity and living conditions comprise the situational context influencing the key barriers. Continued unsanitary living conditions in communities increases *S. stercoralis* exposure. Environmental health policy is necessary for effecting changes in housing infrastructures, functioning plumbing, and enhanced sanitary hygiene and toileting in communities. *S. stercoralis* thrives in unsanitary communal areas (e.g., flooring in housing and outdoor leaking plumbing with exposure to faeces are active agents for strongyloidiasis infection and transfer). *S. Stercoralis* is diagnosed more frequently in rural and remote communities and is often associated with limited access to toilets or non-functioning sewage facilities (Kaminsky, Reyes-Garcia and Zambrano 2016). Concerning racial disparities, racism is perceived by participants in the lack or absence of public policy addressing environmental health issues and funding designed to make changes in affected communities.

Diagnosis and Treatment

Diagnosis continues to be difficult, as Strongyloides has a wide range of symptoms and opposing situations of asymptomology. Hyperinfection, HIV/AIDS, chronic alcoholism, malignancy, tuberculosis, chronic malnutrition, chronic renal failure, and exposure in endemic countries are all found to be factors associated with strongyloidiasis (Kaminsky, Reyes-Garcia and Zambrano 2016). Diarrhea is a significant symptom across patients with strongyloidiasis diagnosis. Strongyloidiasis often appears asymptomatic as presented in a six-year-old child (no abdominal pain, diarrhea, cough, urticarial or pruritus, wheezing, or skin abnormality) and in a survey of stool samples of children in Viti Levu Fiji (Kim et al. 2016; Zubrick et al. 2004). One case presenting at hospital with one week of abdominal pain and distention and vomiting was determined to be hyperinfection symptoms, later including a necrotic jejunal area and respiratory failure. The individual was treated with ivermectin, albendazole, and a broad-spectrum antibiotic. Unfortunately, mortality occurred after 32 days of hospitalization (Figueira et al. 2015). High-risk patients (such as those with the factors above) require mandatory screening prior to steroid treatment for quick and efficient diagnosis and treatment and to clear infection and avoid the hyperinfection and dissemination that can result from prolonged diagnosis (Kaminsky, Reyes-Garcia and Zambrano 2016).

The lack of knowledge among practitioners and community members of *S. stercoralis* and its required treatment strongly indicates the continued need for research, awareness, and policy changes. The findings of this research indicate a notable lack of knowledge about strongyloidiasis. Kaminsky, Reyes-Garcia, and Zambrano (2016) described issues in

Honduras similar to those Miller et al. (2014) described in Australia, including a failure to recognize symptoms, an inadequate knowledge of treatment protocol, and a lack of interest in defining and raising awareness of *S. stercoralis* infection in the community.

Access to Health Care

The 2014 Aboriginal and Torres Strait Islander Health Performance Framework Report (AIHW 2015) supports the perspectives of the participants interviewed for this study. Data on infectious and parasitic diseases (2008–2012 data) report that mortality rates per 100,000 were higher for those identified as Indigenous (19.4) than for those identified as Non-Indigenous (9.2). In addition, 29.9% of those identified as Indigenous aged 15 years or older reported problems accessing services, with 42.0 % located in remote areas and 25.9% in non-remote areas (2008 data). The Health Performance Framework Report (AIHW 2015) reported that the barriers to accessing health care services for remote areas were as follows: "no services in area" (23.7%), "not enough services in area" (20.5%), "waiting time too long or not available at time needed" (15.9%), "services not culturally appropriate" (2.5%), "don't trust services" (3.3%), and "treated badly/discriminated against" (1.4%).

Policy

The perspectives about institutional racism and normalisation reported by the health care professionals in this study present a strong message for policy analysts and developers. Institutional racism refers to the ways in which beliefs and values have been built into institutional operations (e.g., social, health) in a way that discriminates against, controls, and oppresses groups (McConnachie, Hollingsworth and Pettman 1988; Henry, Houston and Mooney 2004). Henry et al. (2004) state that institutional racism can be covert, unrecognized, or unacknowledged by those in the institutions. They outline particular examples in Australian health care, including (1) funding inequality, (2) different performance criteria for black and white, (3) "body part" funding, (4) differences in treatment regimes, (5) inequitable Medicare Primary Health Care (Medicare Benefits Schedule plus Pharmaceutical benefits scheme), and (6) cultural barriers to the Indigenous use of healthcare services (Henry et al. 2004).

The Commonwealth Department of Health and Aging (2001) reported some of the same barriers to access in Indigenous health, including poor, unwelcoming interaction within private, government, and specialist sectors of health services. The National Aboriginal and Torres Strait Islander Health Council (NATSIHC 2003) report lower use/access to health services despite decreased health status and increased health care needs. They point out the need to prioritise allied health care, aged care, and acute care in Indigenous health. In 2002, the National Health and Medical Research Council (NHMRC) suggested areas for reform in Indigenous health and reported specific issues described as barriers to health system access, such as living with racism and poverty. The NHMRC (2002) proclaims that health services delivery is determined as a risk resulting from low levels of trust in health care and a need to understand what effective, accessible health services are and the reasons

why services fail. Further, the focus needs to be on equality in health care and improving health systems and cultural safety.

Although efforts toward policy changes for Indigenous health have been made in Australia, there continues to be a disparity in health and social outcomes (Anderson et al. 2006). Gaps continue to exist in local/regional health information systems in terms of both development and feedback, as well as a lack of Indigenous contribution to health frameworks and indicators for supporting Indigenous health (Smylie et al. 2006). Similarly, Tang and Browne (2008) argued that race and racialisation exist within the Canadian health care system, that health care is not free from discrimination, and thus that issues with socioeconomic contexts result in inequitable access to health care. Hole et al. (2015) suggest that dealing with issues of visibility and voice to foster cultural safety and reporting health care quality improvements such as practice, policy and environmental strategies are needed. In 2010, the NHMRC re-evaluated the continued disparity in the health and social outcome statuses of Indigenous health in Australia and streamlined and redefined the suggested priorities and objectives. The objectives shifted to (1) promoting knowledge transfer at the community level to provide input to service planning; (2) identifying health infrastructure requirements; (3) evaluating increases and risk factors in chronic conditions, and (4) evaluating models of care (NHMRC 2010).

Learning Opportunity

Developing practices in collaboration between health authorities, health professionals, and communities is essential (Hole et al. 2015). Coordination and planning that includes community perspectives and engagement and public health approaches (Einseidel and Woodman 2010; Shield and Page 2008; Miller et al. 2014) will improve health outcomes.

Ideas for Intervention

The data analysis in this study defined cost, knowledge translation, community partnerships, and registration/prevalence as key factors for strategizing interventions. These factors combined would increase intervention successes. Affordable drug costs, permitted by the Australian drug scheme (PBS), would increase access to ivermectin (NPS Medicinewise 2014; NPS Medicinewise 2015), the most effective treatment for strongyloidiasis. Knowledge translation requires active collaboration with communities, public health organisations/agencies, and researchers at all steps in the process—from identification, through procedure and research, and finally to intervention strategies—along with continual feedback for all partners is an elaborate strategy defined and supported by the Canadian Institutes of Health Research (CIHR 2016). To ensure knowledge translation, community partnerships must be developed by identifying each community and their context to ensure the full development of community engagement, recognition, and inclusion by all those in the partnership.

Registration and tracking the prevalence rates of *S. stercoralis* and strongyloidiasis can establish numbers for policy development and assist in the development of intervention

strategies by the community, public health organisations/agencies, and researchers. These factors, either separately or, preferably, as a combined strategy, are significant for policy. Public health policy that develops interventions and guidelines for diagnosis and treatments are essential (Miller et al. 2014; Adam, Page and Speare 2003; Soulsby, Hewagama and Brady 2012; Speare and White 2001; Shield and Page 2008).

Implications

This study offers direct policy implications for Indigenous communities. The need for policy development aimed at the prevention of neglected tropical diseases in Indigenous communities is highlighted. Increased knowledge and understanding of treatment, diagnosis, and healthcare access concerning *S. stercoralis* among health professionals and policymakers are necessary components of positive outcomes for Indigenous health. Raising awareness of systemic institutional racism in the control and prevention of neglected tropical diseases in Indigenous communities is required for effective and sustainable change. A health promotion framework can provide the basis for multiple levels of intervention to control and prevent Strongyloides in Indigenous communities.

Limitations

Few health professionals in Australia have extensive knowledge of the *S. stercoralis* parasite, infection, diagnosis, and treatment or experience with Indigenous communities. The authors interviewed many of these professionals and reached saturation but acknowledge that the sample was limited.

Conclusions

This study highlights the importance of the evidence-based reporting and declaration of strongyloidiasis as a notifiable disease (Speare, Miller and Page 2015). Barriers to controlling strongyloidiasis have been identified in this study, in line with previous research (Miller et al. 2014; Speare and White 2001; Page and Shield 2005; Kaminsky, Reyes-Garcia and Zambrano 2016). In-depth interviews with health service providers active in the field support this evidence. Raising awareness of institutional racism within the health care system, as described by the health professionals in this study, can contribute to policy change. The health care system cannot adequately address the barriers to prevention, treatment, and control until this institutional racism is brought to the forefront of policy development and change.

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In memory of Emeritus Professor Rick Speare, AM, a fearless man of great intelligence, integrity, wisdom, kindness, and humility, with a pragmatic passion for public health and tropical medicine. Amongst his many achievements, Rick's doctoral dissertation on *Strongyloides stercoralis* provided foundational knowledge for understanding the clinical disease. He developed a lifetime commitment to preventing and treating neglected tropical diseases in economically disadvantaged populations in Australia and Oceania.

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5.3.2 Miller, Young, Tye, Cody, Muscat, Sanders, Smith, Judd, & Speare. Community-directed integrated *Strongyloides* control program in Queensland, Australia.

Tropical Medicine and Infectious Disease

MDPI

Review

A Community-Directed Integrated *Strongyloides* Control Program in Queensland, Australia

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Abstract: This paper describes two phases of a community-directed intervention to address strongyloidiasis in the remote Aboriginal community of Woorabinda in central Queensland, Australia. The first phase provides the narrative of a community-driven 'treat-and-test' mass drug administration (MDA) intervention that was co-designed by the Community Health Service and the community. The second phase is a description of the re-engagement of the community in order to disseminate the key factors for success in the previous MDA for *Strongyloides stercoralis*, as this information was not shared or captured in the first phase. During the first phase in 2004, there was a high prevalence of strongyloidiasis (12% faecal examination, 30% serology; $n = 944$ community members tested) that resulted in increased morbidity and at least one death in the community. Between 2004–2005, the community worked in partnership with the Community Health Service to implement a *S. stercoralis* control program, where all of the residents were treated with oral ivermectin, and repeat doses were given for those with positive *S. stercoralis* serology. The community also developed their own health promotion campaign using locally-made resources targeting relevant environmental health problems and concerns. Ninety-two percent of the community residents participated in the program, and the prevalence of strongyloidiasis at the time of the 'treat-and-test' intervention was 16.6% [95% confidence interval 14.2–19.3]. The cure rate after two doses of ivermectin was 79.8%, based on pre-serology and post-serology tests. The purpose of this paper is to highlight the importance of local Aboriginal leadership and governance and a high level of community involvement in this successful mass drug administration program to address *S. stercoralis*. The commitment required of these leaders was demanding, and involved intense work over a period of several months. Apart from controlling strongyloidiasis, the community also takes pride in having developed and implemented this program. This appears to be the first community-directed *S. stercoralis* control program in Australia, and is an important part of the national story of controlling infectious diseases in Indigenous communities.

Keywords: *Strongyloides stercoralis*; aboriginal; indigenous; soil-transmitted helminths; mass drug administration

1. Background and Introduction

1.1. Background

This paper documents two historical phases of a community-directed *Strongyloides stercoralis* control program. The first phase reports on a community-directed *S. stercoralis* control program in the Indigenous community of Woorabinda, central Queensland Australia. The second phase documents the need to have local Indigenous leadership and direction for community-wide health interventions, and the importance of the researchers having cultural humility. Cultural humility is defined as a lifelong process of self-reflection and self-critique whereby the individual not only learns about another's culture, but one starts with an examination of her/his own beliefs and cultural identities [1]. Cultural humility cannot be collapsed into a single workshop; it is commitment and active engagement in a lifelong process 'that individuals enter on an ongoing basis with patients, communities, colleagues, and with themselves' [1] (p. 118). This paper is a testament to Rick Speare's cultural humility across his research career.

Note that this paper is conspicuously published well after the first phase of this project. Following a strongyloidiasis-related fatality, the first phase originally focused on the clinical outcomes of an ivermectin mass drug administration [MDA] intervention to address *S. stercoralis* in the community. However, while it was evident that ivermectin MDA clearly had a significant effect on decreasing the prevalence of *S. stercoralis* among Woorabinda residents, the real success of this intervention lay in the self-determination of the community and the community health team, who drove the health promotion program to address strongyloidiasis in the community. Without this commitment from the community health team, and their relationships and trust with community members, there would have been little chance of the successful implementation of the ivermectin MDA.

This paper forms part of a new study that explores barriers and enablers to addressing infectious diseases in Indigenous Australian communities. The community voiced their concerns regarding participating in this study, as they felt: (i) they received no feedback from the original study relating to the ivermectin MDA in their community, so the community requested some researchers from James Cook University, in particular Rick Speare, to assist them with making sense of the data from the MDA, and (ii) their story regarding the success of the community-driven approach to addressing the issue of *S. stercoralis* received little attention. In their view, this was the most important aspect of the success of this program.

To address this shortcoming and the failure in communication, the results of the MDA were shared. The community felt that the community health team, in partnership with the community's leadership, was the real success of eradicating *S. stercoralis* in Woorabinda. On the community's invitation, a new research team travelled to Woorabinda to re-engage with community health team in order to capture and share the story of their successful community-driven approach to address this infectious disease, which impacted their community's health and well-being.

1.2. Introduction

Strongyloidiasis is considered one of the most neglected tropical diseases and is estimated to affect over 100 million people worldwide including Indigenous Australians [2,3]. Most cases are chronic, while acute strongyloidiasis is more common in children [4,5]. Chronic strongyloidiasis increases the risk of unpredictable fatal hyperinfection when patients become immunocompromised, malnourished, or immunosuppressed. Hyperinfection can be caused by the administration of corticosteroids to patients with strongyloidiasis [4,5].

In Australia, strongyloidiasis is highly prevalent in Indigenous rural and remote communities, and its management at the individual and community level is sub-optimal [6,7]. For *S. stercoralis*, a prevalence greater than 5% is considered to be hyperendemic, and a public health intervention is required [4,5]. However, although many Indigenous Australian communities appear to have above 5% prevalence, no community-wide control program has been reported. This paper describes the outcome from a community-based intervention to control strongyloidiasis, which was driven by the Aboriginal community in partnership with the community health team.

1.3. Context

Woorabinda is a remote, Aboriginal community that is situated approximately 175 km southwest of Rockhampton in Central Queensland, Australia (24°08′05′ S 149°27′22′ E). Woorabinda is the traditional land of the Wadja and Wadjigal people. In 2005, this small discrete Indigenous community had a population of at least 944, with about 191 western-style houses [8].

In 1996, an initial faecal survey for *S. stercoralis* and review of 130 hospital records indicated an overall prevalence of 5% in the community, with the 5–9-year-old age group having the highest prevalence of infection at 14% [9]. In 2000, the testing of patients presenting to the Woorabinda Multipurpose Health Service showed that at least 12% were positive for *S. stercoralis* on faecal testing, and 30% were positive on serology. In addition, a resident who was referred to a tertiary hospital for treatment of another disease, died from hyperinfection.

The Woorabinda Multipurpose Health Service provided health care to the community through a small hospital run by Queensland Health and an active community health team, the Woorabinda Multipurpose Community Health Team. The majority of the team members were Indigenous Australians with ancestral links to the area, and consisted of an Indigenous nurse, a non-Indigenous nurse, several Aboriginal health workers (AHWs), and local residents employed in various roles.

2. Approach

In the original phase, the Woorabinda Multipurpose Community Health Team, in partnership with the community, decided to initiate and lead a program to control *S. stercoralis* by involving the whole Woorabinda community and using a combination of treatment and prevention strategies. The goal of the program was to reduce the prevalence of *S. stercoralis* by at least 75% (from around an estimated 30% prevalence to less than 7.5%), with complete elimination from Woorabinda being the goal. The objectives were to: (i) implement a treatment program using agreed protocols; (ii) increase community participation in strategies related to the prevention of *S. stercoralis*; and (iii) decrease environmental risk factors contributing to *S. stercoralis* infection. The program was managed by a steering committee that had members from the Woorabinda Health Service, Woorabinda Council, and Central Queensland Public Health Unit; the committee also included community representatives, and other people were co-opted as required. An advisory panel with specific technical expertise assisted this steering committee.

A program work plan was co-developed, and is detailed in Table 1 to show as an example. Awareness-raising and education about *S. stercoralis* were the first components of the project, and only after the community was saturated with information did the treatment and testing stage begin. Community-based health promotion is people-centered and collectivist [10]. This program involved multiple stakeholders and worked across the community, as demonstrated by the engagement with school and environmental health officers, the council, and community health service. Facilitation and ownership of the program by the community assists with problem-solving, builds the capacity of the community, and therefore enhances successful and sustainable programs [11].

Table 1. Woorabinda *S. stercoralis* Control Program Work Plan.

Months After Commencement	Action	Responsibility *
3–4 months	Formation of a steering committee	DON
	Adoption of program plan	Steering committee
	Appointment of personnel to conduct program	DON
	Develop consent forms: ivermectin, albendazole, beta-HCG (test for pregnancy), release of information.	PO/RN
	Develop data collection tools for treatment—paper and electronic	PO/RN
	Develop drug recording systems	PO/RN
	Develop management flow chart	PO/RN
	Develop education and awareness-raising materials	PO/RN
	Collect baseline data results from previous studies conducted in Woorabinda and develop evaluation measures for comparison: (a) Environmental health and household survey; (b) Animal census.	PO
	Environmental health program commences	EHO, EH Coordinator/HW's/Council
	Education and awareness-raising commences	HW
6 months	Pilot of initial treatment	DR/RN/HW
	Review and modification of management flow chart	Steering Committee
	Environmental health program continues	EHO, EH Coordinator/HW's/Council
	Initial serology/treatment of community	DR/RN/HW
	Follow-up of community members not presenting for treatment/re-treatment of positive cases at two weeks	RN/HW
	Education and awareness-raising continues	HW
	Environmental health program continues	EHO, EH Coordinator/HW's/Council
	Analysis of results from initial treatment and report	RN
12–13 months	First follow-up serology and treatment of resistant/positive cases.	DR/RN/HW
	Follow-up community members who have not presented for serology and treatment/resistant cases	RN/HW
	Analysis of results from first follow-up and report	RN
	Second follow-up treatment for resistant cases	DR/RN/HW
	Follow-up community members not presenting for serology and treatment	RN/HW
	Education and awareness raising continues	HW
	Environmental health program continues	EHO, EH Coordinator/HW's/Council
	Analysis of results from second follow-up and report	RN
14 months	Third follow-up serology and treatment	DR/RN/HW
	Follow-up community members not presenting for serology and treatment	RN/HW
	Education and awareness raising continues	HW
	Environmental health program continues	EHO, EH Coordinator/HW's/Council
	Analysis of results from third follow-up and report	RN

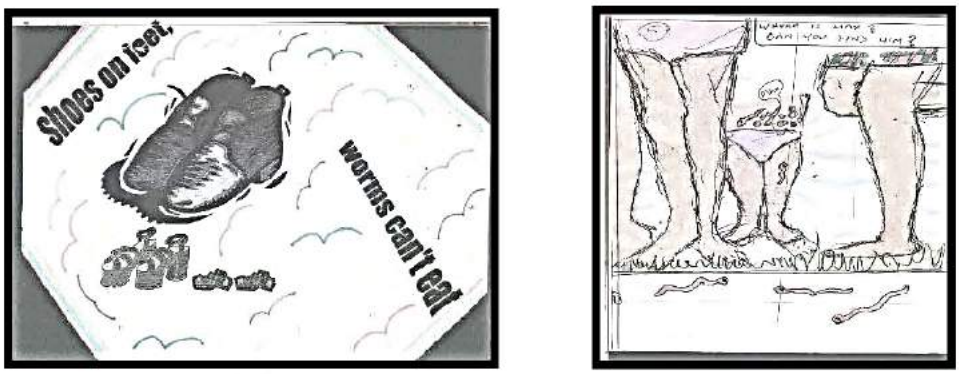
Table 1. *Cont.*

Months After Commencement	Action	Responsibility *
21–24 months	Fourth follow-up serology	DR/RN/HW
	Follow-up community members not presenting for serology and treatment	RN/HW
	Education and awareness raising continues	HW
	Environmental health program continues	EHO, EH Coordinator/HW's/Council
	Analysis of results from fourth follow-up and report	RN
	Refer resistant cases to Dr	RN
	Final report and recommendations	RN
	Second yearly review to confirm eradication	Health Service

* DON—Director of Nursing; PO—Project Officer; EHO—Environmental Health Officer; EH Coordinator—Environmental Health Coordinator; DR—Doctor; Council—Local Shire Council; RN—Registered Nurse; HW—Health Worker.

2.1. Community Participation

The Woorabinda Multipurpose Community Health Team worked with stakeholders to develop health education and promotion material to ensure that all of the resources were culturally appropriate and locally relevant. This material focused on explaining *S. stercoralis* and its lifecycle, symptoms of strongyloidiasis, treatment, and prevention of transmission. Female community elders developed several unique health promotion tools, including posters, a comic strip, and Aunty Val's 'Gunna Story' (Figure 1C). In local Aboriginal slang, 'gunna' means faeces. An explanation of the local treatment program and prevention strategies encouraged people to play an active role in stopping the transmission of *S. stercoralis*. These health promotion strategies used a multiple intervention model and included: improvement of defects in sanitation systems by house-to-house inspection, personal hygiene, safe disposal of nappies, wearing shoes, and responsible dog ownership. All of these strategies were in line with the principles of the Ottawa Charter [12], which emphasises that multiple strategies across sectors will assist in improving the health of peoples, groups, communities, and populations. A recent study found that wearing shoes decreased the likelihood of infection of schoolchildren with *S. stercoralis* [13].



