BEYOND SURVIVAL

NEURODEVELOPMENTAL OUTCOMES FOR NEONATAL INTENSIVE CARE SURVIVORS IN FIJI

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ABSTRACT

BACKGROUND

In low- and middle-income countries (LMIC) where most of the 15.1 million neonates who survive prematurity and serious illness every year reside, neurodevelopmental outcome data are scarce and needed to improve neonatal care including follow-up, developmental monitoring and early intervention. (1) In Fiji, neonatal health policy has shifted from almost exclusive focus on neonatal survival to ensuring that children are also supported to reach their developmental potential.

METHODS

AIM

To examine early childhood neurodevelopmental and health outcomes for neonatal intensive care unit (NICU) survivors in Fiji, to inform improvements in neonatal care and follow-up including developmental monitoring and early intervention.

OBJECTIVES

These were, to:

1. Systematically review existing neonatal outcomes studies in LMIC to understand knowledge gaps related to neurodevelopmental outcomes for high-risk neonates and inform research design and sample size estimates for our neonatal outcomes study

2. Assess early childhood neurodevelopmental and health outcomes for neonates discharged from the Colonial War Memorial Hospital (CWMH) NICU in Suva, compared with control, term neonates born in the same hospital
3. **Evaluate accuracy of nurse-led developmental screening** as a potential tool for early identification of developmental delay and impairment in high-risk neonates, compared with reference standard developmental assessment

**RESULTS**

Systematic review of 60 high-risk neonatal outcome studies in LMIC provided estimates of median prevalence of neurodevelopmental impairment (NDI) for survivors of prematurity/very low birth weight (VLBW) and ‘birth asphyxia’. This highlighted a need for studies that better describe multi-domain neurodevelopment, include hearing and vision and including control data.

Our neonatal follow-up study in Fiji compared early childhood outcomes for high-risk NICU patients (n=149) with those of matched term, normal birth weight neonates (n=147) discharged from Colonial War Memorial Hospital between November 2008 and April 2010. NDI was defined as ≥ 1 of; cerebral palsy, moderate to severe hearing or visual impairment, or global developmental delay using Bayley Scales of Infant and Toddler Development Third Edition (i.e. score <70 in ≥ 2 of cognitive, language or motor domains). At median (IQR) age 36.1 (28.3, 38.0) months, prevalence of moderate to severe NDI % (95% CI, n) in high-risk and control groups was 12 (5 to 17, n=13) and 5 (2 to 12, n=5), respectively, an increased risk ratio (95% CI) of 2.7 (0.8 to 8.9. Risk factors for NDI were identified.

Our nurse-led developmental screening study demonstrated that, while feasibility of a parent-report screening tool was attractive, sensitivity for detection of global developmental delay was poor compared with the reference standard.
CONCLUSION

Our research provided the first neonatal neurodevelopmental outcome data in Fiji, adding to limited international literature on neonatal neurodevelopmental outcomes in LMIC. Measurement challenges highlight a need for international collaboration to improve measurement to better understand neonatal outcomes beyond survival. Negative findings of our developmental screening study indicate a need for longitudinal research to establish developmental monitoring approaches which facilitate early identification of developmental delay and impairment in routine services. Implementation research is also needed to develop innovative models of early intervention which support high-risk neonates in LMIC to thrive.
DECLARATION

I hereby declare that:

i. This thesis comprises my own original work towards the degree of Doctor of Philosophy, except where indicated in the preface,

ii. Due acknowledgement has been made in the text to all other material used,

iii. The thesis is fewer than 100,000 words in length exclusive of tables, maps, bibliographies, and appendices.

Signed: Kate Milner

Date: 13 August 2019
PREFACE

This thesis is my original work.

Research was undertaken in Fiji in collaboration with colleagues in the Fiji Ministry of Health and Medical Services including a local team of medical, nursing, allied health and research staff at the Colonial War Memorial Hospital in Suva. In Australia our project team included paediatricians, speech pathologists and my supervisors, with administrative support through the Centre for International Child Health, University of Melbourne.

I was responsible for the design and completion of the background systematic literature review and research design for both the neonatal outcomes and developmental screening accuracy studies, ethics submissions, database set-up and ongoing data management, project management, staff training and recruitment as well as supervision of data collection and data entry. I was responsible for design and implementation of data analysis for both studies.

I was supervised by Professor Trevor Duke, Associate Professor Gehan Roberts throughout and Prof Andrew Steer up until the final writing phase. My Advisory Committee of Professor Peter Anderson, Professor Katrina Williams and Professor Stephen Graham provided additional input into research design, analysis and thesis structure at scheduled reviews during candidature. In addition, I received the following support:

Support for systematic literature review was provided by Ms Eleanor Neal, Centre for International Child Health, University of Melbourne who assisted with compilation and
review of papers and Ms Poh Chuah, Librarian Royal Children’s Hospital who provided advice regarding search strategy.

The studies in Fiji were supported by members of the research team in Fiji provided who assisted with project management, translation of research materials, identification and recruitment of participants, data collection and data entry. Specifically, support for data collection was provided by: Sr Lanieta Koyamaibole, Associate Professor Susan Woolfenden, Dr Anne Miller, Dr Rakei Kaarira, Dr Kelera Namudu, Ms Kathryn O’Heir and ward nursing staff who undertook developmental assessments and developmental screening. Dr Roger Dethlefs and staff at the Pacific Eye Institute in Suva completed ophthalmological assessments. Audiology assessments were supported by the team at the Carabez Alliance Hearing Clinic in Suva, especially Mrs Bronwyn Carabez, as well as visiting audiologists. In particular, Paediatric Audiologists Ms Linda Zraika, Ms Kelley Graydon and Ms Kathryn Randall provided technical support and equipment for audiology clinics and interpretation of hearing data.

Development of data analysis plans and data analysis was supported by Associate Professor Susan Donath and Ms Suzanna Vidmar at the Clinical Epidemiology and Biostatistics Unit, Royal Children’s Hospital in Melbourne. Ms Eleanor Neal also assisted with data cleaning and analysis.

No component of this work has been submitted for other qualifications.

Initial literature review, design of the research projects and ethics submissions were undertaken prior to my enrolment in the doctoral programme. Systematic literature review and both research projects occurred after I was enrolled.
No third party editorial assistance was provided in preparation of this thesis. My nephew Jakob Bradbeer, who has no content expertise, provided assistance with formatting the manuscript only.

Section 2 includes our systematic review of previous neurodevelopmental outcome studies for high-risk neonates in LMIC, published in Paediatrics and International Child Health on July 3rd 2015.(2) As first author of this paper I was primarily responsible for conceiving and designing the systematic review, analyzing and interpreting data, wrote the first draft and major revisions of the manuscript and approved the final manuscript as submitted. Ms Eleanor Neal supported systematic review of the literature and revision of the manuscript. Professors Trevor Duke, Gehan Roberts and Andrew Steer supervised analysis and reviewed drafts of the manuscript.

Section 4 includes our neonatal outcomes study, published in Archives of Disease in Childhood on August 28th 2017.(3) As first author of this paper I conceptualized, designed and supervised study implementation as noted above, assisted with data collection, analysed data, wrote the first draft and major revisions of the manuscript and approved the final manuscript as submitted. Professors Trevor Duke, Gehan Roberts and Andrew Steer supervised study design, analysis of data, reviewed and revised the manuscript, and approved the final manuscript as submitted. Drs Joseph Kado, Rakei Kaarira, Kelera Namudu, Anne Miller, Sr Lanieta Koyamaibole and Ms Kathryn O’Heir supported and completed data collection at the study site and approved the final manuscript as submitted. Ms Eleanor Neal assisted with data cleaning and analysis and approved the final manuscript as submitted.
All other chapters are entirely my work supervised by Professor Trevor Duke and co-supervised by Professor Gehan Roberts.

Project funding: Both research studies in Fiji were supported by funding through the Australian Agency for International Development (AusAID) Women’s and Children’s Knowledge Hub for Health. Additional funding support for audiology clinics was provided by CureKids Fiji.

Personal funding: I received an Australian Postgraduate Award.
ACKNOWLEDGMENTS

This work is dedicated to the memory of my friend and colleague,

Sr Lanieta Koyamaibole

(28.6.53 – 28.5.17)

Sr La, as she was affectionately known, made a substantial contribution to improvements in quality of neonatal care in Fiji over the course of her lifetime and, without her support as Research Nurse extraordinaire during this research, the work described in this thesis might never have come to fruition. Sr La worked was nursing head of the Neonatal Intensive Care Unit at Colonial War Memorial Hospital in Suva from 1989-2007 and was highly regarded for passionate advocacy for her patients, uncompromising clinical standards, meticulous record keeping and support for professional development of colleagues. In respect for Sr La’s legacy, I hope that this research becomes a small part of many more years of collaboration between our countries, to improve life opportunities for small and sick babies in Fiji.

I am also indebted to the children and families who participated in this study. Throughout this research, I was humbled by the trust, patience and generosity of spirit shown to our team by research participants. We were privileged that during the course of our research, many individual stories of courage, hardship and resilience were shared with us. Our research and ongoing collaborative work with colleagues in Fiji aim to pay tribute to these stories. Vinaka vakalevu.
My doctoral research experience has, like many good things in life, taken far longer than I had hoped or anticipated. As such, it is a great celebration to get to the stage where I can thank colleagues, friends and family for the invaluable support they have provided throughout this endurance event.

When this research journey began, I was living in Fiji, a mother of two small children and paediatrician-in-training. Our young family thrived on the adventure of settling into life in Fiji and getting to know people there. However, shortly after I enrolled in my doctorate, our eldest child became unwell and was diagnosed with leukaemia. We returned back to Australia for his medical care and were thrown into a space where we had to rely on ‘our village’ like never before. In the early days after diagnosis we were unsure whether this research would continue. It is testament to excellent medical care, steady supervision, a phenomenal research team in Fiji and unswerving support of family and friends that it did.

In the years since then, my research work in Fiji, as described in this thesis, has progressed through peaks, ebbs and flows, only through the support of a large team.

I am sincerely thankful my supervisors Professor Trevor Duke and Professor Gehan Roberts without whose support this work would not have been possible. As Primary Supervisor, Trevor’s unwavering commitment to the vision of this research, at a time when the global child health research agenda was firmly focused on child survival, was testament in my mind to both his leadership and genuine support for professional development of junior colleagues. Trevor, has been a supervisor who I could rely on when the chips were down, whether it was being there in the Emergency Department on the day our son was diagnosed or some academic challenge, he was always there and
I am thankful for his guidance. As Co-Supervisor, Gehan’s sage perspectives, timely pearls of advice and wisdom, gentle sharing of his tremendous expertise and patient review of drafts have been invaluable. This work would not have been possible without his resolute positivity and supreme calmness. I am also very thankful to Professor Andrew Steer for his invaluable co-supervision during a substantial period of my candidature. Andrew’s in-depth knowledge of the context in Fiji, collaborative international research partnerships, attention to detail and meticulous planning provided invaluable modelling as a junior researcher.

I was also very fortunate to have a terrific Advisory Committee including Professors Peter Anderson, Katrina Williams and Steve Graham. Peter’s expertise in neurodevelopment and outcomes research were invaluable as were Steve’s experience and understanding of the role of research in quality improvement in global child health.

Prof Katrina Williams, who was also my clinical boss as Head of Neurodevelopment & Disability at the Royal Children’s Hospital for much of my candidature, was a huge support. I am grateful for her long-view of my professional development including my research career while balancing clinical duties. Katrina’s mentorship and friendship have been crucial to both aspects of my career and her encouragement of me as a person has been deeply appreciated. I have learned much from Katrina about supporting leadership development of junior colleagues, especially women in academia.

One of the aspects of this research experience that I enjoyed the most was the establishment and process of working together as an international, multidisciplinary team in Fiji. I am very thankful to have worked with such a committed, skilled and wonderful group of people.
In particular, thanks to Dr Joseph Kado for his leadership and support in developing and carrying this work forwards. Without Dr Kado’s leadership in improving follow-up care and early intervention for children with disabilities in Fiji, this work would not have started. I am now also thankful for the ongoing support of Dr Ilisapeci Tuibeqa, current Head of Department as we build on this work.

Special thanks also to Dr Susan Woolfenden, Dr Anne Miller and Ms Kathryn O’Heir, colleagues and who gave so much to this work and especially stepped up when my son was ill. I am so grateful to have worked with you on this and thankful for our friendship, especially for stepping up when needed the most. I am especially delighted to be continuing research collaboration with Sue, whose commitment to local leadership development in Fiji and solutions-focused approach make working together a pleasure.

Thanks also to paediatric registrars Drs Rakei Kaarira, Kelera Namudu and Raina Prasad for making time in their busy clinical duties to support this work.

There are many other colleagues at CWMH whose enthusiasm and support contributed to successful completion of this work including; Sr Tupou Ratu, Ms Meredani Gunaivalu, Mrs Neomai Hickes, Sr Vijay, Sr Pradeep and Physiotherapy Department staff along with paediatric ward and outpatient teams at CWMH. Thank you to Dr Roger Dethlefs at the Pacific Eye Institute for making time to see our study participants and the Carabez Alliance and University of Melbourne Audiology Departments for providing staff and equipment for audiology testing. Thank you to the following audiologists who travelled to Fiji and volunteered their time and expertise to support our study hearing clinics; Linda Zraika, Kathryn Randall, Anna Ly, Johanna Tan and Kelley Graydon. I would like to thank Associate Professor Susan Donath and Ms Suzanna Vidmar at the Clinical
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Sincere thanks to colleagues at the Centre of International Child Health (CICH), especially Ms Eleanor Neal, Dr Sophie LaVincente and Ms Jane Hawtin for your technical advice in your respective areas of expertise as well as friendship and Ms Caitlyn Robertson for unflappable administrative support. To other past and present CICH doctoral research colleagues Samantha Colquhoun, Amy Gray, Michael Nunan, Hamish Graham, Daniel Engelman and Shidan Tosif, thanks for the collegiality along the way. To Professors Fiona Russell and Kim Mulholland, thank you for your helpful advice and generosity in sharing your wisdom from experience.

I am also deeply appreciative of my colleagues in the Department of Neurodevelopment & Disability at the Royal Children’s Hospital who supported me so much in this work, especially practically in the latter stages of write-up by being generous in covering my roster and excusing me from meetings.

To colleagues at the Maternal, Adolescent, Reproductive & Child Health (MARCH) Centre at the London School of Hygiene & Tropical Medicine, where I worked for 18 months from 2016-2017, it was an honor to work with people so committed to the improving care and long-term outcomes for small and sick babies in vulnerable settings around the world. In particular, I would like to than Professor Joy E Lawn for her leadership, mentorship and sponsorship, Associate Professor Cally Tann for your generosity, friendship and collaborative spirit in sharing your knowledge and experiences, Dr Maya Kohli-Lynch, Ms Jaya Chandna, Ms Vicki Ponce-Hardy and many others for welcoming me in to the team.
Thank you to our major research funder AusAID and to CureKids Fiji for funding our hearing clinics. I am also appreciative of personal funding support through the Australian Postgraduate Award System and the Royal Australasian College of Physicians, through provision of the Eric Burnard Fellowship in Neonatology.

Finally, to my personal ‘village’, I hope that you already know how deeply appreciated you are but I am noting it here so you at least read some of my thesis. To the many wonderful women in my life, including many already noted but especially Drs Sarah McNab, Louise Sterling and Ms Nozipho Khanda, you know more than most what a journey this has been. Thank you for always having my back, for sharing the highs and the lows, for keeping me grounded and for reminding me that we all have limits. I hope we have many more adventures ahead together. To my parents, thanks for your steadfast love and abundant practical support even when you would perhaps prefer I had a more sedate existence. To Auntie Anne, your courage, commitment, generosity to others and wry humour have been a profound inspiration in my life, including this work. To my siblings Andrew, Iain, Kirsty and Sarah, thanks for the life lessons in determination from an early age which set me in good stead to complete this thesis. To Janet, Terence and Alexandra Keefe, thanks for always supporting me and taking an interest in my work. Thanks Maddy, Jakob and Daina for all the babysitting so I could keep writing. To Dr Françoise Mechinaud and team at the Children’s Cancer Centre at the Royal Children’s Hospital in Melbourne, thanks for looking after my boy and using science not only to cure his leukaemia, but to strengthen care beyond survival in your field to improve his opportunities in life. To Alex, thank you for many wonderful shared adventures during this chapter of family life.
Finally, to Artie and Rachel, my thriving children and two of the most courageous and kind humans I know...thank you for being patient while I was writing. I love you more than you can imagine and am so proud of both of you.
PAPERS ARISING FROM THIS THESIS

Peer reviewed papers arising directly from this thesis and published during my candidature include:


Other peer reviewed publications during candidature include:


Related non-peer reviewed publications during candidature include:


- Expert contributor, World Health Organization toolkit for the care and support of people affected by complications of Zika virus, WHO, 2017. Accessible at:

PRESENTATIONS ARISING FROM THIS THESIS

1. Colonial War Memorial Hospital, ‘Toso Vata parent support early intervention for young children with cerebral palsy – research design workshop,’ March 26-28, 2019, Suva. (Oral presentation and workshop lead)

2. Melbourne Children’s Campus, Roundtable discussion – ‘How can we improve care for children with disabilities in low-and middle-income countries in Asia and the Pacific?’ December 3, 2018, Royal Children’s Hospital (Oral presentation and discussion lead)

3. Melbourne Children’s Campus, PhD completion seminar, ‘Survive and thrive – neurodevelopmental outcomes after newborn intensive care in Fiji,’ November 5, 2018, Royal Children’s Hospital (Oral presentation)

4. Melbourne Children’s Campus, 3 Minute Thesis Competition, Royal Children’s Hospital, ‘Survive and Thrive – child development after newborn intensive care in Fiji,’ September 2018, Royal Children’s Hospital (Oral presentation - Heat 4 Winner)

5. Melbourne Children’s Campus, Neurodevelopment & Disability Team Meeting, ‘Neurodevelopment & Disability – a new morbidity in global child health?’ July 17, 2018, Royal Children’s Hospital (Oral presentation)

6. University of Liverpool, ‘Identification of developmental disability for high-risk newborns,’ April 18, 2018 Liverpool. (Oral presentation – co-presentation with Association Professor Cally Tann, London School of Hygiene & Tropical Medicine)
7. WHO Technical consultation on strengthening capacity to enhance detection, care, support and services for complications associated with Zika virus, February 2017, Geneva. Facilitated workshop. (Oral presentation)


11. General Medicine Team Meeting, ‘Care beyond survival – disability and child development in resource-limited settings.’ Royal Children’s Hospital, Melbourne, June 26, 2015. (Oral presentation)

12. Fiji Ministry of Health and Medical Services Meeting, ‘Early childhood health and developmental outcomes for sick newborns in Fiji.’ Colonial War Memorial Hospital Suva, Fiji, November 25, 2014. (Oral presentation)

13. University of Melbourne postgraduate child public health course, annual invited lectures on early child development in resource-limited settings. Nossal Institute for Global Health, 2014-


17. Melbourne Children’s Campus, Campus Research and Education Week, ‘Neurodevelopmental outcomes following serious neonatal illness in low- and middle-income settings’, Royal Children’s Hospital, October 30, 2012. (Oral presentation)


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Textbox 1: Sustainable Development Goal 4, targets and indicators

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<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASQ - Ages and Stages Questionnaire</td>
<td></td>
</tr>
<tr>
<td>Bayley-II - Bayley Scales of Infant and Toddler Development 2nd Edition</td>
<td></td>
</tr>
<tr>
<td>Bayley-III - Bayley Scales of Infant and Toddler Development 3rd Edition</td>
<td></td>
</tr>
<tr>
<td>CP - Cerebral Palsy</td>
<td></td>
</tr>
<tr>
<td>CPAP - Continuous Positive Airways Pressure</td>
<td></td>
</tr>
<tr>
<td>CWMH - Colonial War Memorial Hospital</td>
<td></td>
</tr>
<tr>
<td>CZVS - Congenital Zika Virus Syndrome</td>
<td></td>
</tr>
<tr>
<td>ECD - Early Child Development</td>
<td></td>
</tr>
<tr>
<td>ELBW - Extremely Low Birth Weight</td>
<td></td>
</tr>
<tr>
<td>ENAP - Every Newborn Action Plan</td>
<td></td>
</tr>
<tr>
<td>GMDS – Griffiths Mental Development Scales</td>
<td></td>
</tr>
<tr>
<td>HIC - High Income Countries</td>
<td></td>
</tr>
<tr>
<td>HIE - Hypoxic Ischaemic Encephalopathy</td>
<td></td>
</tr>
<tr>
<td>HMD - Hyaline Membrane Disease</td>
<td></td>
</tr>
<tr>
<td>ICD-10 - International Classification of Diseases Edition 10</td>
<td></td>
</tr>
<tr>
<td>ICF-CY - International Classification of Functioning, health and disease – Child and Youth version</td>
<td></td>
</tr>
<tr>
<td>IMCI - Integrated Management of Childhood Illness</td>
<td></td>
</tr>
<tr>
<td>LBW - Low Birth Weight</td>
<td></td>
</tr>
<tr>
<td>MAS - Meconium Aspiration Syndrome</td>
<td></td>
</tr>
<tr>
<td>MDG - Millennium Development Goal</td>
<td></td>
</tr>
<tr>
<td>MoHMS - Ministry of Health and Medical Services</td>
<td></td>
</tr>
<tr>
<td>NBW - Normal Birth Weight</td>
<td></td>
</tr>
<tr>
<td>NCF - Nurturing Care for Early Child Development Framework</td>
<td></td>
</tr>
<tr>
<td>NDI - Neurodevelopmental Impairment</td>
<td></td>
</tr>
<tr>
<td>NE - Neonatal Encephalopathy</td>
<td></td>
</tr>
<tr>
<td>NEC - Necrotising Enterocolitis</td>
<td></td>
</tr>
<tr>
<td>NGOs - Non-government Organisations</td>
<td></td>
</tr>
<tr>
<td>NHSP - Neonatal Hearing Screening Programmes</td>
<td></td>
</tr>
<tr>
<td>NICU - Neonatal Intensive Care Unit</td>
<td></td>
</tr>
<tr>
<td>NPV - Negative Predictive Value</td>
<td></td>
</tr>
<tr>
<td>PCHL - Permanent Congenital Hearing Loss</td>
<td></td>
</tr>
</tbody>
</table>
PEDS - Parents’ Evaluation of Developmental Status

PEDS: DM - Parents’ Evaluation of Developmental Status: Developmental Milestones

PICU - Paediatric Intensive Care Unit

PPV - Positive Predictive Value

RNDA - Rapid Neurodevelopmental Assessment

ROP - Retinopathy of Prematurity

SBI - Serious Bacterial infection

SDGs - Sustainable Development Goal

SGA - Small for Gestational Age

VLBW - Very Low Birth Weight

WHO - World Health Organization
Section 1

INTRODUCTION
1. **INTRODUCTION**

1.1 **PROBLEM STATEMENT**

Long-term neurodevelopmental data are needed to better understand and improve outcomes for children following neonatal illness and complications, especially in low- and middle-income countries such as Fiji where, until recently, there has been little attention paid to outcomes beyond survival.