(A) (B)

Figure 1. *Cont.*

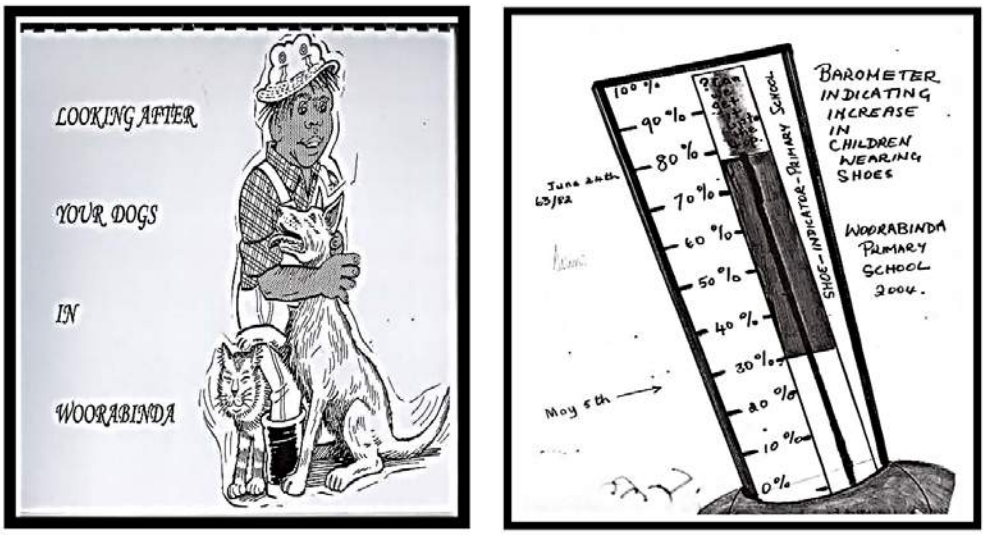


Figure 1. Health promotion material developed during the Woorabinda *Strongyloides* control program. (**A**) Poster on protective footwear; (**B**) Jaime and Aunty June's comic strip described the life cycle and transmission of *S. stercoralis*; (**C**) Aunty Val's Gunna Story; (**D**) Shoe barometer.

2.2. *Involvement of Primary School Children*

Teachers and children at the Woorabinda State Primary School were also actively involved. They developed two very specific items: a shoe barometer that measured the percentage of children wearing shoes to classes (Figure 2), and a *Strongyloides* song that was used on the local radio station, particularly preceding announcements about the control program (Table 2). Health promotion programs are most likely to be effective when they are flexible and responsive to local realities [11].

Table 2. The *Strongyloides* Song Developed and Sung by the Woorabinda State Primary Schoolchildren.

The Strongyloides Song
Words by June Barkworth and adapted by the Woorabinda Schoolchildren. The children and staff of the Woorabinda State School wrote the music. This song was used as a signature tune to herald radio updates on the Strongyloides project.
No, no, no, 'Mr Worm' we don't want you
Travelling through our skin and making us sick,
With boots and shoes on our feet (stamp, stamp)
Blankets on the ground,
We're gon'na stop you from moving around
'Our bodies'
Yes, yes, yes, 'Mr Worm' you have got to go ho, ho, ho, ho,
Go, go, go 'Mr Worm' we're getting tough
You have no place to live in us.
We're gon'na thrash you out, we're gon'na move you on … … then
Woorabinda will say that 'Mr Strongyloides' worm is gone.
Yes, yes, yes 'Mr Worm' you have got to go. Ho, ho, ho, ho, ho.

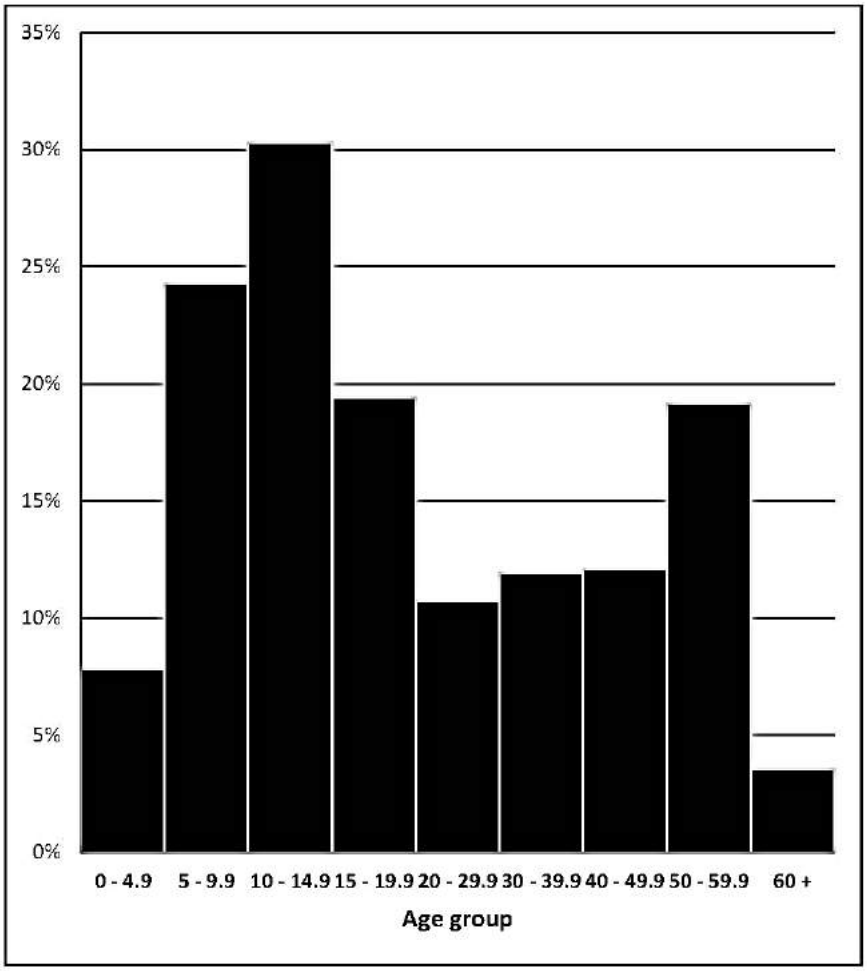


Figure 2. Prevalence of positive *S. stercoralis* serology from an initial survey in phase 1 of the Woorabinda community, July–August 2004.

2.3. Treat-and-Test

All community residents were urged to participate in a 'treat-and-test' survey. Everyone was asked for a sample of blood collected by venipuncture for *S. stercoralis* serology [14], and were treated for *S. stercoralis* at this time. The most effective treatment for *S. stercoralis* is ivermectin [5,15], but ivermectin is not licensed in Australia for treating pregnant women or children with a body weight of less than 15 kg. A less effective alternative option, albendazole, can be used for treatment in the latter category, but was not licensed in Australia for use in pregnant women. The treatment protocol for the Woorabinda program was based on recommendations from the first National Workshop on Strongyloidiasis in September 2001 [16]. This protocol recommended: (1) Children >6 months of age but <10 kg, albendazole: 200 mg daily for three days; (2) Children >6 months of age and 10–15 kg, albendazole: 400 mg daily for three days; and (3) All people except pregnant women >15 kg, ivermectin (Stromectol): 0.2 mg/kg body weight. Women of child-bearing age were offered a pregnancy test prior to treatment with ivermectin. Any person who was subsequently shown to have positive serology for *S. stercoralis* on the initial blood sample was retreated within a month.

2.4. Environmental Risk Factors

Environmental health activities were part of the community-wide program. A housing improvement program as part of a state-wide initiative was operating in Woorabinda using Commonwealth and State government funds. A set of priority areas was developed to address environmental risk factors for *S. stercoralis* in the community. Specific actions included repairing malfunctioning toilets and leaking taps and pipes that could cause areas of persistent damp soil.

2.5. Serological Results

Over a six-week period, 867 people were treated and tested; the group comprised 46% (404/867) males, and 16.6% (144/867) (95% confidence interval 14.2–19.3) had positive serology. The parasite was present in all age groups, with the highest percentage between 5–20 years, with a peak at 10–15 years and a further rise at 50–59 years (Figure 2). The participation rate was approximately 92% (867/944).

Of the participants who tested positive in July and August 2004, 129 were re-tested in February 2005 after treatment, and 103 had reverted to negative: a cure rate of 79.8%. In February 2005, 140 people who had been initially negative for *S. stercoralis* were re-tested, and none had seroconverted over this six-month period, indicating that transmission at Woorabinda appeared to have ceased.

3. Discussion

Most soil transmitted helminth (STH) control programs are driven and managed by health departments, usually from urban centres. Although community-wide control programs for *S. stercoralis* have been advocated since the 1990s [4,17], the only report outside the experimental situation appears to be a Japanese study that monitored and treated a small group of residents on Okinawa, and hence was not a program that engaged the whole community [18]. This Woorabinda program may be the first community-wide program described. It was unusual in that it was initiated, implemented, and managed by the community itself. Woorabinda found the resources—including the funding, person-power, and expertise—that were needed for its successful completion. This was arguably the key factor in achieving a high level of community engagement.

3.1. Impact of the Program

The strategy that was adopted was successful in identifying and treating much of the population. The cure rate after two treatments was high, and transmission of *S. stercoralis* at Woorabinda appeared to have ceased. This is the only description of a successful community-led *S. stercoralis* control program. It appears to be the first to use a 'treat-and-test' strategy where all of the participants were treated initially for *S. stercoralis*, and subsequent management depended on the test result. Although the long-term effect of the program has not been evaluated, the Woorabinda health centre doctor anecdotally reported to the research team that cases of strongyloidiasis are now rare, and strongyloidiasis is no longer considered a public health issue at Woorabinda. Unfortunately, infection with *S. stercoralis* is not notifiable in Australia; hence, the trend in incidence for Woorabinda is unavailable. Making this parasitic infection notifiable is essential for control and elimination [19].

3.2. Local Leadership and Knowledge

The project team used Indigenous and local leadership, with AHW knowledge of the health profile of the local community, the households, and the needs of the community being a very important factor in the success of the mass drug administration program. Additionally, since the AHWs are community members, trust between community members and health staff was high, giving the *S. stercoralis* control program high credibility.

3.3. Big Effort, But Worth It

Members of the health team worked very hard during this program, while still performing their usual work tasks. However, they considered that the effort was worth it, since the disease of concern was controlled, and the health team and the community became united on tackling and solving a significant health problem. Over a decade later, yarns with original members of the health team still reflect their sense of pride in their achievement.

3.4. Knowledge and Understanding of the Parasite

AHWs and other health staff providing information to community members about *S. stercoralis* facilitated the development of localised knowledge and understanding of the parasite. This was contextualised on the community's prior knowledge about hookworm, a STH that had been historically present in the community, but had been eliminated. This allowed the team to develop ways to share new knowledge and understanding about *S. stercoralis* and the benefit of the program. Localised communication strategies were developed and delivered in the form of novel health promotion materials such as a children's song, a children's story in the local language, localised posters, radio advertisements, and a school-based awareness program, which was exemplified by the shoe barometer. The materials developed were a good illustration that in Aboriginal communities, health promotion materials should be localised and humorised [20].

3.5. Development of an Inclusive Governance Model and Skills Development

The team developed a governance model to guide the project, which was a community-driven approach that seconded expert advice at critical points of the program; the steering committee and the advisory panel provided this advice. This approach fostered partnerships between the health and education sectors, researchers, and local government. Strong support for serology tests was provided by Queensland Health laboratory scientists at Rockhampton. AHWs were trained to collect blood (except for infants and babies where phlebotomists were required), and standing orders gave the AHWs authority to administer anthelmintic medications. An implementation protocol with a shared understanding of the commitment required for this program was a core component of the program.

3.6. Aspects to Be Improved

A decrease in the number of people affected meant that momentum for the program to progress to elimination was lost. Although a repeat community-wide survey to document the post-program prevalence of strongyloidiasis would have provided valuable information, owing to lack of further targeted resources, no survey was conducted.

4. Conclusions

This paper illustrates how a community-directed and led *S. stercoralis* control program using a 'treat-and-test' strategy in a remote Australian Aboriginal community brought an outbreak and subsequent high prevalence of strongyloidiasis under control. The use of localised health promotion strategies and materials developed by community members contributed to the program's success, and set out a clear plan for action for other communities needing to address *S. stercoralis*. Since *S. stercoralis* is usually not a health problem in developed countries and is usually associated with poverty, its high prevalence in this community drew attention to the underlying social determinants of health and the need for social solutions, as well as biomedical interventions.

Author Contributions: A.M., J.A.J. and R.S. wrote the paper; E.L.Y., V.T. and R.C. led the mass drug administration, and collected data; R.S. and V.S. analysed the data; V.T. developed and led health promotion resources; M.M. contributed to the paper and lead community engagement; M.L.S. contributed to the paper.

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Ethics and Permissions: All subjects gave their informed consent for inclusion before they participated in the study. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Queensland Health—Rockhampton Health Services District, Human Research Ethics Committee, 'Woorabinda Strongyloides Eradiation Project Plan 2004', Approval Number 04.06.

Conflicts of Interest: There are no conflicts of interests with any authors.

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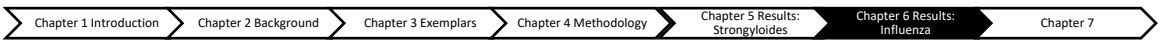
Chapter. 6 Findings: Influenza H1N1



6.1 Chapter Brief

The aim of this chapter is to present results from a study into developing appropriate and effective strategies to reduce risk of pandemic influenza in Indigenous communities and present two further papers from a study that examined the biological risks to new influenza strains for Indigenous peoples.

6.2 Overview

There are three papers included in this chapter; one core to this thesis and two papers additional to the thesis that demonstrate the extension to the influenza research. The core paper presented in this chapter provides a response to the research questions 1 and 2.

6.3 Papers Presented

Massey PD, **Miller A**, Saggers S, Durrheim DN, Speare R, Taylor K, Pearce G, Odo T, Broome J, Judd J, Kelly J, Blackley M, Clough A. Australian Aboriginal and Torres Strait Islander communities and the development of pandemic influenza containment strategies: Community voices and community control. *Health Policy,* 2011, 103, 184–190.

6.3.1 Extension of the Research

Valkenburg SA, Josephs TM, Clemens EB, Grant EJ, Nguyen, THO, Wang GC, Price DA, **Miller A**, Tong S, Thomas PG, Doherty PC, Rossjohn J, Gras S, Kedzierska K. Molecular basis for universal HLA-A*0201 $CD8^+$ T Cell immunity against influenza viruses. *PNAS*, April 19, 113 (16) 4440-4445, 2016.

Clemens EB, Grant EJ, Wang Z, Gras S, Peta Tipping P, Rossjohn J, **Miller A**, Steven Y. C. Tong SYC and Kedzierska K. Towards identification of immune and genetic correlates of severe influenza disease in Indigenous Australians. *Immunology and Cell Biology,* accepted article preview 23 Oct 2015; doi: 10.1038/icb.2015.93.

6.4 Summary

The purpose of the paper by Massey et al. 2011 was to develop culturally appropriate and effective strategies to reduce the risk from pandemic influenza (H1N109) in rural and remote Indigenous Australian communities. We applied a Participatory Action Research (PAR) approach that enabled communities and researchers to work together to develop understanding and take action to reduce risk. Qualitative research methods were used to collect data from Indigenous participants from communities in NSW, Qld and WA. Local Indigenous community researchers were recruited and trained in conducting interviews to collect qualitative data. We also developed effective working relationship with Indigenous health services to enable the research to recruit study participants.

Aboriginal and Torres Strait Islander communities involved in this project raised deep concerns and serious issues because of their experiences during the H1N109 pandemic. The participants expressed distrust and scepticism about current Australian health policies on containment and told the researchers that specific plans for Indigenous peoples were needed. Respondents indicated that policies and plans had been developed without respectful engagement with communities. The strong and recurring themes that emerged from the PAR cycles were: the importance of family; ways of life and realities of living in response to influenza; and key messages to government and health services to focus on communication, understanding and respect.

The essential work of reducing risk of pandemic influenza with Indigenous communities is not straightforward, but this project has highlighted some useful pathways to continue to journey along with communities. Some strategies to reduce the spread of pandemic influenza in Indigenous communities were identified. These strategies would make a good starting point for conversations with communities and health services. In Indigenous communities, the environment, community structures and traditions vary. Respectful engagement with communities is needed to develop effective policy.

This research detailed in Valkenburg et al. revealed Indigenous Australians are at greater risk of severe influenza disease, especially when new influenza strains. However, results suggest that vaccination strategies aimed at generating broad protection should incorporate variant peptides to elicit cross-reactive responses

against other specificities, especially those strains of influenza that may have the potential to become a significant global concern.

The Clemens et al. study discovered Indigenous populations, including Indigenous Australians, are highly susceptible to severe influenza disease, and the underlying mechanisms are unknown. We studied immune and genetic factors that could predicate severe influenza disease in Indigenous Australians enrolled in the LIFT study: Looking into Influenza T cell immunity. To examine CD8+ T cell immunity, we characterised human leukocyte antigen (HLA) profiles. We identified two new HLA alleles (HLA-A*02: new and HLA-B*56: new). Modelling suggests that variations within HLA-A*02: new (but not HLA-B56: new) could affect peptide binding suggesting that the ~15% of Indigenous people that express HLA-A*02:01 have universal influenza-specific CD8+ T cell immunity. Furthermore, the frequency of an influenza host risk factor, IFITM3-C/C, was comparable between Indigenous Australians and Europeans, suggesting that expression of this allele does not explain increased disease severity at a population level. Our study indicates a need to identify novel influenza-specific CD8+ T cell epitopes restricted by HLA-A and HLA-B alleles prevalent in Indigenous populations for the rational design of universal T cell vaccines. The next chapter draws the key messages from core papers to promote five principles for addressing the barriers to effective interventions in Indigenous communities.

6.4.1 Massey, Miller, Saggers, Durrheim, Speare, Taylor, Pearce, Odo, Broome, Judd, Kelly, Blackley & Clough. Australian Aboriginal and Torres Strait Islander communities and the development of pandemic influenza containment strategies: Community voices and community control

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Australian Aboriginal and Torres Strait Islander communities and the development of pandemic influenza containment strategies: Community voices and community control

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ABSTRACT

Objectives: To develop culturally appropriate and effective strategies to reduce the risk from pandemic influenza (H1N109) in rural and remote Australian Aboriginal and Torres Strait Islander communities.
Methods: Participatory Action Research (PAR) approach that enabled communities and researchers to work together to develop understanding and take action to reduce risk.
Results: The H1N109 pandemic raised deep concerns and serious issues in all of the Aboriginal and Torres Strait Islander communities involved in this project. The participants expressed distrust and scepticism in relation to current Australian health policies on containment and told the researchers that specific plans for Aboriginal and Torres Strait Islander peoples were needed. Respondents indicated that policies and plans had been developed without respectful engagement with communities. The strong and recurring themes that emerged from the PAR cycles were: the importance of family; ways of life and realities of living in response to influenza; and key messages to government and health services to focus on communication, understanding and respect.
Conclusion: The essential work of reducing risk of pandemic influenza with Aboriginal and Torres Strait Islander communities is not straightforward, but this project has highlighted a number of useful pathways to continue to journey along with communities. A number of strategies to reduce the spread of pandemic influenza in Aboriginal and Torres Strait Islander communities were identified. These strategies would make a good starting point for conversations with communities and health services. In Aboriginal and Torres Strait Islander communities the environment, community structures and traditions vary. Respectful engagement with communities is needed to develop effective policy.

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1. Introduction

In March 2009 a new influenza A strain (H1N109) was detected in Mexico [1]. This new strain rapidly spread and a pandemic was declared by the World Health Organisation in June 2009 [2].

The H1N109 pandemic resulted in higher attack rates among New Zealand Maori and Pacific Islanders and greater morbidity in Indigenous populations in the Americas, New Zealand and Australia [3]. A three to six fold higher risk of developing severe disease requiring hospitalisation and of dying were recorded [4–7]. Factors that may have contributed to the higher risks of severe disease included a higher prevalence of diabetes, obesity, asthma, chronic obstructive pulmonary disease and pregnancy in Indigenous communities. It has also been speculated that social issues, including larger family size, crowding and poverty were associated with an increased risk of infection [4]. Poor access to culturally appropriate health services have also been reported as a factor contributing to delayed appropriate treatment [4].

In response to the emerging H1N109 pandemic a consultation process with six Aboriginal communities in a rural area of Australia found a number of concerns including: the importance of local trusted people having an understanding of H1N109; clear communication; access to health services; infection control strategies that were culturally appropriate; and Aboriginal people and Torres Strait Islanders having a say in what support was required [8].

In a rural area of northern New South Wales, Australia, a shared understanding of the threats of pandemic influenza has been developing since 2006. Under the direction of the Hunter New England (HNE) Aboriginal Health Partnership – collaboration between Aboriginal Community Controlled Health Services (ACCHS) and the state health service – the process of developing a shared understanding became the basis for a national project. Aboriginal Community Controlled Health Services are services that are governed and directed by local Aboriginal communities to provide primary health care to the community. The services provided include medical, nursing and health promotion programs.

The project aimed to build research capacity within Aboriginal and Torres Strait Islander communities while:

- identifying barriers to implementation of current containment strategies for H1N109 in rural and remote Aboriginal and Torres Strait Islander communities; and
- developing culturally appropriate and effective containment strategies for H1N109 and future pandemics in these communities, modified where possible by experience of the pandemic.

2. Methods

The HNE Aboriginal Health Partnership, and the subsequent communities engaged endorsed a Participatory Action Research (PAR) approach to explore the issues. PAR differs from traditional research in that it seeks to bring about positive change, not simply to investigate an issue. In addition, the research process is based on equal and collaborative involvement of the community in which the issue is located [11–14]. Local research assistants (RAs) were trained in qualitative research techniques using a 'just in time' approach in which RAs and lead researchers worked together as the project progressed.

2.1. Key stakeholders

The community of interest for this project included:

- Anton Breinl Centre for Public Health & Tropical Medicine, James Cook University (Queensland)
- Armajun Aboriginal Medical Service (New South Wales)
- National Drug Research Institute, Curtin University (Western Australia)
- Hunter New England Health (New South Wales)
- Kimberley Aboriginal Medical Service Council (Western Australia)
- Mamu Health Service (Queensland)
- Palm Island Aboriginal Shire Council (Queensland)
- Tamworth Aboriginal Medical Service (New South Wales)
- Torres Strait Island Regional Council (Queensland)

2.2. Participatory action research stages

Within a PAR cycle of planning, action, observation and reflection [12,13] the following stages comprised the method:

2.2.1. Stage 1: Identification of the research problem by communities of interest

Discussions with Aboriginal communities in a regional area of NSW culminated in a workshop in Tamworth with stakeholders in 2007 and confirmed that a PAR approach, with 'giving and learning both ways' [15], was the only way to proceed.

Areas for conducting the research were identified in NSW by the HNE Aboriginal Health Partnership as Tamworth and Inverell. In north Queensland existing community links with an Aboriginal Chief Investigator (AM) were the starting point for engagement with Mamu Health Services Limited, Innisfail, agreeing to participate. The Palm Island Aboriginal Shire Council contacted the researchers and asked to be involved following the death of a foetus of a woman infected with H1N109 from the community. In the Torres Strait, existing links with James Cook University instigated the negotiations and agreement for local community involvement.

2.2.2. Stage 2: Collaborative planning

A detailed research plan was developed with the stakeholders. Ethics approval was provided by the Human Research Ethics Committees in Hunter New England 09/09/16/4.01; NSW Aboriginal Health Medical Research Council; Aboriginal and Torres Strait Islander Research Ethics James Cook University; and Human Research Ethics James Cook University in Queensland.

Aboriginal and/or Torres Strait Islander research-assistants were recruited along with research mentors in each of the areas (NSW and north Queensland). These were people of different ages, gender, backgrounds and stage

of career, all working in either state health services or community-controlled services.

Training for the research-assistants occurred throughout the project and included three intensive 2-day theoretical and practical workshops on qualitative research methods, including PAR and data collection, qualitative data analysis and writing.

2.2.3. Stage 3: Research action (data collection)

Development of the research instruments occurred during the research training sessions and involved preparation of interview and focus group guides. The in-depth interviews explored people's experiences with H1N109 and ways that they believed personal/community risk could be reduced. The focus groups sought to understand what information people wanted about H1N109 and how it should be received.

With informed consent, in-depth interviews of approximately one hour were undertaken by the research assistants in each area. The interview questions explored people's experiences of and responses to pandemic influenza, and strategies to prevent the spread of pandemic influenza at home and at community gatherings. The interviews also explored what the participants would do differently the next time there was a pandemic.

Focus groups were facilitated at each site on the topic of information dissemination. Focus groups included Health Workers in Aboriginal and Torres Strait communities, Community Controlled Health Service Board members, Elders and other community members. Participants were asked about the main things people needed to know about pandemic influenza and the best ways of communicating this information to them.

A purposive sampling technique was used by research assistants to recruit participants from within their existing networks; these included ACCHS staff and Aboriginal and Torres Strait Islander community members of mixed ages and genders. Forty seven interviews and ten focus groups, with an average of five participants per focus group, were completed during the period July 2009–May 2010.

Data from interviews were collected until data saturation occurred and re-occurring themes emerged from people's reported experiences and knowledge about H1N109 and more acceptable approaches to disease control.

2.2.4. Stage 4: Analysis and reflection on research data

Collaborative descriptive and interpretative accounts of the interview and focus group data were developed in a workshop setting. Using a thematic analysis process [16] the data were coded inductively. The researchers and research-assistants identified and defined themes and recurring ideas or concepts based on hermeneutic principles [17]. The data from each area were then compared for common and contrasting themes. As the combined themes and concepts emerged, further data reduction and interpretation occurred, always checking with Aboriginal and Torres Strait Islander understandings of the research-assistants and researchers.

2.2.5. Stage 5: Consultation with Aboriginal and Torres Strait Islander communities and health services, and mainstream health services

The participants reviewed a summary of the collaborative descriptions and interpretive accounts. Further comments were also received from the Aboriginal Community Controlled Health Services involved and these were incorporated into the findings. As required by the HNE Aboriginal Health Partnership the draft findings were also presented back to a Partnership meeting.

2.2.6. Stage 6: Final analysis, dissemination of the results so far and re-drafting of the pandemic plan

The PAR cycles are continuing. Specific areas of concerns identified by some communities are being explored in the light of evidence from other communities and fed back where necessary.

3. Results

The occurrence of H1N109 raised deep concerns and serious issues in all of the Aboriginal and Torres Strait Islander communities involved in this project. The participants expressed distrust and scepticism with the current health policies on containment and told the researchers that specific plans for Aboriginal and Torres Strait Islander peoples are needed, *"There has to be a strategic plan, some sort of plan that is specific for our Indigenous mob in case it may come again"*. It was clear to many respondents that the policies and plans had been developed without respectful engagement with communities and this was a barrier to their acceptance and implementation. The strong and recurring themes that emerged from the PAR cycles described the importance of family; ways of life and realities of living in response to influenza; and key messages to government and health services about needing to focus on communication, understanding and respect in developing pandemic influenza control policies. Specific acceptable ways of reducing the risk of pandemic influenza raised by participants have been developed into strategies.

3.1. Importance of family and ways of life

Families and ways of life were identified as critical determinants of the way communities responded to the threat of pandemic influenza. Keeping families safe; prioritising family above self; respecting family structures; and the need to attend funerals and community events, impacted on how participants responded to pandemic influenza and to the development of more acceptable disease control strategies.

3.1.1. Keeping families safe

The central importance of family to Aboriginal and Torres Strait Islander peoples and keeping them safe was a strong theme. Participants described that in all circumstances, even when they were sick, people would consider their families of greater importance than themselves. A woman from Tamworth reflected, *"That's the way we think, we think more about our families than ourselves."*

A number of strategies were implemented by participants to reduce the risk of infection for their families including: increasing hand washing and using hand gels; keeping a few steps away from others if they were feeling sick; limiting travel of family members when "flu" was around; and creating more safe spaces in homes for people to live when they were sick. One man explained about how *"People stayed away from the house, if they visited they stayed outside"* so that they could "yarn" when they were sick and still keep families safe.

3.1.2. Our families, our ways

Participants shared aspects of family and community life that community members described as "ours".

Grandmothers were identified by many participants as the most important person in the family when dealing with health issues, such as a new influenza strain. At times health information was seen to be in conflict with Grandmothers' ways. One woman described how they integrated new information into their family *"Instead of being in conflict with Grandma, bearer of all knowledge, we try to complement the cultural way with this new improved way"*, and build on Grandmothers' ways.

"Our ways" was referred to as respecting the community as a broader family group and contrasted with the interaction in non-Aboriginal or Torres Strait Islander communities. A participant explained that "*...Your family is us, you, big mob. Your family is not just this little circle.*"

This aspect of 'our families, our ways' was pertinent in descriptions of the importance of family and community events. *"Family funerals are a big thing for Indigenous people, family are an important factor to our mob"* explained a participant from north Queensland. A Torres Strait Islander participant explained, *"your appearance at these events is crucial. It is seen as abusing our own culture"* [if you don't attend]. A participant from Tamworth declared that he *"went to a funeral even though I knew I was sick"*. Being close to people is fundamental at these family and community events. As one participant revealed *"we touch, shake hands or hug – This is a confirmation of our meeting."* Reducing the spread of influenza and keeping families safe in this setting was considered difficult by respondents but some extra measures such as having more tissues was suggested. One woman offered this view about tissues: *"Everyone is crying and blowing their nose, so have them everywhere"* and suggested that tissues and hand gel should be universal *"Have everything out and not behind closed doors. No shame"*.

Attempts to implement home isolation clearly contrasted with described ways of life: *"Murri* [Aboriginal people] *can't stay in the house. We have to go out for that walk."* and *"When I get the flu I go bush, away from the family, so I don't pass it on, just set up camp in the scrub and isolate."* The role of traditional practices and medicine were also reported "*... our people, we got our own medicine.*" Traditional ways have a role in health, "*we just go down the beach for fulgl [traditional food] and fish soup, that's our medicine.*" participant from Palm Island.

3.2. Realities of living

Life in Aboriginal and Torres Strait Islander communities is fulfilling and affirming but the realities of the built environment pose particular challenges. There may be large and extended families living in a relatively small house and there may be more than one house that people call "home."

3.2.1. Big families, small houses

The reality of big families and small houses can contribute to influenza transmission. When describing the challenges of current housing a participant declared that *"Its bad enough now for blacks let alone when they got another problem"*. The result, as a participant explained, is that family are *"Always sharing rooms and utilities"* and that *"Home Quarantine in a house with 14 other people...was particularly difficult for mums and babies."*

3.2.2. Realities of inadequate infrastructure

Participants described infrastructure issues that did not support disease control. Lack of personal and public transport to seek health care was mentioned. In camp areas that people move to, the infrastructure issues become even more pressing. A participant said, *"People in the camps might want water and toilets"* and *"more bins around"*. The community found the lack of infrastructure in the camps "*...very hard*". The same participant pleaded that *"Somebody should help to make a safe place for families to go."*

3.3. Key messages for government and health services

3.3.1. Knowledge is power

People were concerned that there was little Aboriginal community awareness about pandemic influenza, *"There's not much community awareness around Swine Flu in the Murri community and not much in the migaloo* [non-Indigenous] *community."* Fear and panic were described in response to H1N109, *"People got into a panic.... It was all wrong information. Everybody was frightened of this person who first had it"* and *"I was frightened we were going to die from it."* According to a participant from Tamworth:

> *"Knowledge is power, if we knew earlier, we could do more."*

3.3.2. Ask us, listen to us, share with us

Participants provided deep insights into more effective communication between governments, health services and the community. This theme identified the need for government and organisations to enter into a dialogue with Aboriginal and Torres Strait Islander communities, to discover what communities wanted to know before telling them. Respondents reported that it was important that authorities listened to what was really meant, and then shared the information needed. One of the local Aboriginal health professionals interviewed described this process as *"We don't educate – we share"* information with the community. According to another participant *"If information is delivered in an appropriate manner, people will make an appropriate choice."*

For sharing to connect effectively with local people, participants advised to *"localise, personalise and humourise"* the communication, using established local community networks and local languages. The importance of ensuring that information related to community members using identifying colours, people and logos, was reported. As described by participants *"The more you can localise something the better it is received. Use of local people promotes ownership"* and *"If you see an ad with Aboriginal person, you can't wait to see it again."*

Humour was considered an important facilitator for connecting information with communities. A participant suggested to *"make it fun"* as *"Aboriginal people best sense of humour"*.

It was stated that sharing of information about pandemic influenza worked best when it *"flows through the family structure, this way everyone will be prepared next time swine flu comes to our community"*. Participants described how important it was to have Aboriginal and Torres Strait Islander people in communities empowered with an ability to share an accurate understanding about H1N109. *"Aboriginal people need to be the driving force"* and *"Here is not like Sydney. . . we had to deliver the message out to them too"* [outer islands of the Torres Strait].

3.3.3. Partnerships and collaborations are vital

The data revealed that communities placed a high value on partnerships and collaborations. The message to government was that through *"Collaboration. . . people* [are] *more likely to take notice."* A recurrent message for government was that:

> It is really good to sit with community – partnerships, Elders and the younger ones. . .

3.3.4. More responsive health services are needed

A strong recurrent theme across the sites was that health services needed to be more locally responsive to the pandemic threat. Participants felt that there needed to be more community-based clinics that were free and *a "more holistic approach" "treating the whole household"*. An important barrier to treatment was cost.

> *Cost is a big factor for visiting the doctor. . .money is an important factor for a lot of Aboriginal people. . . if you then have to buy medication other things become a priority, food.*

The role of local Aboriginal or Torres Strait Islander health workers was said to be critical. These people are important for *"delivering the health message and they do not frighten the community by keeping the message culturally appropriate by being there to translate immediately any misinterpretation."*

3.4. Acceptable strategies

Participants identified a number of methods to reduce their families' risk of pandemic influenza. These specific strategies are described in Box 1 . Along with a community engagement plan, these strategies would facilitate a broader dialogue with communities. Through this dialogue local plans that are acceptable to communities and Health Services could be developed.

Box 1: Strategies for families to reduce the risk of pandemic influenza

Keeping families safe: ways that can help to reduce the risk of influenza for families

- Vaccination against flu is safe and will help to protect your family, go to your local health service such as AMS or GP
- Cough and sneeze into tissues and throw them out – Catch 'em, Bin 'em, Kill 'em.
- If you don't have tissues, cough or sneeze into your arm, this keeps your hands safer and protects the people around you
- Washing hands with soap and water often will reduce the spread of flu and other germs
- Hand gels are great at getting rid of germs from hands
- Keeping healthy helps to avoid the flu: eat plenty of fruit and veggies, and get some exercise
- If you get a fever and a cough or think that you have the flu:
  - don't hesitate, don't wait, get to the Doctor
  - keep a couple of steps away from others
  - stay away from work and school until have the better
  - get some rest; its good for healing
  - drink plenty of water
- If you are sick with the flu and have to go to an important family or community gathering, here are some things you can do to protect others:
  - stand back if you can, keep a couple of steps away from others, let elders know you are sick so that if you are standing back it is not seen as disrespectful
  - if you cough or sneeze use a tissue or cough into your arm
  - where possible talk with people out in the open, on the verandah or in the fresh air
  - take plenty of tissues and some hand gel with you and use them often
  - less kissing, less hugs, less flu bugs can spread

4. Discussion

Although the Director General of the World Health Organization [23] has declared the H1N109 pandemic over, influenza due to this strain continues to cause illness and deaths in Australian Aboriginal and Torres Strait Islander people. A future pandemic with a new strain is inevitable and we are morally bound to learn from the current pandemic and apply this to our preparation for future infectious disease threats.

Actions to reduce the risk of pandemic influenza transmission in the community need to be driven by the understandings emerging from this research. The current health policies on pandemic influenza have not been developed in partnership with Indigenous communities and do not adequately reflect the issues that emerged in this research.

The importance of family and community ways was a strong and recurring message and must be recognised in developing health policy. Aboriginal and Torres Strait Islander communities differ from non-Aboriginal communities in a number of ways. The social connectedness described by participants is one of these ways. The close social networks are no doubt a generally positive community characteristic, but for pandemic influenza this characteristic increases the risk of transmission.

It is clear from the findings that altering behaviour when people are sick with influenza can be centred on the importance of family. Supporting Grandmothers to share information is a method that may be more acceptable to communities. Infection control advice, restricting movement, keeping a few steps back and seeking medical care early are all strategies that can be acceptable if there is a strong link to "keeping families safe".

The health policies of home isolation of cases and quarantine of contacts are two of the public health measures used in the containment of pandemic influenza [18]. Participants clearly stated that family and community obligations were more important than the national health policy requirement to stay home if sick. The disease control strategies of home isolation of cases and home quarantine of contacts need to be redesigned to allow people to leave their homes. More acceptable strategies could include allowing people to attend family and community events on agreement that they stand back or keep a few steps away from people covering their noses and mouth if sneezing or coughing, and informing Elders of the reasons for this behaviour. Having more tissues, hand gel and information available at community and family events was also recommended.

The reality of life in Aboriginal and Torres Strait Islander communities differs from many non-Aboriginal communities and a clearer understanding may assist policy makers in the design of appropriate strategies. The key messages to government and health services stem from these issues: community engagement and partnership is vital; health services need to be more responsive; and "ask, listen and share".

It has been argued in our previous work that measures to reduce the risk of influenza in Aboriginal and Torres Strait Islander communities need to be developed *with* communities not *for* communities, to maximise their acceptance [8,9]. The current findings reinforce the importance of a process of engagement and ongoing respectful consultation with communities for developing effective and culturally appropriate strategies. This finding mirrors that of Vaughan and Tinker [10] in their work on vulnerable populations.

As described for other communities throughout the world [12,13,19], a PAR approach enabled the close involvement within this work of Aboriginal and Torres Strait Islander communities, as researchers and participants. Sharing of information and ideas resulted in "two way learning" [15]. Parallel to this was the development of the research capacity of a number of Aboriginal people, which will help to build ongoing opportunities for community based health improvements through research. Some of the research assistants involved in this project have gone on to study Indigenous research methods, nursing or public health. Research capacity has increased in the communities involved in the project. Unless Aboriginal and Torres Strait Islander peoples have control of all aspects of the research process, in collaboration with trusted research partners, they are unlikely to participate [20–22].

A number of aspects of this research demonstrate that the PAR approach was central to the outcomes. The research issue initially came from the communities in north-west NSW; the research method was applied collaboratively; researchers were facilitators of knowledge exchange; people from the local Aboriginal communities were trained and mentored in research throughout the study; and feedback to the collaborators and the communities involved was integral in the process. The research process also became health action with a number of the strategies being implemented within communities as a result of the feedback.

Rather than a linear model of researcher-led data retrieval and analysis, PAR is a cyclical process of planning, acting, observing and reflecting. This design ensures that each new collection of data is grounded in reflections formed on the previous data. So the current findings will form the basis of new rounds of research and will see further and deeper exploration of the issues of preventing the spread of influenza in families and homes.

5. Conclusion

The essential work of reducing risk of pandemic influenza with Aboriginal and Torres Strait Islander communities is not straightforward, but this project has highlighted a number of useful pathways to continue to journey along with communities. A number of strategies to reduce the risk of pandemic influenza in Aboriginal and Torres Strait Islander communities were identified. Strategies included the need for health services to undertake respectful engagement with communities; modifying home isolation and quarantine policies; family centred prevention; and communicating with and through Grandmothers. These strategies would make a good starting point for dialogue with communities and health services. In Aboriginal and Torres Strait Islander communities the environment, community structures and traditions vary. Respectful engagement with communities is needed to develop effective policy.

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6.4.2 Valkenburg , Josephs, Clemens, Grant, Nguyen,Wang, Price, Miller, Tong, Thomas, Doherty, Rossjohn, Gras & Kedzierska. Molecular basis for universal HLA-A*0201 CD8+ T Cell immunity against influenza viruses.

Molecular basis for universal HLA-A*0201–restricted CD8+ T-cell immunity against influenza viruses

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Memory CD8+ T lymphocytes (CTLs) specific for antigenic peptides derived from internal viral proteins confer broad protection against distinct strains of influenza A virus (IAV). However, immune efficacy can be undermined by the emergence of escape mutants. To determine how T-cell receptor (TCR) composition relates to IAV epitope variability, we used ex vivo peptide–HLA tetramer enrichment and single-cell multiplex analysis to compare TCRs targeted to the largely conserved HLA-A*0201-$M1_{58}$ and the hypervariable HLA-B*3501-NP_{418} antigens. The TCRαβs for HLA-B*3501-NP_{418}^+ CTLs varied among individuals and across IAV strains, indicating that a range of mutated peptides will prime different NP_{418}-specific CTL sets. Conversely, a dominant public TRAV27/TRBV19+ TCRαβ was selected in HLA-A*0201+ donors responding to $M1_{58}$. This public TCR cross-recognized naturally occurring $M1_{58}$ variants complexed with HLA-A*0201. Ternary structures showed that induced-fit molecular mimicry underpins TRAV27/TRBV19+ TCR specificity for the WT and mutant $M1_{58}$ peptides, suggesting the possibility of universal CTL immunity in HLA-A*0201+ individuals. Combined with the high population frequency of HLA-A*0201, these data potentially explain the relative conservation of $M1_{58}$. Moreover, our results suggest that vaccination strategies aimed at generating broad protection should incorporate variant peptides to elicit cross-reactive responses against other specificities, especially those that may be relatively infrequent among IAV-primed memory CTLs.

influenza infection | human CD8+ T cells | T-cell receptor

Preexisting CD8+ T-lymphocyte (CTL) immunity directed at peptides derived from internal viral proteins is known to confer protection against specific strains of influenza A virus (IAV) (1–5). Recalled memory CTLs generated by seasonal variants can also expedite virus elimination and host recovery following infection with H1N1, H2N2, H3N2, H5N1, and H7N9 IAVs (2, 3, 6–9). However, it is unclear why such cross-strain responses vary among individuals. The ability of αβ T-cell receptors (TCRαβs) to recognize antigenic epitopes from distinct IAVs and circumvent immune escape relies on peptide sequence conservation and/or structural homology (10–12). A detailed understanding of cross-strain reactivity in relation to defined TCRαβ interactions may therefore inform the rational development of a universal vaccine against IAV.

The conserved HLA-A*0201–restricted $M1_{58\ 66}$ (GILGFVFTL, referred to hereafter as "$M1_{58}$") (13) and variable HLA-B*07 superfamily-restricted $NP_{418\ 426}$ (LPFERATVM, referred to hereafter as "NP_{418}") (10) peptides are the most immunogenic IAV epitopes described in humans. The $M1_{58}$ epitope has remained unchanged in seasonal and pandemic IAVs since 1918 (1, 8, 14, 15), although viruses with single-alanine-substitution mutants of $M1_{58}$ generated by reverse genetics are replication competent (16). Accordingly, the $M1_{58}$ peptide is an ideal vaccine candidate for >1 billion people globally who express HLA-A*0201. In contrast, the NP_{418} epitope is hypervariable, encompassing >20 different naturally occurring sequences. Analysis of HLA-B*07/B*35–restricted NP_{418}-specific CTLs in the wake of the 2009 pandemic revealed at least two distinct responses to this prominent epitope (12).

In this study, we used ex vivo tetramer enrichment combined with single-cell multiplex RT-PCR to dissect TCRαβ signatures within CTL populations specific for the HLA-A*0201-$M1_{58}$ and HLA-B*07/B*35-NP_{418} epitopes. Our data indicate that public A*0201-TCRαβs use molecular mimicry to recognize distinct IAVs.

Results

Natural IAV $M1_{58}$ Variants Emerge in HLA-A2.1 Transgenic HHD Mice. The HLA-A*0201–restricted $M1_{58}$ peptide is broadly conserved across IAVs, although the M1-I2M and M1-L3W variants have been found in 21% of H5N1 sequences (7). Using the influenza resource database at the National Center for Biotechnology Information, we aligned 1,000 full-length sequences representing IAV subtypes infecting different species between 1918 and 2010 to conduct an in-depth validation of $M1_{58}$ conservation.

Significance

Influenza is a rapidly spreading acute respiratory infection that causes profound morbidity and mortality. Established CD8+ T-lymphocyte (CTL) immunity directed at conserved viral regions provides protection against distinct influenza A viruses (IAVs). In this study, we show that public T-cell receptors (TCRs) specific for the most prominent human CTL epitope ($M1_{58-66}$ restricted by HLA-A*0201) are capable of recognizing sporadically emerging variant IAVs. We also identify the structural mechanisms that enable promiscuous TCR recognition in this context. Our analysis suggests that preexisting cross-reactive TCRs may limit the spread of newly emerging pandemic IAVs.

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The authors declare no conflict of interest.

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Data deposition: Crystallography, atomic coordinates, and structure factors reported in this paper have been deposited in the Protein Data Bank (PDB) database [PDB ID codes 5HHQ (HLA-A*0201-M1-L3W), 5HHP (HLA-A*0201-M1-G4E), 5HHN (HLA-A*0201-M1-F5L), 5HHO (JM22-TCR-HLA-A*0201-M1-G4E), and 5HHM (JM22-TCR-HLA-A*0201-M1-F5L)].