Globally, there has been important progress in improving neonatal survival although mortality remains far too high. Every year, an estimated 2.7 million of 5.9 million deaths (i.e. 45.1%) of children under the age of 5 years occur in the neonatal period.(4) The major causes of neonatal deaths are complications of preterm birth, 0.9 [uncertainty range 0.8-1.1] million, intrapartum related 0.6 [uncertainty range 0.6-0.7] million and pneumonia and meningitis 0.4 [uncertainty range 0.3-0.5] million deaths.(4) The majority of these deaths occur in low and middle-income countries and are preventable.(5)

Reducing preventable neonatal mortality is a strategic priority in the World Health Organization’s (WHO) ‘Global Strategy for Women’s Children’s and Adolescent Health (2016-2030).’(6) This aims to reduce neonatal mortality in every country to <12/1000 live births by 2030.(6) Additionally, the ‘Every Newborn Action Plan’ endorsed by 194 United Nations member states, provides a ‘road-map’, targets and indicators for tracking country-level progress towards mortality reduction goals.(7) Alongside this there has been a substantial increase in donor investment in programmes to improve neonatal survival and development of a high-level global research agenda.(8, 9) In Fiji, as in many
middle-income countries reducing preventable neonatal mortality has been an increasing strategic focus in policy and programmes.\(^{(10)}\)

Since the launch of the Sustainable Development Goals (SDGs) in 2015, global child health has increasingly also aimed to ensure that all children are enabled to thrive, reach their developmental potential.\(^{(6, 11)}\) This is recognised in SDG 4.2.1 which aims for all children to have equal early child development opportunities and access to early learning opportunities.\(^{(11)}\) In spite of this, what has been almost invisible on the global child health agenda until recently are outcomes for the 15.1 million neonates worldwide, who experience preterm birth, intrapartum related neonatal encephalopathy, serious bacterial infections and other complications and survive.\(^{(12-15)}\)

In high income countries (HIC) large, well-established research programmes on neonatal outcomes have provided a detailed knowledge base regarding the long-term health, and developmental consequences of a diverse range of neonatal conditions throughout the life course. For example, preterm birth is known from a large body of evidence to be associated with increased early mortality, health service utilisation, neurodevelopmental impairment (including motor, cognitive and sensory impairments), behavioural and socioemotional dysfunction, educational difficulties and chronic health conditions throughout childhood and into adult life.\(^{(16-20)}\)

The broader impact of prematurity has also been demonstrated through research; for example, on quality of life, and family well-being.\(^{(21)}\) In addition, research evidence has been important in highlighting the public health and economic rationale for increased investment in improving quality obstetric and neonatal care as well as development of
Section 1 - Introduction

follow-up care that is appropriate and effective in addressing children’s anticipated health and developmental needs.(17, 18, 22) While preterm birth is perhaps most studied, there are similar substantial bodies of research related to many other neonatal conditions in high-income settings.(23)

However, outcome research from HIC cannot be directly translated to predict outcomes for neonates in LMIC where broader child health epidemiology, health and education systems, demographic and cultural contexts are often markedly different from HIC and also vary from one LMIC to another. Therefore, there is an urgent need for local neonatal outcomes data in LMIC that can inform improvements in neonatal and obstetric care and inform effective and appropriate models of care for neonates who survive complications in such contexts.

This thesis will address the need for improved local, long-term neonatal outcome data in the context of Fiji, a small geographically dispersed island country in the South Pacific. Specifically, I undertook the research described in subsequent chapters because paediatric colleagues in Fiji were concerned about long-term outcomes for children who required intensive care support as neonates but were difficult to follow-up after they were discharged from hospital, often to geographically remote villages and islands. Prior to this study, no data on the long-term health and developmental outcomes of these children were available and follow-up services in Fiji were very limited.

The geographic focus of this work builds on institutional linkages between the Department of Paediatrics, University of Melbourne and the Fiji Ministry of Health. The University of Melbourne, Department of Paediatrics has a strong track record of child health research in collaboration with colleagues in Fiji. While this thesis outlines a new
technical area of research within the Department, I hope that over time it will, like collaborative research initiatives before it, translate into meaningful improvements in care, in this case for ‘small and sick’ neonates in Fiji.

1.2 PURPOSE AND AIMS

The overall goal of this research is to provide quality local data on early childhood health and developmental outcomes for neonatal intensive care unit (NICU) survivors in Fiji, to inform improvements in neonatal care and follow-up, including early intervention, in that setting. The body of research described in this thesis has three main elements which contribute to achieving this goal;

1.2.1 Systematic review of existing neonatal outcome studies in LMIC

A systematic literature review of published neonatal outcomes studies in LMIC undertaken as background to research in Fiji; to inform sample size estimates of the prevalence of neurodevelopmental impairment for high-risk neonates in these settings and to better understanding gaps in the literature, at the outset of this work.

1.2.2 Neonatal outcomes study

A retrospective cohort study which aimed to assess and compare early childhood neurodevelopmental and health outcomes for neonates discharged from the CWMH NICU in Suva, Fiji compared with outcomes for ‘healthy’ control neonates born at term in the labour ward of the same hospital. Specifically, this research aimed to describe the prevalence of neurodevelopmental impairment in early childhood and potentially modifiable risk factors for adverse developmental outcomes in both groups.
CWMH Neonatal Intensive Care Unit (NICU) is the major neonatal referral service in Fiji and as such, provides care for most seriously ill neonates in the country. Within the scope of available funding, study participants were retrospectively recruited from CWMH and assessed from 18 months up to approximately four years of age.

1.2.3 Developmental screening accuracy study
A second study, nested within the main observational follow-up study, which explored the accuracy of nurse-led developmental screening compared with comprehensive developmental assessment, as a potential approach for early identification of developmental delay and impairment in this high-risk newborn population.

1.2.4 Implications for research and programmes
Building on these elements, we explore implications of this research for prevention, early identification, intervention and follow-up care for sick neonates in Fiji and, more broadly, also consider implications for improving measurement of developmental outcomes for sick neonates in Fiji and other similar contexts.

1.3 Potential significance

1.3.1 Data to improve obstetric, neonatal and follow-up care for high-risk neonates
Local developmental outcome data have potential to inform improvements in multiple aspects of care for high-risk neonates in Fiji. This thesis will especially focus on the potential for outcome data to strengthen prevention, early identification and intervention for neonates at increased risk of developmental impairment as a result of neonatal complications or illness.
1.3.2 Understanding the developmental needs of other young children

Prior to this research, data on early child development status and disability in childhood in Fiji was very limited. (Section 2.2.4) Although small scale and hospital based, this research adds to the available pool of data to better understand the epidemiology of childhood disabilities in Fiji.

1.3.3 Improved understanding of the what is needed to improve neonatal neurodevelopmental outcome data

This research also has the potential to inform the understanding of the challenges in measurement of child development outcomes within the health sector, cross culturally, in a multi-lingual and resource-limited setting where financial resources and staff technical capacity in child development are limited and where many existing measurement tools have neither been adapted nor validated. As will be further described elsewhere, limitations in current approaches to child development outcome measurement in LMIC not only create difficulties in high-risk newborn follow-up, but also in many other interventions where understanding child development impact is a priority. (Section 2.4)

1.3.4 Practical experience in follow-up to inform future models of care

This research has the potential to inform understanding about enablers and barriers to improved care including follow-up and early intervention for high-risk neonates in Fiji. Specifically, the process of undertaking this research provides a unique opportunity to better understand the structure and capacity of health and education services and referral pathways. Such knowledge is crucial to the future development and strengthening of contextually appropriate models of care for high-risk neonates in Fiji.
1.3.5 Implications for other low- and middle-income settings

While the major focus of this research is in Fiji, these findings have relevance to care of high-risk neonates in other middle-income and Pacific Island countries. In particular, since Fiji represents a regional focal point for newborn and child health in the South Pacific, findings are also relevant to other small Pacific Island Countries facing similar transitions in Neonatal Health. More broadly, this research adds to the limited pool of quality developmental outcome data for neonates in LMIC worldwide. It also provides detailed exploration of neurodevelopmental measurement challenges with potential to inform ongoing efforts to better measure impact of global efforts to improve newborn health ‘beyond survival’.

1.4 Thesis Overview

To achieve the above aims the thesis is divided into sections as outlined below. For orientation, each section also begins with its own brief outline and ends with a short section summary.

Section 1 - Introduction and overview of thesis including key definitions

This section has outlined the overall problem this thesis seeks to address, described the thesis purpose and aims and potential research significance. After providing an overview of the thesis in this section, definitions used throughout the thesis for key developmental and neonatal terms will also be outlined in Section 1.5.

Section 2 - Background

The background section provides a multidimensional description of the research context in Fiji, available developmental outcome data for high-risk neonates worldwide, our
published systematic review of similar previous studies in LMIC, and narrative review of challenges with defining both neonatal exposures and developmental outcomes for neonates in LMIC.

Section 3 - Neonatal outcomes study research design

Building on background provided in the previous section, this section details the research design for our neonatal outcomes study including an overview and detailed rationale for design choices made related to; study participants, primary and secondary outcome measures, sample size, procedures, data analysis plan, and ethics.

Section 4 - Neonatal outcomes study results

Results of the neonatal outcomes study are provided in the form of our paper published in Archives of Diseases in Childhood (2017).(3) Additional details of findings related to hearing and vision and outcomes which were not able to be included within the published article are also provided.

Section 5 - Neonatal neurodevelopmental outcomes study discussion

This section considers what our study adds to the existing neonatal outcomes literature in LMIC, limitations and how these were addressed. It also outlines implications of our study for informing improvements in neonatal care and follow-up in Fiji, as well as for improving neurodevelopmental outcomes measurement moving forwards.

This section also contextualizes the outcomes study within the bigger picture of global child health in the so-called Sustainable Development Goal era arguing for the need to improve neurodevelopmental outcome measurement to track change in global neonatal
and child development. Within this section, I will use the example of the Zika crisis to highlight the public health importance of addressing this measurement challenge.

The section will close by suggesting next steps and research priorities for improving neonatal neurodevelopmental outcome measurement in Fiji and other LMIC moving forwards.

**Section 6 - Nurse-led developmental screening accuracy study**

This section begins by outlining knowledge and implementation gaps related to developmental monitoring and early identification of children with developmental delay and impairment in LMIC, including in Fiji. It then describes our developmental screening accuracy study aims and objectives, potential significance, research design, procedures and data analysis. We then discuss findings of the study including which screening tools were selected for piloting and measured accuracy compared with the Bayley-III for detection of developmental delay and impairment. We consider what these findings mean in Fiji, allowing for study limitations.

The section closes with consideration of next steps and future research within which I highlight the example of EN-SMILING, a multi-country neonatal follow-up and developmental monitoring study exploring these developmental monitoring challenges in routine services.

**Section 7 - Follow-up care and early intervention – practical experiences and future directions**

While the core research completed within this doctorate was observational, in this section we consider practical experiences gained relevant to follow-up care including
early intervention for high-risk neonates in LMIC. It will include reflections on our practical experiences as a team related to; communication, transport, referral pathways, and responding to identified needs of children and families in research in LMIC. We will also consider, from the broader literature, requirements for follow-up health care and the substantial evidence and implementation gap related to follow-up care and early intervention for children with or at risk of developmental delay or impairment in these settings. To close this section, we will consider ongoing implementation research relevant to this area in Fiji, particularly Toso Vata (Moving Together), a pilot feasibility and acceptability study of a parent support and early intervention programme for young children with cerebral palsy which I am leading in Fiji.

Section 8 - Research translation in Fiji

In the penultimate section of this thesis we consider research translation activities related to this work in Fiji including relevance of our neonatal outcomes and developmental screening accuracy studies to national level neonatal and child development policies, service development and strengthening referral pathways. We also consider how this research collaboration has complemented other activities and supported leadership development in child development and disability in Fiji.

Section 9 - Conclusion

We conclude by drawing together key findings of our systematic review of previous neonatal outcomes literature, Fiji neonatal outcomes and developmental screening accuracy studies, summarizing how research aims and objectives have been answered. Implications for high-risk neonatal follow-up and early intervention in Fiji and ongoing
knowledge and implementation gaps warranting further research, to improve care of high-risk neonates in Fiji and other LMIC are highlighted.

1.5 Key definitions

This section provides definitions for relevant key terms used throughout the thesis including neonatal exposure variables (i.e. neonatal conditions, interventions) and outcomes. Standard definition and measurement of many of these factors, especially in LMIC, can be difficult and presents a major challenge to understanding neonatal outcomes in diverse settings. These challenges are described in more detail in subsequent sections of the thesis. (Sections 2.4 and 3.4)
Table 1: Key definitions used throughout thesis

<table>
<thead>
<tr>
<th>Term (Abbreviation)</th>
<th>Definition used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonatal</td>
<td></td>
</tr>
<tr>
<td>Neonate</td>
<td>Infant in the first 28 days after birth</td>
</tr>
</tbody>
</table>
| High-risk neonate                | A general term, variously defined in the literature with the broad aim of identifying neonates who warrant increased health and/or developmental surveillance and early intervention across a number of health, developmental and/or social domains. (24) Previously defined (2008) by the American Academy of Pediatrics as including: preterm infants; infants with special health care needs; infants at risk because of social issues and/or infant with an anticipated early death. (25)  
In this thesis the term is used broadly, except for where it directly refers to children enrolled in the neonatal outcomes study in Fiji, in which case the term high-risk group refers to children who had previously required admission at the CWMH NICU and met inclusion criteria for our study. |
| Preterm                          | Infant born < 37 completed weeks of gestation (or fewer than 259 d since the first day of the woman’s last menstrual period)                                                                                     |
| Extremely                        | Infant born < 28 weeks gestation                                                                                                                                                                             |
| Very                             | Infant born 28 - <32 weeks gestation                                                                                                                                                                          |
| Moderate/late                    | Infant born 32 - 36 weeks gestation                                                                                                                                                                            |
| Post-term                        | Infant born ≥42 weeks gestation                                                                                                                                                                              |
| Normal birth weight (NBW)        | Weight of 2,500 – 4,000g, irrespective of age                                                                                                                                                                |
| Low birth weight (LBW)           | Weight of <2,500g, irrespective of gestational age                                                                                                                                                            |
| Very low birth weight (VLBW)     | Weight of 1000 – 1,499g, irrespective of gestational age                                                                                                                                                      |
## Section 1 - Introduction

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extremely low birth weight (ELBW)</td>
<td>Weight of &lt;1000g, irrespective of gestational age (26)</td>
</tr>
<tr>
<td>Macrosomia</td>
<td>High birth weight, usually equal or greater than 4,000g but variously defined in the literature (26, 27) Within our neonatal outcomes study we used a cut-off of 4,200g.</td>
</tr>
<tr>
<td>Small for gestational age (SGA)</td>
<td>Infant below the 10th percentile of birth weight for gestational age, using local growth charts(26)</td>
</tr>
<tr>
<td>Neonatal encephalopathy (NE)</td>
<td>Neurological dysfunction in neonate &gt;35 weeks gestation which may be due to a number of causes, manifested by difficulty initiating and maintaining respiration, depression of tone and reflexes, abnormal level of consciousness and often by seizures, following and intrapartum hypoxic insult.(14)</td>
</tr>
</tbody>
</table>
| Hypoxic ischaemic encephalopathy (HIE)    | Neonatal encephalopathy likely due to intrapartum related events, further defined as; Onset within 2 days of birth of severe or moderate neonatal encephalopathy in infants born at 34 weeks or more gestation  
Acute perinatal event, and/or a 10min APGAR less than 5 or assisted ventilation for more than 10 minutes  
Ideally also the following: Evidence of metabolic acidosis (pH <7 or less or base deficit <12 mmol per litre)  
Other identifiable aetiologies (e.g. trauma, coagulation disorder, infectious conditions or genetic disorders excluded) (14, 23) |
| Birth asphyxia                             | Largely an historical term in high-income countries but still used in many LMIC including in Fiji. In this thesis it is used where is was recorded as a diagnosis in Colonial War Memorial Hospital Medical records. |
| Meconium aspiration syndrome (MAS)        | Respiratory distress in an infant born through meconium-stained amniotic fluid with chest x-ray findings consistent with MAS and whose symptoms could not be otherwise explained.(26) |
| Serious bacterial infection (SBI)          | Invasive bacterial infections including sepsis, meningitis and pneumonia ideally include isolation of bacteria from an otherwise sterile site in the body (e.g. blood or cerebrospinal fluid culture.(28) |
| Pneumonia                                 | Respiratory distress, especially with other clinical signs of sepsis, in a term infant who does not meet criteria for meconium aspiration syndrome or preterm respiratory distress syndrome,(29) |
| Sepsis                                    | Positive blood culture  
Clinical definition of neonatal sepsis based on an accepted algorithm(28)                                                                                                                          |
| Meningitis                                | Cerebrospinal fluid (CSF) positive for a causative organism OR positive antigen test                                                                                                                 |
### Section 1 - Introduction

| White cell count in cerebrospinal fluid of >50 cells per microlitre |
| Positive blood culture and/or gram stain |
| Blood glucose/CSF ration <0.1(23) |

| Hyperbilirubinaemia |
| Based on bilirubin level for aged and weight of newborn based on internationally accepted criteria.(30) Extreme hyperbilirubinaemia is defined at total plasma/serum bilirubin >25mg/dl/ (428 μmol/l) or those who require treatment with exchange blood transfusion.(30) |

| Hypoglycaemia |
| A persistent blood glucose level <2.6mmol/L or hypoglycaemia requiring bolus intravenous treatment although noting lack of evidence for specific biochemical cut-offs for diagnosis.(31) |

### Neurodevelopmental

#### Neurodevelopmental impairment (NDI)

| Impairment refers to loss or abnormality in body structure or physiological function (including mental functions), where abnormality means significant variation from established statistical norms.(4) Neurodevelopmental impairment was further defined as at least one of; |
| Score in ≥ 2 of cognitive, language AND/OR motor composite scales of <-2 standard deviations below standardised mean on the Bayley Scales of Infant and Toddler Development Third Edition® (Bayley-III)(32) |
| AND/OR diagnosis of cerebral palsy(33) |
| AND/OR hearing loss (an unaided hearing threshold in the better ear of 31dBHL or more)(34) |
| AND/OR visual acuity of <6/18 in the better eye(35) |

#### Developmental delay

| The condition in which a child’s development lags behind established normal ranges for his or her age. Delay is determined relative to normative development within a given population.(1) Defined according to performance on developmental assessment as; |

| Global: |
| Score in ≥ 2 of cognitive, language AND/OR motor composite scales of <-2 standard deviations below standardised reference mean (i.e. score <70) on the Bayley Scales of Infant and Toddler Development Third Edition® (Bayley-III)(32) |

| Mild global developmental delay |
### Section 1 - Introduction

<table>
<thead>
<tr>
<th>Condition</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Score in ≥ 2 of cognitive, language AND/OR motor composite scales of ≥-2 and &lt; -1 standard deviations below standardised mean (i.e. score ≥70 and &lt; 85) on the Bayley Scales of Infant and Toddler Development Third Edition® (Bayley-III)(32)</td>
<td></td>
</tr>
<tr>
<td>Domain specific (i.e. single domain): Score in one of cognitive, language or motor composite scales of &lt;-2 standard deviations below standardised reference mean on the Bayley Scales of Infant and Toddler Development Third Edition® (Bayley-III)(32)</td>
<td></td>
</tr>
</tbody>
</table>
| Hearing impairment | An unaided hearing threshold in the better ear of 31dBHL or more using pure tone average over octave frequency levels of 0.5, 1, 2, 4 Hz, further subdivided in children < 15 years into:  
  - Mild - audiometric hearing threshold of 26-30dB HL  
  - Moderate - audiometric hearing threshold of 31-60dB HL  
  - Severe - audiometric hearing threshold of 61dB HL or greater.(34) |
| Vision impairment | WHO use the following definitions of visual impairment;  
  - Mild - visual acuity of <6/12 in the better eye  
  - Moderate - visual acuity of <6/18 in the better eye  
  - Severe - visual acuity of <6/60 in the better eye  
  - Blind - visual acuity of <3/60 in the better eye(35) |
<p>| Cerebral palsy (CP) | A group of developmental disorders of movement and posture, causing activity restriction or disability, attributed to disturbances occurring in the foetal or infant brain.(33) In cerebral palsy, the primary neuromotor impairment is accompanied to varying extents, by a range of health morbidity, sensory and intellectual disabilities (e.g. seizures, feeding difficulties, respiratory disease, hearing and vision impairment.(33) |</p>
<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disability</td>
<td>An umbrella term for impairments, activity limitations, and participation restrictions, denoting the negative aspects of the interaction between an individual (with a health condition) and that individual’s contextual factors (environmental and personal factors). (36)</td>
</tr>
<tr>
<td>Developmental screening test</td>
<td>A brief measure used to identify children who are at risk of developmental problems in one or more domains. (37)</td>
</tr>
<tr>
<td>Developmental assessment</td>
<td>An assessment, typically longer in duration and more detailed than a screening test, which provides a range of scores representing children’s skill levels across and within domains, usually in comparison to a reference population. (37)</td>
</tr>
<tr>
<td>Developmental monitoring</td>
<td>Often used interchangeably with developmental surveillance in global child development literature, the term developmental monitoring is used throughout this thesis, to describe approaches in which a health care provider, who follows the child and family regularly, uses standardized instruments to monitor the child’s developmental functioning in all areas. (38) In this model, the child’s cognitive, language, social-emotional and motor development is followed on a regular basis, in conjunction with other aspects of the child’s health and the family’s functioning. Monitoring also includes working with the family to provide special support when needed to ensure the child’s optimal development. (38)</td>
</tr>
<tr>
<td>Early identification</td>
<td>The process by which risk factors associated with developmental difficulties and developmental delays, disabilities and disorders are identified in order to facilitate early intervention. (38)</td>
</tr>
<tr>
<td>Early intervention</td>
<td>A systematic and planned effort to promote development through a series of manipulations of environmental or experiential factors, initiated during the first five years of life. (38) Involves strategies which aim to intervene early in the life of a problem and provide individually tailored solutions. It typically focuses on populations at a higher risk of developing problems, or on families that are experiencing problems that have not yet become well established or entrenched. (36)</td>
</tr>
</tbody>
</table>
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2. BACKGROUND

2.1 SECTION OUTLINE

So far, we have introduced the central challenge this thesis seeks to address, namely a lack of long-term neonatal neurodevelopmental outcome data in Fiji. We have noted how in Fiji, as in many other middle-income countries, there has been substantial attention over several decades to the importance of reducing neonatal mortality. However, data to understand the long-term outcomes and needs of high-risk neonates who survive prematurity, neonatal encephalopathy (NE), serious bacterial infection (SBI) and other morbidity has been lacking. As such, neurodevelopmental outcome data are needed to inform improvement in obstetric and neonatal care and follow-up including early identification and intervention for children who experience long-term developmental complications.

This section provides further background to understand the research context in Fiji (Section 2.2), considers what is already known about neonatal outcomes for high-risk neonates worldwide (Section 2.3) and then explores the challenges in neonatal neurodevelopmental outcomes measurement in LMIC. (Section 2.4)

Section 2.2 provides a multidimensional description of the research context including consideration of sociocultural, demographic, neonatal and child health, child development and disability policy and programming factors. It highlights how neonatal and child health in Fiji is in transition which creates increasing need and opportunity to focus increased attention on beyond survival outcomes for high-risk neonates. The section also draws on the WHO, UNICEF and World Bank Nurturing Care Framework for early child development to provide a structure for situational analysis with regards to
Section 2: Background

existing policies and programmes for child development and disability including existing approaches to high-risk newborn follow-up, early identification and early intervention.(39)

Section 2.3 explores in more depth what is already known about mortality and neurodevelopmental outcomes for high-risk neonates worldwide. Specifically, we consider global modelled estimates (Section 2.3.2) and, although the focus of this research is mostly on Fiji and other LMIC, also briefly consider the evolution and lessons learned from neonatal outcomes research in HIC. Our systematic review, published in *Paediatrics and International Child Health*, is presented in whole to provide a detailed analysis of existing neonatal neurodevelopment outcome studies in LMIC and what data are already known from this.(2) (Section 2.3.3) It also provides an important structure for understanding key data gaps and beginning to explore challenges in collecting quality, comparable neurodevelopmental outcome data in LMIC. (Section 2.3.3)

Section 2.4 continues a more detailed overview of measurement challenges in considering neurodevelopmental outcomes across contexts, which becomes an underlying thread throughout the thesis. Specifically, this section provides an overview of challenges and approaches to measuring key neonatal exposure variables, especially gestational age and common neonatal conditions. It then also provides a description of the epidemiology of specific neurodevelopmental impairments, previously defined in Section 1.5, and approaches and challenges in assessing these across contexts.

Finally, in Section 2.5, this section closes with a summary of the key findings and implications for design of our neonatal outcomes and developmental screening accuracy studies in Fiji, which are then described in detail in Section 3.
2.2 **FIJIAN RESEARCH CONTEXT**

2.2.1 **Sociodemographic**

The Republic of the Fiji Islands (‘Fiji’) is a middle-income Pacific Island country with a population of 884,887 people (2019 data). Fiji consists of 322 geographically spread islands although approximately 75% of the population now live on the main Island of Viti Levu with the population particularly concentrated in and around the capital Suva. Fiji is increasingly urbanised with 55.9% of the population living in or around urban centres. An estimated 300 islands in Fiji are inhabited with many remote rural islands and the interior of the larger islands being difficult to access by road or boat.

The two main ethno-cultural groups in Fiji are the ‘iTaukei’ (Indigenous Fijians) (57%) and those of Indian descent (i.e. Indo-Fijians) (38%). The three predominant languages are English, the official national language, Fijian and Fijian-Hindi. Dominant religions in Fiji are Christianity, Hinduism and Islam.