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Table 1. Newly identified naturally occurring $M1_{58}$ peptide variants

GILGFVFTL	Mutant	No.	%	Source	Year	Subtype	Strain
A- - - - - - - -	G1A	1	0.1	Human	2009	H3N2	A/Tomsk/02/2009
W- - - - - - - -	G1W	1	0.1	Swine	2005	H3N2	A/swine/Guangdog/01/2005
-V- - - - - - -	I2V	19	1.9	Avian	1999–2008	H3N2, H5N1, H7N7, H7N2, H7N3, H9N2, H2N1	A/Hanoi/TN405/2005
-M- - - - - - -	I2M*	35	3.5	Avian	1999–2008	H5N1, H6N2, H9N2	A/duck/Hong Kong/140/1998
-T- - - - - - -	I2T	1	0.1	Avian	2002	H5N1	A/duck/Fujian/13/2002
- -W- - - - - -	L3W*	0	0.0	Avian		H5N1	Described in ref. 7
- - -E- - - - -	G4E	1	0.1	Avian	1998	H9N2	A/chicken/Anhui/1/1998
- - - -V- - - -	F5V	2	0.2	Human, avian	1946, 2000	H1N1, H9N2	A/Cameron/1946
- - - -L- - - -	F5L	9	0.9	Human, avian	1983–2009	H1N1, H5N2, H7N3, H11N2	A/Canterbury/236/2005
- - - - -I - - -	V6I	12	1.2	Human, avian	1967–2006	H2N2, H13N6, H1N2, H3N1, H1N1	A/England/10/1967
- - - - - -Y- -	F7Y	1	0.1	Human	1999	H3N2	A/New South Wales/15/1999
Total mutations	82						
Total sequences	998	8.2					

Mutations were found in 8.2% of IAVs, and 11 distinct $M1_{58}$ substitutions were identified across all positions bearing the C-terminal P8 and P9 residues (Table 1). The most frequent $M1_{58}$ mutations occurred at the anchor residue (p2), accounting for nearly 67% of all substitutions in the database (M1-I2M, 42%; M1-I2V, 23%; M1-I2T, 1.2%). Although these $M1_{58}$ variants were detected mainly in avian IAVs (H2, H5, H6, H7, H9, H11, and H13), 8 of the 82 mutant sequences were derived from human isolates.

An established mouse model of IAV escape (17) was used to probe the emergence of $M1_{58}$ mutants. As in humans, the $M1_{58}$ epitope is immunodominant in HLA-A2.1 HHD mice (Fig. S1 *A* and *B*). Amino acid substitutions in $M1_{58}$ were encoded by viral RNA extracted from the lungs of three of seven mice 15 d after infection (Fig. S1 *C*–*E*), a lower mutation rate compared with the immunodominant H2-$D^b$$NP_{366}$ epitope in WT B6 mice (17). Engineered PR8 viruses carrying the M1-I2M, M1-F5L, M1-V6I, and M1-F7Y mutations grew to similar titers in embryonated eggs and MDCK cell cultures (Fig. S1 *F* and *G*). However, it remains possible that subtle differences in viral fitness may counterselect against $M1_{58}$ mutants in the natural setting. The absence of epitope-specific immune pressure also may lead to the occurrence of viral refugia in individual cases, a phenomenon widely recognized in the ecology field.

Sequence variation within $M1_{58}$ therefore occurs in IAVs recovered from humans (8.2%) and from experimentally infected HLA-A2.1 HHD mice (7.3%). However, unlike the frequent and persistent mutations in NP_{418} (10), these $M1_{58}$ variants are not readily fixed in circulating human IAVs. To determine whether the contrasting patterns of viral variation within $M1_{58}$ and NP_{418} reflect immune selection, we undertook a detailed cellular and molecular evaluation of the corresponding CTL responses.

HLA-A*0201-$M1_{58}$$^+$ CTLs Are Immunodominant and Recognize $M1_{58}$ Variants. Using direct ex vivo tetramer-based magnetic enrichment (4, 18) to minimize selection bias, we analyzed CTL responses specific for HLA-A*0201-$M1_{58}$ (A2-$M1_{58}$) and HLA-B*3501-NP_{418} (B35-NP_{418}) in individual subjects expressing both HLA-A*0201 and HLA-B*3501 (Fig. 1 and Table S1). A2-$M1_{58}$$^+$ CTLs were identified with a single conserved tetramer, and B35-$NP_{418}$$^+$ CTLs were identified with a tetramer pool corresponding to the main variants from 1918, 1934, 1947, 1980, and 2002 (12). The A2-$M1_{58}$$^+$ CTL population was consistently larger (17 ± 9.2-fold) than the B35-$NP_{418}$$^+$ CTL population (Fig. 1*A*), which frequently predominates in HLA-A*0201 donors (Fig. S2). Furthermore, the polyclonal A2-$M1_{58}$$^+$ CTLs recognized all detected mutants, although response frequencies varied and the M1-G4E mutant was weakly immunogenic in five donors (Fig. 1*B*). Conversely, the polyclonal B35-$NP_{418}$$^+$ CTLs recognized a limited number of variants (Fig. 1*C*), in line with previous reports of immune escape (10, 12). Thus, $M1_{58}$-specific TCRs cross-react with a broader spectrum of naturally occurring epitope variants compared with NP_{418}-specific TCRs. It is notable in this regard that NP_{418} variants are often composite, incorporating up to three amino acid substitutions, whereas single mutations are more common in $M1_{58}$.

Dissection of A2-$M1_{58}$ and B35-NP_{418} TCRαβ Repertoires. Consistent with previous reports (19–21), direct ex vivo single-cell sequencing of the A2-$M1_{58}$$^+$ TCRαβ repertoire showed a heavy bias toward T-cell receptor β variable 19 (TRBV19) use across all eight donors, coupled with a dominant T-cell receptor α variable 27 (TRAV27) segment in seven of eight donors (Fig. 2 *A* and *B* and Fig. S3 *A* and *B*). The averaged frequency for TRBV19 was 91.6% (range 44–100%), compared with 49.2% (range 0–91%) for TRAV27. The most common TCRαβ signature was the public clonotype

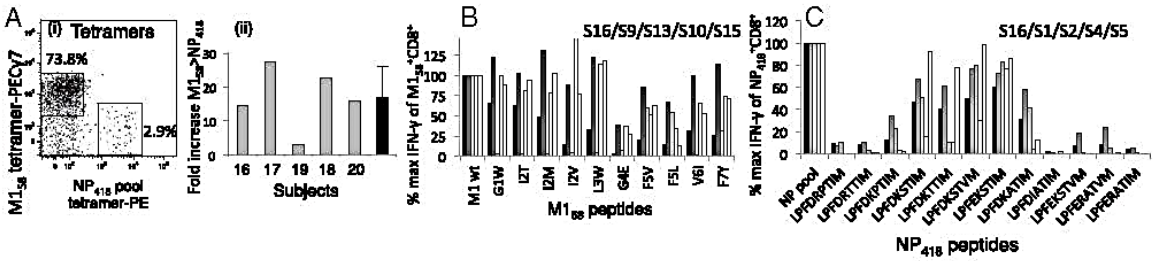


Fig. 1. Ex vivo immunodominance of A2-$M1_{58}$$^+$ over B35-$NP_{418}$$^+$ CTLs. (*A*) Costaining of A2-$M1_{58}$$^+$ and B35-$NP_{418}$$^+$ CTLs directly ex vivo by tetramer enrichment showing (*i*) single tetramer$^+$CD8$^+$CD4$^-$CD14$^-$CD19$^-$ cells and (*ii*) fold-increase of the A2-$M1_{58}$ above the B35-NP_{418} CTL response. (*B* and *C*) Recognition of naturally occurring $M1_{58}$ (*B*) and NP_{418} (*C*) variants by human PBMCs from A2$^+$B35$^+$ donors was assessed 10 d after restimulation using intracellular staining for IFN-γ production in response to the indicated peptides. Data show individual subjects (*S*).

TRBV19/complementarity-determining region (CDR)3β-SIRSSYEQ paired with TRAV27/CDR3α-GGSQGNL (Fig. 2*C* and Fig. S3 *C*–*E*). In subject 23, the public TRBV19/CDR3β-SIRSSYEQ paired with a similar TRAV27/CDR3α-ASGSSNTGKL (44% of sequences), whereas subject 22 exhibited a limited TCRαβ repertoire in which an alternate TCRβ (TRBV19/CDR3β-GAGGPLNEQ) paired with a non-TRAV27 TCRα (TRAV12.3/CDR3α-SERNNARL). Public TCRαβ clonotypes can therefore be generated in the majority of HLA-A2$^+$ individuals across different ethnicities, including Indigenous Australians.

Reflecting the prevalence of low-frequency private clonotypes, the $M1_{58}$-specific TCRαβ repertoire was more diverse (12.4 ± 6.0 CDR3αβ pairs per donor) than previously reported. Furthermore, the AGA(G_n)GG CDR3α motif (22) (in which "$_n$" denotes any number of residues) found by others following long-term culture was not consistently present in our direct ex vivo dataset, although two glycines (GG) featured in 20 of the 45 CDR3α sequences. The CDR3β IRS motif, which forms the basis for "peg–notch" JM22 TCR recognition of the "plain vanilla" $M1_{58}$ epitope (21), was used in 11/45 CDR3β sequences across five donors.

In contrast, analysis of the B35-$NP_{418}{}^+$ TCR repertoire using pooled B35-NP_{418} tetramers (Fig. S4) revealed distinct CDR3α/CDR3β sequences incorporating diverse TRAV and TRBV segments. A preference for TRBV20-1/TRBJ5-1 rearrangements with a CDR3β length of 7 or 10 amino acids was observed in the TCRβ repertoire, whereas the predominant TCRα chains favored TRAV8-1 and TRAJ18 with a CDR3α length of 8–10 amino acids (Table S2). However, only one common sequence (TRAV8-1/CDR3α-NEGGSTLGRL) was found among individuals (Fig. S4).

There was no overlap between the B35-$NP_{418}{}^+$ TCR datasets, generating a Morisita–Horn statistic of 1 (zero interindividual similarity). However, the A2-$M1_{58}{}^+$ TCR datasets overlapped considerably, driven by the public TRBV19/CDR3β-SIRSSYEQ sequence (averaged Morisita–Horn statistic of 0.6). These differences were statistically significant (P = 0.0056, Wilcoxon signed tank test). In addition, the Simpson diversity index was higher for B35-$NP_{418}{}^+$ TCRαβs (0.97 ± 0.03) than for A2-$M1_{58}{}^+$ TCRαβs (0.75 ± 0.27) (Table S2).

Thus, dominant public TCRαβ clonotypes (TRBV19/TRAV27) are selected in HLA-A*0201$^+$ donors responding to the relatively invariant A2-$M1_{58}$ epitope, whereas TCRαβ clonotypes directed at the hypervariable B35-NP_{418} epitope are more diverse across individuals.

Public $M1_{58}$-Specific TCRαβ Clonotypes Cross-Recognize Newly Identified Variants. How do A2-$M1_{58}{}^+$ CTLs recognize naturally occurring $M1_{58}$ variants? To investigate this question, peripheral blood mononuclear cells (PBMCs) were stimulated with the mutant peptide (M1-L3W, -G4E, or -F5L) for 10 d and then stained with the $M1_{58}$ WT tetramer. In this way, variant-specific CTLs were amplified by the mutant peptide, and cross-reactive clonotypes identified by reactivity with the $M1_{58}$ WT tetramer were characterized using single-cell CDR3αβ TCR repertoire diversity analysis (Fig. 3 and Table S3). The variant M1-L3W, M1-G4E, and M1-F5L peptides represent naturally occurring $M1_{58}$ mutants, with a CTL response magnitude hierarchy of M1-L3W > M1-F5L > M1-G4E in subject 9 and subject 16 (Fig. 3).

The public HLA-A*0201-$M1_{58}{}^+$ TCR (CDR3α-GGSQGNL; CDR3β-SIRSSYEQ) recognized all three peptide variants (Table S3), although the frequency was slightly lower for the M1-G4E mutant (47% of the WT). Higher-frequency public TCRαβ use correlated with larger mutant-specific CTL responses (Fig. 1*B*), indicating that public HLA-A*0201-$M1_{58}{}^+$ TCRs play an important role in variant cross-recognition. Overall, the mutant $M1_{58}$ peptides selected a TCRαβ repertoire comparable to that of WT $M1_{58}$ with similar TRAV27, TRAJ42, TRBV19, and TRBJ2-7 use (except for M1-G4E in subject 16, which used TRAV23DV/6 instead of the typically dominant TRAV27), suggesting that WT HLA-A*0201-$M1_{58}{}^+$ TCRs are largely cross-reactive with $M1_{58}$ variants.

HLA Presentation and TCR Recognition of $M1_{58}$ Variants. To determine the impact of peptide mutation on HLA binding and T-cell recognition, we assessed the extent to which the naturally occurring $M1_{58}$ mutant peptides M1-F5L, M1-G4E, and M1-L3W stabilize HLA-A*0201. We refolded the HLA-A*0201 molecule with the $M1_{58}$ peptide and each of the three variants to determine the thermal stability of the corresponding peptide-HLA (pHLA) complexes. In complex with the $M1_{58}$ peptide, HLA-A*0201 exhibited a thermal melt point (Tm, the temperature required to unfold 50% of the protein) of ~66 °C; the Tm was similar for the three $M1_{58}$ variants (Table S4), indicating that the mutations directly affect TCR binding rather than pHLA complex stability.

To understand the mode of recognition of $M1_{58}$ mutants by public HLA-A*0201-$M1_{58}{}^+$ TCRs, we conducted surface plasmon resonance studies with the previously characterized $M1_{58}$-specific JM22 TCR (TRAV27/CDR3α-AGSQGNL; TRBV19/CDR3β-SSRSSYEQ) (21). We confirmed that the JM22 TCR binds with high affinity (1.79 μM) to the HLA-A*0201-$M1_{58}$ complex (21, 23), but measured substantially lower affinities for the three $M1_{58}$ variants (Table S5). Namely, weak binding (K_d >200 μM) characterized the JM22 TCR interaction with M1-G4E and M1-F5L, and this was further diminished (K_d >600 μM) for M1-L3W, presented by HLA-A*0201 (Table S5). Thus, although the JM22 TCR can recognize all $M1_{58}$ variants, the binding affinity is lower for the mutant epitopes (24).

$M1_{58}$ Variants No Longer Form Plain Vanilla Epitopes. To understand the impact of the naturally occurring $M1_{58}$ mutations on epitope presentation and T-cell recognition, we determined the structures of three binary pHLA complexes (M1-F5L, M1-G4E, and

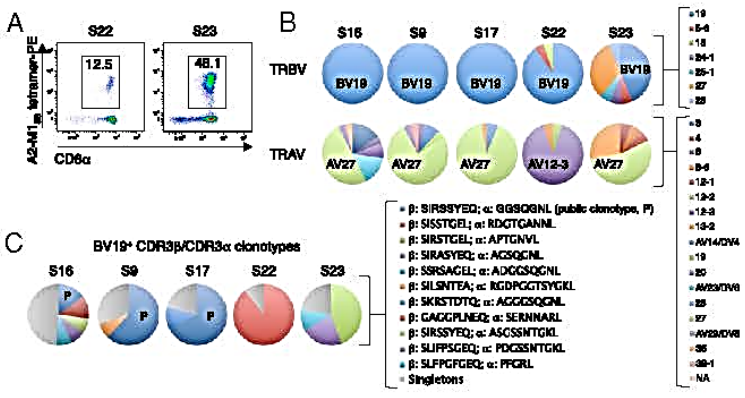


Fig. 2. The A2-$M1_{58}{}^+$ TCRαβ repertoire is dominated by a public clonotype. A2-$M1_{58}{}^+$ CTLs were isolated directly ex vivo from non-Indigenous healthy donors (n = 5) by magnetic enrichment and flow cytometric sorting of single tetramer$^+$ cells. Populations were gated on viable Dump$^-$tetramer$^+$CD3$^+$CD8$^+$ events. (*A*) Representative flow cytometry profiles showing tetramer$^+$CD8$^+$ T cells after ex vivo enrichment. (*B*) TRBV and TRAV use. (*C*) Frequency of CDR3αβ clonotypes. Corresponding data for healthy Indigenous Australian donors (n = 3) are shown in Fig. S3. P, public.

M1-L3W) (Fig. 4 and Table S6) and compared these structures with the previously solved structure of HLA-A*0201-$M1_{58}$ (23). The $M1_{58}$ epitope is considered plain vanilla because the $M1_{58}$ epitope adopts a flat surface in the cleft of HLA-A*0201 (25) (Fig. 4*A*). Indeed, despite containing two aromatic residues (P5-Phe and P7-Phe), these side chains are buried inside the antigen-binding cleft, leaving the P6-Val solvent exposed. The overall structure of the M1-G4E mutant complex is similar to that of the $M1_{58}$ complex, with rmsds of 0.25 Å for the antigen-binding cleft and 0.27 Å for the peptide (Fig. 4*A*). Although the replacement of the glycine residue by glutamic acid does not disturb the backbone conformation for M1-G4E, it allows P6-Val to move deeper into the HLA-A*0201 antigen-binding cleft (Fig. 4*A*). As a result, P5-Phe and P7-Phe are mobile and adopt several conformations, most of which are solvent exposed (Fig. 4*A*).

More dramatic rearrangements were observed for the M1-L3W (Fig. 4*B*) and M1-F5L (Fig. 4*C*) variants. The P3-Leu of the WT $M1_{58}$ peptide is buried in the cleft and interacts with the B pocket of HLA-A*0201, whereas the larger P3-Trp of M1-L3W is accommodated in the B pocket without modification of the overall antigen-binding cleft structure (rmsd of 0.33 Å). However, the M1-L3W peptide must rearrange dramatically due to the presence of the large tryptophan residue at P3 (rmsd of 0.61 Å) (Fig. 4*B*). The P5-Phe side chain swings out of the antigen-binding cleft to avoid steric clashes with P3-Trp and hence becomes solvent exposed. As a consequence, P6-Val is buried in the antigen-binding cleft, and P7-Phe is again mobile and solvent exposed (Fig. 4*B*). Thus, in the HLA-A*0201-M1-L3W structure, the two large aromatic side chains at P5 and P7 are directly available for TCR interaction.

Similarly, the M1-F5L variant adopts a different peptide conformation (rmsd of 0.44 Å) without distorting the antigen-binding cleft (rmsd of 0.29 Å) (Fig. 4*C*). Even though P5-Leu is smaller than P5-Phe, the rotamer of the leucine side chain (like P5-Phe) does not allow docking inside the antigen-binding cleft without changing the overall backbone of the peptide. The P3-Leu therefore no longer interacts with the B pocket of HLA-A*0201 and instead becomes mobile and solvent exposed. The new conformation of the P5-Leu residue also impacts the P6-Val conformation, which becomes buried in the antigen-binding cleft, whereas P7-Phe is now solvent exposed and mobile (Fig. 4*C*).

Overall, these surprising structures of the $M1_{58}$ variants demonstrate that interplay between peptide residues constrains the conformation of the $M1_{58}$ epitope, with any alterations reflecting either the inherent flexibility of particular residues (in M1-G4E and M1-F5L) or steric hindrance (in M1-L3W). As a consequence, single substitutions at different positions in the peptide can transform the plain vanilla $M1_{58}$ epitope into a more featured antigen.

The Public JM22 TCR Recognizes $M1_{58}$ Variants via Induced-Fit Molecular Mimicry. To understand how HLA-A*0201-$M1_{58}^+$ CTLs recognize the naturally occurring epitope variants (Fig. 1*B*), we determined the structures of the JM22 TCR (21) in complex with HLA-A*0201-M1-G4E and HLA-A*0201-M1-F5L (Table S7). As in the WT $M1_{58}$ complex (Fig. 4 *D*–*F*), the JM22 TCR docks orthogonally on the two $M1_{58}$ variant peptides presented by HLA-A*0201 (rmsd of 1.1 Å and 0.7 Å with the M1-G4E and M1-F5L complexes, respectively). The M1-G4E and M1-F5L peptides change conformation upon JM22 TCR binding (Fig. 4 *G* and *H*) to mimic that of the WT $M1_{58}$ peptide (Fig. 4*I*). These structural rearrangements allow key residues (23) from the JM22 TCR β-chain (identified via mutagenesis), namely D32, Q52, and R98, to maintain critical interactions with both the peptide and HLA-A*0201. The requirement for conformational change also explains why the JM22 TCR binds HLA-A*0201-M1-G4E and HLA-A*0201-M1-F5L with lower affinities than HLA-A*0201-$M1_{58}$ (Fig. 4 *G* and *H*).

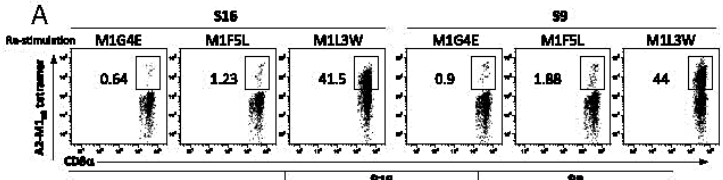
The leucine substitution at p5 (M1-F5L) is accommodated without rearrangements of the JM22 TCR CDR loops (Fig. 4*I*) (23), whereas the JM22 TCR docking angle is slightly different when in complex with $M1_{58}$ and M1-G4E (78° and 80°, respectively) (Fig. 4 *D* and *F*). This difference is a direct result of the P4-Glu substitution, which causes a 1-Å shift of the CDR3α loop to avoid steric clashes with the P4-Glu (Fig. 4*K*). The key JM22 TCR β-chain residues identified via mutagenesis (23), namely D32, Q52, and R98, conserve their critical interactions with both the peptide and the HLA molecule despite the P4-Glu and P5-Leu substitutions. Thus, the lower affinity of the JM22 TCR for HLA-A*0201-M1-F5L and HLA-A*0201-M1-G4E can be attributed to structural changes in the corresponding peptides, as well as to the CDR3α loop in the case of M1-G4E, following TCR binding (Fig. 4 *G* and *H*, respectively). Given the structural rearrangement of the M1-G4E and M1-F5L peptides, it is anticipated that large changes would occur in the M1-L3W peptide, resulting in an even lower affinity for the JM22 TCR (Table S5).

These ternary structures show that a public TCRαβ can recognize naturally occurring $M1_{58}$ variants via induced-fit molecular mimicry, potentially explaining why this epitope is conserved among influenza viruses circulating in the human population.

Discussion

Diversity in the TCR repertoire has been associated with high-avidity recognition of MHC-peptide antigens, effective viral clearance, and the containment of immune escape (26, 27). In this study, we used a multiplex single-cell RT-PCR (28, 29) to determine whether TCRαβ diversity and/or composition are associated with immune escape in influenza virus infection. The broad recognition spectrum of a public TRAV27/TRBV19$^+$ TCR within the $M1_{58}$-specific CTL repertoire correlated with the relative scarcity of naturally occurring epitope variants. Such public A2-$M1_{58}^+$ TCRs were found to be highly prevalent across donors, including HLA-A*0201$^+$ non-Indigenous donors and Indigenous Australians (HLA-A*0201 frequency of 30–50% and 10–15%, respectively). It is notable in this regard that Indigenous Australians are at greater risk of severe influenza disease, especially when new IAVs emerge (9, 30, 31). Nonetheless, preexisting CTL memory characterized by best-fit public TCRs may confer protection in the context of HLA-A*0201.

The ternary structure of a public TCR bound to the plain vanilla HLA-A*0201-$M1_{58}$ complex (21, 23) showed previously that the central arginine residue within the predominant CDR3β IRS motif (21) is required to allow a peg–notch interaction. We extended this analysis to naturally occurring $M1_{58}$ mutants and found that the



B

	S16				S9			
	M1	G4E	F5L	L3W	M1	G4E	F5L	L3W
Total sequences	26	24	20	16	33	18	20	20
% public TCR usage	15	9	15	19	67	28	45	70
% public TCR usage relative to wt		53.3	100	125		41.4	67.2	104.5

Fig. 3. The A2-$M1_{58}^+$ TCRαβ repertoire cross-recognizes $M1_{58}$ peptide variants. (*A*) A2$^+$ PBMCs were restimulated for 10 d in vitro with the $M1_{58}$ variant peptides M1-G4E, M1-F5L, or M1-L3W and then stained with the $M1_{58}$ WT tetramer. Thus, TCRs were selected to recognize the mutant by the 10-d restimulation and to recognize the cross-reactive WT epitope by tetramer sort. Representative flow cytometry plots are shown gated on CD8$^+$ T cells after the exclusion of CD4$^+$CD14$^+$ CD19$^+$ events. (*B*) Summary of public TCRαβ use.

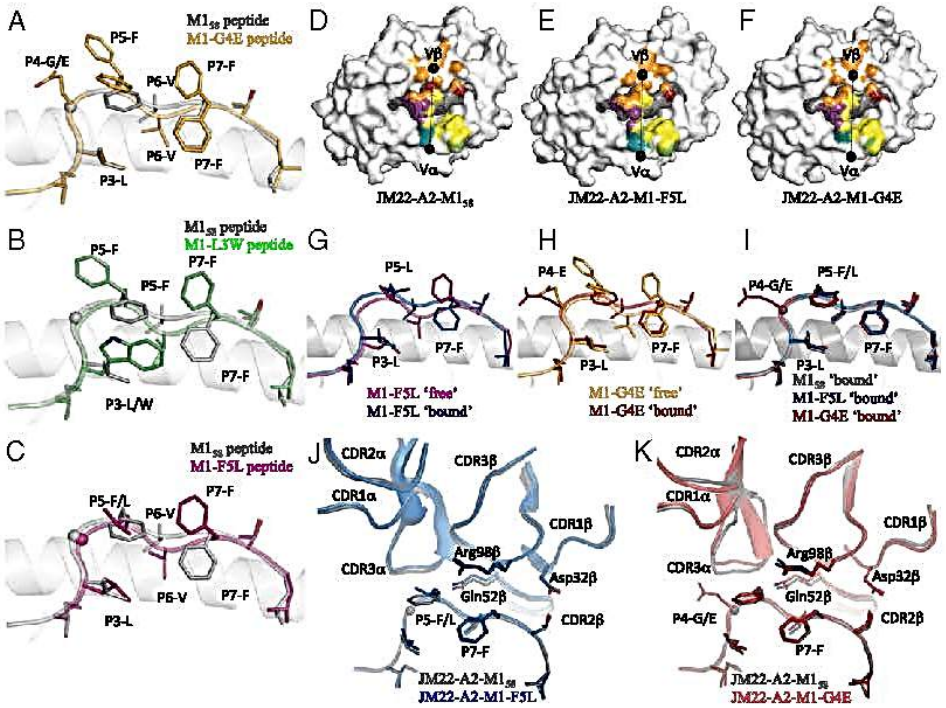


Fig. 4. Structural analysis of $M1_{58}$ variants in complex with HLA-A*0201 and the JM22 TCR. (*A–C*) HLA-A*0201 is represented as a white cartoon with the peptide in stick form ($M1_{58}$ in white, M1-G4E in orange, M1-L3W in green, M1-F5L in pink). The glycine Cα is represented as a sphere. (*D–F*) The JM22 TCR footprint on the surface of HLA-A*0201 (white) in complex with $M1_{58}$ (*D*), M1-F5L (*E*), and M1-G4E (*F*) peptide (gray). The HLA and peptide atoms are colored teal, green, and purple when contacted by CDR1α, CDR2α, and CDR3α, respectively, and red, orange, and yellow when contacted by CDR1β, CDR2β, and CDR3β, respectively. The black spheres represent the JM22 TCR center of mass for the Vα and Vβ domains. (*G*) Superimposition of HLA-A*0201-M1-F5L free (pink) and bound to the JM22 TCR (blue). (*H*) Superimposition of HLA-A*0201-M1-G4E free (orange) and bound to the JM22 TCR (red). (*I*) Superimposition of HLA-A*0201-$M1_{58}$ (gray), HLA-A*0201-M1-F5L (blue), and HLA-A*0201-M1-G4E (red) bound to the JM22 TCR. (*J* and *K*) Superimposition of JM22 TCR-HLA-A*0201-$M1_{58}$ (dark gray) with the JM22 TCR-HLA-A*0201-M1-F5L (blue) and JM22 TCR-HLA-A*0201-M1-G4E (red) complexes.

same public TCR can recognize naturally occurring variants via induced-fit molecular mimicry, incurring a penalty in terms of binding affinity and T-cell activation. Moreover, the extent of variant recognition correlated with the prevalence of public TCRs, possibly explaining the hierarchical differences in TCR affinity (G4E/F5L > L3W) and T-cell activation (L3W > F5L > G4E). Donors with prominent public TCR use (e.g., subject 9, 67%) recognized the majority of $M1_{58}$ mutants, and the converse was true for donors with limited public TCR use (e.g., subject 16, 15%). These observations suggest that public TCRs may limit, at least to some extent, the establishment of mutant strains within the circulating pool of human IAVs. This idea is consistent with an earlier report in which public Mamu-A*01-$CM9_{181}$–specific TCRs were shown to predict the outcome of simian immunodeficiency virus infection in rhesus macaques (32).

Mutant peptides incorporating substitutions at TCR contact sites within the B35-NP_{418} epitope (reflecting nine decades of natural selection) can be recognized by at least two distinct sets of cross-reactive CTLs specific for either ER or DK motifs at P4-5 (11). In theory, accurate identification of the key solvent-exposed residues and motifs that allow variable peptides to elicit cross-reactive CTL responses could inform the development of rationally designed peptide-mosaic vaccines against unpredicted IAVs (1, 33). Unlike the A2-$M1_{58}^{+}$ CDR3αβ repertoire, however, the NP_{418}^{+} CDR3αβ repertoire in $B7^{+}$ and $B35^{+}$ donors is diverse and private, potentially facilitating the emergence of novel NP_{418} variants. In turn, these mutated epitopes will likely elicit de novo TCR repertoires. Successive waves of variant exposure and diverse TCR recruitment may therefore favor the emergence and perpetuation of NP_{418} mutant IAVs (34).

Structural analyses revealed that single-amino acid substitutions within the $M1_{58}$ peptide can transform this rather flat epitope into conformations that are no longer plain vanilla (25). Although the featureless morphology of HLA-A*0201-$M1_{58}$ determines the character of the highly biased TCR repertoire (21, 25), our data show that structurally prominent $M1_{58}$ variants select a similar array of TCRs. This counterintuitive finding can be explained, at least in part, by the observation that public TCRs (exemplified by JM22) can reshape such variants into conformations that resemble the WT $M1_{58}$ epitope, which is optimal for immediate binding without the need for structural rearrangements. Such induced-fit molecular mimicry was reported previously for an Epstein–Barr virus-specific TCR (35).

In summary, we show here that HLA-A*0201–restricted public TCR clonotypes elicited by the WT $M1_{58}$ epitope can cross-recognize naturally occurring peptide variants. Conversely, the HLA-B*3501–restricted NP_{418} epitope selects a diverse and largely private CDR3αβ repertoire, which correlates with frequent mutational escape and the ongoing circulation of variant IAVs (12, 16). The ability of vaccine-induced CTL responses to protect against variable pathogens should therefore be considered in the context of individual peptides and individual TCRs.

Methods

PBMC Isolation. PBMCs were processed and HLA-typed from randomly selected buffy packs (Melbourne Blood Bank) and healthy donors, with informed written consent (Table S1). Experiments conformed to the National Health and Medical Research Council Code of Practice and were approved by the University of

Melbourne Human Research Ethics Committee and the Human Research Ethics Committee of the Northern Territory Department of Health and Menzies School of Health Research.

Ex Vivo Tetramer Enrichment and Phenotypic Analysis. Lymphocytes ($1–8\times10^6$) were stained with HLA-A*0201-$M1_{58}$ or HLA-B*3501-NP_{418} tetramers conjugated to phycoerythrin (PE) or PE-Cy7. The NP_{418} response was represented by the 1918 (LPFERATIM), 1934 (LPFDRTTIM), 1947 (LPFDKTTIM), 1980 (LPFEKSTVM), and 2002 (LPFEKSTIM) variants (12). Samples were incubated with anti-PE microbeads and tetramer-PE/PE-$Cy7^+$ cells were enriched via magnetic separation (36), then stained with anti–CD4-APC-H7, anti–CD8-PerCP-Cy5.5, anti–CD14-APC-Cy7, anti–CD19-APC-Cy7, anti–CD27-APC, and anti–CD45RA-FITC for 30 min, washed, resuspended, and analyzed/sorted by flow cytometry.

Single-Cell Multiplex RT-PCR. Single tetramer$^+$CD8$^+$CD4$^-$CD14$^-$CD19$^-$ cells were sorted using a FACSAria (BD Biosciences) into 96-well plates. CDR3$\alpha\beta$ regions were determined using a single-cell multiplex RT-PCR (28, 29). Sequences were analyzed with FinchTV, and V/J regions were identified by IMGT.

Intracellular Cytokine Staining (ICS). PBMCs were stimulated with peptides for 10 d, and IAV-specific CTLs were quantified using IFN-γ/TNF-α ICS (12, 33). C1R-A*0201 cells, HLA-B*0702$^+$ PBMCs, or C1R-B*3501 cells were used to present antigen. Mouse spleen and bronchoalveolar lavage (BAL) cells were stimulated with $M1_{58}$ (GILGFVFTL), PA_{46} (FMYSDFHFI), or NS_{122} (AIMDKKIIL) for 5 h (17).

HLA-A2.1 Transgenic HHD Mice and de Novo IAV Epitope Mutations. HLA-A2.1 transgenic HHD mice were developed by François Lemonnier (37) and provided by the Pasteur Institute. Experiments were approved by the University of Melbourne Animal Ethics Experimentation Committee. Mice were lightly anesthetized and infected with 10^3 pfu HK (H3N2) virus intranasally. Viral RNA was extracted from lungs 15 d after infection and reverse transcribed to cDNA (17). The M1 region was amplified and sequenced.

Recombinant Influenza Viruses. Influenza viruses with amino acid substitutions in the $M1_{58}$ peptide (M1-I2M, M1-F5L, M1-V6I, and M1-F7Y) were generated using reverse genetics and amplified in embryonated eggs (38).

Protein chemistry and structural biology are described in *SI Methods*.

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6.4.3 Clemens, Grant, Wang, Gras, Tipping, Rossjohn, Miller, Tong and Kedzierska. Towards identification of immune and genetic correlates of severe influenza disease in Indigenous Australians.

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ORIGINAL ARTICLE

Towards identification of immune and genetic correlates of severe influenza disease in Indigenous Australians

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Indigenous populations, including Indigenous Australians, are highly susceptible to severe influenza disease and the underlying mechanisms are unknown. We studied immune and genetic factors that could predicate severe influenza disease in Indigenous Australians enrolled in the LIFT study: looking into influenza T-cell immunity. To examine CD8$^+$ T-cell immunity, we characterised human leukocyte antigen (HLA) profiles. HLA typing confirmed previous studies showing predominant usage of HLA-A*02:01, 11:01, 24:02, 34:01 and HLA-B*13:01, 15:21, 40:01/02, 56:01/02 in Indigenous Australians. We identified two new HLA alleles (HLA-A*02:new and HLA-B*56:new). Modelling suggests that variations within HLA-A*02:new (but not HLA-B56:new) could affect peptide binding. There is a relative lack of known influenza epitopes for the majority of these HLAs, with the exception of a universal HLA-A*02:01-M1$_{58}$ epitope and proposed epitopes presented by HLA-A*11:01/HLA-A*24:02. To dissect universal CD8$^+$ T-cell responses, we analysed the magnitude, function and T-cell receptor (TCR) clonality of HLA-A*02:01-M1$_{58}$$^+$CD8$^+$ T cells. We found comparable IFN-γ, TNF and CD107a and TCRαβ characteristics in Indigenous and non-Indigenous Australians, suggesting that the ~15% of Indigenous people that express HLA-A*02:01 have universal influenza-specific CD8$^+$ T-cell immunity. Furthermore, the frequency of an influenza host risk factor, IFITM3-C/C, was comparable between Indigenous Australians and Europeans, suggesting that expression of this allele does not explain increased disease severity at a population level. Our study indicates a need to identify novel influenza-specific CD8$^+$ T-cell epitopes restricted by HLA-A and HLA-B alleles prevalent in Indigenous populations for the rational design of universal T-cell vaccines.
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Indigenous populations are at substantially higher risk of hospitalisation and morbidity from influenza infection. Up to 10–20% of Indigenous Australians died from pandemic influenza in 1919 compared with <1% of non-Indigenous Australians.[1] Similarly, although Indigenous Australians comprise 2.5% of the Australian population, they accounted for 16% of patients hospitalised with pandemic (p) H1N1 and 9.7% of those admitted to ICU.[2] Studies from the Northern Territory, Queensland and Western Australia have found that Indigenous Australians are 3–12 times more likely to be hospitalised than non-Indigenous Australians. Similar patterns have been observed in Indigenous populations from New Zealand, Canada and the United States.[3–5] Such greater risk of hospitalisation could reflect higher infection rates due to crowded living conditions, and also increased rates of chronic disease and comorbidities that lead to more severe outcome. In this setting, pre-emptive vaccination is clearly of significant benefit. However, prior administration of the currently available vaccines confers no protection against newly emerged unpredicted influenza viruses. Ultimately, the capacity to clear influenza virus and recover depends on the immune status of the individual.

Immune factors and host genetics can lead to increased severity of influenza disease in some ethnicities. This is exemplified by the expression of an interferon-induced transmembrane protein 3 (IFITM3) single-nucleotide polymorphism (SNP) rs12252, with the IFITM3 rs12252-C/C genotype (versus C/T or T/T) being predictive of early hypercytokinemia and severe influenza-induced disease.

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The IFITM3 C/C genotype is highly prevalent in the Asian population and correlates with severe pH1N1 and H7N9 disease.[6,7] The prevalence of the IFITM3-C/C genotype in Indigenous Australians has not yet been documented.

Differences in influenza-specific T-cell immunity, especially the protective $CD8^+$ T-cell responses,[8–10] can be affected by distinct human leukocyte antigen (HLA) profiles (HLA restriction) found across different ethnicities.[11] Our recent work showed that Indigenous populations, including Indigenous Australians and Alaskans, are at greater risk from severe influenza disease caused by newly emerged influenza viruses due to a lack of $CD8^+$ T cells directed at universal influenza epitopes.[11] Thus, prolonged and more severe influenza infection in the Indigenous population might reflect differences in $CD8^+$ T-cell immunity associated with specific HLA profiles expressed. Indeed, the computational data suggest a strong correlation between pH1N1 influenza-induced mortality and the expression of HLA-A24,[12] an allele highly prevalent in Indigenous Australians and Alaskans.[13] Previous studies also suggest that some HLA molecules of Indigenous Australians differ from those that predominate in non-Indigenous Australians.[14–16] Thus, HLAs expressed in Indigenous populations may bind different viral peptides and induce distinct $CD8^+$ T-cell responses in comparison with non-Indigenous individuals. To date, there are no data on influenza-specific $CD8^+$ T-cell responses, in the context of HLA restriction, in Indigenous Australians. Given the recent emergence of new influenza viruses capable of infecting humans (H7N9, H6N5 and H10N8), there is an urgent need to understand the immune correlates, and especially the effectiveness of $CD8^+$ T-cell immunity within the vulnerable Indigenous communities.

Here we studied influenza-specific $CD8^+$ T-cells epitopes in a cohort of Indigenous Australians enrolled in the LIFT study: looking into influenza T-cell immunity. Our HLA analysis verified previous reports of predominant usage of HLA-A*02:01, 11:01, 24:02, 34:01 and HLA-B*13:01, 15:21, 40:01/02, 56:01/02 in Indigenous Australians, and identified new HLA-A*02 and HLA-B*56 alleles. We showed a relative lack of known epitopes for these highly represented HLAs and analysed the magnitude, quality and clonality of $CD8^+$ T cells directed at a universal HLA-A*02:01-$M1_{58}$ epitope. We found comparable characteristics of HLA-A*02:01-$M1_{58}$$^+$$CD8^+$ T cells in Indigenous and non-Indigenous Australians. Further, we determined low population frequency of IFITM3-C/C alleles in Indigenous Australians. We propose that identification of novel immunodominant influenza-specific $CD8^+$ T cell epitopes restricted by HLA alleles prevalent in the Indigenous populations should be a priority for the rational design of new influenza vaccine strategies.

RESULTS

'Looking into inFluenza T cell immunity' (LIFT) cohort

We recruited 82 Australian Indigenous donors (LIFT01-LIFT083; Supplementary Table S1) in Darwin, Northern Territory, Australia. Participants included Indigenous patients at the Royal Darwin Hospital admitted with non-influenza related diagnoses and healthy volunteers in the Darwin region. The study was explained to potential

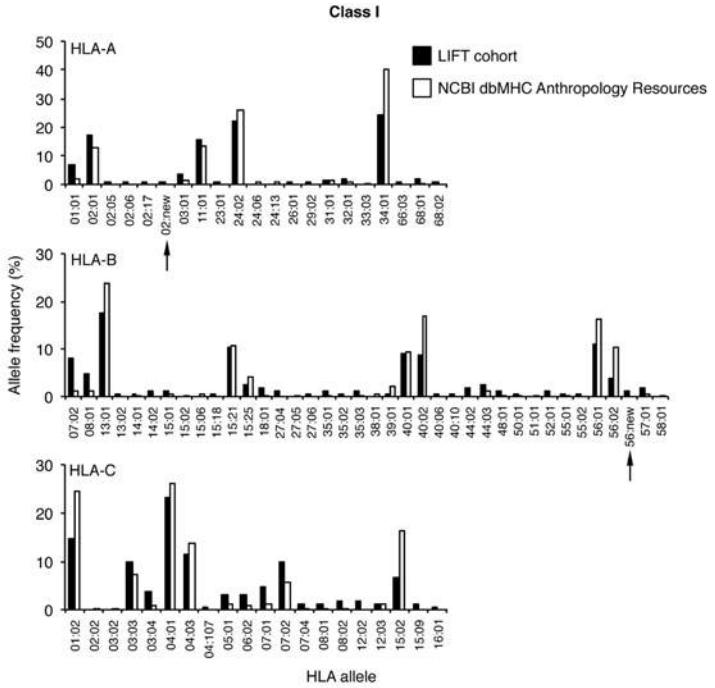

Figure 1 HLA class I allele expression in Indigenous Australians from the Top End. DNA typing of HLA-A, -B and -C alleles was performed for 82 Indigenous Australian individuals from the Top End of the Northern Territory in Australia (LIFT cohort; $2n=164$). The range and frequency of HLA class I allele expression are shown compared against previous studies of HLA class I expression in Indigenous Australians obtained from NCBI dbMHC Anthropology Resources (available online at www.ncbi.nlm.nih.gov/gv/mhc/ihwg.cgi?cmd=page&page=AnthroMain) (HLA-A, $2n=810$; HLA-B, $2n=812$; HLA-C, $2n=764$). The sample size was $2n$ as each individual donor contributed two separate alleles to the analysis.

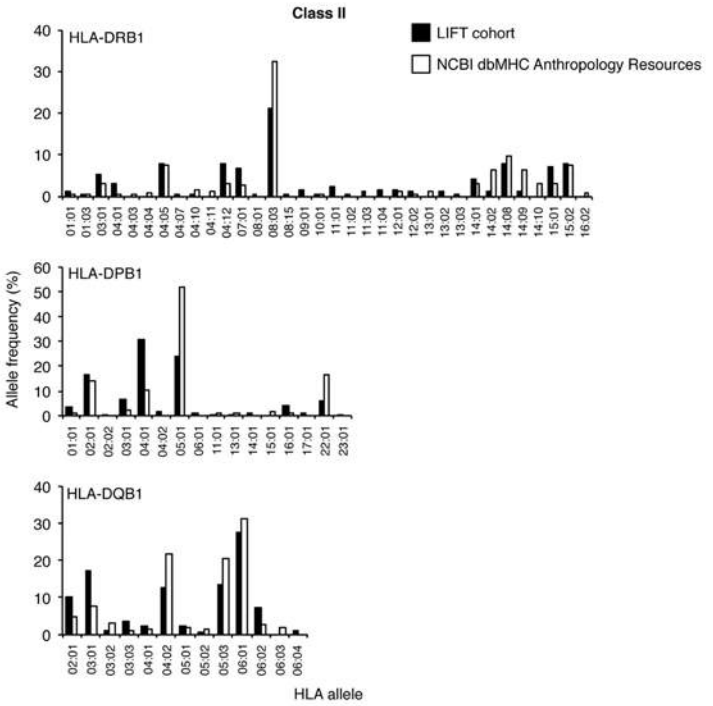

Figure 2 HLA class II allele expression in Indigenous Australians from the Top End. DNA typing of HLA-DRB1, -DPB1 and -DQB1 was performed for Indigenous Australian individuals (LIFT cohort; $2n=164$). Allele expression is shown as described in Figure 1. Data from NCBI dbMHC Anthropology Resources represent: HLA-DRB1, $2n=280$; HLA-DPB1, $2n=268$; HLA-DQB1, $2n=280$.

participants by Indigenous research staff with the use of culturally appropriate flipcharts and all participants provided written informed consent. The study was approved by the Human Research Ethics Committee (HREC) of the Northern Territory Department of Health and Menzies School of Health Research, and included review by the Aboriginal Ethics Sub-committee of the HREC. The median age of participants was 45 years (interquartile range 30, 55) and 42 (52%) were male.