The Fijian population is demographically young with a median age of 27.5 years. An estimated 29% of the population are aged less than 15 years and 40% less than 18 years. Average life expectancy is 67 years for males and 73 years for females.

Estimated gross national income per capita in 2013 was $7610 (PPP international, 2013). An estimated 15% of the population live in poverty, according to national standards, which is most pronounced in urban slum settlements and rural areas.

2.2.2 **Neonatal health**

When this research was established, the Millennium Development Goals (MDG) framed national child health policies and programming in Fiji, as in many other LMIC at that
In particular, in line with MDG 4, the primary goal of Fiji Child Health Policy (2010-2015) was to reduce childhood morbidity and mortality by two-thirds between 1990-2015. (10)

Around that time, the overall under 5 mortality rate was 25/1000 live births and since the neonatal mortality rate was 8-10/1000 live births, neonatal deaths accounted for approximately 44% of all deaths of children under the age of five years. (10) As such, in order to accelerate progress towards MDG 4, the Fiji Ministry of Health and Medical Services (MoHMS) prioritised efforts to improve neonatal survival. (10) In particular, the first area of strategic focus for national child health policy for the period 2010-2015 was to improve neonatal services, including follow-up care.

The National Child Health Plan (2010-15) listed the most common causes of neonatal mortality although definitions of terms were not provided. (10) For term/late preterm and NBW infants these included; ‘perinatal asphyxia’, meconium aspiration syndrome and sepsis. (10) For the estimated 10% of all infants born low birth weight (LBW) or those born moderate to extremely preterm these included; hyaline membrane disease, ‘perinatal asphyxia’, meconium aspiration syndrome and sepsis were the most common causes. (10)

In 2009, more than 98% of all deliveries in Fiji occurred in three divisional hospitals. Of these, approximately 40% of all deliveries (i.e. 7215 live births) occurred at the Colonial War Memorial Hospital (CWMH) in Suva. (10) Two intensive care units at CWMH in Suva and in Lautoka, on the west side of the main island Viti Levu, provided specialist care for sick neonates in Fiji. See Figure 1 below.
At CWMH a 25 bed NICU provides care to inborn neonates and the CWMH is also the major referral centre for ‘outborn’ neonates. For infection control purposes, outborn neonates are generally nursed separately in the adjacent Paediatric Intensive Care Unit (PICU), rather than the NICU itself. In 2009, the CWMH provided intensive care to a total of 571 neonates including 452 NICU patients and an additional 119 outborn neonates who were admitted to the CWMH PICU. Throughout the remainder of this document the term ‘NICU’ will be used to refer to any neonate receiving intensive care at the CWMH, in either the neonatal or general paediatric intensive care units.

Between 2006-2009 the estimated mortality rate for all NICU admissions was 10-13%. In 2009, survival rates were greater than 90% for neonates with a birth weight >2500g but remained less than 20% for <1000g (extremely low birth weight, ELBW)
neonates. (45) Neonates estimated to be 28 weeks gestation at delivery were not actively resuscitated unless independent respiratory effort was demonstrated. (45) For comparison, in Victoria, Australia in the 1970’s an estimated 25% of ELBW neonates survived but by the 1990’s this had increased to approximately 75%, an increase which has persisted in subsequent decades. (46, 47)

Care provided by CWMH NICU includes ventilatory support (continuous positive airways pressure (CPAP) and conventional ventilation), inotropic support and limited surgery. However, at the time this research was undertaken, surfactant therapy, important for prevention and management of lung disease associated with prematurity, was not available. In addition, allied health support, concepts of developmental care and monitoring for evolving developmental concerns and impairments among NICU patients, such as hearing and ophthalmology screening, were inconsistently applied or lacking. Specifically, although ophthalmology services existed, screening criteria and protocols were based on the American Academy of Pediatrics Guidance without local adaptation and capacity for corrective treatment (e.g. of retinopathy of prematurity if identified) was limited. (48) There were no pathways for neonatal hearing screening among NICU patients when this research was established.

Identified challenges in NICU included limited staff numbers, lack of staff specialist neonatal training, inadequate equipment and consumables and recurrent outbreaks of hospital acquired infections. (10) Further, after discharge, although there was nominally a neonatal follow-up clinic, in discussion with senior paediatric staff at CWMH, it was perceived to be inadequate for clinical need. After discharge, preterm neonates were provided with appointments to a weekly weigh clinic at CWMH until they reached 2.5kg, and other sick neonates were referred to the CWMH paediatric outpatient clinic on an
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as needs basis. However, clinicians reported that attendance at neonatal follow-up was poor and staffing was inadequate to support quality assessments and follow-up care. For example, we observed that one paediatric registrar would often see upward of twenty patients in a half-day clinic.

Additionally, at the initiation of this study, we observed that there was limited capacity to provide follow-up care or early intervention for neonates who subsequently developed neurodevelopmental complications. At the time that this research started, paediatric trainees received very little training in child development and although a physiotherapy clinic existed, to which children could be referred, it was our experience that many physiotherapists staffing the clinic had received little paediatric training and very little training in early motor intervention for children with physical disability. There were no permanent speech pathologists or occupational therapists in government child health services. (See also Section 2.2.4)

2.2.3 Child health and nutrition

Child health in Fiji is in an epidemiological transition. There are now high-levels of coverage of primary health care services (e.g. immunisation) and there have been important reductions in the overall burden of vaccine preventable disease although this remains an important ongoing cause of childhood mortality and morbidity.(43)

In addition to the previously described increasing emphasis on neonatal health, non-communicable diseases are also an increasing priority for the MoHMS. For example, although prevalence of stunting (i.e. height for age <-2SD) and wasting (i.e. weight for height <-2SD) are relatively low overall (8% and 6% respectively), there remain substantial geographic, ethnic and economic inequities.(49) In particular, over the past several years there have been increasing concerns among clinicians about hospital
admission rates for under-nutrition among vulnerable population sub-groups including urban poor, children living in remote areas and children with disability. Dietary diversity is poor with the 2004 National Nutrition Survey (NNS) indicating 50% prevalence of anaemia in children under five years of age. There have since been national public health initiatives to address this although follow-up data on prevalence of anaemia are not yet publicly available.(49) Exclusive breast feeding rates are low, estimated to be <40% at six months of age.(41)

2.2.4 Child development and disability

Previous sections have provided broad descriptions of the sociodemographic, neonatal and child health context in Fiji. In this section, we further explore the situation for early child development programming in Fiji. To do this we systematically consider the current situation in Fiji, relative to five domains of action, described in the WHO & UNICEF Nurturing Care for Early Child Development Framework (NCF) to promote child development in diverse settings.(39) The NCF is a policy framework which has been developed to accelerate country-level action to promote and support early child development in LMIC.(39) Early child development (ECD) is defined by the World Health Organization (WHO) as ‘children’s cognitive, physical, language, motor, and social and emotional development, between conception and 8 years of age.’(39) Nurturing care, a more recently defined term, refers to ‘the environment created by a caregiver which supports children’s health and nutrition, protects them from threats, and gives them opportunities for early learning, through interactions that are emotionally supportive and responsive’. (39) Within the NCF five key domains for action to support ECD include; health, nutrition, early learning, responsive caregiving and safety and security, as well
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as emphasising the importance of an enabling policy environment. (See Figure 2 below)(39)

Figure 2 Domains of WHO, UNICEF and World Bank Nurturing Care Framework


Since the context in Fiji with regards to child health and nutrition has already been described (Sections 2.2.2 and 2.2.3) in this section, we elaborate on the situation regarding early learning and responsive caregiving, safety and security and the broader policy environment.

2.2.4.1 Responsive caregiving and early learning

The NCF defines responsive caregiving as care which recognises and responds to children’s developmental cues including responsive feeding and primary caregiver-child
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interactions. It incorporates but goes beyond the scope of terms such as ‘psychosocial stimulation’ and/or ‘responsive stimulation’ that have been used to describe similar concepts in peer-reviewed ECD literature in the past. Early learning refers to formal and informal learning opportunities before primary school age.

Although national level indicators for responsive caregiving are lacking, UNICEF uses a range of indicators to describe opportunities for early learning, which are tracked in an increasing number of LMIC (e.g. access to books and objects for play in the home). However, to date data on these indicators are not available at national level and there are no universal parenting programmes in Fiji. Nevertheless, in recent years, there has been increasing national government support for and roll out of early childhood education services in Fiji although data on overall enrolment rates are not available. Primary school enrolment in Fiji is almost universal and 40% of 18 year old youths are enrolled in secondary school which represents a significant improvement over the course of several decades. School enrolment rates are comparable for males and females and adult literacy, as estimated from recent census data, is 94%.

2.2.4.2 Safety and security

The NCF considers ‘safety and security’ in terms of both the extent to which children and families have their basic needs met and protection of children from trauma, abuse and neglect.

World Bank data suggest that for the period 2002-2013, 34-40% of the population of Fiji lived below the national poverty line. There has been substantial improvement in household-level access to improved water and adequate sanitation and hygiene (WASH) over several decades which is important not only to health, but also child development with better WASH being associated with improved school attendance.
than 90% of households have access to improved drinking water (which is piped in almost 70% of households) and sanitation. Available UNICEF data suggest a high prevalence of ‘violent discipline’ (72%) of children.(51, 52) However, overall national level data on child trauma, abuse and neglect are limited.(52)

In spite of this, there has been progress with inter-agency service development to prevent and improve secondary prevention and management of child trauma, abuse and neglect in Fiji over the past several years. In 2008 a baseline report indicated the need for improved inter-sectoral action, in 2010, a National Child Welfare Decree was introduced, in 2012, the Fiji Ministry of Health released national ‘Child Protection Guidelines for Health Workers’ and subsequently there has been ongoing review of both progress and challenges.(53)

2.2.4.3 Epidemiology: early child development and disability prevalence data

In Fiji, there are no national level data on child development for children below school age and data on disability in childhood are also very limited. A baseline survey, undertaken by the Fiji National Council for Disabled persons in 2010 suggested that 3,019 children aged 5-19 years, and 1.4% of the total population, lived with a disability.(54) However, this is considered to be a substantial under-estimate, with a prevalence of 10% being closer to that expected from global survey data, although also dependent on definitions of disability used. (55, 56) Previous research on prevalence of vision impairment in Fiji suggested a prevalence of 1.1 per 1,000 (95% CI 1.1-1.2) for low vision and 0.4 per 1,000 (95% CI 0.3-0.4) for blindness.(57) Consistent with the situation in other LMIC, limited available data suggest that children with disability in Fiji, especially girls, are more likely to live in poverty or be excluded from educational opportunities.(55)
2.2.4.4 Policy and plans

There is no over-arching inter-sectoral national policy or coordinated plan for early child development in Fiji.\(^{(58)}\) While there is a national level early childhood education policy, this is not integrated with health.\(^{(59)}\) There are however, a number of policies and strategic plans related to the above areas (i.e. child protection, nutrition, disability) which are relevant to child development.\(^{(10, 49, 53, 58, 60)}\) The 2010-2015 National Child Health Policy and Strategy emphasised neonatal health as a strategic priority while child development and disability were noted as areas needing baseline situational assessment.\(^{(10)}\) (See also Sections 2.2.2 and 2.2.3)

2.2.4.5 Programmes and services

Within neonatal and child health programmes in Fiji, programmes for universal promotion of early child development are lacking.\(^{(10, 61)}\) To date, there are no formal national or scaled-up parenting programmes, although non-government organisations such as Save the Children Fiji, provide parenting support through facilitated community groups in some vulnerable communities (e.g. remote and periurban settlements).\(^{(61)}\)

Approaches to early identification of developmental difficulties (i.e. developmental surveillance) for children below school age are weak.\(^{(61)}\) Developmental surveillance from birth to 24 months is structured around a milestone based checklist which is included as part of maternal and child health checks. However, the checklists used are not validated and clinicians report poor completion and referral of children with concerns who often first present with difficulties when they start primary school. Further, there is very limited formal training for medical and nursing staff in child development including the principles and practice of developmental screening, surveillance and early intervention. Additionally, pathways for referral are often unclear,
as indicated by discussions during the course of this research, with both child health and education personnel.

Until recently, childhood hearing screening in Fiji was limited to two non-government organisations (NGOs), based in Suva. One of these provided screening and fitting of hearing aids to primary school aged children (i.e. Project Heaven, Hearing and Vision Enhancement Project) and the other which provided more detailed audiology assessments and hearing follow-up which has not been active for several years (i.e. the Carabez Alliance). Project Heaven also provided vision checks for primary school aged children and the Pacific Eye Institute, co-located with CWMH, also provided ophthalmology assessments for children referred from CWMH.

Early intervention services existed in Fiji, but were limited. In particular, there were physiotherapy and dietetic services for children at CWMH but these were more limited or lacking at other divisional and subdivisional hospitals. Further, even when allied health services existed, staff training in paediatrics was variable. There were no paediatric speech or occupational therapy personnel at CWMH or other hospitals in Fiji.

In Suva, there was one early intervention centre, with capacity to enrol 60 children aged 18 months-8 years. (62) For school-aged children there were 17 special developmental schools nationally, although these were typically under-resourced with allied health typically being provided by temporary, voluntary, NGO staff. (60) There were national level policies on inclusive education although anecdotally there remain many challenges in implementing these in practice. (63)
2.3 NEURODEVELOPMENTAL OUTCOMES FOR HIGH-RISK NEONATES WORLDWIDE: WHAT IS ALREADY KNOWN?

2.3.1 Global estimates of neurodevelopmental impairment among survivors of common neonatal conditions

Global epidemiological data highlight the public health importance of increased focus on long-term outcomes for neonates who survive illnesses and complications. Specifically, estimates published by Blencowe H et al. and Mwaniki MK et al. in 2012 and in the ‘Beyond Survival’ series in 2013 provided landmark global estimates of the numbers of neonates who experience preterm birth, neonatal encephalopathy, serious bacterial infections or severe hyperbilirubinaemia worldwide every year and survive. (Table 2) (13-15, 23, 30, 64) This section highlights these estimates, using key definitions provided in relevant reference publications, which may differ slightly to those outlined earlier in Section 1.5, which are used throughout this thesis. Challenges in defining neonatal conditions and outcomes in LMIC are discussed further in Section 2.4, including the rationale for selection of definitions used throughout this thesis.
## Table 2: Global estimates of survivorship and impairment following common neonatal conditions

<table>
<thead>
<tr>
<th>Condition</th>
<th>Definition used in reference publication</th>
<th>Global estimated total number of neonates with condition n (millions)* (95% uncertainty range)</th>
<th>Number of neonates with condition surviving into post-neonatal period (i.e. &gt;28 days of life) n (millions) (95% uncertainty range)</th>
<th>Global estimated total number of neonates with moderate to severe NDI (thousands)* (95% uncertainty range)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prematurity</strong></td>
<td>Infant born before 37 completed weeks of gestation</td>
<td>14.9 (12.3-18.1)</td>
<td>13 (12.7-14.3)</td>
<td>345,000 (269,000–420,000)</td>
</tr>
<tr>
<td><strong>Extreme</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very</td>
<td>Infant born &lt; 28 weeks gestation</td>
<td>0.8 (0.8-0.9)</td>
<td>0.14 (0.1-0.2)</td>
<td></td>
</tr>
<tr>
<td>Infant born 28 - &lt;32 weeks gestation</td>
<td></td>
<td>1.6 (1.5-1.7)</td>
<td>0.86 (0.8-1.0)</td>
<td></td>
</tr>
<tr>
<td><strong>Moderate to late</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infant born 32 - 36 weeks gestation</td>
<td></td>
<td>12.6 (12.3-14.0)</td>
<td>12 (11.6-13.2)</td>
<td></td>
</tr>
<tr>
<td><strong>Neonatal encephalopathy due to intrapartum related events</strong></td>
<td>‘Disturbance of neurological function in the earliest days of life in a term infant manifested by difficulty initiating and maintaining respiration, depression of tone and reflexes, abnormal level of consciousness and often by</td>
<td>1.1 (0.9-1.6)</td>
<td>0.9 (0.5-1.4)</td>
<td>233,000 (163,000–342,000)</td>
</tr>
</tbody>
</table>
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<table>
<thead>
<tr>
<th>Possible severe bacterial infection (pSBI) (&gt;32 weeks gestation)</th>
<th>‘As defined by the WHO Young Infant Study 2: Any one of the following: a history of difficulty feeding, convulsions, movement only when stimulated, respiratory rate of 60 breaths per min or more, severe chest indrawing, temperature ≥ 37.5 or ≤35.5°C’</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sepsis</strong></td>
<td>Clinical signs of pSBI, with a blood culture positive for a pathogenic organism</td>
</tr>
<tr>
<td><strong>Meningitis</strong></td>
<td>Clinical signs of pSBI with a CSF culture positive for a pathogenic organism or a raised leucocyte count (&gt;50 ×10⁶/ml) in cerebrospinal fluid</td>
</tr>
<tr>
<td><strong>Pneumonia</strong></td>
<td>Clinical signs of pneumonia (fast breathing, indrawing) and informed by chest x-ray</td>
</tr>
<tr>
<td></td>
<td>1.7 (1.4-2.4)</td>
</tr>
<tr>
<td></td>
<td>0.2 (0.0-0.4)</td>
</tr>
<tr>
<td></td>
<td>0.5 (0.2-0.9)</td>
</tr>
<tr>
<td></td>
<td>0.9 (0.5-1.2)</td>
</tr>
<tr>
<td></td>
<td>0.1 (0.0-0.2)</td>
</tr>
<tr>
<td></td>
<td>0.3 (0.1-0.5)</td>
</tr>
<tr>
<td></td>
<td>No data</td>
</tr>
<tr>
<td>No data</td>
<td>18,000 (2,700–35,000)</td>
</tr>
</tbody>
</table>

Section 2: Background

Overall, an estimated one in five of the world’s neonates require additional special or intensive care in hospital every year and 15.1 million neonates survive serious illness, the majority in LMIC.(1, 13-15, 30, 65)

Modelled estimates provided by Mwaniki MK et al. suggest that worldwide, 18.5% of neonates who survive complications such as prematurity, birth asphyxia or serious bacterial infection experience severe NDI including cerebral palsy, cognitive, hearing or visual impairment.(23) These and estimates later provided in the 2013 Beyond Survival Series Pediatric in Research (Table 1) highlight the substantial number of children worldwide affected by common neonatal conditions every year, who survive and experience long-term developmental complications as a result of neonatal conditions.(13, 15, 30, 65, 66) These landmark modelled estimates have been important in advocating for the need to both improve care in order to reduce neonatal deaths and also to improve longer-term outcomes for the substantial number of children who experience these conditions and survive.(67)

However, there are also important limitations to these data, such as limitations in the primary data from which they are derived and challenges in standardising definition and measurement of these conditions across settings, which are discussed further in Section 2.4.2). These limitations, highlight the need to improve the availability and quality of primary data from LMIC to strengthen understanding of the needs of children who experience neonatal complications in these settings moving forwards.(67)

2.3.2 Long-term outcomes following neonatal illness and complications in high income countries

Given the paucity of primary neonatal outcome data from LMIC, our research hypotheses related to neonatal neurodevelopmental outcomes in Fiji were not only informed by data
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from similar LMIC, but also informed by a broader understanding, based on data from HIC, of the spectrum of neurodevelopmental outcomes children experience following diverse neonatal conditions in those contexts.

In this section key concepts and the scope of evidence available from neonatal neurodevelopmental outcomes research in HIC are highlighted, drawing especially on data related to neurodevelopmental outcomes following preterm birth. In so doing, I acknowledge that it is beyond the scope of this thesis to more systematically review the vast available data across a wide range of neonatal conditions, now available through neonatal outcomes research in HIC.

Historically, neonatal neurodevelopment outcome studies in HIC initially studied survival to hospital discharge and then, once post-discharge neurodevelopment was considered, focused predominantly on diagnosis of NDI commonly defined by at least one of; cerebral palsy, hearing or vision impairment or global developmental delay on standardised developmental assessments in early childhood (i.e. 0-3 years). Using these criteria, data from diverse HIC have shown that preterm infants are at increased risk of a range of NDI such as cerebral palsy and sensory impairments (e.g. hearing and visual impairment) and/or global developmental delay with risk increasing in inverse proportion to gestational age and rising rapidly at or below 32 weeks gestation.(14, 68) Of note, in many HIC settings, long-term neurodevelopmental outcome data are available for gestational ages, considered borderline for viability (i.e. 22-25 weeks), which are not compatible with life in many LMIC. For example, by contrast, in Fiji when this research was undertaken it was not standard practice to resuscitate children <1,000g or <28 weeks gestation.
However, as neonatal outcomes research in HIC has evolved, outcomes measured have expanded in scope and the time periods for which data are available. In particular, there has been a recognition of increased risk following neonatal morbidity for longer-term, milder ‘impairments’ in a broader range of developmental domains than were considered in the past.\(^{(18)}\) For example, there are effects on emotion, behaviour, attention, social and adaptive functioning, cognition and educational performance.\(^{(69-71)}\) Data demonstrate that 50-70\% of very low birth weight infants (i.e. infants born <1500gm) in HIC experience this sort of ‘low severity’ neurodevelopmental dysfunction.\(^{(18)}\) While identification of this sort of dysfunction is often delayed, it is also important for predicting longer term social outcomes, academic achievement and quality of life.\(^{(69, 71)}\) Hence there has been increased recognition of the prevalence and population level importance of such high prevalence, low severity neurodevelopment outcomes for high-risk neonates.

Literature from high-income settings also demonstrates that infants born preterm, even late preterm infants are at increased risk, compared with the broader paediatric population, of a range of health problems through childhood into adult life.\(^{(72)}\) In early childhood, preterm infants have increased health care utilisation and risk of respiratory illness and growth and nutritional issues. \(^{(72)}\) Increasingly, links between neonatal complications, including prematurity and chronic adult health issues such as the metabolic syndrome are also documented.\(^{(72, 73)}\) Even in HIC, there is an inverse association between gestational age and mortality which, although it fluctuates over time, has been shown to persist into adult life.\(^{(18)}\) In addition, population level data mostly from Scandinavia, demonstrates a long-term association between preterm birth and other adult outcomes including education and socioeconomic status.\(^{(74)}\)
Of course, as noted earlier, while we have focused here on outcome data for preterm survivors, in HIC as neonatal care has improved, long-term neurodevelopmental outcome data for neonates with a diverse range of conditions (e.g., surgical conditions, rare genetic disorders) have also been increasingly well described. Such data, typically shared in HIC through large multi-institution and international research networks, has made a major contribution to improving the quality of care including; obstetric, neonatal and developmental care for high-risk neonates including early identification and intervention adverse neurodevelopmental and sensory outcomes (i.e., hearing and vision impairment).

2.3.3 Systematic review of neonatal neurodevelopmental outcome studies in LMIC (Published paper)

Although collection of local neonatal outcome data is key to improving the quality of neonatal care and follow-up in LMIC, as it has been in HIC in the past, there are many challenges to obtaining meaningful long-term neonatal outcome data in such settings.

To better understand what neonatal neurodevelopmental outcome data are available in LMIC and how others in the field have approached common measurement challenges, we undertook a systematic review of the published literature to inform the design of our research in Fiji. The systematic review, as published in Paediatrics and International Child Health is included below. Following the paper, challenges in measuring neonatal exposure and neurodevelopmental outcomes in LMIC will be discussed in more detail. (Section 2.4)
Long-term neurodevelopmental outcome in high-risk newborns in resource-limited settings: a systematic review of the literature

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1Centre for International Child Health, Department of Paediatrics, The University of Melbourne, Parkville, Australia, 2Royal Children’s Hospital Melbourne, Parkville, Australia, 3Murdoch Children’s Research Institute, Parkville, Australia

Background: Improving outcomes beyond survival for high-risk newborns in resource-limited settings is an emerging challenge. Global estimates demonstrate the scale of this challenge and significant gaps in morbidity outcome data in high mortality contexts. A systematic review was conducted to document the prevalence of neurodevelopmental impairment in high-risk newborns who were followed up into childhood in low- and middle-income countries.

Methods: High-risk newborns were defined as low, very or extremely low birthweight, preterm infants or those surviving birth asphyxia or serious infections. Electronic databases were searched and articles screened for eligibility. Included articles were appraised according to STROBE criteria. Narrative review was performed and median prevalence of key neurodevelopmental outcomes was calculated where data quality allowed.