Restricted HLA allele expression in Indigenous Australians from the Top End

Our analysis of 82 LIFT donors showed that HLA allele expression in Top End Indigenous Australians is relatively restricted for both HLA class I (Figure 1) and HLA class II (Figure 2). LIFT donors expressed a more restricted range of HLA alleles compared with Australian Caucasians . The four main HLA-A alleles in LIFT Indigenous donors (HLA-A*02:01, 11:01, 24:02 and 34:01) accounted for 79% of HLA-A alleles, whereas the four main HLA-B alleles (HLA-B*13:01, 15:21, 40:01/02, 56:01/02) accounted for 47% of HLA-B alleles (Figure 1). The main HLA-C alleles were HLA-C*01:02, 04:01/02, 07:02 and 15:02.

Similarly, expression of HLA class II alleles was largely limited (Figure 2). The most dominant HLAs were HLA-DRB1*06:03, HLA-DPB*102:01, 04:01, 05:01 and HLA-DQB1*03:01, 04:02, 05:03 and 06:01. Our data are in accordance with previous reports.[17] Overall, HLA distribution in our LIFT cohort was similar to those found in previous Indigenous cohorts from Cape York, Groote Eylandt, Kimberley and Yuendumu regions (NCBI dbMHC Anthropology Resources; Supplementary Table S2). Thus, there appears to be a HLA conservation between geographically distinct Indigenous groups that were unlikely to have had extensive interaction.

New HLA-A*02 and HLA-B*56 alleles in Indigenous Australians

Molecular sequencing of donors LIFT026 and LIFT053 identified two new HLA alleles thus far unique to Indigenous Australians. In LIFT053, the new HLA-A*02 allele differed from HLA-A*02:35:01 at four nucleotide positions affecting three codons. The first nucleotide substitution occurs at codon 62 (GGG to CGG) and results in an amino-acid (aa) change of glycine to arginine. The second and third nucleotide substitutions at codon 63 (GAG to AAC) result in an aa change from glutamic acid to asparagine. A change in a nucleotide at codon 90 (GCC to GAC) results in an aa change from alanine to aspartic acid. Sequencing was verified on two occasions by the analysis of two independent samples. Position 90 is located in one of the loops outside the antigen-binding cleft of the HLA molecule, and therefore is unlikely to change the bound peptide repertoire of the new HLA-A*02 allele. On the other hand, positions 62 and 63 are located within the antigen binding cleft (Figure 3a), with position 62 exposed to the solvent and readily available for TCR contact, whereas position 63 is buried within the cleft and likely interacts with the residue at position 1 of the peptide. The larger arginine 62 of the new HLA-A*02 allele (Figure 3b) will most likely affect TCR interaction. In the HLA-A*02:35:01 molecule, Glu 63 makes a hydrogen bond with the main chain of the first residue of the peptide, stabilizing the bound

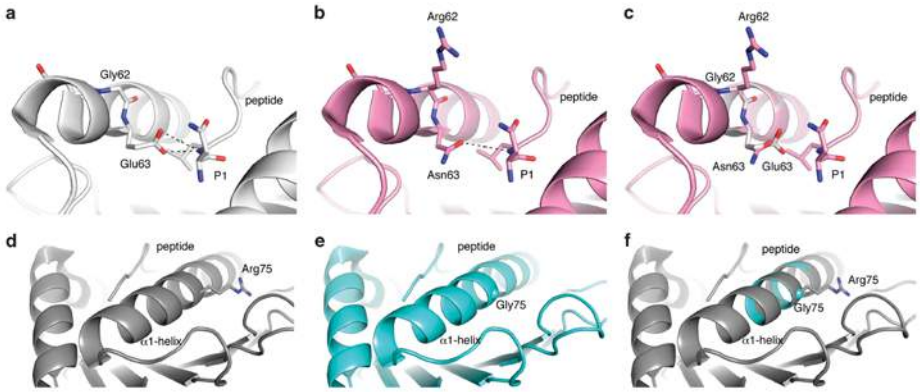

Figure 3 Modelling of new HLA class I alleles identified in Top End Indigenous Australians. The top panels show (**a**) the HLA-A*02:01 cleft, (**b**) HLA-A*02:new and (**c**) a superposition of both HLAs. The HLA cleft is represented in cartoon and the key residues as stick, coloured in white for HLA-A*02:01 and pink for HLA-A*02:new. The dashed lines represent the interaction between the HLA residue 63 and the peptide residue 1. The bottom panels represent the (**d**) HLA-B*56:01 in grey, (**e**) HLA-B*56:new in cyan and (**f**) a superposition of both HLAs. The sphere represents the Cα atom of the glycine 75.

peptide. In the new HLA-A*02 allele, the Glu 63 is replaced by an Asn 63, which might not be as suited to strongly bind position 1 of the peptide owing to a smaller side chain (Figure 3c). The change at position 63 might potentially impact on peptide binding and change the peptide repertoire of the HLA-A*02:new compared with that of the HLA-A*02:35:01 molecule. Further studies will determine the peptide repertoire presented by this new HLA-A02 allele and test their immunogenicity.

HLA-B*56:new was identified in donor LIFT026. This new allele differs from B*56:01:01G or B*56:02 at codon 75 (CGA to GGA) and results in an aa change from arginine to glycine. The Arg75 of HLA-B*56:01 is located on the α1-helix of the cleft (Figure 3d), outside the cleft and therefore the change to glycine (Figure 3e) should not impact T-cell recognition. The HLA residue 75 does not contact the bound peptide, and the substitution from arginine to glycine (Figure 3f) is unlikely to impact the peptide repertoire. Therefore, the HLA-B*56:new and HLA-B*56:01 alleles are likely to bind the same peptide repertoire.

Dissection of influenza epitopes restricted by HLA-A and HLA-B alleles prevalent in Indigenous Australians

To understand the breadth of potential $CD8^+$ T-cell epitopes restricted by HLAs expressed in Indigenous Australians, we analysed epitopes corresponding to the immunogenic influenza proteins: nucleoprotein (NP), matrix 1 (M1) and polymerase basic 1 (PB1),[18] as outlined in the Immune Epitope Database (www.immuneepitope.org). We found that influenza-specific $CD8^+$ T-cell epitopes were previously proposed for four HLAs common to non-indigenous populations and identified within our LIFT cohort, including HLA-A*02:01 (40 epitopes), HLA-A*11:01 (20 epitopes), HLA-A*24:02 (10 epitopes) and HLA-B*40:02 (5 epitopes; Table 1). In contrast, no influenza-specific epitopes have been identified for the remaining HLAs (HLA-A*02:new, HLA-A*15:25, HLA-A*34:01, HLA-B*13:01, HLA-B*15:21, HLA-B*40:02, HLA-B*56:01, HLA-B*56:02, HLA-B*56:new) prominent in our LIFT cohort or described as distinct to Indigenous Australians (Table 1). Thus, no influenza-specific $CD8^+$ T-cell epitopes have been yet proposed for 71% of class I HLA alleles identified in Indigenous Australians. This suggests a need to identify prominent influenza epitopes restricted by HLAs associated with Indigenous populations in order to accurately determine the extent of $CD8^+$ T-cell immunity in this population. Furthermore, our findings suggest that the immunodominant epitopes in Indigenous Australians are likely to differ from dominant $CD8^+$ T-cell specificities in Caucasian populations.

Universal $CD8^+$ T-cell immunity directed at the universal HLA-A*02:01-restricted $M1_{58-66}$ epitope

To the best of our knowledge, there are currently no data published on influenza-specific $CD8^+$ T-cell responses in the Indigenous Australian population. It is, however, well documented that HLA-A*02:01-positive individuals generate prominent $CD8^+$ T-cell responses towards the viral $M1_{58-66}$ peptide, highly conserved amongst distinct influenza strains and subtypes.[11,19] To understand how robust and functional $M1_{58}{}^+CD8^+$ T cells are in the ~15% of Indigenous donors who express HLA-A*02:01, we analysed peripheral blood mononuclear cells (PBMCs) from HLA-A*02:01-positive LIFT donors stimulated with the $M1_{58}$ peptide, a method used routinely to amplify influenza-specific memory $CD8^+$ T cells.[20,21] $M1_{58}{}^+CD8^+$ T-cell numbers and their functional capacities were assessed on d10 after the *in vitro* stimulation. Analysis of 7 LIFT individuals of various ages revealed the presence of prominent $M1_{58}{}^+CD8^+$ T-cell responses in 6 HLA-A*02:01 donors (LIFT07, LIFT09, LIFT011, LIFT022, LIFT027, and LIFT029), but not LIFT03, who expressed HLA-A*02:05 (rather than HLA-A*02:01) positive (Figure 4a). Staining with the A2-$M1_{58}$ tetramer showed robust expansion of influenza-specific $CD8^+$ T cells on d10 after *in vitro* stimulation (mean of 4.2% of $CD8^+$ T cells; range 1.23–9.48%).

We next determined the qualitative characteristics of $M1_{58}{}^+CD8^+$ T cells in the LIFT cohort. As high-quality $CD8^+$ T cells simultaneously produce multiple cytokines and display killing capacity, we assessed the production of interferon (IFN)-γ and tumour necrosis factor (TNF) together with CD107a degranulation following short-term stimulation (5 h) with the $M1_{58}$ peptide and detection by

Table 1 Influenza epitopes presented by HLA-A and -B alleles that are highly prevalent and/or display an ethnic association with Indigenous Australians

Allele	*Frequency (LIFT cohort/ NCBI database)*	*Number of Influenza epitopes identified*[a]
Highly prevalent:[b]		
A*02:01	17%/13%	40
A*11:01	16%/14%	21
A*24:02	22%/26%	10
A*34:01	24%/40%	0
B*13:01	18%/24%	0
B*15:21	10%/11%	0
B*40:02	8%/17%	5
B*56:01	11%/16%	0
B*56:02	4%/10%	0
Ethnic association:[c]		
A*02:new	1%/0%	0
A*24:06	0%/1%	0
A*24:13	0%/1%	0
B*15:25	2%/4%	0
B*56:new	1%/0%	0

Abbreviation: LIFT, looking into influenza T-cell immunity.
[a]Number of different Influenza epitopes defined in the Immune Epitope Database and Analysis Resource (available online at http://www.iedb.org/home_v2.php).
[b]Frequency ⩾ 10% within the LIFT cohort or NCBI database (for Indigenous Australians).
[c]Alleles that are unique to Indigenous Australians or particularly associated with this ethnic group (according to the IPD IMGT/HLA Database available online at http://www.ebi.ac.uk/ipd/imgt/hla/).

an intracellular cytokine secretion (ICS) assay. Our data showed that $M1_{58}^{+}CD8^{+}$ T cells in the LIFT cohort were polyfunctional and 56.68% ± 16.3% produced both INF-γ and TNF (Figure 4b). A high proportion of those cells (66.8% ± 18.3%, representing 40.1 ± 15.7% of all $M1_{58}^{+}CD8^{+}$ T cells) also expressed CD107a (Figure 4c).

Clonal characteristics of the universal $CD8^{+}$ T cells directed at HLA-A*0201-restricted $M1_{58-66}$ epitope

TCR usage has an important role in determining the quality of the $CD8^{+}$ T-cell response to viruses and the outcome of infection.[22–25] Previous analyses of $M1_{58}^{+}CD8^{+}$ T cells, using mainly T-cell clones, have described the $M1_{58}$-specific TCR repertoire as highly conserved[26,27] and identified clones shared across different HLA-A*02:01^{+} individuals. Using *in vitro* cultures of three Indigenous and three non-indigenous donors, we dissected the TCRαβ repertoire utilised by $M1_{58}^{+}CD8^{+}$ T cells using a novel single-cell multiplex PCR for simultaneous amplification of the TCRα and TCRβ chains (Figure 5).[21,28] The repertoires were compared in terms of TCRαβ gene segment usage, CDR3αβ loop characteristics (important for the peptide-HLA specificity) and clonal diversity.

Similar to previous reports and our non-indigenous donors (Figures 5c and d), HLA-A*02:01-restricted $M1_{58}^{+}CD8^{+}$ T cells isolated from our LIFT cohort were characterised by a strong bias for *TRBV19* gene segment in TCRβ chain (frequency of 94.49 ± 2.11%) and a bias for TRAV27 in the TCRα chain (39.55 ± 11.30%, Figures 5a and b, Table 2). As seen in non-indigenous donors, individuals in the LIFT cohort also displayed

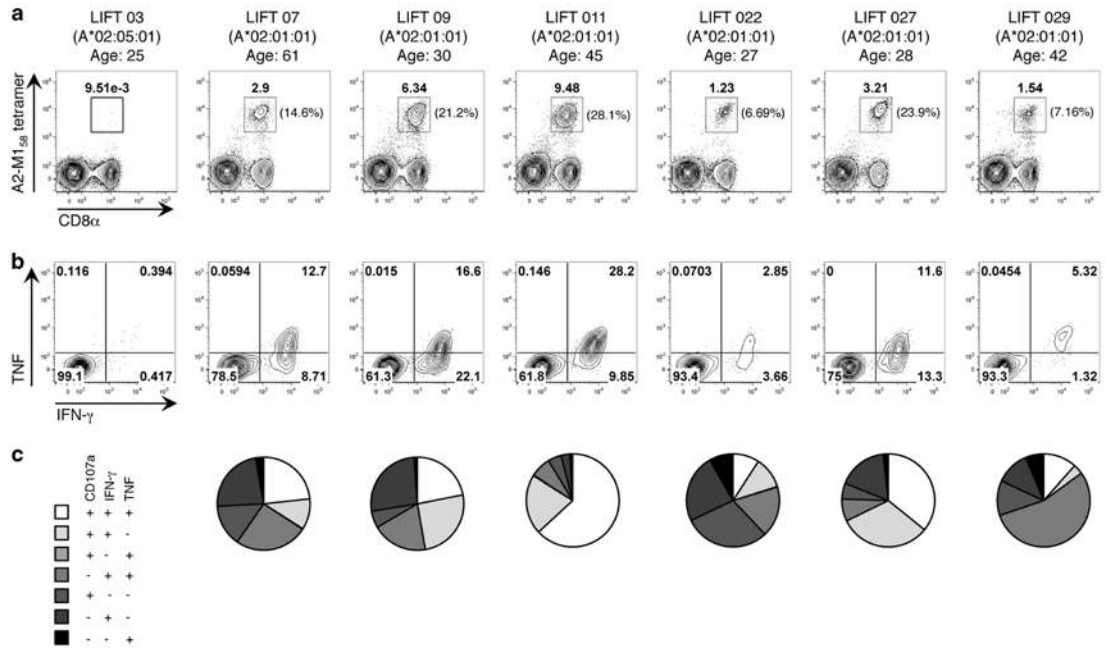

Figure 4 Establishment of robust A2-$M1_{58}$-specific $CD8^{+}$ T-cell responses in A*02^{+} Indigenous Australians. A2-$M1_{58}$-specific $CD8^{+}$ T-cell lines were generated by pulsing PBMCs from A*02^{+} donors with $M1_{58-66}$ peptide for 10 days in the presence of rIL-2. Plots (**a**) show A2-$M1_{58}$ tetramer-PE and anti-CD8-PerCPCy5.5 staining of $CD3^{+}$ T cells. Values in parenthesis indicate the proportion of $CD8^{+}$ T cells that bound A2-$M1_{58}$ tetramer. The function of A2-$M1_{58}$-specific $CD8^{+}$ T cells was assessed following peptide stimulation in an ICS assay examining expression of IFN-γ, TNF and CD107a (**b, c**). Plots (**b**) show anti-IFN-γ-V450 and anti-TNF-APC staining of $CD3^{+}CD8^{+}$ T cells. The polyfunctional profile of $M1_{58}$-specific $CD8^{+}$ T cells is compared in **c**.

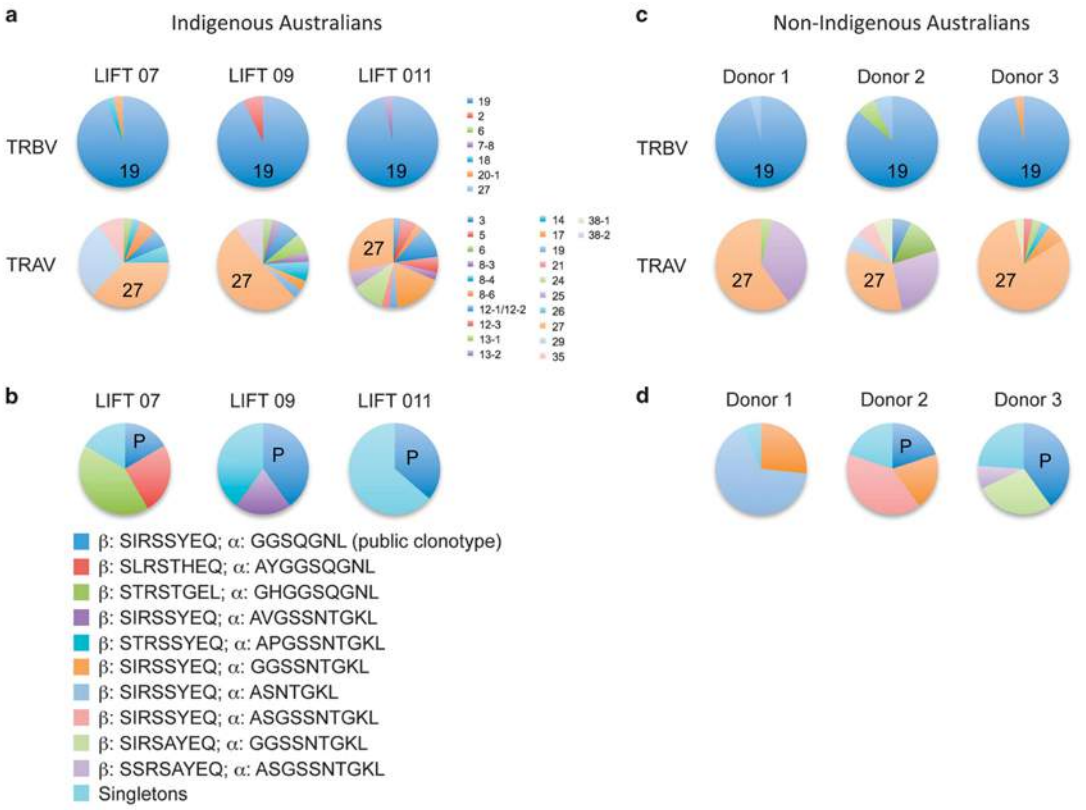

Figure 5 A2-M1$_{58}$-specific CD8$^+$ T cells from Indigenous Australians display characteristic TCRαβ repertoire usage. Single A2-M1$_{58}$-specific CD8$^+$ T cells from (**a, b**) three representative Indigenous and (**c, d**) three representative non-Indigenous donors were sorted from day 10–19 *in vitro* cultures for analysis of the TCRαβ repertoire using a multiplex PCR and sequencing protocol. (**a, c**) *TRBV* and *TRAV* gene usage was compared across donors and (**b, d**) clonotype usage with the prominent BV19/AV27$^+$ subset was further dissected to reveal common usage of a well-defined public A2-M1$_{58}$-specific TCRαβ clonotype.

a preference for TRBJ2-7 segment within the TCRβ chain (41.96 ± 18.14% of clones) and TRAJ42 within the TCRα chain (54.53 ± 12.59% of clones). The predominant length of the complementarity-determining region 3 of TCRβ chain (CDR3β loop), generally positioned over the centre of the antigenic peptide bound to HLA class I was of 8 aa (80.21 ± 9.02% of clones).

Analysis of specific CDR3β and CDR3α sequences showed that SIRSSYEQ and GGSQGNL were the most common signatures within the TCRβ–TRBV19 and TCRα–TRAV27, respectively, in accord with previous reports. Conversely, LIFT donors displayed a preference for CDR3α lengths of 7 aa (28.97 ± 14.76% of clones), 9 aa (19.04 ± 8.33% of clones) and 10 aa (19.99 ± 9.27% of clones) in comparison to non-indigenous individuals, which preferentially selected CDR3α loops of 9 aa in length (41.75 ± 17.24 of clones), followed by 7 aa (28.46 ± 18.88 of clones) and 10 aa (23.20 ± 16.63 of clones).

Interestingly, there was a trend towards a higher level of TCR diversity in Indigenous donors as compared with non-indigenous donors, shown by an increased number of unique CDR3α (18.33 ± 2.31 versus 10.33 ± 4.73 clonotypes) and CDR3β clones (15.67 ± 2.52 versus 8 ± 2.65 clonotypes) and CDR3αβ pairs (17.67 ± 4.04 versus 11.33 ± 4.62 pairs) per donor. However, these trends were not significant ($P > 0.05$ by a Mann–Whitney test and a non-parametric *t*-test), most likely owing to a limited number of donors.

Overall, our data from Indigenous LIFT donors suggest that in HLA-A*02:01-positive donors A2-M1$_{58}$-specific CD8$^+$ T cells are numerically, functionally and clonally comparable to those providing universal immunity to distinct influenza strains and subtypes in non-Indigenous populations.[11,19,29]

Similar pattern of Rs12252-IFITM3 distribution in Indigenous Australians and Europeans

Rs12252 in interferon-induced transmembrane protein 3 (IFITM3) can prevent endocytosed virus particles from entering the host cytoplasm and thus, to some extent, control the viral infection.[6] The SNP rs12252-C variant (C/C genotype), on the other hand, leads to a 21 aa truncation of IFITM3 and is associated with severe outcome of viral diseases, including influenza A virus, HCV and VSV infections.[6,7,30] High prevalence (30.1%) of rs12252-C/C in East Asia correlates with influenza disease severity[6,7] and indicates that East Asian populations historically experienced different infection disease patterns from European people who have an rs12252-C/C frequency of <1% (Figure 6). Thus, it was of importance to understand the patterns of SNP rs12252 in Indigenous Australians. Our analysis of rs12252 distribution patterns in Indigenous people showed similar patterns in Europeans and Indigenous people (Figure 6), suggesting that IFITM3-C/C genotype is an unlikely immune correlate for high

Table 2 A2-M1$_{58}$-specific TCR$_{\alpha}\beta$ repertoire of Indigenous and non-indigenous Australians

TRBV	*CDR3β*	*Aa length*	*TRBJ*	*TRAV*	*CDR3α*	*Aa length*	*TRAJ*	*Indigenous (%)*			*Non-indigenous (%)*		
								LIFT 7	*LIFT 9*	*LIFT 11*	*Donor 1*	*Donor 2*	*Donor 3*
19	**SIRSSYEQ**	**8**	**2-7**	**27**	**GGSQGNL**	**7**	**42**	**6.3**	**17.9**	**9.4**		**6.7**	**32.3**
19	SQRSTDTQ	8	2-3	17	DGGGGSQGNL	10	42			3.1			6.5
19	SIRSSYEQ	8	2-7	27	AGSQGNL	7	42			3.1			3.2
19	SIRSAYEQ	8	2-7	27	AVGSSNTGKL	10	37			3.1			3.2
19	SIRSSYEQ	8	2-7	27	GGSSNTGKL	9	37				16.0	6.7	
19	SMFGGAEA	8	1-1	35	PDRPNGGSQGNL	12	42	25					
19	STRSTGEL	8	2-2	27	GHGGSQGNL	9	42	15.6					
19	SLRSTHEQ	8	2-1	27	AYGGSQGNL	9	42	9.4					
19	SIGVYGY	7	1-2	38-1	MSSPGGTSYGKL	12	52	9					
19	SIRSSYEQ	8	2-7	8-6	GGSQGNL	7	42	6.3					
19	SIAGGAARPQ	10	1-5	26-2	RDGGSSNTGKL	11	37	6.3					
19	STRSGWEQ	8	2-1	27	AGSSNTGKL	9	37	3.1					
20	RGAPGPQ	7	1-5	6	HTTRDDKI	8	30	3.1					
18	SLVGGPGDEQ	10	2-1	8-4	ARL	3	31	3.1					
19	SSRSAYEQ	8	2-7	12-1	NIGGGSQGNL	10	42	3.1					
19	SIRSSYEQ	8	2-7	12-1	GGDGGSQGNL	10	42	3.1					
19	SSRSAYEQ	8	2-7	27	ALGSSNTGKL	10	37	3.1					
19	SITRNEQ	7	2-1	35	FFRDDKI	7	30	3.1					
19	SVRSSYEQ	8	2-7	27	GGSQGNL	7	42		14.3				
2	SDWDRVKGPDTQ	12	2-3	14	REDNQGGKL	9	23		7.1				
19	STRSSYEQ	8	2-7	27	APGSSNTGKL	10	37		7.1				
19	SIRSSYEQ	8	2-7	27	AVGSSNTGKL	10	37		7.1				
19	SIGTYGY	7	1-2	38-2	SVNAGGTSYGKL	12	52		7.1				
19	SIRAADTQ	8	2-3	6	DMGGGSQGNL	10	42		3.6				
19	STRSGVEQ	8	2-7	8-3	GGSQGNL	7	42		3.6				
19	SMRSSYEQ	8	2-7	12-2	NDQGGKL	7	23		3.6				
19	SMAINEQ	7	2-1	12-2	SVSKTSYDKV	10	50		3.6				
				17	SRGEGAQKL	9	54						
19	SGRSGETQ	8	2-5	13-1	QNQGGKL	7	23		3.6				
19	STRSLEPQ	8	1-5	13-1	TYNQGGKL	8	23		3.6				
19	SQRSSYEQ	8	2-7	13-2	NGGGSTLGRL	10	18		3.6				
19	SIHSGSNNEQ	10	2-1	19	VGGSYIP	7	6		3.6				
19	SIRSDYTL	8	1-6	27	AGGGSQGNL	9	42		3.6				
19	SLRSDGEL	8	2-2	27	ASGGSQGNL	9	42		3.6				
19	SIGLYGY	7	1-2	38-2	ATNAGGTSYGKL	12	52		3.6				
19	SGLSNQPQ	8	1-5	24	YGGSNYQL	8	33			12.5			
19	SLRSDYEQ	8	2-7	12-2	SSNTGKL	7	37			9.4			
19	SIRAGTEA	8	1-1	12-3	SGDGGSQGNL	10	42			6.3			
19	SIRSGVEQ	8	2-7	5	SIGRGSQGNL	10	42			6.3			
19	SVYSNQPQ	8	1-5	17	DEYGNYGGSQGNL	13	42			6.3			
19	SSRSSYEQ	8	2-7	8-6	SSNTGKL	7	37			3.1			
19	SSRSAYEQ	8	2-7	12-2	GGSQGNL	7	42			3.1			
19	GPLSTDTQ	8	2-3	3	RDGTGANNL	9	36			3.1			
19	STRSTGEL	8	2-2	25	SGGGSQGNL	9	42			3.1			

Table 2 (Continued)

TRBV	*CDR3β*	*Aa length*	*TRBJ*	*TRAV*	*CDR3α*	*Aa length*	*TRAJ*	*Indigenous (%)*			*Non-indigenous (%)*		
								LIFT 7	*LIFT 9*	*LIFT 11*	*Donor 1*	*Donor 2*	*Donor 3*
19	SIRSSYEQ	8	2-7	27	PGSNTGKL	8	37			3.1			
7-8	SLVWWGADSNQPQ	13	1-5	13-2	INSGNTPL	8	29			3.1			
				17	RENQGGKL	8	23						
19	SMRSTDTQ	8	2-3	17	DGGGGSQGNL	10	42			3.1			
19	SPFGGGPNEQ	10	2-1	17	DAWGYGGSQGNL	12	42			3.1			
19	SRRSTDTQ	8	2-3	21	L	1	20			3.1			
				25	SGGGSQGNL	9	42						
19	SIRSAYEQ	8	2-7	27	GSSNTGKL	8	37			3.1			
19	SARSADTQ	8	2-3	27	AGGGSQGNL	9	42			3.1			
19	SVRSSYEQ	8	2-7	27	AVGSSNTGKL	10	37			3.1			
19	SILTGPRTEA	10	1-1	27	APRTSGTYKY	10	40			3.1			
19	SIRSSYEQ	8	2-7	27	ASNTGKL	7	37				40.0		
19	SGRSTDTQ	8	2-3	25	TYGGSQGNL	9	42				32.0		
19	SVRSQETQ	8	2-5	13-1	SGGGSQGNL	9	42				4.0		
27	SLYGPMSTGEL	11	2-2	25	TYGGSQGNL	9	42				4.0		
19	SIRSAYEQ	8	2-7	27	THGSSNTGKL	10	37				4.0		
19	SIRSSYEQ	8	2-7	27	ASGSSNTGKL	10	37					13.3	
19	SGTAVEKL	8	1-4	3	RDGTGANNL	9	36					6.7	
19	SRRSTDTQ	8	2-3	6	DIGGGSQGNL	10	42					6.7	
19	SIFGSSGNTI	10	1-3	6	DNTNAGKS	8	27					6.7	
19	SARSTDTQ	8	2-3	25	NYGGSQGNL	9	42					6.7	
19	STRSTDTQ	8	2-3	25	SSGGSQGNL	9	42					6.7	
19	STRSTDTQ	8	2-3	25	VGGGSQGNL	9	42					6.7	
19	SLRSTDTQ	8	2-3	25	SYGGSQGNL	9	42					6.7	
19	SIRSSYEQ	8	2-7	27	GGHGGSQGNL	10	42					6.7	
6	SYSAAAGTSLDIQ	13	2-4	29	SDPNQGGKL	9	23					6.7	
27	SLIFPSGEQ	9	2-7	35	PDGSSNTGKL	10	37					6.7	
19	SIGSYGY	7	1-2	38-1	MNDAGGTSYGKL	12	52					6.7	
19	SIRSAYEQ	8	2-7	27	GGSSNTGKL	9	37						22.6
19	SSRSAYEQ	8	2-7	27	ASGSSNTGKL	10	37						6.5
19	SVRSSYEQ	8	2-7	27	SGSQGNL	7	42						3.2
19	SIRSAYEQ	8	2-7	27	ASGSSNTGKL	10	37						3.2
19	SIRSSYEQ	8	2-7	27	AIGSSNTGKL	10	37						3.2
19	SVRSSYEQ	8	2-7	27	AIGSSNTGKL	10	37						3.2
20-1	RTSGDFGEQ	9	2-1	13-1	RGYGGATNKL	10	32						3.2
19	STRSTDTQ	8	2-3	12-3	TGDGGSQGNL	10	42						3.2
19	SIYGNTEA	8	1-1	14	REDPGGTSYGKL	12	52						3.2
19	SIGVYGY	7	1-2	38-1	MIGAGGTSYGKL	12	52						3.2
					Total number of sequences	32	28	32	25	15	31		

Abbreviations: Aa, amino acid; LIFT, looking into influenza T-cell immunity.
A2-M1$_{58}$ tetramer-binding CD8$^+$ T cells were single-cell sorted. Populations were gated as viable Dump$^-$CD3$^+$CD8$^+$A2-M1$_{58}$ tetramer$^+$ cells. Paired amino-acid CDR3αβ diversity analysis was performed for non-Indigenous donors ($n=3$) and Australian Indigenous LIFT donors ($n=3$). Data show *TRBV* and *TRAV* gene usage and the frequency of CDR3α–CDR3β clonotypes. The abundance of particular CDR3β/CDR3α clonotypes with the prominent BV19$^+$ population is given in bold. TCRαβ repertoires were performed using a TCRαβ multiplex protocol.

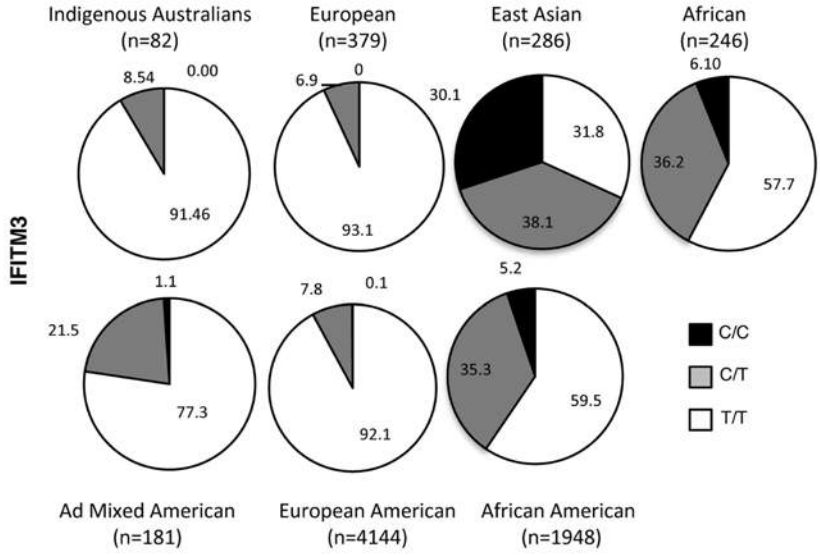

Figure 6 Expression of IFITM3 genotype associated with increased influenza disease severity across different ethnicities. Sequencing of the exon 1 region of IFITM3 containing rs12252 was performed for Indigenous Australians to determine allele frequencies of the SNP rs12252-C variant (in contrast to the WT rs12252-T variant) associated with increased influenza disease severity. Occurrence of the C/C, T/C and T/T genotypes was determined for this study population and compared with data for other ethnicities obtained from the 1000 genomes project (available on line at www.1000genomes.org).

influenza disease severity in Indigenous Australians. Furthermore, it is interesting that while our HLA results (Figures 1–3) showed that Indigenous people share some similarity in HLA patterns with Asian populations, which suggests an ancestral link, the IFITM3 genotypes (Figure 6) are distinct. Considering that African Americans (AFR_AMR, 5.2%, C/C) have similar rs12252-C/C patterns to their ancestor Africans (AFR, 6.1%, C/C), it seems that mixing of AFR and European populations in America two centuries ago did not impose significant changes in rs12252-C/C distribution. Perhaps distinct disease burdens have selectively shaped rs12252-C/C distribution in Asian and Indigenous Australian populations, whereas similar HLA patterns have been retained.

DISCUSSION

Indigenous populations, including Indigenous Australians and Alaskans, are at high risk of severe influenza disease.[11] In the case of an emergence of a new influenza viral strain, including avian-derived influenza viruses such as A/H7N9,[9] $CD8^+$ T cells can have an important role in host recovery. However, pre-existing influenza-specific $CD8^+$ T-cell responses recognising distinct influenza strains and subtypes vary greatly across ethnicities[11] and HLA profiles. We found that while ~15% of Indigenous Australians (HLA-A*02:01-positive) would have robust universal $CD8^+$ T-cell pools, epitopes associated with other HLA types prominent in Indigenous people are unknown.

Our analysis of the LIFT cohort found that Indigenous Australians display a restricted and distinct HLA profile in accordance with previously published serological studies.[14–16] Our molecular HLA typing verified the predominant usage of HLA-A*02:01, 11:01, 24:02, 34:01 and HLA-B*13:01, 15:21, 40:01/02, 56:01/02. Such restriction in HLA diversity and HLA usage is likely to have arisen from an evolutionary bottleneck that established a small ancestral pool with limited HLA diversity. As diversity of HLA alleles evolves rapidly, it is intriguing that there is a high degree of conservation in Indigenous Australians. This could be partly explained by limited mixing with other populations, long-term adaptation to local pathogens, and minimal exposure to new pathogens that might drive selection and/or emergence of new variants. Limited or no exposure to influenza prior to European contact in the eighteenth century may explain a low prevalence of protective HLA variants for influenza.

In addition, we identified two new HLA alleles, HLA-A*02:new and HLA-B*56:new, in 2 out of 82 LIFT donors. The aa changes in HLA-A*02:new could potentially impact the repertoire of bound epitopes. In HLA-A*02:01, Glu 63 is buried in the cleft and likely interacts with the first residue of the peptide via a network of hydrogen bonds. Asn 63 of the HLA-A*02:new appears to be too short to form the same network and may contact the peptide residue 1 via hydrophobic interaction only. Potentially, the HLA-A*02:new might not be able to bind, or not as stably, the $M1_{58}$ epitope compared with the HLA-A*02:01 molecule.

Establishment of robust HLA-A*02:01-$M1_{58}$-specific $CD8^+$ T-cell responses with a typical magnitude, function and TCR$\alpha\beta$ repertoire structure in HLA-A*02:01-positive Indigenous Australians suggests that at least ~15% of Indigenous Australians would have cross-strain protective $CD8^+$ T-cell immunity. Once established, $M1_{58}{}^+CD8^+$ T cells can recognise any influenza strain and subtype owing to the high level of conservation of this epitope.[11,19,29] We thus provide the first data on influenza-specific T-cell immunity in the Indigenous population. Our findings suggest that where there are shared HLA profiles between Indigenous Australians and non-Indigenous populations, they display similar $CD8^+$ T-cell responses to known, well-characterised influenza epitopes.

With the exception of HLA-A*02:01, little is known about the peptides presented by HLAs specific to Indigenous Australians (Table 1). Further studies are required to identify and characterise epitopes restricted by these unique HLA alleles, in particular HLA-A*34:01 (frequency of 24% of HLA-A alleles), HLA-B*13:01, 15:21,

56:01 and 56:02 (together accounting for 43% of HLA-B alleles), to provide insights into the effectiveness of $CD8^+$ T-cell immunity in this population. Furthermore, as there is a strong correlation between the expression of HLA-A*24 and pH1N1 influenza-induced mortality,[12] analyses of $CD8^+$ T-cell responses to epitopes restricted by HLA-A*24 alleles in Indigenous Australians are a priority.

Apart from HLA distribution, the expression of IFITM3-C/C SNP rs12252 represents the only other host factor known to be associated with increased influenza disease severity across different ethnicities. Following influenza A virus infection, the expression of IFITM3-C/C SNP rs12252 is related to an early hypercytokinemia, especially in the Asian population.[6,7] The rs12252-C genotype is reasonably infrequent in Indigenous Australians, suggesting that compromised IFITM3 function appears not to be linked to the increased susceptibility to severe influenza disease in this population.

To support the rational design of an effective, broad-spectrum universal vaccine, it is essential to define the dominant influenza-specific T-cell responses focused on the allelic HLA variants characteristic of Indigenous Australians.[15,16] Identification of immune and host factors underlying severe influenza disease in Indigenous Australians, highly susceptible to influenza, is of an enormous importance. Understanding which individuals within the Indigenous populations (globally) are at risk of developing severe influenza disease (for example, HLA-A24-expressing individuals[12]) will inform our future prognostic strategies for the treatment and management of severe influenza pneumonia and for designing the vaccination programmes that target specific groups for routine influenza immunisation.

METHODS

Human ethics

All the experiments conformed to the NHMRC Code of Practice and were approved by the University of Melbourne Research Human Ethics Committee (Applications #1441452.1 and #0931311.5) and the Human Research Ethics Committee of Northern Territory Department of Health and Menzies School of Health Research (Application # HREC-2012-1928).

Recruitment of Indigenous Australian donors (LIFT cohort)

To understand influenza-specific responses in the Indigenous population, participants ⩾18 years of age were recruited from the Royal Darwin Hospital and also from healthy volunteers in Darwin as a 'looking into influenza T-cell immunity' (LIFT) cohort. We ensured representation of different age groups across the main regions of the Top End (Darwin urban, Darwin rural, West Arnhem/Daly, Tiwi Islands, East Arnhem, Katherine). This permitted sampling from a range of language and people groups so as not to bias the population HLA distribution. For hospital inpatients, permissions were requested from the treating clinical team for the research team to approach potential participants. Patients were then approached to discuss the study and seek informed consent for access to medical and immunisation records and to obtain a 50-ml venous blood sample. Participants were excluded if they had a diagnosis of Systemic Inflammatory Response (SIRS) (defined as satisfying ⩾2 SIRS criteria–temperature <36 °C or >38 °C; heart rate>90 b.p.m.; respiratory rate>20 b.p.m.; white blood cell count $<4\times10^9$ per l or $>12\times10^9$ per l) or a haemoglobin below the normal range. Participant recruitment, sample collection, isolation by Ficoll Paque density centrifugation (GE Healthcare, Uppsala, Sweden)[20] and storage of PBMCs were performed at the Menzies School of Health Research. PBMCs were cryopreserved for further use at University of Melbourne. DNA was isolated from granulocytes using a QIAGEN QIAamp DNA Mini Kit (QIAGEN, Hilder, Germany) according to manufacturer's instructions.

PBMC isolation from buffy packs

PBMCs were isolated also from buffy packs (obtained from the Blood Bank, Melbourne, VIC, Australia) for HLA-A*02:01$^+$ non-Indigenous donors. PBMCs were isolated by Ficoll Paque density centrifugation,[20] then cryopreserved for future use. Viability of the PBMCs derived from the Indigenous donors was >80% (80–95%) upon thawing out. Furthermore, a viability stain (Live/dead stain) was used in all ICS assays to confirm that all detected responses are from viable $CD8^+$ T cells. A >85% viability was detected in all $CD8^+$ T-cell lines derived from Indigenous donors following the ICS assay.

HLA typing and IFITM3 genotyping

HLA class I and class II molecular genotyping was performed from genomic DNA by the Victorian Transplant and Immunogenetics Service (Parkville, Melbourne, VIC, Australia). For IFITM3 sequencing, the *exon 1* region of IFITM3 containing rs12252 was amplified from genomic DNA by PCR with forward (5′-GGAAACTGTTGAGAAACCGAA-3′) and reverse (5′-CATACG CACCTTCACGGAGT-3′) primers, as previously described.[7]

Generation of $M1^{58}$-specific $CD8^+$ T-cell lines

To amplify influenza-specific $CD8^+$ T cells directed at the immunodominant HLA-A*02:01-restricted $M1_{58-66}$ epitope, PBMCs from HLA-A*02 donors were stimulated with the $M1_{58-66}$ (GILGFVFTL) peptide and then cultured for 10 to 19 days, as previously described.[20,31] Cultures were supplemented twice weekly with 10 U ml^{-1} rIL-2 and $CD8^+$ T-cell lines from non-indigenous donors were restimulated once weekly with gamma-irradiated $M1_{58}$-pulsed C1R-A*02:01 cells.

Intracellular cytokine staining (ICS)

At d10, HLA-A*02-$M1_{58}{}^+CD8^+$ T cells from Indigenous donors were assessed by an IFN-γTNF/CD107a ICS assay. C1R-A*02:01$^+$ were used as antigen presenting cells (APCs) in an ICS assay to restimulate PBMCs. APCs (at $1–3\times10^7$ cells per ml) were pulsed with 10 μM peptide in 100 μl serum-free media RPMI for 60 min at 37 °C. Subsequently, 1×10^5 peptide-pulsed APCs were co-cultured with 2×10^5 restimulated PBMC samples for 5 h at 37 °C in U-bottom 96-well plates in the presence of IL-2 (10 U ml^{-1}), 2 μl GolgiPlug (BD Biosciences, Franklin Lakes, NY, USA; final dilution of 1:1000) and 1.33 μl Golgi-Stop (BD Biosciences, final dilution of 1:1500) and 1 μl anti-CD107a-AF488 (eBiosceinces, San Diego, CA, USA). Following stimulation, cells were washed with FACS buffer (1% bovine serum albumin (Gibco, Waltham, MA, USA) and 0.02% sodium azide (Sigma, St Louis, MO, USA) in phosphate-buffered saline (PBS)) and stained with anti-CD3-PeCy7 (eBiosceinces) and anti-CD8α-PerCP-Cy5.5 (BD Biosciences) and Live/Dead-NIR (Invitrogen, Carlsbad, CA, USA) in PBS, and then washed twice. Cells were fixed and permeabilised using the BD Cytofix/Cytoperm Plus Fixation/Permeabilisation Kit (BD Biosciences), and intracellularly-stained with anti-IFN-γ-V450 (BD Horizon, Franklin Lakes, NY, USA), anti-TNF-APC (BD Biosceinces) in perm-wash buffer. Samples were washed and acquired by flow cytometry on a BD FACS Canto II (BD Biosciences) and analysed by FlowJo software (Treestar, Ashland, OR, USA). Cytokine production was calculated by subtracting background fluorescence using 'no peptide' C1R-A*02:01$^+$ controls.

Tetramer staining

D10-19 $M1_{58}$ cultures were stained with HLA-A*02:01-$M1_{58}$ tetramer conjugated to PE or APC at a 1:100 dilution in FACS buffer (PBS with 0.1% bovine serum albumin) or PBS. Cells were then washed twice with cold FACS buffer and stained with a cocktail of antibodies including anti-CD3-PB (Biolegend) or anti-CD3-PeCy7 (eBiosciences), anti-CD8-PerCPCy5.5 or anti-CD8-PerCP (both BD Biosciences), CD27-APC or APC-Cy7 (BD Biosciences), CD45RA-FITC (BD Pharmingen, San Diego, CA, USA) and Live/Dear-NIR (Invitrogen) (Indigenous donors only), washed twice with FACS buffer or PBS. Cells were then resuspended in 200 μl of sort buffer and passed though a 40-μm sieve prior to flow cytometric analysis or sorting.