Results: 6959 articles were identified with sixty included in final review. At follow-up in early childhood, median estimated prevalence (inter-quartile range) of overall neurodevelopmental impairment, cognitive impairment and cerebral palsy were: for survivors of prematurity/very low birthweight 21.4% (11.6–30.8), 16.3% (6.3–29.6) and 11.2% (5.9–16.1), respectively, and for survivors of birth asphyxia 34.6% (25.4–51.5), 11.3% (7.7–11.8) and 22.8% (15.7–31.4), respectively. Only three studies reporting outcomes following newborn serious bacterial infections were identified. There was limited reporting of important outcomes such as vision and hearing impairment. Major challenges with standardised reporting of key exposure and developmental outcome variables and lack of control data were identified.

Conclusion: Understanding the limitations of the available data on neurodevelopmental outcome in newborns in resource-limited settings provides clear direction for research and efforts to improve long-term outcome in high-risk newborns in these settings.

Keywords: Newborn infant, Preterm infant, Birth asphyxia, Very low birthweight, Meningitis, Sepsis, Developmental disabilities, Hearing and vision impairment

Introduction

Worldwide, an estimated 2.9 million newborns die each year, predominantly from prematurity, birth asphyxia, serious bacterial infection and congenital malformations.1 A further estimated 15.1 million neonates survive prematurity, birth asphyxia, serious bacterial infection every year, and these children are at high risk of adverse neurodevelopmental outcome.2–4 Most of these newborns live in resource-limited settings in which occur more than 90% of preterm births and birth asphyxia, and which bear the greatest burden of serious bacterial infections.2–5

Research from high-income settings highlights the long-term increased risk of neurodevelopmental sequelae in survivors of prematurity and very low-birthweight (VLBW)-infants compared with their term/normal birthweight peers.6 Specifically, preterm and VLBW survivors are at increased risk of poorer cognitive outcomes, cerebral palsy, hearing and vision impairments, adverse emotional–behavioural and academic outcomes, and the risk increases with decreasing gestational age and birthweight.6 Similarly, outcome research in high-income settings highlights that newborns who survive neonatal encephalopathy, including hypoxic ischaemic
encephalopathy or serious bacterial infection such as neonatal meningitis, have a significant long-term risk of adverse neurodevelopmental, academic and behavioural sequelae.\textsuperscript{7,8}

For this reason, newborns who survive prematurity, VLBW, birth asphyxia and serious bacterial infections are considered to be at ‘high risk’ of adverse developmental outcomes. In many high-income settings, guidelines have been developed for follow-up care including screening, evaluation and early intervention for developmental complications when they are identified.\textsuperscript{9}

By contrast, until recently, long-term outcomes for high-risk newborns in resource-limited settings have received little attention in the global health literature because the challenge of newborn health in these settings has traditionally been defined almost exclusively as survival.

Recent publications have highlighted the scale of the emerging challenge of outcomes ‘beyond survival’ in resource-limited contexts. In particular, it has been estimated that, worldwide, 18.5% of newborns who survive complications such as prematurity, birth asphyxia or serious bacterial infection develop severe neurodevelopmental impairment including cognitive impairment, cerebral palsy and hearing or visual impairment.\textsuperscript{10} Published reviews have also highlighted the major gap in primary data from settings with the highest morbidity.\textsuperscript{11-13} Better understanding of outcomes in high-risk newborns in resource-limited settings is therefore needed to guide development of newborn health policy, including systems of follow-up and early intervention which are feasible, effective and appropriate.

The aim of this review is to systematically describe studies of long-term neurodevelopmental outcome in high-risk newborns in low- and middle-income countries. It is hoped that this might help in considering the next steps required to improve outcome metrics, and assist in strategies to improve developmental outcome in these newborns.

\section*{Methods}

\subsection*{Search strategy}

Medline via Ovid, Cumulative Index to Nursing and Allied Health Literature, and Cochrane and Embase from January 1996 to end of April 2012 were searched. Studies describing post-neonatal (\textgreater{}28 day) health and developmental outcome in infants who were premature (\textless{}37 weeks gestation), of low birthweight (\textless{}2500 g), very low birthweight (\textless{}1500 g) or extremely low birthweight (\textless{}1000g) or who experienced intrapartum-related events (‘birth asphyxia’) or serious infections (i.e. sepsis, pneumonia or meningitis) were included. Only studies which included overall measures of child development were included. Studies of only hearing or visual outcome in high-risk newborns were not the primary focus of this review.


Available abstracts were screened by two independent reviewers (EN, KM) who assessed suitability for inclusion. Inclusion criteria were defined as prematurity, low birthweight, intrapartum-related events (‘birth asphyxia’) or serious newborn infections as per definitions above with subsequent measurement of health and developmental outcomes beyond the neonatal period.

The following were excluded: case reports, case series where less than 30 patients were included, narrative reviews or opinion pieces, studies focusing on outcomes in the neonatal period (days 0–28) only, studies with HIV, malaria, tuberculosis, congenital infections, congenital anomalies or surgical conditions as the primary subject area, studies based in high-income countries and those without the full text available in English.

Articles which focused on neurodevelopmental status as a key outcome measure for the final review were selected. Disagreements about inclusion were resolved by discussion between EN and KM (Fig. 1).

\subsection*{Quality assessment and data extraction}

Methodological quality was assessed according to the STROBE statement checklist for observational studies including assessment of study design, sampling methods, sample size, outcome measurement and follow-up rate.\textsuperscript{14} An adapted version of a quantitative grading system used in previously published studies by the Public Health Agency of Canada was applied.\textsuperscript{15} This grading system assigns a score of 0–8 for study quality.\textsuperscript{15} Quality scores were assigned by KM and tabulated (Appendices 1 and 2, Tables 1–4).

\subsection*{Data synthesis}

Because of the heterogeneity and variable quality of the studies available, a systematic summary rather than meta-analysis was performed. For prematurity/VLBW and birth asphyxia follow-up studies, the overall prevalence of key neurodevelopmental outcomes was expressed as median and interquartile
range, taking into account studies with a quality score of five or more. For the limited available outcome studies of serious bacterial infections, mixed neonatal intensive care unit cohorts and population-based birth cohorts, a narrative review was undertaken because limitations of the data made summary statistics less meaningful.

**Results**
The search strategy identified 6959 article titles of which 6032 were excluded on the basis of the title and abstract; 927 articles therefore underwent abstract or full-text review, 866 of which were excluded because they were not directly relevant to the topic (Fig. 1).

Sixty studies were included in the final review. Of these, the majority (33) were pre-term or low-birthweight (LBW) populations. A smaller number focused on newborns with birth asphyxia (17) or heterogeneous ‘high risk’ cohorts (i.e. neonatal intensive care populations) (6). One study followed neonates with meningitis and two followed survivors of sepsis. (Tables 1–4, references in Appendix 2)
## Table 1: Studies of pre-term and very/low-birthweight infants: summary

<table>
<thead>
<tr>
<th>Author</th>
<th>Country</th>
<th>Newborn sub-group</th>
<th>Quality score 0–8</th>
<th>Cases</th>
<th>Age, mths</th>
<th>Cognitive impairment</th>
<th>Cerebral palsy</th>
<th>Language impairment</th>
<th>Hearing impairment</th>
<th>Visual impairment</th>
<th>Seizures</th>
<th>Overall NDI</th>
</tr>
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<tbody>
<tr>
<td>Ballot**</td>
<td>South Africa</td>
<td>VLBW</td>
<td>7</td>
<td>178</td>
<td>16</td>
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<td>9.4</td>
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<td>–</td>
<td>–</td>
<td>15.1</td>
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<tr>
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<td>VLBW</td>
<td>7</td>
<td>127†</td>
<td>12</td>
<td>‡</td>
<td>†‡</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>19.7 (severe)</td>
</tr>
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<td>31.2</td>
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<tr>
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<td>131†</td>
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<td>‡</td>
<td>†‡</td>
<td>–</td>
<td>–</td>
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<td>–</td>
<td>–</td>
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<tr>
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<tr>
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<td>247†</td>
<td>24</td>
<td>–</td>
<td>‡‡</td>
<td>2.6</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>3.9 (severe)</td>
</tr>
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<td>‡‡</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
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</tr>
<tr>
<td>Silveira**</td>
<td>Brazil</td>
<td>VLBW/pre-term</td>
<td>6</td>
<td>86</td>
<td>18</td>
<td>‡</td>
<td>‡‡</td>
<td>–</td>
<td>–</td>
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<td>–</td>
<td>4.7 (severe)</td>
</tr>
<tr>
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<td>20</td>
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<td>8</td>
<td>8</td>
<td>23</td>
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<td>12</td>
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<td>35</td>
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<td>–</td>
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<td>–</td>
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<td>83†</td>
<td>96</td>
<td>‡‡</td>
<td>††</td>
<td>0.0</td>
<td>††</td>
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<td>4</td>
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<tr>
<td>Ho</td>
<td>Malaysia</td>
<td>VLBW</td>
<td>5</td>
<td>83†</td>
<td>24</td>
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<td>–</td>
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<td>–</td>
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<td>Procianoy**</td>
<td>Brazil</td>
<td>VLBW</td>
<td>5</td>
<td>121</td>
<td>24</td>
<td>48†</td>
<td>28†</td>
<td>–</td>
<td>–</td>
<td>16.8</td>
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</tr>
<tr>
<td>Procianoy**</td>
<td>Brazil</td>
<td>VLBW (massage RCT)</td>
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<td>73</td>
<td>24</td>
<td>0.3</td>
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<td>Stoinska**</td>
<td>Poland</td>
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<td>1.7</td>
<td>4.8</td>
<td>3.1</td>
<td>30.7</td>
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<td>175</td>
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<td>9.2</td>
<td>11.7</td>
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<td>–</td>
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<td>–</td>
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<td>Afzal</td>
<td>Pakistan</td>
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<td>87</td>
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<td>–</td>
<td>16.6</td>
<td>9</td>
<td>4.5</td>
<td>–</td>
<td>6</td>
<td>94 (severity not stated)</td>
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<td>Cooper</td>
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<td>113</td>
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<td>–</td>
<td>–</td>
<td>–</td>
<td>17.4</td>
</tr>
<tr>
<td>Manaceros</td>
<td>Brazil</td>
<td>Pre-term</td>
<td>4</td>
<td>37</td>
<td>14</td>
<td>–</td>
<td>‡‡</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Metgud</td>
<td>India</td>
<td>VLBW</td>
<td>4</td>
<td>45</td>
<td>12</td>
<td>–</td>
<td>‡‡</td>
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<td>–</td>
<td>–</td>
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<tr>
<td>Modrusan-Mozetic**</td>
<td>Croatia</td>
<td>VLBW/pre-term</td>
<td>4</td>
<td>49</td>
<td>48</td>
<td>34.7</td>
<td>43.5</td>
<td>–</td>
<td>2.1</td>
<td>39.1</td>
<td>–</td>
<td>36.9</td>
</tr>
</tbody>
</table>
Study quality was variable. Thirty-seven of the 60 studies had a quality score of five or more. Common methodological issues that reduced the quality score included studies which were single-institution rather than population-based, regional or multi-centre ones; small sample sizes; high rates of loss to follow-up; lack of control newborns to facilitate meaningful interpretation of results; poor quality assessment of developmental outcome measures and assessors who were not blinded.

Studies were heterogeneous with regard to details of exposure and outcome measurements, as outlined further below, making comparison between studies challenging.

Pre-term and low-birthweight studies (n = 33) (Table 1, references in Appendix 2)

Pre-term/LBW studies were from many regions and spanned a number of decades. Most studies were small (median sample size n = 122, IQR 84–171), hospital-based and observational with only seven including control populations. Only one study followed a cohort of community-born pre-term newborns. There were three randomised controlled trials. Duration of follow-up in these studies varied from 6 months to 13 years.

The majority of studies which defined subjects primarily according to birthweight focused on outcome in VLBW populations. While some of these studies included an extremely low-birthweight (ELBW) sub-group, only one focused exclusively on ELBW infants, consistent with the high overall mortality profile of ELBW infants in many resource-limited settings but in contrast with many contemporary outcome studies in high-income countries.

In studies which assessed outcome in VLBW and/or pre-term infants, the prevalence of cognitive impairment at follow-up varied significantly with a median of 16.3% (IQR 6.3–29.6). As would be expected, the prevalence of cognitive impairment in the single high-quality LBW follow-up study was low compared with the prevalence in VLBW studies (e.g. 0.1% in Charpak et al.). The median prevalence of cerebral palsy in studies in this group was 11.2% (IQR 5.9–16.1). The median overall prevalence of moderate-to-severe neurodevelopmental impairment was 21.4% (11.6–30.8). A minority of studies also reported other outcome measures including language, hearing and visual impairment and seizures.

Birth asphyxia (n = 17) (Table 2, references in Appendix 2)

Most birth asphyxia follow-up studies (i.e. 12/17) were small (median sample size n = 90, IQR 57–108), single-institution cohort studies, and only...
<table>
<thead>
<tr>
<th>Author</th>
<th>Country</th>
<th>Newborn sub-group</th>
<th>Quality score 0–8</th>
<th>Cases</th>
<th>Age mths</th>
<th>Neurodevelopmental impairment</th>
<th>Cognitive impairment</th>
<th>Cerebral palsy</th>
<th>Language impairment</th>
<th>Hearing impairment</th>
<th>Vision impairment</th>
<th>Seizures</th>
<th>Overall NDI</th>
</tr>
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<tr>
<td>Carlo†‡§</td>
<td>India</td>
<td>Birth asphyxia‡</td>
<td>8</td>
<td>123</td>
<td>36</td>
<td>4.1†</td>
<td>–</td>
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<td>–</td>
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<td>–</td>
<td>–</td>
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<td>Bhareja†‡§</td>
<td>India</td>
<td>Birth asphyxia‡</td>
<td>6</td>
<td>130</td>
<td>6</td>
<td>11.3</td>
<td>–</td>
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<td>–</td>
<td></td>
</tr>
<tr>
<td>Boo†§</td>
<td>Malaysia</td>
<td>Birth asphyxia‡</td>
<td>6</td>
<td>104†</td>
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<td>–</td>
<td>22.8</td>
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<td>–</td>
<td>27.1 (severe), 44.2 (any)</td>
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<tr>
<td>Nair†‡ §</td>
<td>India</td>
<td>Birth asphyxia‡</td>
<td>6</td>
<td>108†</td>
<td>12</td>
<td>–†</td>
<td>–</td>
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<td>–</td>
<td>–</td>
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<tr>
<td>Zhou†</td>
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<td>–</td>
<td>15.9       60–100</td>
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<td>Thompson†</td>
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<td>El-Ayouty†</td>
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<td>18</td>
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<td>72†§§</td>
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<td>Hallioglu†</td>
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<td>Birth asphyxia‡</td>
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<td>57</td>
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<td>20</td>
<td>–</td>
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<td>–</td>
<td>–</td>
<td>11.7       20</td>
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<td>Jiang†</td>
<td>China</td>
<td>Birth asphyxia‡</td>
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<td>48–144</td>
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<td>18</td>
<td>10.8 (hypothermia), 24.4 (control)</td>
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<td>–</td>
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<td>3.5        26.1</td>
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<td>Begun†</td>
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<td>Birth asphyxia‡</td>
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<td>24</td>
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<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>60 Any NDI, severe NDI 16.6</td>
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<tr>
<td>Calkavu†‡</td>
<td>Turkey</td>
<td>Birth asphyxia‡</td>
<td>3</td>
<td>40</td>
<td>12</td>
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<td>–</td>
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<td>–</td>
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<td>Birth asphyxia‡</td>
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<td>Birth asphyxia‡</td>
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<td>–</td>
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<td>–</td>
<td>18.3 (severe) 16.7 (mild)</td>
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*Overall neurodevelopmental impairment: moderate-to-severe unless stated otherwise; †prevalence of motor scores on standard testing <70 provided; ‡randomised trial, includes intervention and control arms; §study includes low-risk control group; ¶high risk/scores on developmental screening test; †mean developmental scores only provided.
### Table 3 Summary of sepsis and meningitis studies

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<th>Author</th>
<th>Country</th>
<th>Newborn sub-group</th>
<th>Quality score 0–8</th>
<th>Cases</th>
<th>Age mths</th>
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<th>%</th>
<th>%</th>
<th>%</th>
<th>%</th>
<th>%</th>
<th>%</th>
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<td>Brazil</td>
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<td>86</td>
<td>12</td>
<td>Cerebral palsy</td>
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<td>Daoud53</td>
<td>Jordan</td>
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<td>3</td>
<td>53</td>
<td>16</td>
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* Neurodevelopmental impairment: moderate-to-severe unless stated otherwise; † prevalence of motor scores on standard testing > 70 provided.

### Table 4 Summary of mixed NICU and population-based cohort studies

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<th>%</th>
<th>%</th>
<th>%</th>
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* Neurodevelopmental impairment: moderate-to-severe unless stated otherwise; † prevalence of ‘abnormal neurological examination’ less than 6 months given only; ‡ study also includes low-risk control group
two had a healthy newborn control group. Five studies were randomised controlled trials, mostly relating to trials of therapeutic hypothermia. Duration of follow-up in these studies varied from 6 months to 12 years.

For birth asphyxia follow-up studies, median measured prevalence of cognitive impairment was 11.3% (IQR 7.7–11.8). The prevalence of cerebral palsy in these studies varied widely with a median of 22.8% (IQR 15.7–31.4). The overall estimated median prevalence of neurodevelopmental impairment in this sub-group was 34.6% (IQR 25.4–51.5), although there was notable variability and difficulty in ascertaining the severity of neurodevelopmental impairment in a number of studies. Other outcomes including language, hearing and visual impairment and the prevalence of seizures were measured in a very small minority of studies.

Serious infections (i.e. meningitis, sepsis, pneumonia) (n = 3) (Table 3, references in Appendix 2)

There were very few studies of this newborn sub-group. One study by Daoud et al. in Jordan evaluating neurodevelopmental sequelae up to 2.5 years after neonatal meningitis was identified. This was a small, two-institution cohort, with no control group to identify background neurodevelopmental risk. It reported an overall neurodevelopmental impairment prevalence of 39%. Two prospective, hospital-based studies in Brazil explored outcome in VLBW infants with sepsis. Both were single-institution cohort studies with a VLBW control group. Ferreira et al. estimated a very high prevalence (47.7%) of cognitive impairment at 12 months in VLBW infants following sepsis. In both this and the study by Hentges et al., the prevalence of adverse neurodevelopmental outcome was greater in VLBW infants than in non-affected VLBW infants. Hentges et al. assessed the prevalence of cerebral palsy in VLBW following sepsis to be 3.2%. Ferreira et al. noted a very high (i.e. 33.7%) prevalence of neuromotor impairment on standardised testing. Hentges et al. reported the overall prevalence of neurodevelopmental impairment following sepsis in VLBW infants at 2 years to be 6.1%. No studies of neurodevelopmental outcome following neonatal pneumonia were identified.

Heterogeneous neonatal intensive care cohorts (n = 6) (Table 4, references in Appendix 2)

Six studies included heterogeneous cohorts defined on the basis of admission to hospital neonatal intensive care units. One was a multi-centre cohort study and the others focused on single institutions. Only one of these studies included a control group. Duration of follow-up varied from 2 months to 6 years.

Overall prevalence of cognitive impairment in these studies varied markedly, from 5.8 to 52%, with results at the upper end of this range often reflecting a lower cut-off for definition of cognitive delay (e.g. reporting of standard scores ≤85 rather than scores <70). The reported prevalence of cerebral palsy varied from 5% to 9.4%. Paul et al. and Molteno et al. reported the overall prevalence of neurodevelopmental impairment, variably defined, to be 10% and 15%. The prevalence of hearing and visual impairment was measured in only one study in this sub-group.

Birth cohort studies (n = 1) (Table 4, see Appendix 2)

One large birth cohort study by Halpern et al. in Pelotas, Brazil was identified which included two cohorts of newborns from 1993 and 2004, followed up until the age of 12 months. This study measured population prevalence (74.7%, 1993 and 43.8%, 2004) for the proportion of the LBW population at developmental risk, rather than with neurodevelopmental impairment.

Discussion

This review highlights the high prevalence of neurodevelopmental impairment in early childhood in high-risk newborns in resource-limited settings. This high estimated prevalence of overall neurodevelopmental impairment, cognitive impairment and cerebral palsy in pre-term and VLBW infants and in those with birth asphyxia is of clinical and public health relevance for newborn health policy-makers in these settings.

The estimates are similar to previously published overall pooled estimates of neurodevelopmental impairment in places where newborn mortality is moderate to high. These previously published pooled estimates have suggested that, overall, 24.6% of moderately pre-term infants (i.e. <32 weeks sub-group) and 26.9% of survivors of birth asphyxia develop moderate-to-severe neurodevelopmental impairment in settings where overall neonatal mortality is >5/1000 live births. Similar to this review, authors of recent global estimates series have also noted broad confidence intervals around these estimates, reflecting limitations in the raw data available.

The results confirm that adverse developmental outcomes in early childhood are more common in high-risk newborns than in the general population. For example, the median prevalences of cerebral palsy in high-risk newborns in this review are high compared with the limited available estimates for the general population in resource-limited settings. Population studies in India and China suggest an
overall prevalence of cerebral palsy of 2–2.8/1000 children, which is much lower than the reported median prevalence of cerebral palsy in survivors of prematurity/very low birthweight (VLBW) and birth asphyxia in this review (11.2% and 22.8%, respectively). Similarly, when using standardised, norm-referenced methods of assessing cognition, 2.5% of a population would be expected to have cognitive scores ≤2 standard deviations below the mean. Therefore the estimated prevalence of cognitive impairment in survivors of prematurity/VLBW and birth asphyxia in this review (16.3% and 11.3%, respectively) are also likely to be comparatively high, despite the scarcity of normative data for resource-limited settings.

Comparison of our data from low- and middle-income countries with those from high-income contexts is challenging because of the significant differences in health systems, inclusion criteria within newborn population sub-groups and differences in condition-specific survival. For example, Blencowe et al. estimated that in low-mortality settings (i.e. neonatal mortality rate <5/1000 live births), the case fatality rate for newborns with a gestational age of 28–31 weeks is 5.8%. By comparison, in higher mortality settings with only limited basic or special care, the estimated case fatality rates for the same gestation are much higher (41.3–61.4%).

This review has a number of limitations including restriction to English-language articles and a restricted focus on causes of neonatal mortality. As newborn mortality decreases and morbidity profiles change, tracking outcomes for other causes of morbidity, such as congenital anomalies, will become increasingly important. Grading of study quality in this review is also limited by the tools available for quantitative grading of observational studies, and is potentially subjective.

However, by focusing specifically on the data available for resource-limited settings, this review highlights the challenges and provides a useful insight into the next steps required to improve newborn outcome in low- and middle-income countries. Specifically, it indicates where further research is needed to improve newborn care and outcome in resource-limited settings.

In particular, only a small number of the studies explored outcome after birth asphyxia and there is a serious deficiency of developmental outcome data for survivors of serious newborn infections. Since global data indicate high levels of neurodevelopmental morbidity in newborns surviving these conditions, improving outcome data for these conditions in resource-limited settings is an important step in improving the care of affected newborns.

Most studies in this review were single-institution, hospital-based studies. There is a strong argument for multi-institutional or regional studies as a part of efforts to standardise and improve care across settings, and a need for high-quality research into outcomes in community settings, in which almost half of global pre-term births still occur.

Additionally, a major challenge in understanding and comparing outcome in high-risk newborns in different contexts is differences in defining exposure and outcome variables. For example, gestational age is known to be a key determinant and to be inversely proportional to the prevalence of adverse neurodevelopmental outcomes. Yet, in this review, many studies provided no methods of estimating gestational age, many used last menstrual period or clinical assessment, and only one from Malawi used the gold standard of first trimester obstetric ultrasound, which remains unfeasible in many contexts. Similarly, although WHO definitions of birthweight categories are well established, definitions used in the studies were not consistent with their application. Definitions of birth asphyxia also varied, with some studies using Apgar scores or the WHO definition of failure to initiate or maintain respiration at birth, and others using the American Academy of Pediatrics’ more comprehensive definition of hypoxic ischaemic encephalopathy.

Studies in this review also varied in terms of outcome measures assessed, tools used and timing of assessments. For example, globally adverse cognitive outcomes are one of the most prevalent sequelae of newborn illness and are considered to be a key outcome measure. However, in this review, just over half of the studies included an assessment of cognitive impairment or developmental delay. Furthermore, very few studies assessed key developmental outcomes such as hearing and visual outcome. This is in spite of the fact that retinopathy of prematurity has become a major preventable cause of blindness in many low- and middle-income countries, and it has been estimated that 13.4% of children globally who experience newborn complications develop long-term hearing impairment. A broader range of outcomes including of seizures, and linguistic, academic and neurobehavioural outcomes also require more attention, and there is also a need for greater focus on potentially modifiable health and social risk factors for adverse outcomes as potential targets for intervention in future research.

There was significant variation between the studies in the methods of assessing and reporting outcomes in specific developmental domains. For example, the developmental or cognitive assessment tools used in many studies were psychometrically inadequate (e.g. Denver Developmental Screening Test) or not translated or adapted for the local context. In addition, reporting was not consistent:
some studies reported mean scores and others reported prevalence of scores one or two standard deviations below a reference mean.

This lack of standardisation of key exposure and outcome variables, combined with a lack of reference population data for developmental disabilities in resource-limited settings makes comparison of outcome data across regions and over time very difficult. As newborn survival improves, improving long-term outcome data for high-risk newborns in resource-limited settings will be increasingly important in order to monitor efforts to improve quality of newborn care, to inform families of affected newborns, and to guide development of strategies to improve long-term follow-up care.

To improve measurement of developmental outcomes for high-risk newborns in resource-limited settings, collaboration is needed to define key risk factors, outcomes and relevant minimum datasets in different contexts, to develop standardised, reliable, appropriate, affordable and effective developmental screening and assessment tools, and to improve screening for sensory impairments. More investment to build whole-population early child development data and use of controls in future studies is also important because, without it, meaningful interpretation of high-risk newborn outcome data and prioritisation of this within broader child health and early child development policy will remain challenging. Such efforts will require collaboration between clinicians, researchers and newborn health and early child development professionals in both resource-limited and high-income settings.

While not the primary focus of this review, the even greater challenge of improving newborn care and developing effective pathways for follow-up including early detection and intervention for high-risk newborns in resource-limited settings is also crucial. Systems of developmental screening, surveillance and assessment are a standard part of high-risk newborn follow-up in high-income settings and are key to enabling children to access early intervention in order to improve their long-term outcomes. However, the numerous challenges to the development of such systems in resource-limited settings need to be further explored in order to improve developmental outcomes for high-risk newborns.

Implementation research is needed to determine which models of early intervention will improve outcomes for these children. In high-income settings, early intervention has been shown to improve cognitive and motor outcome in pre-term infants. In resource-limited settings, an increasing body of evidence highlights strategies for early intervention which might improve developmental outcomes in the paediatric population in general. For example, parent-focused early intervention strategies enhance their responsiveness to a child’s developmental needs, and have been shown to be effective. However, there are major knowledge gaps around implementation of such strategies for sick newborns. The limited available studies suggest that parent-focused interventions might improve early childhood cognitive and motor development in newborns of low birthweight or who have experienced birth asphyxia. However, more research is required in several settings and we are not aware of any studies which have assessed the effects of such interventions following serious bacterial infection.

There are also specific conditions such as retinopathy of prematurity and hearing impairment for which evidence of the benefit of early detection and intervention is strong but also highly technical and difficult to implement in resource-limited contexts. In particular, improvements in neonatal care, including the appropriate use and monitoring of oxygen and locally adapted guidelines for screening and treatment of retinopathy of prematurity are needed to prevent worsening of the epidemic of retinopathy of prematurity which is now a major cause of childhood blindness in many middle-income settings. Similarly, WHO has published guidelines for developing newborn hearing screening programmes, and these programmes have been introduced in a number of resource-limited settings. Greater awareness of these, improved quality of newborn care and further development of such programmes including early detection, intervention and specialist educational support for affected children are required.

There are significant challenges in preventing and detecting adverse developmental consequences in high-risk newborns, including the provision of ongoing follow-up and early intervention in resource-limited settings. To address this and effectively move ‘beyond survival’, stronger collaboration between the newborn health and early child development sectors is required.

Newborns who survive the major causes of newborn mortality in resource-limited settings are at high risk of adverse neurodevelopmental outcomes in early childhood and beyond. If not adequately addressed, there are important clinical and public health consequences for those affected, their families and health and education systems. Consideration of outcome in high-risk newborns ‘beyond survival’ is therefore a major emerging global health challenge. This review has highlighted the high prevalence of adverse developmental outcomes for high-risk newborns in resource-limited settings as well as the need for improved data from areas with the highest morbidity. Ongoing efforts to better describe and improve long-term outcomes for these children are essential.
Disclaimer Statements

Contributors Kate Milner - primary role in conceiving and designing review, analysing and interpreting data and writing and revising the text. Eleanor Neal - role in literature review and revision of the text. Ghean Roberts, Andrew Steer and Trevor Duke - role in analysing and interpreting data and revision of text.

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Conflicts of interest None declared.

References

37 Prociangoy RS, Mendes EW, Silveira RC. Massage therapy improves neurodevelopment outcome at two years corrected age for very low birth weight infants. Early Hum Dev. 2010;86:7–11.

41 Cooper PA, Sandler DL. Outcome of very low birth weight infants at 12 to 18 months of age in Soweto, South Africa. Pediatrics. 1997;99:537–44.


### Appendix 1: Review of study quality

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<th>First author</th>
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<th>Unbiased sampling frame</th>
<th>Adequate sample size</th>
<th>Measures were the standard</th>
<th>Outcomes measured by unbiased assessors</th>
<th>Adequate response rate (&gt; 70%)</th>
<th>Confidence intervals and subgroup analysis</th>
<th>Study subjects described</th>
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Appendix 2: Reference list – included studies

Studies of pre-term and very/low birthweight infants


36 Procianoy RS; Koch MS; Silveira RC. Neurodevelopmental outcome of appropriate and small for gestational age very low birth weight infants. J Child Neurol. 2009;24:788–94.

37 Procianoy RS; Mendes EW; Silveira RC. Massage therapy improves neurodevelopmental outcome at two years corrected age for very low birth weight infants. Early Hum Dev. 2010;86:7–11.


41 Cooper PA, Sandler DL. Outcome of very low birth weight infants at 12 to 18 months of age in Soweto, South Africa. Pediatrics. 1997;99:537–44.


Sepsis and meningitis studies


Birth asphyxia studies

54 Carlo WA, Goudar SS, Pasha O, Chomba E, Wallander JL, Biasini FJ, et al. Randomized Trial


Mixed NICU and population–based cohort studies


2.4 Measuring neonatal exposures and neurodevelopmental outcomes in LMIC: What are the Challenges?

In Section 2.3.3, systematic review of the literature demonstrated a high prevalence of NDI among survivors of prematurity/very low birth weight and intra-partum related events in LMIC although there was a substantial gap in studies reporting outcomes following severe bacterial infection. (2) Importantly, systematic review also revealed limitations of the existing literature with regards to research design, standardised reporting of exposure and outcome variables. Although these limitations and challenges were discussed in part within the preceding paper, we discuss them more systematically here, to frame decisions made and subsequently described in Section 3, with regards to measurement of these variables within our Fiji neonatal outcomes study.

2.4.1 Neonatal exposure variables

Accurate definition and measurement of neonatal variables is crucial to understanding neonatal outcomes in research and practice. However, as noted above (Section 2.3) this is often challenging in LMIC.

For example, data from HIC has clearly demonstrated the importance of gestational age in relation to neurodevelopmental outcomes with an established inverse relationship between these variables. (68) However, our systematic review highlighted the frequent use of birth weight, rather than gestational age in neonatal outcome studies in LMIC. This is problematic but typical in settings where accurate means for assessing gestational age (e.g. first trimester ultrasound) are frequently lacking. (2, 76)

In high-income settings, first trimester ultrasound is considered standard of care and the reference standard for assessment of gestational age. (76) In LMIC where early antenatal
ultrasound may not be readily available, aside from using birthweight as a surrogate, other commonly used approaches to assess gestational age are recall of last menstrual period and clinical neonatal assessment (e.g. using the Dubowitz or New Ballard score).(76) Unfortunately, a recent systematic review highlights the inaccuracy of these methods and the need for investment in innovative methods to improve accuracy of gestational age assessment in LMIC as well as increasing coverage of antenatal ultrasound.(76)

However, unfortunately there are no easy solutions and Section 3.3.2 will describe the hierarchical approach we took, within our neonatal outcomes study in Fiji, to make best use of available methods for gestational age assessment in that setting.

Similarly, although key definitions for common neonatal conditions (e.g. neonatal encephalopathy, serious bacterial infection and severe hyperbilirubinaemia) were defined in Section 1.5, our research inclusion and exclusion criteria, detailed in Sections 3.3.2-3.3.3, reflect the fact that defining these conditions in practice, was often challenging, especially with retrospective identification of patients from medical records. For example, limitations of available laboratory diagnostic support and ancillary tests (e.g. microbiological data, serum bilirubin monitoring) increased our reliance on clinical diagnoses rather than more objective measures of describing neonatal status.

2.4.2 Child development outcomes

Earlier (Section 2.3.2), we described the evolution in approaches regarding neonatal neurodevelopmental outcome measurement in high-income settings. (See Section 1.2.2) Current approaches to neonatal neurodevelopmental outcome measurement in HIC typically involve multidisciplinary assessment with trained specialists using measurement tools that are standardised and validated in similar contexts.
However, in LMIC, the measurement context is different and varies between and within countries. While there are many tools available that could be used to measure developmental outcomes in LMIC, there are many barriers to meaningful measurement of neurodevelopmental outcomes across such contexts. These are outlined here, before methodological choices made within our Fiji neonatal outcomes study are described in more detail in subsequent sections (See Section 3.4). For simplicity, these challenges will be considered according to developmental domains and tool selection, tester and broader systems constraints. Please note that this section refers to a number of key definitions, outlined in Section 1.5.

Please note, that due to constraints of available resources, we focused on outcomes in early childhood and cognitive, language, motor and hearing and vision outcomes. We did not measure socio-emotional, functional or behavioural outcomes.

2.4.2.1 Developmental domains and assessment tool selection

There is a plethora of tools for measuring child development outcomes. The first version of the World Bank toolkit for ‘Examining early child development in low-income countries’ published in 2009, systematically reviewed numerous available child development assessment and screening tools and described a number of key issues in their selection and use in LMIC.

Firstly, Fernald et al highlighted the important of tool selection being guided by the purpose of testing. In the context of high-risk newborn follow-up, there are potentially multiple reasons to measure child development often including measurement of outcomes in response to particular exposures or interventions and/or to identify developmental delays or impairments in neonates who are known to be at increased risk of developmental
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complications. In this research, the primary purpose of ECD measurement was to measure outcomes in response to certain neonatal conditions. This overlaps with but is somewhat different to measurement of child development within a longitudinal process of developmental monitoring or surveillance for the purpose of facilitating early identification of developmental delay or impairments.(78) Measurement for the purpose of developmental monitoring is discussed more Section 6, which describes our exploration of the accuracy of a parent report tool for identification of developmental delay in our study population.

As Fernald et al highlighted, being clear on why measurement is being undertaken is important in order to determine what domains of development are assessed and what tools are used.(78) In terms of domains to be tested, Section 2.3.2 described how in HIC an increasing spectrum of developmental domains are measured in neonatal outcomes research and programmes. However, in LMIC measurement of a broad range of outcomes over prolonged timeframes is often not readily feasible due to challenges such as cost, limitations of staff training and lack of locally appropriate and effective tools.(77, 79-81)

Conversely, in LMIC such as Fiji where ancillary health services (e.g. neonatal hearing and retinopathy of prematurity screening) are often lacking, inclusion of measures of sensory impairment within broader child development outcome measurement may arguably be more important since child development assessment provides an opportunity for checking progress in these areas, which would otherwise be missed in these contexts.(2) In addition, understanding hearing and vision functioning or impairment is crucial to understanding performance in other developmental domains.
Types of tools for measuring child development include both screening and assessment tests. (Section 1.5) Mode of testing may include parental, observational or performance based through testing in standardised conditions.

In HIC, in order to measure outcomes in response to an exposure (e.g. neonatal illness or complications or intervention), formal child developmental assessment rather than use of a screening tool is considered best practice. (37) Commonly used tools for this purpose include the Bayley Scales of Infant and Toddler Development® Second and Third Editions (Bayley-II and III) and the Griffiths Mental Development Scales Second and Third Editions (GMDS). (32, 82, 83) While the Bayley-III is the most commonly used tool for diagnosis of developmental delay, it is important to note this reference standard is not without limitations, even when used in HIC. In particular, Anderson et al. have recently critically reviewed the Bayley-III suggesting that its cognitive, language and motor skills overestimate development (i.e. under-estimate developmental delay) as well as being a poor predictor of long-term cognitive and motor impairment. (84)

Further, the psychometric properties of tools (i.e. the effectiveness of measures to assess characteristics they purport to measure) are crucial to meaningful outcome measurement, yet these are often unknown in LMIC. (77) Effective measurement requires that tools are both reliable (i.e. consistently produce the same results for groups of children with repeated measurement over time) and valid (i.e. the degree to which a tool measures the characteristics it is designed to measure) in the population in which they are being used. (37) Most child development tools have been extensively tested in HIC but are infrequently reassessed when used in LMIC to establish their reliability and validity across contexts. (77) This means that in settings such as our research context in Fiji, the use of control groups, to
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provide a reference for understanding results observed within our study population, is crucial.

In addition to re-establishing psychometric properties when tools are used across settings, it is also important to consider requirements for translation, back-translation and cultural adaptation. Without this, use of tools which assess concepts which are foreign to local children may not accurately assess their developmental abilities.(85)

There are many practical issues which influence tool selection in LMIC including tool cost, accessibility (e.g. online access, copyright limitations), time for administration and interpretation and training requirements.(77) Most of the commonly used child developmental assessment tools in HIC are relatively costly, time consuming, have proprietary restrictions and time-consuming training requirements with test administration typically being undertaken by specialist psychologists, health or allied health professionals.(37, 77) These issues make use of such tools challenging, even in research settings, in LMIC, which partially explain our observation, in systematic review of the literature, that screening tools were commonly used as outcome measures in LMIC neonatal outcome studies. (Section 2.3.3)

2.4.2.2 Human resources

Quality measurement of child development requires human resources not only for test administration but also for training, supervision, referral and follow-up. In many LMIC, such as Fiji, pre-service training of the child health work force remains focused on acute health issues with little background training in child development, let alone training in specific developmental assessments. As described in Section 2.2 above, in Fiji, specialist child development and allied health services are lacking with child health services still mostly
focused on acute child health needs. Further, existing staff typically have high caseloads and limited time for training and follow-up in each individual episode of care. Thus, in high-risk newborn follow-up, having developmental monitoring approaches that are robust but feasible for use in existing services will be crucial for sustainable service development. Specifically, development of processes to identify neonates who are at highest risk of developmental delay or impairment on the basis of risk factors or screening, using brief tools that could be administered by non-specialist health professionals are appealing in terms of ability to target resources to those most in need, likely feasibility and sustainability.

2.4.2.3 Systems

Giving adequate consideration to the broader system in which child development measurement occurs is also crucial, not only to the feasibility and quality of child development assessment, but also to ensure the ethical acceptability of measurement. In particular, understanding resources for follow-up including referral pathways and early intervention services for children identified with developmental delays or impairment is crucial. While this is true across all settings, it is especially important in LMIC such as Fiji where referral pathways and early intervention through government services may be limited.

2.4.3 Measurement of vision and hearing impairment

2.4.3.1 Vision

Definitions of varying degrees of visual impairment, according to the International Classification of Disease Version 2010 (ICD-10) have been described above (Section 1.5) Using these definitions, in 2010 an estimated 19 million children aged between 0-14 years were visually impaired with an estimated three quarters of these children living in LMIC.(86) In LMIC, approximately half of all childhood blindness is considered avoidable, with
Section 2: Background

Retinopathy of prematurity (ROP) being an increasingly common cause, especially in middle-income countries. (86) Overall global estimates for the numbers of preterm neonates affected by ROP have been provided in Section 2.3.1 above. Of note these estimates suggest that 6% of neonates born at less than 32 weeks gestation in LMIC develop ROP. (12) This is higher than would be expected for similar gestation in HIC. Indeed data show that neonates in LMIC are at increased risk of ROP across a wider range of gestational ages and birth weights and are more likely to develop ROP requiring treatment than in HIC. (87)

Further, preterm neonates and term neonates who experience other causes of morbidity (e.g. NE, SBI) are also at increased risk of visual impairment due to other causes (e.g. cortical visual impairment, refractive errors, amblyopia). (86)

In high-income countries, systems to prevent and facilitate early treatment of ROP among preterm infants have been developed which include titrating use of supplementation oxygen to levels safe levels according to best available evidence, neonatal screening by specialist ophthalmologists and early intervention as indicated.

In many LMIC, where the so-called third epidemic of ROP is occurring, such systems of prevention, early identification and management are lacking. (12) However, there are examples, such as India, where there has been rapid scale-up of such systems, showing that this can be done, with potential to prevent or curtail an epidemic of ROP among preterm neonates in such context. (88, 89) Local data on visual outcomes are considered key to the development of quality, contextually appropriate ROP screening programmes. (12)

Beyond hospital discharge, many preterm and other high-risk neonates require follow-up visual assessment. Early detection of conditions that can lead to amblyopia requires targeting pre-school age children to assess their vision for refractive errors and visual
acuity.

Guidance is available for screening vision in infants and young children in LMIC, including by non-specialist health workers, including App-based technologies (e.g. ‘Peekaboo vision’) for visual acuity testing in young children although these technologies were less widely used when this research was being established.

2.4.3.2 Hearing

The WHO definition of hearing impairment in childhood has been provided in Section 1.5. However, this definition is likely to result in under-estimation of disability due to hearing loss in LMIC, since as Olusanya et al. note, this definition fails to account for conductive hearing loss, unilateral hearing loss or more mild degrees of hearing impairment that may still have functional impacts on children’s learning and development.

Section 2.3.2 provided global estimates of hearing impairment following neonatal conditions in LMIC. More generally, an estimated 737,000 children or 6/1000 live births every year worldwide are affected by permanent congenital hearing loss (PCHL). This is three times the prevalence of PCHL in HIC. Although the cause of PCHL is unknown in a substantial proportion (38-62%) the remainder are attributable to a combination of genetic, infective, neonatal and postnatal factors including prematurity, NE and SBI. As for other vision impairment, timely identification of hearing impairment in infants and young children is crucial to allow early intervention and minimise impact on other areas of development and broader functional and educational outcomes.

In HIC, the benefits of early identification of PCHL on language outcomes through neonatal hearing screening programmes (NHSP) are well established and NHSP, which are either universal or targeted to ‘high risk’ populations, are now considered standard of care. NHSP are designed to allow early identification and management of PCHL (i.e. within the
first year of life) since later detection or poor management is known to be associated with poorer speech, language and cognitive outcomes in childhood as well as later educational and employment outcomes.(95) However, a review by Olusanya BO based on 2011 data showed that only 15% (n=16/110) LMIC had NHSP in place.(94)

The WHO guiding principles of action on newborn hearing screening resolution NHSPs will vary both according to need and resources at country level.(96) NHSPs require not only the right technology or tools but also broader resourcing of infrastructure in terms of human and other resources for follow-up when concerns are identified. For many LMIC, it has been suggested that development of targeted rather than universal NHSPs may be the most feasible first step.(96, 97)

A variety of instruments can be used to screen hearing in infants including otoacoustic emission and auditory brainstem responses, usually with set criteria for re-testing and referral for formal audiological assessment. These are short, minimally invasive tests which are performed when the infant is in a quiet state and can be conducted by trained but non-specialist staff. For children who have an abnormal result, arrangements may be made either for repeat screening, using the same approach, and/or follow-up for more detailed assessment by an audiologist or, in LMIC, an audiometrist.(96)

If PCHL is ascertained through this approach, standard of care in HIC would include ENT referral, consideration of aides or cochlear implant depending on findings, further assessment for cause, counselling of the family and referral for developmental assessment and early intervention including specialist communication support.(98, 99) In LMIC, even when NHSPs exist, structured pathways for follow-up assessment, referral and intervention are often weak.(94)
2.4.4 Cerebral palsy

The most commonly used consensus definition of cerebral palsy, as outlined by Rosenbaum et al. has been provided in Section 1.5. Data from LMIC is variable but available estimates suggest and overall prevalence of cerebral palsy ranging from approximately 2-4/1000 live births, twice the prevalence typically observed in HIC.(100-102) Additionally, in Australia and a number of other HIC where more robust epidemiological data typically from population registers are available, population prevalence has been shown to be decreasing.(103, 104)

Cerebral palsy is further described according to the predominant motor disorder and topography.(105) In Australia, recent registry data indicate that by motor type: spastic (85%-91%), dyskinetic (4%-7%), ataxic (4%-6%) and hypotonic (2%), noting that motor types are frequently mixed.(103) Topography describes which parts of the body are predominantly affected and may include quadriplegia (all four limbs and trunk), hemiplegia (unilateral upper and lower limb) or diplegia (where both sides are affected but with lower limbs more than upper limbs).(33, 105, 106) Most cases of cerebral palsy in HIC are thought to be pre- or perinatally acquired and the majority (58%) occur in term neonates.(105, 106) Risk factors such as male sex, lower gestational age and birth weight and multiple births are well known.(106, 107) However, while in some cases these and other clinical risk factors such as neonatal encephalopathy may be identifiable, there is typically no one clear identifiable causal pathway.(106, 107)

In systematic review of the literature related to the prevalence, types and aetiology of cerebral palsy in LMIC, Gladstone M. noted a proportionately higher prevalence of spastic quadriplegic and dyskinetic and relatively lower prevalence of dyskinetic cerebral palsy.
than typically observed in HIC. (101) Although noting the substantial difficulties of determining cause of cerebral palsy in these settings, Gladstone M. postulated that the difference in subtypes observed could reflect the higher incidence of neonatal encephalopathy, serious bacterial infections and jaundice and lower rates of survival for preterm infants in these LMIC.

Cerebral palsy is primarily a clinical diagnosis. In high-income countries diagnosis typically entails standardised neuromotor assessments and magnetic resonance imaging. (108) Increasingly, protocols for high-risk neonates in high-income countries use a combination of standardised neurological and motor assessments (e.g. Prechtl’s qualitative Generalised Movement Assessment, Hammersmith Infant Neurological Examination) and neuroimaging to facilitate early diagnosis and access to diagnosis specific intervention. (108) In LMIC, algorithms for early diagnosis, with less emphasis on neuroimaging have been suggested but are not yet well studied and diagnosis specific interventions are typically limited. (100)

2.5 Section summary

This section has provided a multidimensional description of the research context in Fiji including consideration of sociocultural, demographic, neonatal and child health, child development and disability policy and programming factors. We have highlighted how neonatal and child health in Fiji is in transition which creates increasing need and opportunity to focus increased attention on beyond survival outcomes for high-risk neonates.
Section 2: Background

We have systematically reviewed available similar literature from LMIC, identifying a need for high-quality research which measures multi-domain neurodevelopmental outcomes including hearing and vision, for high-risk neonates and control healthy neonates in LMIC.

We have also discussed anticipated challenges from the field more broadly, related to measurement of both neonatal and neurodevelopmental outcome variables in LMIC.

In Section 3, informed by the key findings of this section related to detailed local situational analysis; evolving evidence in the emerging field of global neonatal neurodevelopmental outcomes research and equipped with a detailed understanding of anticipated challenges in measurement, we describe the research design for the next component of this research, our neonatal neurodevelopmental outcome study for NICU graduates in Fiji.
Section 3
NEONATAL OUTCOMES
STUDY – RESEARCH
DESIGN
3. NEONATAL OUTCOMES STUDY - RESEARCH DESIGN

3.1 SECTION OUTLINE

This section builds on background described in Section 2 and provides a detailed description of the overall research design for our neonatal neurodevelopmental outcomes study in Fiji; a retrospective cohort study comparing long-term neurodevelopmental outcomes for high-risk neonatal intensive care unit (NICU) patients and matched control neonates at Colonial War Memorial Hospital (CWMH) in Suva, Fiji.