Single-cell multiplex RT-PCR for paired CDR3β and CDR3α analysis

$CD8^+$ T cell lines were tetramer-stained as above and single HLA-A*02:01-$M1_{58}$-tetramer$^+$ $CD3^+$dump$^-CD8^+$tetramer$^+$ cells were single-cell sorted on a FACS Aria III (BD Biosciences) into 80 wells of a 96-well twin-tec plate (Eppendorf, Hamburg, Germany). The CDR3αβ regions were determined by a

novel single-cell multiplex reverese transcription PCR (RT-PCR) protocol.[21,28] mRNA transcripts were reverse-transcribed to cDNA, using a VILO kit (Invitrogen). For the internal round of PCR, 2.5 µl of the external product was used as template, with either a set of TRAV or TRBV internal primers.[28] The internal PCR reaction included the two different primers sets at 5 pmol ml^{-1} (TRAV and TRAC, or TRBV and TRBC). Positive PCR products were purified with Exo-SAP-IT (Affymetrix, Santa Clara, CA, USA) and sequenced using TRAC or TRBC internal primers with BigDye v3.1 (Applied Biosciences, Foster City, CA, USA). Sequences were cleaned using DyeEx sequencing plates (QIAGEN) and sequencing was performed at the Sequencing and Genotyping facility within the Department of Pathology at the University of Melbourne. Sequences were analysed using FinchTV, and V and J region usage was identified by IMGT query (www.imgt.org/IMGT_vquest).

New HLA class I modelling

The HLA-A*02:new model was made using the published HLA-A*02:01 structure (PDB code: 3GSO[20]) and mutating the corresponding residues: glycine 62 to arginine, glutamic acid 63 to asparagine. The HLA-B*56:new was modelled using the HLA-B*57:01 structure (PDB code: 3VRI[32]) and mutating the residue 75 from arginine to glycine. All the mutations have been generated in Pymol.[33]

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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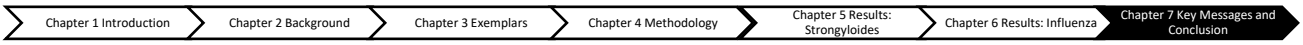
The Supplementary Information that accompanies this paper is available on the Immunology and Cell Biology website (http://www.nature.com/icb)

Chapter. 7 Key Messages and Conclusion



7.1 Chapter Brief

This chapter aims to address the third research question: How does this research inform Indigenous communities, researchers and public health policy makers about the barriers to controlling infectious diseases in Indigenous communities? A discussion about the benefits, limitations and significance of this research is included and the main outcome the development of key messages to inform communities, researchers and health professionals and government that have emerged from the research. The key messages are framed in my research standpoint framework in Dyirbal langauage as ***nyali nyinda nyambayirijnu* -** that we can collaboratively think of solutions to complex problems in Indigenous health is explained in this chapter.

7.2 Overview

This thesis, given its development over time, describes my research journey from novice to more experienced researcher and presents as an empirical thesis with peer reviewed journal articles and book chapters. The focus of studies is centred on two infectious diseases, Strongyloides and Influenza H1N1, as exemplars to provide a better understanding of barriers to effective interventions for infectious diseases in selected Indigenous Australian communities. The research centred around three research questions about Strongyloides and Influenza H1N1: (two separate studies).

1. What are, and have been, the barriers that have prevented effective of control and treatment of Strongyloides and H1N1 swine influenza in Indigenous Australian communities?
2. How are these barriers understood and articulated by Aboriginal communities/people, health staff and researchers? and
3. How does the outcome of this research inform Indigenous communities, researchers and public health policy makers about the barriers of controlling infectious diseases in Indigenous communities?

The Strongyloides study applied qualitative methods to investigate the views and perspectives of Indigenous community members, health professionals and

researchers to the barriers of controlling and treating Strongyloides in Indigenous Australian communities. Interviews were undertaken using purposive sampling; qualitative data was recorded and verified with participants and transcripts were thematically analysed.

The influenza H1N1 study applied a qualitative PAR framework to better understand community members' perceptions and risks of pandemic influenza. The outcomes of applying this qualitative PAR framework was to gain a depth of knowledge and understanding from participants. Aboriginal and Torres Strait Islander community controlled organisations and health services were involved in the implementation, interpretation and monitoring of the project. As a result, novel features of PAR with Aboriginal and Torres Strait Islander communities and organisations emerged. These novel features included:

- the importance of working in a multi-disciplinary team with Aboriginal and Torres Strait Islander researchers;
- the complexities and importance of obtaining multi-site human research ethics approval processes;
- the importance and value of building the research capacity of both experienced and novice researchers in PAR;
- the need to use localised sampling protocols; and the process of undertaking a collective research process and enacting action research and feedback.

The most effective responses of this project are in pre-existing relationships that had been established over a long period between Aboriginal Medical Services and investigators, while research relationships established specifically for the projects, were less successful. These papers on Strongyloides and H1N1 were included in this thesis as a response to research questions 1 and 2.

Five key messages were synthesised from these publications to inform Indigenous communities, researchers and public health policy makers about the barriers of controlling infectious diseases in Indigenous communities.

As explained in Chapter 1, significant progress has been undertaken, in the form of additional funded research, to further investigate the impact of Strongyloides and influenza has had on Indigenous communities. Some of the outcomes from this

continued research are included in this thesis led by some of Australia's leading researchers in the field. I have been included in this research for provide advice and guidance in particular aspects of the study design pertaining to Indigenous research, in particular, gaining ethics approvals, capacity building for Indigenous researchers in gaining bio-samples and cultural protocols in Indigenous research. Three papers are included to demonstrate that apart from socio-economic and cultural factors impacting the control of these infectious diseases, immunologic factors specific to Indigenous populations play a significant role in the control of pandemic influenza (Qui Quinones-Parra 2014, Clements 2016, Valkenburg 2016). These papers identify specific immunologic differences in vaccine effectiveness between Indigenous and non-Indigenous populations, the discovery of gene responsiveness to influenza infection in Indigenous peoples and the need to develop targeted vaccine for specific Indigenous populations.

7.3 Significance

There are five main reasons this research has significance. Firstly, the use and application of qualitative research methods to investigate infectious diseases in Indigenous communities is novel. Typically epidemiology, the science of public health research, is commonly used to investigate infectious diseases in human populations. This research applied qualitative research methods to gain insight into knowledge, experience and perceptions of barriers to controlling infectious diseases in Indigenous communities from a unique group of participants.

Secondly, this research targeted a unique group of participants; Indigenous people, researchers and health professionals, to document their knowledge, insights and perceptions of barriers to controlling infectious diseases in Indigenous communities. The research questions were designed to ensure collecting and analysing this important information was at the centre of this research by providing opportunities for Indigenous peoples to be involved in making sense of the data and research approaches.

Thirdly, the research projects had a substantial amount of Indigenous participation and leadership, and a strong focus on research capacity building. As an Indigenous Chief Investigator I led the application of Indigenous research protocols, had leadership of the grants and played an important role in the recruitment and training of the Indigenous researchers. Two approaches were used to recruit and employ Indigenous researchers. The first approach was payment to primary healthcare

services to second staff time for the project and the second approach was directly recruiting from local Indigenous communities. The strong focus on building and sustaining research capacity benefited the Indigenous organisations, communities and researchers. It's important to note this research was guided by and reported to Aboriginal Community Controlled Health Service Boards, adding to Indigenous leadership of the projects.

The fourth point of significance is that this research ocurred across three states (NSW, QLD and WA) which required rigorous attention to detail within ethics applications at both community-controlled organisational and institutional levels. A significant amount of effort was devoted to applying, responding and reporting to ethics committees. In some cases, manuscripts were required to be reviewed and approved by an ethics committee before submitting for publication.

Finally, the coordination and administration of three category one grants, two NHMRC and one ARC, that formed the basis of this research was led by myself as the Indigenous leader and cultural advisor in these teams.

7.4 Benefit

The benefits of this research were to provide a large body of evidence on the barriers to controlling or addressing infectious diseases in Indigenous Australian communities. This evidence was developed using two infectious disease exemplars; Strongyloides and H1N1 Influenza and published in open access journals. To assist in translating this benefit into practice, a substantial amount of dissemination, presentation and reporting was undertaken in addition to peer reviewed and community reports (see Box 1.1 Presentations and Dissemination). Additionally, there were community-based presentations to local government and community controlled health services. Research undertaken on H1N1 influenza during 2009 and 2010 drew a large amount of media attention which was used to share our research intentions and the reasons why the research was important to Indigenous communities, health professionals and government agencies. A major outcome of the H1N1 influenza study resulted in changing the Australian Health Management Plan for Pandemic Influenza and the Queensland Health Pandemic Influenza Plan – letter received from the Chief Health Officer of Queensland, Dr Jeannette Young. This change meant a stronger focus and better inclusion of vulnerable populations, in particular, Aboriginal and Torres Strait Islander people within both plans. Feedback from presentations to community organisations indicated that this

research should be included or considered in local government disaster management planning.

7.5 Limitations

The perceived limitation of this research is that qualitative research in infectious diseases in particular communities cannot be generalised beyond those communities, particularly to diverse Indigenous communities and health service contexts. However, the development of key messages from this research is generic enough to guide, engage and inform Indigenous community members, health professionals and researchers on reducing risk, clinical matters, research processes and guide government agencies on public policy development with Indigenous peoples. This research has already proven that qualitative research with Aboriginal and Torres Strait Islander communities has influenced pandemic influenza planning nationally and within Queensland.

There is also a perceived limitation that this research was conducted over a long period which may have impact on the relevance of the information in today's understanding of health and wellbeing. Overall, since this research began in 2009, there has been limited research output in publications that centre on barriers to infectious disease within the topics of strongyloides and influenza in Australian Aboriginal and Torres Strait Islander communities.

Finally, there could be a perception that my contribution in this research is not explicitly evident, given the involvement of co-authors, co-investigators and research assistants in two funded studies. I can confirm that I have, along with my collaborators, have conformed to international conventions of authorship, which has been declared in some publications included in this thesis. I have provided Indigenous leadership and have been actively involved in study design, methodology, the quality of the data and analysis and led and contributed significantly to publications and presentations. The outcomes are grounded in Indigenous research protocols and communicated back to communities and stakeholders within my research framework standpoint that has been detailed in Chapter 4.

7.6 Key Messages: *djilbay* and *wiraway*

In Dyirbal language, *djilbay* is knowing how to do something and *wiyamay* is knowing what to and how to do it, these form the two conceptual ways to categorise key

messages from this research. There are two categories of key messages resulting from this research: generic key messages (*djilbay*) and specific key messages (*wiraway*) relating directly to the two infectious disease exemplars. *The generic key messages djilbay* include models of capacity building, community engagement, applying Indigenous ethical standards and organisational engagement that were driven from this research should inform other research. These generic key messages can broadly be applied to other infectious diseases including sexually transmitted infections and other immerging, neglected and tropical diseases impacting on Indigenous communities. As a leader in Indigenous research, these generic key messages (*djilbay*) should inform any research or policy makers to consider when approaching infectious diseases in Indigenous populations and influence design, approach and potential outcomes.

The specific key messages *wiraway* are synthesised from the research and the publications in this thesis. An analysis of each paper's conclusion are listed in Box 7.1 and 7.2 with bolded crucial phases. The specific key messages are listed separately into the two exemplars and themed into three areas: communities, researchers and health professionals and government. These key messages are distilled (*wayu*) further to compile research and engagement principles about improving interventions to infectious disease in Indigenous Australian communities.

Box 7.1. Key Messages – Strongyloides

For Communities

To address and lead community based infectious disease control programs, communities need to:

- **Establish testing and treatment** initiatives within communities (Miller et al. 2018);
- **Increased knowledge and understanding of the risks** to health for Indigenous community members (Miller et al. 2018);
- Effective and sustainable changes can be made by using a **health promotion framework** that can provide the basis for multiple levels of interventions to control and prevent Strongyloides in Indigenous communities (Miller et al. 2018); and
- The importance of **local Aboriginal leadership and governance** and a high level of community involvement increases success in a mass drug administration program to address *S. stercoralis* (Miller, Young, Tye, Cody, Muscat, Sanders, Smith, Judd, Speare, 2018).

For Researchers / Health Professionals

To ensure quality services and health outcomes for Indigenous Australian patients:

- **Test all Indigenous Australian patients**, immunocompromised patients and those exposed in areas with *S. stercoralis* (Miller et al. 2014).
- **Health professionals require detailed information** on strongyloidiasis and the potential for exposure for Indigenous Australian people (Miller et al. 2014).
- The **emergence, development and recognition of Indigenous methodologies** in research should be considered in all types of study designs (Evans, Miller, Hutchinson & Dingwall 2014).
- Health professionals and policymakers who work within Indigenous health need **increased knowledge and understanding of treatment, diagnosis and healthcare access** for *S. stercoralis* (Miller et al. 2018).
- A **community-driven 'treat-and-test'** mass drug administration (MDA) intervention needs to be co-designed with the Community Health Service and the community (Miller, Young, Tye, Cody, Muscat, Sanders, Smith, Judd, Speare, 2018).
- Health staff providing information to community members about *S. stercoralis* can facilitate the development of **localised knowledge and understanding** of the parasite. This process allows research teams to develop ways to share new knowledge and understanding about *S. stercoralis* **leading to localised communication strategies** development and delivered in the form of novel health promotion materials (Miller, Young, Tye, Cody, Muscat, Sanders, Smith, Judd, Speare, 2018).
- Develop a **community-driven governance model** to guide the project that can second expert advice at critical points of the program/project (Miller, Young, Tye, Cody, Muscat, Sanders, Smith, Judd, Speare, 2018).

For Government

In order to develop effective public health policies and frameworks, governments need to:

- **Develop reporting protocols** between health care system and communities (Miller et al. 2014).
- **Measure and report prevalence** rates specific to communities and act with initiatives based on these results (Miller et al. 2014).
- We urge the Australian Government Department of Health to consider **placing strongyloidiasis on the National Notifiable Diseases Surveillance System** (NNDSS), to establish an accurate estimate of incidence that will inform the necessary public health action at community, regional and national levels. (Speare, Miller & Page 2015).
- We propose that all reported cases of Strongyloides be laboratory confirmed, based on faecal examination or serology. These data can be collated and used to guide implementation of a **National Strongyloidiasis Elimination Program** (Speare, Miller & Page 2015).
- There is a need for **prevention policy development for neglected tropical diseases** in Indigenous Australian communities (Miller et al. 2018).

– There is a need **to raise awareness of systematic institutional racism** in the control and prevention of neglected tropical diseases in Indigenous communities (Miller et al. 2018).

– There is a need for the **incorporation of local leadership and knowledge** in community wide interventions (Miller, Young, Tye, Cody, Muscat, Sanders, Smith, Judd, Speare, 2018).

Box 7.2. Key Messages – Influenza H1N1

For Communities

To address and lead community based infectious disease control programs, communities need to advocate for:

- Australian Indigenous people may be particularly vulnerable to the H7N9 influenza disease (Quiñones-Parra 2014).
- An effective way to engage with Indigenous communities is through **pre-existing relationships** with individuals within organisations that were established over a long period between Aboriginal medical services and investigators. However, research relationships established specifically for the project were less successful because of changes in personnel and organisational support (Miller et al. 2015).
- Decisions on appropriate pandemic containment measures need to be made in **genuine partnership** with communities, recognising that some cultural practices may amplify or reduce infection risk (Massey et al. 2009).
- **Families and ways of life** were identified as critical determinants of the way communities responded to the threat of pandemic influenza (Massey, Miller et al. 2011).
- **Keeping families safe; prioritising family above self**; respecting family structures; and the need to attend funerals and community events, impacted on how participants responded to pandemic influenza and the development of more acceptable disease control strategies (Massey, Miller et al. 2011).
- Life in Aboriginal and Torres Strait Islander communities is fulfilling and affirming, but the realities of the **built environment pose particular challenges**. There may be large and extended families living in a relatively small house, and there may be more than one house that people call “home” (Massey, Miller et al. 2011)

For Researchers / Health Professionals

To ensure quality services and health outcomes for Indigenous Australian patients are achieved through:

- **Public health experts must work with communities in genuine and respectful partnership** to define what pandemic containment measures are culturally appropriate and acceptable (Massey, Miller et al. 2009).
- Lessons learnt from this study by implementing a **PAR research framework with Aboriginal and Torres Strait Islander communities,** and organisations include:
- The importance of working in a multidisciplinary team with Aboriginal and Torres Strait Islander researchers;
    - The complexities and importance of obtaining multi-site human research ethics approval processes;

    - The importance and value of building the research capacity of both experienced and novice researchers in PAR;
    - The need to use localised sampling protocols; and the process of undertaking a collective research process and enacting action research and feedback (Miller et al. 2015).

- The participatory approach used in this study has the potential to be applied to vulnerable populations in other countries (Miller et al. 2015).
- A strong recurrent theme across the sites was that **health services needed to be more locally responsive** to the pandemic threat (Massey, Miller et al. 2011).
- The role of local Aboriginal or Torres Strait Islander health workers was said to be critical. These people are important for ***"delivering the health message, and they do not frighten the community by keeping the message culturally appropriate by being there to translate immediately any misinterpretation"*** (Massey, Miller et al. 2011).

For Government

In order to develop effective public health policies and frameworks, governments need to:

- There is a fundamental need for governments to **acknowledge and respond effectively** to the specific requirements of Aboriginal and Torres Strait Islander people in public policy development (Miller & Durrheim 2010).
- Prevention and preparedness must include government support of planning in **respectful partnerships** with Aboriginal and Torres Strait Islander communities, health organisations and representative bodies. Mandating this support and partnership at all levels of government will allow a greater understanding of infection risk and identification of cultural, social, economic and health service factors that may contribute to poor health outcomes, and ensure culturally safe and effective prevention and mitigation strategies (Miller & Durrheim 2010).
- A strong theme emerging from this work is the message to government: **"Ask us, listen to us, share with us"** (Miller & Durrheim 2010).
- Solutions to limit the burden on Aboriginal and Torres Strait Islander populations exist, but **respectful partnership** is necessary to unearth them. The partnership must not be a token one, but one developed through engagement with communities, and with the flexibility to be localised to meet the specific needs of diverse urban, rural and remote Aboriginal and Torres Strait Islander communities in all states and territories. Health information delivered with a local flavour is a key message from the project. "Ask us, listen to us, share with us" is a strong message that governments must heed if the impact of pandemic influenza on Aboriginal and Torres Strait Islander communities is to be limited (Miller & Durrheim 2010).
- Indigenous participants is this study provided deep insights into **more effective communication** between governments, health services and the community. This theme identified the need for government and organisations to enter into a dialogue with Aboriginal

and Torres Strait Islander communities, to discover what communities wanted to know before telling them. Respondents reported that it was important that authorities listened to what was 'really' meant, and then shared the information needed (Massey, Miller et al. 2011).

- For sharing information, to connect effectively with local people, participants advised to ***"localise, personalise and humourise"*** the communication, using established local community networks and local languages. The importance of ensuring that information related to community members using identifying colours, people and logos, was reported (Massey, Miller et al. 2011).
- The data revealed that communities placed a high value on **partnerships and collaborations** (Massey, Miller et al. 2011).

7.7 Principles to Address Barriers to Infectious Disease Interventions: *wayu*

I have synthesised (*wayu*) these key messages into 5 principles to address barriers for infectious disease interventions in Indigenous communities. These are:

1) Increase knowledge and information about the diagnosis and treatment of the disease and share this information with communities.
2) Collaboratively work with local leadership to support a community-driven model that has genuine and respectful partnerships between local Indigenous people, health professionals and government agencies.
3) Develop and adopt effective communication strategies to share knowledge and information about infectious diseases to different stakeholders to respond effectively.
4) Plan, develop and implement public policy about infectious diseases interventions that addresses institutionalised racism and incorporates local Indigenous knowledge.
5) Indigenous engagement strategies must identify and use pre-existing relationships that incorporates Indigenous people's values.

7.8 Conclusion: nyali nyinda nyambayirijnu (ŋali ŋinda ŋambayiriɲu)

This research used qualitative methods that focused on two infectious diseases: Strongyloidiasis and H1N1 Influenza and aimed to use these diseases as exemplars to provide a better understanding of the barriers to effective interventions for

infectious diseases in selected Indigenous Australian communities. The research investigated these diseases in two studies to answer three research questions. These are:

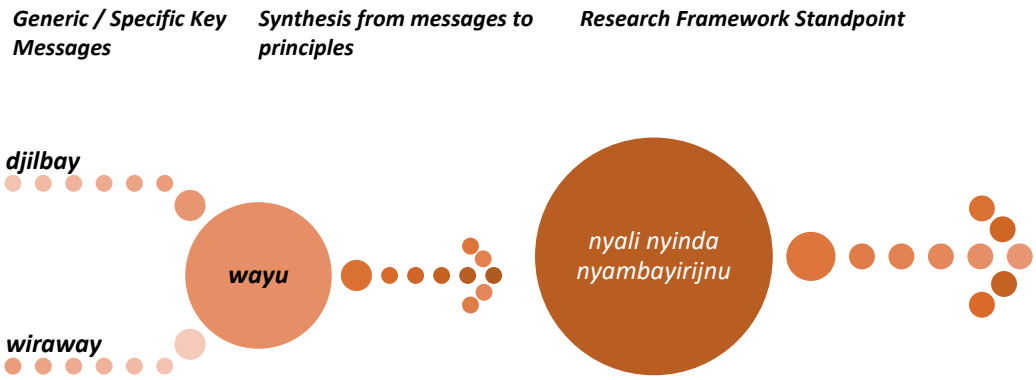
1. What are, and have been, the barriers that have prevented effective of control and treatment of Strongyloides and H1N1 swine influenza in Indigenous Australian communities?
2. How are these barriers understood and articulated by Aboriginal communities/people, health staff and researchers? and
3. How does the outcome of this research inform Indigenous communities, researchers and public health policy makers about the barriers of controlling infectious diseases in Indigenous communities?

The major outcomes of this research were presented in publications as 3 book chapters and 11 peer reviewed journals that formed the structure of the thesis. Additionally, there were 3 articles as an extension to the influenza part of this study. The purpose of including the extension research is to highlight the trajectory of the original research to include biological and immunological barriers within Indigenous peoples for influenza prevention and treatment.

The Strongyloides study and related articles used qualitative methods to investigate the views and perspectives of Indigenous community members, health professionals and researchers about the barriers of controlling and treating Strongyloides in Indigenous Australian communities. Interviews were undertaken using purposive sampling, and qualitative data was recorded and verified with participants and thematically analysed. The findings were categorised into major and minor themes.

The Influenza H1N1 study applied a PAR framework to better understand community members' perceptions and risks of pandemic influenza. The outcome of using a qualitative PAR framework was an effective way to gain a greater depth of knowledge and understandings from participants. Aboriginal and Torres Strait Islander community controlled organisations and health services were involved in the implementation, interpretation and monitoring of the project. As a result, novel features of PAR with Aboriginal and Torres Strait Islander communities and organisations emerged.

Figure 7.1 Research Framework Standpoint



I envisage, that this research has shed light, through ***djilbay*** and ***wiraway***, on the important issues affecting the barriers to Indigenous community participation in infectious disease research, clinical interventions and public policy development. The principles and outcomes, ***wayu***, of this research not only answer the research questions posed but confirms my research framework standpoint - ***nyali nyinda nyambayirijnu*** that we can collaboratively think of solutions to complex problems in Indigenous health (See Figure 7.1).

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