Section 3.2 provides an overview of the research design including research aims, hypotheses, objectives and the overall study design. Section 3.3 describes the study population and inclusion and exclusion criteria, acknowledging the complexity in defining a number neonatal exposure and neurodevelopmental outcome variables in LMIC, as discussed in Section 2.4. Section 3.4 outlines choices made for selection for primary neurodevelopmental and secondary health outcome measures, again balancing acknowledged complexities. Sections 3.5-3.7 provide details of sample size calculations, study procedures and the data analysis plan. Section 3.8 describes processes undertaken to obtain ethical approvals for the study in Australia and Fiji while broader ethical issues raised by this study are discussed later in this thesis. (Section 7.3) A summary of research design is provided in Section 3.9.

Please note that methods and results for the developmental screening accuracy study, which explores approaches to developmental monitoring in the same high-risk neonatal population in Fiji, are described in Section 6.
3.2 OVERVIEW OF RESEARCH DESIGN

3.2.1 Study design

This was a retrospective cohort study comparing early childhood neurodevelopmental and health outcomes in high-risk NICU survivors with a group of matched, term, normal birth weight controls. A cohort study design was used to enable description of early childhood neurodevelopmental outcomes relative to a broad range of child, maternal and family health and sociodemographic factors in early life (i.e. from pregnancy to early childhood). A retrospective method of identification of participants from medical records rather than prospective recruitment was chosen because a prospective design was not feasible within the constraints of available funding.

3.2.2 Aims

The main aim of this study was to assess the early childhood neurodevelopmental and health outcomes for a cohort of high-risk neonatal intensive care patients compared with matched, term, normal birthweight controls in Fiji.

A secondary aim of this research was to pilot and assess the accuracy of nurse-administered developmental screening for identification of developmental delay and impairment among the same population, through a nested developmental screening accuracy study. (Section 6)

3.2.3 Objectives

In order to achieve the above aims, the objectives of this research were as follows:

Primary:
To assess, in a cohort of children previously discharged from CWMH NICU and a comparison control group who were not admitted to the NICU, the prevalence of moderate to severe NDI at age approximately two years

**Secondary:**

To also assess in the same children;

- Prevalence of stunting, wasting and anaemia
- Immunisation rates
- Feeding practices
- Number of contacts with government health service

Specific objectives of the developmental screening accuracy study are described in Section 6.3.

### 3.2.4 Hypotheses

Based on review of neonatal neurodevelopmental outcomes literature and understanding of the local context, as described in Section 2, we hypothesised that;

- Neonates who were seriously ill and required NICU admission would have a higher prevalence of neurodevelopmental and health morbidities in early childhood than term, normal birth-weight neonates who did not require intensive care in the neonatal period.

- A range of potentially modifiable social and biological risk factors for adverse long-term neurodevelopmental outcomes would exist and provide potential targets for preventive, primary and secondary neurodevelopmental interventions.
• Nurse-led developmental screening would be feasible and accurate for identification of developmental delay and impairment among the study population, comparable to specialist developmental assessment. (Section 6)

3.3 PARTICIPANTS

This section describes the rationale for choices made regarding the sampling frame, inclusion and exclusion criteria and selection of the control group for our neonatal outcomes study.

3.3.1 Sampling frame

Choice of participating health facility

Our research was based out of CWMH since that is the primary neonatal referral centre in Fiji. We chose to undertake a facility rather than community-based study since, in Fiji, in contrast to many lower-income countries, 98% of all deliveries now occur in one of three major divisional hospitals.(10) (Section 2.2.2) As noted earlier, based on 2009 data approximately seven thousand live births or 40% of all deliveries occurred at CWMH.(10) (Section 2.2.2) This means that a substantial proportion of neonates were also born at the other divisional hospitals in Lautoka and Labasa. While a multi-institution follow-up study would therefore have been ideal in terms of understanding high-risk neonatal outcomes across all three major neonatal referral centres, this was not possible within the resources available for this research.

Neonatal population

Participants in this research included a group of children who had been admitted to CWMH NICU as neonates as well as a control group of children born at CWMH and
admitted to the post-natal ward during the same period. As noted earlier, in 2009 571 neonates received intensive care at CWMH of whom 452 (n=79%) were born at CWMH and the remaining 119 (n=21%) were born elsewhere but referred to CWMH. The majority (i.e. 94%) of neonates born at CWMH did not require intensive or special care and typically had brief admissions to the postnatal ward with their mothers before discharge home. (10) (Section 2.2.2)

Among NICU survivors, study participants were selected on the basis of inclusion criteria defined to further identify neonates thought likely to be at high-risk of NDI and therefore warranting additional follow-up even in a resource-constrained setting. (Section 2.2.2) That is, in discussion with CWMH clinicians we were made aware of a common practice of admitting children to NICU for less severe conditions such as temperature instability requiring antibiotics and brief periods of phototherapy. In a context where follow-up of all NICU patients was not likely to be possible from a health service perspective, we were therefore keen for our inclusion criteria to focus on those neonates admitted to NICU who were clinically considered to be more seriously unwell and more likely to require follow-up after hospital discharge.

However, from systematic review of existing literature (Section 2.3.3) we were also aware of the substantial knowledge gap across diagnoses in LMIC. That is, in addition to an overall lack of data regarding neurodevelopmental outcomes for neonates in these settings, there was a specific lack of data on outcomes for neonates with neonatal encephalopathy, SBI in addition to prematurity and VLBW, which constituted the majority of previous studies in similar settings. (2) (Section 2.3.3)
As such, we chose to include children with a range of neonatal diagnoses and aimed to collect outcome data for a group of children who broadly reflected the diverse clinical group cared for at CWMH rather than potentially selecting a more homogeneous research population. Our inclusion criteria therefore included the most common causes of neonatal mortality and morbidity in Fiji as well as a number of other conditions that we considered, on the basis of broad understanding of the field and/or preceding literature review to represent ‘serious illness’. (2)

### 3.3.2 Inclusion criteria

Based on this rationale, we reviewed medical records of patients discharged from CWMH NICU between November 2008 and April 2010 with the aim of assessing children at approximately two years of age. (Section 3.4.2) Among patients discharged from CWMH NICU during this period, we selected a convenience sample at potential higher risk of long-term morbidity and adverse neurodevelopmental outcomes. This included children discharged from CWMH during the above time period with the pre-determined inclusion criteria.

Building on international definitions outlined in Section 2.4, this section will consider definitions used to define neonatal exposure and outcome variables within our neonatal outcomes study in Fiji and how decisions about those definitions were reached.

Definitions used for these conditions within our outcomes study (Table 3) represent our best efforts within the limitations of data retrospectively available in routine health services in Fiji, to use the most robust and standardised definitions possible. Where internationally accepted definitions (e.g. World Health Organization [WHO] or
International Classification of Diseases Edition 10 [ICD-10]) existed, these were used as a baseline. (Table 3)

3.3.3 Definitions used in case ascertainment from medical records

3.3.3.1 Gestational age

In addition, in Section 2.4.1 we discussed the importance of accurate definition of gestational age in neonatal outcomes research since gestational age, rather than birth weight, is recognised as having the major effect on newborn survival and long-term morbidity. (109) However, we also discussed a number of challenges with measurement of gestational age in LMIC, where the reference standard of a first or early second trimester ultrasound dating scan is often not available.

Globally, an estimated 44 million of 1140 million annual live births occur at home without contact with formal health services. (2017 data)(1) For these neonates, improving birth registration, let alone further details such as birth weight or gestational age, remains a major challenge. (1)

In Fiji, where 98% of deliveries occur in health facilities vital registration is less problematic yet antenatal care is inconsistent and access to ultrasounds limited. (10) (Section 2.2.2 and 2.2.3) As such, other less accurate measures of gestational age assessment including last menstrual period, fundal height and clinical measures of gestational age after birth are commonly used for estimation of gestational age in obstetric and neonatal practice.

Since recruitment in our neonatal outcomes study was retrospective, gestational age allocation relied on the use of these measures as documented within medical records, using definitions of prematurity as previously outlined in Section 1.5.
We were aware of the limitations of this approach including potential misclassification of neonates who were either small or large for their gestational age. (76)

Therefore, to enable the best possible estimate of gestational age within the limitations of retrospective data, medical records were reviewed by a paediatrician who assigned gestational age on a case by case basis using best available data which was prioritized in the following order;

1. Ultrasound determination of the estimated date of delivery, measured during a first or early second trimester ultrasound scan

2. Ballard, New Ballard Score or Dubowitz as assigned by the NICU team

3. Last menstrual period estimation as per the delivery record

3.3.3.2 Birth asphyxia

In Section 1.5 we described how in current terminology, especially in HIC, the term neonatal encephalopathy (i.e. neurological dysfunction in neonate >35 weeks gestation) is preferred over use of the term birth asphyxia, which is considered less precise or predictive in terms of long-term neonatal neurodevelopmental outcomes.(14)

In HIC, the association between NE due to hypoxic-ischaemia and long-term neurodevelopmental complications such as cerebral palsy, cognitive impairment, seizures, hearing and vision impairment is well established.(14) In such settings, in addition to clinical neonatal assessment, cardiotocograph monitoring during labour, umbilical arterial blood gases and neuro-imaging are typically available, alongside clinical methods, to assist clinicians to understand potential associations between NE and intrapartum events.(14)
However, in LMIC, such as Fiji, sophisticated laboratory and biomedical engineering resources are often not available to support diagnosis of NE due to hypoxic-ischaemic brain injury. In Fiji, when this study was undertaken, cardiotocograph monitors were in short supply and while blood gas machines were available to the NICU, MRI brain imaging and electrical monitoring for seizures (i.e. electroencephalography [EEG]) were not. In addition, we were unable to retrieve full maternal obstetric records for the purposes of this study.

Further, in Fiji, at the time this study was undertaken, the term birth asphyxia which has previously been broadly defined by the WHO as ‘failing to initiate or maintain regular breathing at birth’, was widely used by health professionals.

As such, for inclusion to this research we used medical records documentation of a diagnosis of ‘birth asphyxia’ as the closest approximation of NE. However, noting that on occasions, neonates seemed to be admitted to NICU for monitoring on the basis of low-Apgar scores alone, where birth asphyxia was the primary inclusion criterion, we further reviewed the medical records in an attempt to verify other features of NE using the following definition:

- Onset within 2 days of birth of severe or moderate neonatal encephalopathy in infants born at 34 or more weeks of gestation
- Acute perinatal event, and/or a 10 minute Apgar less than 5 or assisted ventilation for more than 10 minutes.
- Ideally also the following:
  - Evidence of metabolic acidosis (pH < 7 or less or base deficit < 12 mmol per litre)
• Other identifiable aetiologies such as trauma, coagulation disorders, infectious conditions, or genetic disorders were excluded

This approach represented our best effort to be rigorous in case assignment within the limitations of data available through routine health information systems in Fiji.

3.3.3.3 Serious bacterial infection (SBI)

Formal diagnosis of serious or invasive bacterial infections in neonates including sepsis, meningitis and pneumonia ideally include isolation of bacteria from an otherwise sterile site in the body (e.g. blood or cerebrospinal fluid culture [CSF]). (28)

However in Fiji, these conditions were variably defined according to clinical assessment and inconsistently supported by microbiological culture. From the review of medical records and from discussion with CWMH clinicians, we noted that some were admitted to NICU for presumptive treatment with antibiotics because they were considered on the basis of risk factors (e.g. maternal prolonged rupture of membranes, maternal fever during labour) as being at increased risk of sepsis. As such, when clinical diagnoses of risk of sepsis were recorded in NICU records, we reviewed medical records in more detail, on a case by case basis to ensure that the following conditions were met, before inclusion in the study:

• Sepsis – positive blood culture or clinical definition of neonatal sepsis based on an accepted algorithm or two or more risk factors for sepsis and treated with antibiotics(28)

• Pneumonia –suspected in neonates with respiratory distress, especially with other clinical signs of sepsis, in a term infant who does not meet criteria for meconium aspiration syndrome or preterm respiratory distress syndrome(29)
- Meningitis - CSF culture positive for a causative organisms OR positive antigen test OR white cell count in cerebrospinal fluid of more than 50 cells per microliter

3.3.3.4 Definition of other serious illness

Table 3 outlines other definitions used to define serious illness within our neonatal neurodevelopmental outcomes study. As previously discussed (Section 3.3.1) we were keen for the sampling frame to be inclusive of neonates with a broad range of diagnoses, as encountered by NICU clinicians at CWMH on a day to day basis. As for previously described neonatal diagnoses, all definitions represent our best efforts to standardise case definitions within the context of existing services and health information systems.

For example, while the internationally accepted definition of severe hyperbilirubinaemia is usually based on bilirubin level for age and weight (e.g. total plasma/serum bilirubin >25mg/dl)/ (428 µmol/l), we also included any child who required exchange transfusion (30) We made this decision because access to serum bilirubin testing was somewhat inconsistent and we assumed that clinicians would not usually make the decision to proceed to exchange transfusion unless they considered jaundice to be severe, even if serum bilirubin was not available.
### Table 3: Definitions used in inclusion criteria for Fiji neonatal outcomes study

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Case ascertainment from medical records</th>
</tr>
</thead>
</table>
| Gestational age <34 weeks and/or;                      | 1. Ultrasound determination of the estimated date of delivery, measured during a first or early second trimester ultrasound scan  
2. Ballard, New Ballard Score or Dubowitz as assigned by the NICU team (111, 112 {Vik, 1997 #1976 {Vik, 1997 #1976})  
3. Last menstrual period estimation as per the delivery record |
| Birthweight <1800 grams and/or;                        | As assigned in CWMH labour ward records                                                                                                                                                                                                 |
| Required surgery and/or;                               | As outlined in CWMH NICU records                                                                                                                                                                                                          |
| **Other serious illness, defined to include clinical diagnosis in CWMH NICU records of one or more of the following:** |                                                                                                                                                                                                                                       |
| Diagnosis of birth asphyxia                            | A diagnosis of birth asphyxia with CWMH NICU records, with detailed record review to verify other features of neonatal encephalopathy including: onset within 2 days of birth of severe or moderate neonatal encephalopathy in infants born at 34 or more weeks of gestation and acute perinatal event, and/or a 10 minute APGAR less than 5 or assisted ventilation for more than 10 minutes or diagnosis by treating paediatrician. |
| Seizures or encephalopathy of any cause                 | As outlined in CWMH NICU records, with encephalopathy manifested by difficulty initiating and maintaining respiration, depression of tone and reflexes, abnormal level of consciousness and often by seizures, following and intrapartum hypoxic insult’. (14) |
| Meningitis                                             | Cerebrospinal fluid (CSF) culture positive for a causative organisms or clinical diagnosis by treating paediatrician. (23)                                                                                                                                 |
| Risk of sepsis                                          | Positive blood culture or clinical diagnosis of sepsis based on an accepted algorithm or two or more risk factors for sepsis and treated with antibiotics. (28)                                                                                           |
| Pneumonia                                              | Respiratory distress, especially with other clinical signs of sepsis, in a term infant who does not meet criteria for meconium aspiration syndrome or preterm respiratory distress syndrome. (29)                                                                 |


Hyaline membrane disease (HMD) | Respiratory distress in a preterm infant with characteristic radiological features (e.g. diffuse reticulogranular pattern with air bronchograms) and requirement for supplemental oxygen, continuous positive airway pressure or invasive ventilator support. (26)

Meconium aspiration syndrome (MAS) | Respiratory distress in an infant born through meconium-stained amniotic fluid with chest x-ray findings consistent with MAS and whose symptoms could not be otherwise explained. (26)

Severe respiratory distress of any cause (requiring CPAP or invasive ventilation) | Clinical evidence of increased work of breathing, tachypnoea, requirement for supplemental oxygen or ventilatory support

Necrotising enterocolitis (NEC) | Gastrointestinal dysfunction and systemic instability using Modified Bell’s criteria (113)

Severe erythroblastosis | Haemolytic disease of the newborn resulting in severe jaundice as defined above or anaemia requiring transfusion (30)

Severe jaundice | Significant jaundice based on bilirubin level for age and weight of newborn based on internationally accepted criteria or treated with exchange transfusion (30)

Severe hypoglycaemia | Persistent blood glucose level <2.6mmol/L or hypoglycaemia requiring bolus intravenous treatment (31)

Infants who are clinically ill for other reasons and need careful nursing and medical care
3.3.4 Exclusion criteria

Neonates discharged from CWMH NICU between January 2008 and January 2010 who were diagnosed with major congenital anomalies were excluded from the study. This decision was taken because we considered that the causative pathways to NDI in these children were likely to be different compared with NDI following other neonatal conditions. As such, although congenital anomalies are a major cause of neonatal mortality and morbidity in LMIC, they were not included within this study.(114)

3.3.5 Comparison group

We considered it crucial to have a comparison group for this neonatal outcomes study since in Fiji there was no prior population level data on early child development outcomes or disability. Additionally, since child development assessment tools that were used for outcome measurement had not been normed in Fiji (Section 3.4), having a local comparison group was important to enable meaningful interpretation of outcomes observed in the high-risk neonatal group in particular.

We included controls neonates who were discharged from CWMH postnatal ward between January 2008 and January 2010 who were;

- 37-42 weeks gestational age
- AND birthweight 2500-4200 grams
- AND Matched with NICU case for all of the following;
  - Expected date of delivery
  - Sex
  - Rural/urban location
  - Ethnicity
AND No major congenital abnormalities

We specified that control infants needed to be term and normal birth weight because, in discussed with CWMH clinicians we learned that in Fiji it is common practice for low birth weight, moderately preterm infants to be managed on the postnatal ward. Additionally, we included an upper limit for both weight and gestational age because data, including from LMIC shows that macrosomia and post-term birth are associated with increased neonatal morbidity.\(^{(115)}\)

In order to match NICU and control populations for potential confounders, controls were individually matched to NICU recruits on the basis of several sociodemographic factors which may be associated with variations in long-term health and developmental outcomes including; sex, ethnicity and place of residence.\(^{(116, 117)}\)

Controls were also matched to NICU recruits by expected date of delivery in order to account for any variations in outcomes which may have occurred over time (e.g. seasonal variation, with changes in services).

3.4 PRIMARY AND SECONDARY OUTCOME MEASURES: WHAT, WHEN AND HOW?

In the previous section we described the rationale for choices made regarding the study population within our neonatal neurodevelopmental outcomes study. In this section we move on to discuss choices made regarding primary and secondary outcome measurement, informed by previously described background literature on measurement of neurodevelopmental outcomes in both HIC and LMIC including our systematic review similar neonatal outcome studies in LMIC (Sections 2.3 and 2.3.3) and consideration of challenges in measuring neurodevelopmental outcomes across contexts.\(^{(2)}\) (Sections 2.4.2-2.4.4) Specifically we describe decisions made with regards
to selection of what primary neurodevelopmental and secondary health outcomes to measure, when and how to measure them. As for measurement of neonatal exposures, inevitably the outcome measurement choices we made represented efforts to balance what we understood to be preferred practice with what was feasible within the constraints of measuring child development outcomes across cultural and linguistic contexts, in a resource-limited setting.

3.4.1 Developmental domains

Building on findings of our systematic review and broader understanding of child development, we considered that there were several key domains to test in our study cohort including cognition, language and motor development.(2, 78)

In addition, recognising the potential for increased prevalence of sensory impairment in this high-risk neonatal population; the importance of hearing and vision function in interpreting findings in other developmental domains and relative neglect of measurement of these areas in existing LMIC neonatal outcomes literature, we determined that formal assessment of hearing and vision should also be included. (Sections 3.4.7 and 3.4.8)

We also considered measurement of other developmental domains which are known to be closely associated with long term cognitive and educational outcomes, in particular socioemotional development and executive functioning.(118-121) However, given limitations in measuring these constructs cross-contextually with available tools, we did not include these latter two domains in testing within this study.(122)
3.4.2 Child age

Several factors influenced our decision to assess children within our neonatal outcomes study at two years corrected age, or as close as possible. We chose to use corrected age to allow for prematurity of some children within the study population. We chose to assess children’s development at as close to two years corrected age as possible to allow for best comparability of results with previous similar LMIC neonatal outcomes studies which, although variable, mostly measured neurodevelopmental outcomes in early childhood. We also considered that this would be more feasible than follow-up in later childhood. In particular, we were concerned about the feasibility of being able to retrospectively identify and recruit children to the study cohort at older ages, since we expected that many children would be lost to follow-up within existing services in Fiji at older ages. Assessing children in early childhood was also important to the longer goal of this research, to form a platform for early intervention service development in Fiji. (Section 3.2.2)

However, we also understood limitations of assessment at this age and in particular, evidence that demonstrates that later (i.e. late preschool/early primary school) neurodevelopmental assessment is more predictive than earlier testing for long-term cognitive and educational outcomes. (123, 124)

3.4.3 Mode of testing (screening or assessment)

In Section 2.4.2 we described different modes of measuring child development including developmental screening and assessment by direct and proxy measures.

Within our neonatal outcomes study, for the purposes of testing cognitive, language and
motor outcomes, we decided to undertake a direct assessment of child development, rather than use a shorter parent report or observational developmental screening tool. Although undertaking direct assessments on every child had substantial implications for the duration and cost of the study, we considered that this was best practice, based on the broad neonatal outcomes literature from HIC and existing guidance of measuring early child development outcomes in LMIC. Use of proxy measures (e.g. parent report) would have substantially reduced the resources required for this research. However, we did not consider this an appropriate mode of testing for the primary aim of this research to measure neurodevelopmental outcomes in the study population.

However, since we also recognised the need to develop approaches to monitoring child development for high-risk neonates in Fiji that were likely to be feasible beyond the duration of this research, we also decided to explore the accuracy of less resource-intensive measures of child development within the study population. We therefore used the opportunity provided by our cohort study, to explore the feasibility and accuracy of nurse-led parent report measures for identification of developmental delay and impairment, within the study population, as described in Section 5.

Our direct assessment of child development in cognitive, language and motor domains was supplemented with clinical neurological examination by paediatric doctors for diagnosis of cerebral palsy and specialist testing for hearing and vision impairment. The decision to undertake formal audiology assessments in every child and refer all children with vision concerns for specialist assessment had substantial resources implications, even within a research context. However, based on
understanding of existing literature on the sensitivity and specificity of less resource-intensive approaches (e.g. clinical screening by a community health worker) we did not consider these alternatives adequate for measuring outcomes within our study. (90)

3.4.4 Definition of neurodevelopment impairment

Building on the above, our chosen primary outcome measure for this research was the prevalence of moderate to severe NDI at aged approximately two years corrected age and defined as;

- Score in ≥ 2 of cognitive, language AND/OR motor composite scales of < -2 standard deviations below standardised mean on the Bayley Scales of Infant and Toddler Development Third Edition® (Bayley-III)(32)
- AND/OR diagnosis of cerebral palsy(33)
- AND/OR hearing loss (an unaided hearing threshold in the better ear of 31dBHL or more)(34)
- AND/OR visual acuity of <6/18 in the better eye(35)

3.4.5 Global and domain specific developmental delays

3.4.5.1 Global developmental delay

As noted above, we chose to undertake direct assessments of child development in study participants at age 2 years corrected age to assess performance in cognitive, language and motor domains. Commonly used tests for assessing development in infants and young children include the Bayley Scales of Infant and Toddler Development (Second or Third Editions) (Bayley-II or III), the Griffiths Mental Development Scales (GMDS), among others. (32, 83) Of these, we chose to use the Bayley-III as the most up to date version of the Bayley Scales at the time and also the most commonly used child
development assessment tool in neonatal outcomes research. We therefore defined global developmental delay as:

- Score in ≥ 2 of cognitive, language AND/OR motor composite scales of < -2 standard deviations below standardised mean on the Bayley-III (Section 1.5)

Unlike formal cognitive assessments in older children (e.g. Weschler Intelligence Scales for Children) the Bayley-III and other direct developmental assessment tests in children aged 0 to 3 years, do not enable calculation of intelligence quotients. Instead they enable calculation of developmental scores per domain and across domains compared to the mean scores in a reference population. (32, 125)

Therefore, in young children, estimates of global developmental delay (i.e. a score ≥ 2 of cognitive, language AND/OR motor composite scales of < -2 standard deviations below standardised mean test scores) are used as a standard measure of delayed development rather than diagnosing intellectual impairment in young children (i.e. less than five years of age) in this age group. (126) Hence we used this definition as a key component of our composite definition of NDI.

The Bayley-III tests cognitive, motor (fine and gross), language (expressive and receptive), socioemotional and adaptive domains. (32) However, we chose not to test socioemotional development or adaptive behaviour given that these are assessed by lengthy parental questionnaire. We anticipated that reliable translation and adaptation of this would be difficult and likely to yield unreliable results given documented difficulties assessing socioemotional development in young children cross-culturally. (122)
We were also aware that, in spite of the Bayley-III being the reference standard child development assessment measure in young children, there were a number of actual and potential limitations in its use, especially cross-culturally.

Firstly, as noted in Section 2.4.2.1, although being widely accepted as a reference standard, the Bayley-III has been shown across a number of settings to under-estimate delays in cognitive, language and motor development as well as being a poor predictor of long-term cognitive and motor impairment.(84)

Secondly, the reference population for the Bayley-III included a sample of 1700 children of varying ages, representative of the United States population between the years 2000 and 2004.(32) Clearly, this sample was substantially different to the study population in Fiji. As such, we considered that it was crucial to have a local healthy neonatal comparison group, to enable us to interpret scores in the local context, rather than relying on data from the US Bayley-III norming sample.

Finally, as discussed in Section 2.4.2, there are many challenges, beyond lack of local validation, in the use of child development assessment tools across contexts. While we were not able to formally translate or adapt the Bayley-III for Fiji, within the constraints of this research, Section 3.6.2 describes procedures used to ensure to ensure best standardisation and quality of testing within the local context. Key findings related to these challenges will also be discussed more in Section 5.4.2 of this thesis.

**3.4.5.2 Domain specific and mild global developmental delay**

Within this research, we also chose to measure, as secondary outcomes, specific delays in language, motor and cognitive development in isolation which was defined as;
• Score in one of cognitive, language or motor composite scales of $<-2$ standard deviations below standardised mean (i.e. score $<70$) on the Bayley-III(32) (Section 1.5)

We were also interested in more mild adverse developmental outcomes and as such, mild global developmental delay, was also measured and defined as;

• Score in $\geq 2$ of cognitive, language AND/OR motor composite scales of $\geq -2$ and $<-1$ standard deviations below standardised mean (i.e. scores $\geq 70$ and $<85$) on the Bayley-III(32) (Section 1.5)

3.4.6 Vision impairment

We used the WHO definition of moderate or greater vision impairment within for this study, which meant that children with a visual acuity of $<6/18$ in the better eye were classified as having at least moderate visual impairment.(35)

Section 2.4.3.1 described approaches to ROP screening and early identification of amblyopia among young children in LMIC. As described in that section, App based technologies for rapid assessment of visual acuity in young children are increasingly widely available.(66) However, since these were less widely used at the time this research study was undertaken, we took expert ophthalmology advice regarding best initial vision screening in our study population and decided to do this by;

• Checking for strabismus and visual acuity by asking children to fix and follow an object, held at 30cm distance from their face, through an H-shape, each eye separately.(91, 127)

• Asking about parental concerns(128)
Since it was not feasible to offer every child in the study formal ophthalmology assessment, any child with concerns on initial eye screening or parental or clinical concerns was referred to see a trained ophthalmologist for formal assessment at the Pacific Eye Institute.

### 3.4.7 Hearing impairment

We used the WHO definition of moderate to severe hearing impairment within this study and therefore considered a child to have at least moderately severe hearing impairment if their unaided hearing threshold in the better ear was 31dBHL or more using pure tone average over octave frequency levels of 0.5,1,2,4 Hz.(34) (Section 1.5)

In Section 2.4.3.1 we outlined methods for hearing screening and assessment in childhood, including resource requirements and practical challenges commonly experienced with hearing screening and follow-up in LMIC.

Within our neonatal outcomes study, in order to obtain the most robust hearing data possible, we chose to offer tympanometry and formal diagnostic audiology assessments to all study participants. At the time this study was undertaken, since there were no local audiology services for children below primary school age, hearing tests were conducted by visiting audiologists at the Carabez Alliance audiology clinic in Suva. This was located a short bus ride away from CWMH. Where initial testing was inconclusive or raised concerns, repeat testing and follow-up through the Carabez Alliance and CWMH Ear, Nose and Throat surgical referral were offered.

### 3.4.8 Cerebral Palsy

We used the definition of CP provided by Rosenbaum et al within our definition of NDI for this study.(33) (Section 1.5) Within this internationally accepted definition, CP
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describes a group of developmental disorders of movement and posture, causing activity restriction or disability, attributed to disturbances occurring in the foetal or infant brain. (33) In cerebral palsy, the primary neuromotor impairment is accompanied to varying extents, by a range of health morbidity, sensory and intellectual disabilities (e.g. seizures, feeding difficulties, respiratory disease, hearing and vision impairment.

Diagnosis of cerebral palsy in young children is based on clinical neurological assessment by appropriately trained health professionals. This often requires follow-up over time and can be challenging in infancy, especially in ex-preterm children for whom there is an increased prevalence of motor tone abnormalities which resolve over time. Delineating the severity and type of cerebral palsy often also requires repeat and multidisciplinary assessment as does assessment of commonly associated co-morbidities including hearing and vision impairments, seizure disorders, nutritional and other health difficulties. (33)

In this research, the diagnosis of cerebral palsy was made on the basis of clinical neurological assessment by three practicing Australian paediatricians, (KM, SW, AM who were all part of the study team). Given that classifications such at the Gross Motor Function Classification System (GMFCS) for describing severity of CP are based on data from HIC where early access to physiotherapy, orthopaedic and rehabilitation are vastly different to services available in Fiji, we did not apply the GMFCS within our study population. (129)

3.4.9 Severity of impairment

In this research, we chose to focus on measurement of moderate to severe rather than mild NDI for several reasons.
Firstly, given the lack of baseline developmental data in Fiji and that tools used for measurement had not previously been used in that setting, it seemed sensible to focus on those outcomes which were most likely to be reliably identifiable using available tools in the local context.

Secondly within available resources, the larger sample size that would likely have been needed to detect mild differences between NICU survivors and the control neonatal group were not considered feasible. Similarly, a longer duration of follow-up is needed to ascertain mild neurodevelopmental sequelae, for example, around the time of school entry, and this was not feasible.

Finally, in a context where resources for follow-up were limited, even within a relatively small research study, we were mindful of health system and other sectoral ability to respond to the needs of children identified with developmental concerns. As such we decided to focus on identification of moderate to severe impairments, which, even in a resource-constrained setting, could be supported by follow-up through local services.

3.4.10 Health related outcomes

Secondary health outcomes assessed for study participants included comparison between cases and controls with regards to health conditions which were either highly prevalent in Fiji, considered likely on the basis of previous literature to be more prevalent in the high-risk group or particularly important to developmental outcomes. These included;

- Nutrition factors:
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- Prevalence of stunting, wasting and/or microcephaly – using WHO Child Growth reference curves, with correction for prematurity. (130)
- Anaemia – diagnosed as haemoglobin <10g/dL according to WHO definition for at least moderate anaemia in young children and using Hemocue® (131, 132)
- Feeding practices – as assessed using a WHO Infant & Young Child Feeding questionnaire. (133)

- Immunisation rates, based on parental report and cross checked with medical records where possible
- Childhood illnesses using the WHO Integrated Management of Childhood Illness (IMCI) guidelines as well as presence/absence of seizures. (134) In Fiji adapted IMCI guidelines include consideration of respiratory difficulties, diarrhoea, fever, ear and skin problems. (10)
- Number of contacts with government health service - based on parental report and cross checked with medical records where possible

3.5 Sample size

A total sample size of approximately 320 children including both the high-risk (n=160) and matched control (n=160) neonatal groups was determined based on conservative estimates of the expected prevalence of the primary outcome measure (i.e. moderate to severe NDI) according to review of the published literature, specifically, we estimated a prevalence of moderate to severe NDI in the control population of 5% and 15% in NICU survivors. (2) (Section 2.3) Using these estimates, we calculated that a total sample size
of 319 children would be needed to have 80% power to detect a difference of 10% in rates of moderate to severe NDI at follow-up in early childhood between the high-risk and the control neonatal groups (i.e. 15 vs. 5 %) with a significance level of 0.05.

### 3.6 Procedures

#### 3.6.1 Overall

Outcome data for this study were collected between February 2011 and July 2014. During this time, eligible patients discharged from CWMH NICU between November 2008 and April 2010 and a comparison control, term normal birthweight group discharged from the postnatal ward during the same period were identified from medical records.

Parents/guardians of eligible children were approached and informed consent obtained (Appendix 1 Plain language statement and third party consent form)

Baseline demographic and perinatal data for the cohort were retrieved from medical records and by parent report and recorded on relevant data collection forms (See Appendix 2 Baseline perinatal data collection form)

As close as possible to 24 months corrected age, a health and developmental assessment was undertaken by the research team (paediatric clinician and research nurse) at the Colonial War Memorial Hospital and Carabez Alliance Audiology Clinic for audiology assessment. This assessment was typically undertaken over two to three visits and included:

- Review of past history and current health status
- Measurement of growth parameters (height, weight and head circumference)
• Structured developmental screening using the Parents’ Evaluation of Developmental Status (See Section 6)(135)

• Assessment of immunization status and feeding practices

• Capillary blood sampling using an automated haemoglobinometer (i.e. Hemocue®) with referral of children with haemoglobin <10g/dL for formal venipuncture and treatment per local protocol(131)

• Physical examination by the study doctor including clinical neurological examination and vision screening (i.e. eliciting parental concerns, fix and follow using for each eye separately in H-shape at 30cm and assessment for strabismus). Children with vision concerns on clinical review were referred to ophthalmologists at the Pacific Eye Institute, CWMH for formal ophthalmological assessment.

• Comprehensive developmental assessment using the Bayley III by trained researchers, blinded to neonatal history with verbal translation by research and hospital staff as needed. Details for ensuring the quality and standardisation of child development assessment are covered in further detail below (Section 3.6.2)

• Formal audiology assessment conducted by visiting specialist audiologists including tympanometry and behavioural observation and play-based or visual reinforcement audiometry depending on each participant’s developmental abilities. This included repeat testing when initial audiology results were inconclusive.

(See Appendix 3 General Follow-up Data collection form for further details)
3.6.2 Child development assessment procedures

The quality of developmental assessment test includes both reliability and validity.(37) *Reliability* refers to how consistently a measure produces similar results for a child or group of children with repeated measurement.(37) *Validity* refers to the degree to which a measure accurately assesses behaviours or abilities that reflect the underlying construct being tested.(37) Ensuring test reliability and validity in turn depends on the tester, environment and testing procedures.(37)

3.6.2.1 Testers

All testers were trained and directly supervised by the primary assessor (KM) until they were competent in administration and scoring of the Bayley-III and PEDS tests. This included several supervised practice tests with children attending CWMH child development clinic before assessing study participants. Testers were supervised with intermittent review of assessments throughout the data collection period. Research staff responsible for developmental testing were blinded to the neonatal status of children at the time of testing.

Since some children within the study population had limited prior exposure to foreigners, we also recognised that the appearance of testers may have been novel and potentially affected their initial comfort with the test situation. However, all children had a parent or primary caregiver present as well as a local staff member translating.

3.6.2.2 Testing procedures

All children received test instructions in their first language, either directly by the tester or through translation into their first language by local staff members. Staff members were trained only to provide instructions and not to coach children to perform tasks.
Since many children within the study population travelled a substantial distance to attend study clinics, families were reimbursed for travel and light refreshments were provided to study participants and attending family members.

3.6.2.3 Testing environment
Bayley-III and most PEDS assessments were undertaken in CWMH outpatients. Although it was not always possible to secure the same room for testing, we aimed to keep the assessment area quiet.

3.6.2.4 Follow-up response and referral for children with health or developmental concerns
All children participating in the study received a written report and were counselled at the time of assessment, regarding any concerns about their child’s health or development. (See Appendix 4 Report for caregivers) In addition, follow-up for health, developmental or other concerns was arranged as per Table 4 below.
### Table 4: Follow-up care and referral for children with health, developmental or social concerns

<table>
<thead>
<tr>
<th>Domain of concern</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Developmental delay or impairment</td>
<td>Counselling of caregiver by a study doctor, referral to CWMH outpatients for review, further investigation and management by local paediatrician, formal audiology and ophthalmology assessment offered through study. Referral to existing local early intervention services.</td>
</tr>
<tr>
<td>Hearing impairment</td>
<td>Repeat testing was offered where initial testing was inconclusive. Caregivers were counselled by a study doctor regarding abnormal results and follow-up arranged including: Referral to an Ear, Nose and Throat specialist through CWMH, fitting of hearing aids through the Carabez Alliance Audiology Clinic in Suva if appropriate (at no cost to family), referral to early intervention services including a local school for children with hearing impairment that taught Fiji sign language if appropriate and follow-up paediatric care through CWMH outpatients.</td>
</tr>
<tr>
<td>Vision impairment</td>
<td>If initial clinical assessment raised concerns about a child’s vision or there were parental concerns about a child’s vision, that child was referred to the Pacific Eye Institute for further assessment and management by a specialist ophthalmologist</td>
</tr>
<tr>
<td>Anaemia on haemoglobin screening</td>
<td>Caregivers of children with a haemoglobin on initial screen of &lt;10g/dL were counselled and the child referred to CWMH outpatients on the same day for a full blood examination and management as indicated by a member of the paediatric team.</td>
</tr>
<tr>
<td>Health concerns</td>
<td>Children with other health concerns were referred to CWMH outpatient or inpatient service for further assessment and management.</td>
</tr>
<tr>
<td>Other concerns</td>
<td>While we did not specifically screen for child abuse or neglect, staff members were trained to notify the study doctor on the same day if they had any concerns in this domain, which were then managed in accordance with local protocol.</td>
</tr>
</tbody>
</table>
3.7 DATA ANALYSIS PLAN

Data were entered into an Epidata Version 3.1 database with double entry of variables relevant to the primary outcome. Data were cleaned and exported to StataIC Version 14 for analysis. Zanthro was used for analysis of anthropometric data. Demographic data for high risk and control groups were compared for any baseline differences between groups. Primary developmental and health outcomes at follow-up were described according to mean (SD) (parametric data), median (IQR) (non-parametric data) and odds ratios (95% CI) using McNemar’s test to allow for paired research design, paired t-tests and X² statistic as indicated.

Secondary developmental outcome measures including proportion of children with Bayley-III score ≥ 70 and < 85 and mean scores in each developmental domain were also assessed. Biological and social risk factors for adverse neurodevelopmental outcomes were explored through univariate and logistic regression analysis. Logistic regression included all study participants to explore potential risk factors for NDI, allowing interaction between gestational age and birth weight. This included covariates identified as significant at univariate analysis and socioeconomic status, which was considered potentially relevant on the basis of face validity.

Sensitivity analysis was undertaken to account for missing hearing data and to assess effect of conductive hearing loss on primary outcomes.

3.8 ETHICS

Informed consent was obtained from children’s parents/guardians prior to recruitment. Caregivers were reimbursed for costs of travel only. Approval was obtained from the Fiji
National Health Research, Fiji National Research Ethics Review and University of Melbourne Human Research Ethics Committees.

One particular ethical issue that we considered from very early on in research design, was the need to ensure best available local care for children with identified NDIs. This meant gaining an understanding of local referral pathways not only in health, but also education and working in collaboration with local government health staff throughout the study. Table 4 above summarises protocols that were established for follow-up of children with concerns in different domains.

Towards the end of this thesis the practical ethical challenges of conducting neurodevelopmental outcomes research in LMIC and implications of this research for improving follow-up care of high-risk neonates and care of children with developmental delay and impairment are discussed in more detail. (Section 7)

3.9 **SUMMARY OF METHODS**

This section has provided a detailed description of the research design for our neonatal neurodevelopmental outcomes study in Fiji and the rationale for design choices made. The overall aim of the research was to describe the prevalence and risk factors for moderate to severe NDI in high-risk and matched control neonates in Fiji at two years corrected age, or as close thereto as possible.

To achieve this, we completed a retrospective cohort study with comparison of early childhood neurodevelopmental and health outcomes in high-risk NICU and a group of matched, term, normal birth weight controls neonates discharged from CWMH between January 2008 and January 2010. The high-risk NICU group included children with a
diverse range of neonatal morbidities based on pre-defined inclusion and exclusion criteria. Control neonates, selected from CWMH postnatal ward were matched for potential confounders (age, sex, expected date of delivery).

Research participants underwent detailed developmental and health assessment including direct developmental assessment using the Bayley-III, hearing and vision assessment and a structured health review, including neurological examination by a paediatrician for cerebral palsy. Based on existing literature review, we estimated a sample size of 160 children for each group based on estimated prevalence of moderate to severe NDI of 15% and 5% in the ‘high-risk’ and control group respectively, with 80% power and significance level of 0.05. Univariate and logistic regression analysis of primary and secondary outcome measures and covariates was undertaken to answer research objectives. Children with identified health, developmental or other concerns were provided with follow-up care, according to study protocol, within existing services.

Results of this study, subsequently published in *Archives of Disease in Childhood*, are provided in the next section of this thesis together with additional findings on hearing, vision and health which were covered in less detail in the published paper.(3)
Section 4

NEONATAL OUTCOMES
STUDY - RESULTS
4. NEONATAL OUTCOMES STUDY - RESULTS

4.1 SECTION OUTLINE

Earlier sections of this thesis have described the background and research design for our high-risk neonatal outcomes study in Fiji. In this section, the results of this study are presented in Section 4.2 as published in *Archives of Disease in Childhood* including:

- Description of the high-risk and comparison control group populations (Table 1);
- Neurodevelopmental outcomes (Table 2);
- Hearing outcomes (Figure 2);
- Health outcomes (Table 3);
- Analysis of risk factors for adverse neurodevelopmental outcomes

Sections 4.3 then provides further detail, unable to be included within the word limits of the published results paper, regarding hearing and vision outcomes.

The published paper also includes discussion of the significance of results, comparison with existing literature, interpretation of findings related to risk factors, limitations of the study and its importance and implications for ongoing neonatal and child development research and programming in LMIC. This provides a basis for the discussion in Section 5 of this thesis, which elaborates on and extends themes raised in this paper.

4.2 NEURODEVELOPMENTAL OUTCOMES - PUBLISHED PAPER

Results of the neonatal outcomes study were published in *Archives of Disease of Childhood* as an original study paper entitled, ‘Neurodevelopmental outcomes for high-risk neonates in a low-resource setting’ which is provided below.(3)
Neurodevelopmental outcomes for high-risk neonates in a low-resource setting

Kate M Milner,1,2,3 Trevor Duke,1,2,4 Andrew C Steer,1,2,4 Joseph H Kado,5,6 Lanieta Koyamaibole,5 Rakei Kaarira,7 Kelera Namudu,5 Susan Woolfenden,7,8 Anne E Miller,1 Kathryn E O’Heir,1 Eleanor F G Neal,1,4 Gehan Roberts4,9

ABSTRACT
Worldwide, most neonates who survive prematurity and serious illness reside in low-resource settings where developmental outcome data and follow-up care are limited. This study aimed to assess in Fiji, a low-resource Pacific setting, prevalence and risk factors for moderate to severe neurodevelopmental impairment (NDI) in early childhood among high-risk neonates compared with controls. Retrospective cohort study comparing long-term outcomes for high-risk neonatal intensive care unit patients (n=149) compared with matched term, normal birth weight neonates (n=147) discharged from Colonial War Memorial Hospital between November 2008 and April 2010. NDI was defined as one or more of cerebral palsy, moderate to severe hearing or visual impairment, or global developmental delay using Bayley Scales of Infant and Toddler Development Third Edition (ie, score <70 in ≥1 of cognitive, language or motor domains). At median (IQR) age 36.1 (28.3, 38.0) months, prevalence of moderate to severe NDI 95% CI n) in high-risk and control groups was 12 (5 to 17, n=13) and 5 (2 to 12, n=5), respectively, an increased risk ratio (95% CI) of 2.7 (0.8 to 8.9). Median gestational age (weeks (median, IQR)) in the high-risk group was 37.5 (34–40) weeks. Among high-risk neonates, gestational age, birth weight, asphyxia, meningitis and/or respiratory distress were significantly associated with risk of NDI. Prevalence of NDI was high among this predominantly term high-risk neonatal cohort compared with controls. Results, including identified risk factors, inform efforts to strengthen quality of care and models of follow-up for high-risk neonates in this low-resource setting.

INTRODUCTION
Modelled estimates suggest that worldwide, 18.5% of neonates who survive complications such as prematurity, birth asphyxia or serious bacterial infection experience severe neurodevelopmental impairment (NDI), including cerebral palsy, cognitive, hearing or visual impairment.1 However, in low-resource settings where most of the 15.1 million neonates who survive serious illness every year reside, developmental outcome data are scarce.2–5 Improved data are needed to guide programming, including models of follow-up for these children. Specifically, recent review of available outcome studies from low-income and middle-income settings highlights the need for high-quality studies that describe multidomain neurodevelopmental outcomes for very low birth weight (VLBW) infants and for neonates who survive other causes of neonatal morbidity.6

In Fiji, a middle-income Pacific Island country, national neonatal health policy has shifted, alongside the Global Strategy for Women’s Children’s and Adolescent’s Health, from almost exclusive focus on neonatal survival to increased emphasis on helping every neonate, including those who survive complications, to ‘thrive’.7 8 Efforts to reduce neonatal mortality have been successful, national neonatal mortality rates are low by global standards (ie, 9.9/1000 live births) and neonatal services are in transition with increasing capacity to support care for preterm and unwell infants.9 The Colonial War Memorial Hospital (CWMH) neonatal intensive care unit (NICU), the major national neonatal referral centre, has 40–50 admissions per month and provides increasing acute interventions, including conventional ventilation, but post-discharge follow-up remains limited.7 Long-term developmental outcome data are not available but needed to inform service development.

This study aimed to assess early childhood neurodevelopmental and health outcomes for a cohort of high-risk neonates, defined on the basis of NICU admission, relative to control healthy, term neonates from Fiji, specifically:
1. prevalence of moderate to severe NDI at approximately 2 years of age
2. prevalence of stunting, wasting, anaemia, other health morbidity, immunisation rates and health service usage.

PATIENTS AND METHODS
Study design
This is a retrospective cohort study comparing long-term outcomes for high-risk NICU patients and matched control neonates. We reviewed medical records of patients discharged from CWMH NICU between November 2008 and April 2010 with the aim of assessing children at approximately 2 years of age. Among patients discharged from CWMH NICU during this period, we selected a convenience sample at potential higher risk of long-term morbidity and adverse neurodevelopmental outcomes on the basis of pre-existing literature from other settings (online supplementary appendices 1 and 2).8 In response to broad concerns of local clinicians, this included a diagnostically heterogeneous group according to the following predetermined inclusion criteria: gestational age <34 weeks and/or birth weight <1800 g and/or requiring surgery and/
Global child health

or having other serious illness (online supplementary appendices 1 and 2). We excluded children with major congenital anomalies. Gestational age was determined hierarchically from medical records using first-trimester or early second-trimester ultrasound, postnatal clinical assessment (ie, Ballard, New Ballard Score or Dubowitz) or last menstrual period. Control, term, normal birth weight neonates discharged from postnatal wards during the same period were identified from medical records, matched for potential confounders including expected date of delivery, gender, ethnicity and place of residence.

Study procedures
Outcome data for this study were collected between February 2011 and July 2014. Demographic and health data were retrieved from medical records and by parental report. Between 18 and 42 months, developmental assessment using Bayley Scales of Infant and Toddler Development Third Edition (Bayley-III) was completed by trained researchers, blinded to participants’ neonatal history, with verbal translation as needed.

Visiting audiologists conducted assessments, including tympa-nometry and behavioural observation, and play-based or visual reinforcement audiometry depending on children’s developmental abilities. Repeat testing was offered when initial audiology results were inconclusive.

Children were reviewed by a doctor for medical history, cross-checked with medical records, and physical examination including anthropometry, general systems, neurology and clinical screening for strabismus was completed. Children with strabismus, inability to fix and follow an object in H-shape at 30 cm for each eye separately, or parental vision concerns were referred for ophthalmology assessment. HemoCue haemoglobin screening was performed.

Outcome measures
Moderate to severe NDI was defined as presence of ≥1 of:
- clinical diagnosis of cerebral palsy per Rosenbaum et al1
- Bayley-III score ≥1 on cognitive, language composite or motor composite scales <−2 SD below reference mean
- moderate to severe hearing impairment per WHO criteria (ie, unaided hearing threshold in better ear 31 decibels hearing loss (dBHL) or worse)12
- moderate to severe visual impairment per WHO criteria (ie, visual acuity <6/18 in better eye).13

Sample size
We calculated a target sample size of 160 children for each of the high-risk and control groups using estimates of the primary outcome measure derived from previous published literature (ie, 15% vs 3% prevalence of moderate to severe NDI in high-risk and controls, respectively), with 80% power and significance level of 0.05.14–21

Data analysis
Data were entered into EpiData V.3.1, with double entry of variables relevant to primary outcome, cleaned and exported to StataIC V.14 for analysis. Zanthro was used for anthropometric data. Demographic data were compared between groups for baseline differences. Primary developmental and health outcomes were described according to mean (SD), median (IQR) and ORs (95% CI) using McNemar’s test to allow for paired research design, paired t-tests and X² statistic as indicated. Secondary developmental outcome measures including proportion of children with Bayley-III score ≥70 and ≤85 and mean scores in each domain were also assessed. Biological and social risk factors for adverse neurodevelopmental outcomes were explored through univariate and regression analyses. Logistic regression included all study participants to explore potential risk factors for NDI, allowing for interaction between gestational age and birth weight. This included covariates identified as significant at univariate analysis and socioeconomic status, which was considered potentially relevant on the basis of face validity. Sensitivity analysis was undertaken to assess the effect of missing hearing data and conductive hearing loss on primary outcomes.

Informed consent and ethics approval
Informed consent was obtained from children’s parents/guardians prior to recruitment. Caregivers were reimbursed for cost of travel. Approval was obtained from Fiji National Health Research, Fiji National Health Research Ethics Review and University of Melbourne Human Research Ethics Committees.

RESULTS
Seven hundred and fifty-four infants were discharged from CWMH NICU between November 2008 and April 2010 (figure 1). Study participants were retrospectively identified from medical records, with potential participants approached for recruitment until the target sample size was reached. This included 149 NICU patients matched to a control group of 147 children (figure 1). Appropriate controls for two NICU patients could not be allocated in a timely manner. Recruited NICU patients had similar gestational age, birth weight and ethnicity profiles to the broader NICU population during the sampling period.

Population characteristics
Most high-risk neonates had normal birth weight (table 1). Among high-risk neonates, a higher proportion of families resided in rural areas and were relatively more socially disadvantaged according to parental income and maternal education status (table 1). Median age at neurodevelopmental assessment was approximately 36 months for high-risk and 37 months for control participants (table 1).
High-risk neonates had a trend towards increased overall prevalence of moderate to severe NDI compared with controls (risk ratio 2.7 (0.8–8.9, p=0.09); table 2). Four per cent (0.8–7.2, p=0.01) of high-risk children had cognitive delay and 4.7% (1.3–8.1, p=0.02) had cerebral palsy compared with zero-affected controls (table 2).

**Table 1**  Population characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>High-risk group (n=149)</th>
<th>Control group (n=147)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, %</td>
<td>42</td>
<td>40</td>
</tr>
<tr>
<td>Birth weight, g, median (IQR)</td>
<td>2610 (1750–3500)</td>
<td>3350 (3000–3650)</td>
</tr>
<tr>
<td>Gestational age, week, median (IQR)</td>
<td>37.5 (34–40)</td>
<td>39.6 (38.5–40)</td>
</tr>
<tr>
<td>Age at neurodevelopmental assessment, month(mth) (SD)</td>
<td>35.8 (6.8)</td>
<td>36.8 (5.5)</td>
</tr>
</tbody>
</table>

**Birth weight group**

| Low birth weight (1500–2500 g), n (%)            | 47 (32)                     | Not applicable |
| Very low birth weight (1000–1499 g), n (%)      | 18 (12)                     |              |
| Extremely low birth weight (1000 g), n (%)      | 3 (2)                       |              |

**Gestational age group**

| Late preterm (32–37 weeks), n (%)              | 52 (36)                     | Not applicable |
| Moderate preterm (28–32 weeks), n (%)         | 10 (7)                      |              |
| Extremely preterm (<28 weeks), n (%)          | 2 (1)                       |              |

**Neonatal diagnoses**

| Birth asphyxia *, n (%)                        | 15 (11)                     | Not applicable |
| Meningitis†, n (%)                            | 11 (8)                      |              |
| Risk of sepsis‡, n (%)                        | 84 (65)                     |              |
| Severe jaundice§, n (%)                       | 44 (33)                     |              |
| Respiratory distress¶, n (%)                  | 100 (72)                    |              |
| Nosocomial infection**, n (%)                  | 19 (14)                     |              |

**Age (corrected) at follow-up, mth (IQR)**

| High-risk group (n=149)                         | 36.6 (26.1–38.1)            | 35.7 (30.5–37.9) |

**Ethnicity**

| Indo-Fijian, n (%)                             | 50 (34)                     | 48 (33)        |
| Itaukei, n (%)                                 | 92 (62)                     | 93 (64)        |

**Maternal age, year, median (IQR)**

| 26 (18–41)                                    | 26 (19–37)                  |              |

**Residence at birth, rural, %**

| 35                                            | 19                           |              |

**Maternal education, primary school only, %**

| 5                                             | 2                            |              |

**Family income, <FJ$100 per week combined family income, %**

| 20                                            | 11                           | 20             |

*Birth asphyxia: onset within 2 days of birth of severe or moderate neonatal encephalopathy in infants born at 34 or more weeks of gestation and acute perinatal event, and/or a 10 min Apgar less than 5 or assisted ventilation for more than 10 min or diagnosis by treating paediatrician.
†Meningitis: cerebrospinal fluid culture positive for a causative organisms or clinical diagnosis by treating paediatrician.
‡Risk of sepsis: positive blood culture or clinical diagnosis of sepsis or two or more risk factors for sepsis and treated with antibiotics.
§Severe jaundice: significant jaundice based on bilirubin level for age and weight of newborn based on internationally accepted criteria.
¶Respiratory distress: clinical evidence of increased work of breathing, tachypnoea, requirement for supplemental oxygen or ventilatory support.
**Microbiologically confirmed or treatment for clinically diagnosed infections acquired while neonate is receiving treatment for another condition.

**Table 2**  Neurodevelopmental outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Children with completed assessment, n</th>
<th>Prevalence of neurodevelopmental impairment, % (95% CI) (n)</th>
<th>Risk ratio (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate to severe neurodevelopmental impairment, % (95% CI) (n)</td>
<td>207</td>
<td>12 (5 to 17) (13/109) 5 (2 to 12) (5/98)</td>
<td>2.7 (0.8 to 8.9)</td>
<td>0.09</td>
</tr>
<tr>
<td>Moderate to severe neurodevelopmental impairment, % (95% CI) (n)</td>
<td>296</td>
<td>4 (6/149) 0 (0/147)</td>
<td>ns</td>
<td>0.01</td>
</tr>
<tr>
<td>Composite score &lt;70 in ≥2 domains, % (n)</td>
<td>296</td>
<td>4 (5/149) 1 (2/147)</td>
<td>3.5 (0.7 to 16.8)</td>
<td>0.1</td>
</tr>
<tr>
<td>Cerebral palsy, % (95% CI) (n)</td>
<td>295</td>
<td>5 (1/149) 0 (0/146)</td>
<td>Not specified (ns)</td>
<td>0.02</td>
</tr>
<tr>
<td>Hearing impairment (moderate-severe), % (n)</td>
<td>212</td>
<td>6 (6/107) 5 (5/102)</td>
<td>1.7 (0.5 to 5.8)</td>
<td>0.41</td>
</tr>
<tr>
<td>Vision impairment (moderate-severe), % (n)</td>
<td>289</td>
<td>3 (4/145) 0 (0/144)</td>
<td>ns</td>
<td>0.05</td>
</tr>
<tr>
<td>Bayley-III scores</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Domain</td>
<td>Children with completed assessment, n</td>
<td>High-risk group (n=149)</td>
<td>Control group (n=147)</td>
<td>p</td>
</tr>
<tr>
<td>Cognitive composite score, mean±SD</td>
<td>296</td>
<td>90 (11) 92 (13)</td>
<td>95 (10)</td>
<td>0.04</td>
</tr>
<tr>
<td>Language composite score, mean±SD</td>
<td>296</td>
<td>92 (13) 103 (11)</td>
<td>0.08</td>
<td></td>
</tr>
<tr>
<td>Motor composite score, mean±SD</td>
<td>295</td>
<td>98 (16) 103 (11)</td>
<td>0.00</td>
<td></td>
</tr>
</tbody>
</table>

Health outcomes

High-risk children had lower height for age and head circumference than controls (table 3). Risk ratio of active respiratory symptoms was also 1.9 (1.0–3.6, p=0.04) times higher among high-risk children (table 3). There was no significant difference in prevalence of anaemia or other measured health indices (table 3). Children with NDI had poorer height for age, head circumference and had 3.6 (1.8–7.2, p=0.00) times higher risk ratio of respiratory symptoms compared with peers without NDI (table 3).

**DISCUSSION**

This study shows a high prevalence of moderate to severe NDI impairment in early childhood among a diagnostically heterogeneous, predominantly term cohort of high-risk neonates in a middle-income setting.

Previous similar studies have varied in quality and have often not included a control group, which we considered important in a setting where population developmental outcome data were lacking.22 We found a difference in overall prevalence of NDI relative to control neonates. This difference was higher and statistically significant once common childhood causes of hearing loss (ie, middle ear disease) were excluded from analysis.

Previous similar studies, focusing on diagnostically heterogeneous cohorts, have tended to include a higher proportion of VLBW infants.6 13 23–27 In our study, 14% of the cohort was very or extremely low birth weight, and 12.8% (7.2%–20.6%) of the high-risk group had moderate to severe NDI. This is comparable to 15% prevalence of NDI noted by Paul et al24 at follow-up of a NICU cohort in New Delhi, which had a much higher proportion (ie, 52%) of VLBW infants.

Prevalence of cerebral palsy in similar NICU follow-up studies is variable, ranging from 5% to 9.4% in cohorts of predominantly VLBW infants.6 13 26 27 Using a standard definition of cerebral palsy, this study showed a similar prevalence of 4.7% (SD 1.3–8.1) in spite of a smaller proportion of VLBW infants.

Most previous NICU follow-up studies in low-resource settings have not included assessments of hearing and vision.6 22 Among comparable studies that have reported visual outcomes, Paul et al estimated a 4% prevalence of visual impairment in their New Delhi NICU cohort, although details of ophthalmological definitions used are unclear.24 Mwaniki et al previously estimated a median prevalence of severe visual impairment following ‘neonatal insults’ globally of 2.4% (IQR 0.6–10.0). As such, overall observed prevalence of visual impairment in our study population appears in keeping with previous literature. However, as expected, observed prevalence among this high-risk group was higher than previous estimates of visual impairment among the broader paediatric population in Fiji of 1 per 1000 children.28

We did not identify ROP. However, we again note the gestational age profile of the cohort and that our study was not powered to assess causes of visual impairment as an isolated outcome. A previous survey of childhood visual impairment in Fiji observed that 30% of preventable blindness is due to ROP.30 Global estimates also suggest that in middle-income settings with similar neonatal health profiles, the median prevalence of ROP among neonates with gestational age 32–36 weeks is much higher than in high-income settings at 7.7% (95% CI 6.7% to 8.7%).3

Observed prevalence of moderate to severe hearing impairment was high for both high-risk (5.6%, n=41) and control (4.9%, n=5) groups. In both groups, this was multifactorial, and middle ear disease was noted in 45% (n=106) of the children assessed. This is comparable to findings of an unpublished survey of 773 children aged 3–13 months in Fiji in 2004, in which prevalence

Figure 2  Audiometry testing flow chart and results.
Table 3  Health outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>High-risk group (n=149)</th>
<th>Control group (n=147)</th>
<th>Risk ratio (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height for age z-score, mean±SD</td>
<td>−0.5±1.2</td>
<td>−0.1±1.2</td>
<td>na</td>
<td>0.02</td>
</tr>
<tr>
<td>Weight for height z-score, mean±SD</td>
<td>−0.3±1.4</td>
<td>0.1±1.3</td>
<td>na</td>
<td>0.09</td>
</tr>
<tr>
<td>Head circumference z-score, mean±SD</td>
<td>−0.6±1.5</td>
<td>−0.1±1.2</td>
<td>na</td>
<td>0.05</td>
</tr>
<tr>
<td>Haemoglobin, median g/dL (IQR)</td>
<td>11.7 (10.7–12.5)</td>
<td>11.3 (10.6–12.2)</td>
<td>na</td>
<td>0.09</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Symptoms (parental report), % (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory symptoms</td>
</tr>
<tr>
<td>15 (22/149)</td>
</tr>
<tr>
<td>8 (11/145)</td>
</tr>
<tr>
<td>1.9 (1.0 to 3.6)</td>
</tr>
<tr>
<td>0.04</td>
</tr>
<tr>
<td>Diarrhoea</td>
</tr>
<tr>
<td>4 (5/149)</td>
</tr>
<tr>
<td>1 (1/145)</td>
</tr>
<tr>
<td>5.0 (0.6 to 42.8)</td>
</tr>
<tr>
<td>0.10</td>
</tr>
<tr>
<td>‘Skin problems’</td>
</tr>
<tr>
<td>11 (16/149)</td>
</tr>
<tr>
<td>14 (20/145)</td>
</tr>
<tr>
<td>0.8 (0.4 to 1.5)</td>
</tr>
<tr>
<td>0.49</td>
</tr>
<tr>
<td>Fever</td>
</tr>
<tr>
<td>5 (7/149)</td>
</tr>
<tr>
<td>4 (5/145)</td>
</tr>
<tr>
<td>1.4 (0.5 to 4.0)</td>
</tr>
<tr>
<td>0.53</td>
</tr>
<tr>
<td>Seizures</td>
</tr>
<tr>
<td>7 (11/148)</td>
</tr>
<tr>
<td>8 (11/144)</td>
</tr>
<tr>
<td>0.9 (0.4 to 2.1)</td>
</tr>
<tr>
<td>0.83</td>
</tr>
<tr>
<td>9-Month immunisation completion (parental report), % (n)</td>
</tr>
<tr>
<td>99 (146/149)</td>
</tr>
<tr>
<td>100 (143/143)</td>
</tr>
<tr>
<td>1.0 (0.9 to 1.0)</td>
</tr>
<tr>
<td>0.15</td>
</tr>
<tr>
<td>Hospital admissions (at least one postnatal) (parental report), % (n)</td>
</tr>
<tr>
<td>26 (38/147)</td>
</tr>
<tr>
<td>17 (25/143)</td>
</tr>
<tr>
<td>1.5 (0.9 to 2.4)</td>
</tr>
<tr>
<td>0.09</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Children with NDI (n=20)</th>
<th>Children without NDI (n=268)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height for age z-score, mean±SD</td>
<td>−0.8±1.2</td>
<td>−0.3±1.2</td>
<td>0.03</td>
</tr>
<tr>
<td>Weight for height z-score, mean±SD</td>
<td>−0.4±1.9</td>
<td>0.1±1.3</td>
<td>0.06</td>
</tr>
<tr>
<td>Head circumference z-score, mean±SD</td>
<td>−0.9±2.5</td>
<td>−0.3±1.2</td>
<td>0.02</td>
</tr>
<tr>
<td>Haemoglobin, median g/dL (IQR)</td>
<td>11.6 (11.3–12.5)</td>
<td>11.4 (10.7–12.3)</td>
<td>0.85</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Symptoms (parental report), % (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory symptoms</td>
</tr>
<tr>
<td>35 (7/20)</td>
</tr>
<tr>
<td>10 (26/267)</td>
</tr>
<tr>
<td>0.00</td>
</tr>
<tr>
<td>Diarrhoea</td>
</tr>
<tr>
<td>5 (1/20)</td>
</tr>
<tr>
<td>2 (5/267)</td>
</tr>
<tr>
<td>0.35</td>
</tr>
<tr>
<td>Fever</td>
</tr>
<tr>
<td>0 (0/20)</td>
</tr>
<tr>
<td>5 (12/267)</td>
</tr>
<tr>
<td>0.33</td>
</tr>
<tr>
<td>Seizures</td>
</tr>
<tr>
<td>10 (2/20)</td>
</tr>
<tr>
<td>8 (20/265)</td>
</tr>
<tr>
<td>0.69</td>
</tr>
<tr>
<td>9-Month immunisation completion (parental report), % (n)</td>
</tr>
<tr>
<td>95 (19/20)</td>
</tr>
<tr>
<td>99 (263/265)</td>
</tr>
<tr>
<td>0.07</td>
</tr>
<tr>
<td>Hospital admissions (at least one postnatal) (parental report), % (n)</td>
</tr>
<tr>
<td>25 (5/20)</td>
</tr>
<tr>
<td>22 (57/263)</td>
</tr>
<tr>
<td>0.73</td>
</tr>
</tbody>
</table>

NDI, neurodevelopmental impairment; na, not applicable.

of middle ear disease was 38%. Further research is required to explore this observed high prevalence of hearing impairment.

We identified several risk factors for adverse developmental outcomes among high-risk infants consistent with pre-existing literature, including lower gestational age, birth weight, and diagnoses of ‘birth asphyxia’, ‘meningitis’ or ‘respiratory distress’. Absence of identification of social risk factors in our study also requires further investigation. Given the importance of psychosocial variables on child development, it is possible that measures of psychosocial risk used lacked sufficient detail. In future studies, more in-depth assessments of psychosocial variables may be warranted.

We also note the substantial proportion of children in both NICU and control groups (28% and 19%, respectively) with Bayley-III scores in the mildly delayed range. Further research is required to determine the extent to which this reflects limitations of the Bayley-III in the local context, as discussed further below, or factors that may contribute to developmental risk in the paediatric population generally and therefore warrant a programming and policy response.

There are a number of limitations to our study. First, the retrospective study design, used because it was most feasible, introduces potential confounding, which was addressed through use of a matched control group and on analysis. Second, there was substantial loss to follow-up for audiology assessments, although on sensitivity analysis this did not substantially alter primary outcomes. We also took a two-tiered approach to ophthalmological assessment (ie, clinical screening followed by specialist review) because it was not possible to offer formal assessments to every participant. Given that children in both groups with clinical concerns were referred, it is unlikely that this substantially affected the results.

More generally, as for neonatal outcomes research in low-resource settings more broadly, there were potential limitations with accuracy and reliability of both exposure and outcome variables. Accurate gestational age assessment, central to measurement of developmental outcomes, was challenging in a setting where women have poor access to antenatal ultrasound. Similarly, the need to rely on clinical diagnosis of exposure variables (eg, ‘birth asphyxia’, ‘serious bacterial infections’) had inherent limitations, although unlikely to affect primary results. There are also clear limitations in the use of developmental assessment tools developed and normed in high-income settings. Steps were taken to limit impact of this on the validity of results through piloting, use of interpreters and a control group. However, in future studies formal adaptation, translation and revalidation in the local context would strengthen understanding of measured outcomes. Similarly, in this study, due to the need for assessments to be supported by visiting specialists, recruitment was temporally spread. This is, however, unlikely to have substantially affected the primary results.
Since this study was undertaken, neonatal intensive care provided in Fiji has further advanced with provision of artificial surfactant for preterm neonates. Such interventions are likely to improve overall and gestation-specific survival. It is also possible that there may be associated changes in the prevalence of neurodevelopmental sequelae among high-risk neonates, as has been observed historically in high-income settings, for example with epidemics of ROP, in the past. In order to monitor neonatal outcomes through transitions in care, there is urgent need for programming that includes methods for monitoring long-term developmental outcomes in low-resource settings that are feasible, appropriate, valid and appropriately referenced for such contexts. Prospective cohort studies, which continue to explore risk factors for adverse neurodevelopmental outcomes among high-risk neonates in low-resource settings, are warranted.

Finally, this study raises the question of what can be done to improve long-term health and developmental outcomes for high-risk newborns in resource-limited settings, such as Fiji where neonatal healthcare is in transition. Primary prevention of adverse neurodevelopmental sequelae through increased focus on the quality of antenatal, obstetric and neonatal care for preterm and seriously ill neonates is critical, including systems for prevention, early detection and management of hearing impairment and ROP. Postdischarge, a stratified approach to follow-up based on local outcome data may be warranted. Implementation research to explore models of follow-up, including developmental monitoring and early intervention that are feasible, appropriate and effective in settings where resource-intensive multidisciplinary models of care are not possible, is also needed.

CONCLUSION

We observed a high prevalence of moderate to severe NDI in a predominantly term high-risk neonatal cohort in Fiji. This informs efforts to improve quality of neonatal care and identifies risk factors that could be used to stratify follow-up in a setting where resources are limited. As neonatal care in Fiji and other similar middle-income settings improves, there is an urgent need to strengthen systems for monitoring long-term outcomes and further research to determine models of follow-up that are effective in supporting high-risk neonates achieve their best developmental potential.

Acknowledgements

In publishing this work we acknowledge our profound respect for colleague and co-author Sr Lanieta Koyamaiboile (28.6.53 – 28.5.17) who made a substantial contribution to improvements in quality of neonatal care in Fiji over the course of her lifetime. Without Sr Koyamaiboile this research would not have been possible. After registering as a nurse and midwife in 1974, Sr Koyamaiboile worked throughout Fiji and was nursing head of the Neonatal Intensive Care Unit at Colonial War Memorial Hospital in Suva from 1989-2007. As a result of passionate advocacy for her patients, uncompromising clinical standards, meticulous record keeping and her support for professional development of colleagues, Sr Koyamaiboile was highly regarded as a champion for neonatal health. We are indebted to the children and families who participated in this study. We would also especially like to extend our thanks to the staff at CWMH who supported coordination of the study, including CWMM Neonatal Intensive Care Unit, Children’s Outpatients nurses including Sns Vijay and Pradeep; Mrs Neomai Hickes; the Paediatric Physiotherapy Department; Dr Roger Dethlefs and staff at the Pacific Eye Institute; Mrs Bronwyn Carabez and staff at the Carabez Audiology Clinic; visiting audiologists Ms Linda Zralka, Ms Kathryn Randall, Ms Anna Ly, Ms Johanna Tan and Ms Kelley Graydon; as well as office staff in both Suva and Melbourne whose support with coordination of this study was invaluable, including Mrs Tupou Ratu, Mrs Meresdni Gunaiwalu and Mrs Caitlyn Robertson. We would also like to than Susan Donath and Suzanna Vidmar from the Clinical Epidemiology and Biostatistics Unit, Murdoch Children’s Research Unit, for their support.

Contributors

AEM conceptualised and designed the study, assisted with data collection, analysed data, revised the manuscript and approved the final manuscript as submitted. TD, ACS and GR supervised study design and analysis of data, reviewed and revised the manuscript, and approved the final manuscript as submitted. JHK, RK, KN, SW, AEM and LX and KEO supported, coordinated and completed data collection at the study site and approved the final manuscript as submitted. EFGN assisted with data cleaning and analysis and approved the final manuscript as submitted.

Funding

Australian Agency for International Development and Cure Kids Fiji.

Competing interests

None declared.

Patient consent

Parental/guardian consent obtained.

Ethics approval

Fiji National Health Research Committee, Fiji National Health Research Ethics Review Committee and University of Melbourne Human Research Ethics Committees.

Provenance and peer review

Not commissioned; externally peer reviewed.

Data sharing statement

Primary data related to this study and a related substudy exploring developmental screening instruments within the study cohort are stored at Colonial War Memorial Hospital Suva, Fiji, and the Centre for International Child Health, University of Melbourne. Data retention, storage and management are per University of Melbourne stipulations.

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REFERENCES


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Global child health


4.3 **HEARING AND VISION - ADDITIONAL FINDINGS**

Hearing testing in our neonatal outcomes study occurred during specially arranged clinics with visiting audiologists who brought in equipment and we also borrowed equipment from a non-government organisation with a clinic in Suva, the Carabez Alliance. In spite of all participants being offered appointments, almost 1/3 of children in both high-risk and control groups did not attend an audiology appointment (i.e. 27% (n=40) and 30% (n=43) respectively). Additionally, 13% of children tested (n=38/296) needed repeat testing to clarify results. Children with hearing impairment were then referred for follow-up through a combination of visiting audiology and local health services.

For vision testing, we used initial clinical assessment as the decision point for referral, based on expert ophthalmology advice in the research design phase. (See also 3.4.6) On the basis of initial clinical vision screens, 11% (n=32) children were referred for ophthalmology assessment which was attended by 84% (n=27) of children referred. Of these 3% (n=4/145) high-risk but no control neonates had moderate to severe vision impairment at follow-up. Children with moderate-severe visual impairment had cortical visual impairment in the context of multi-domain NDI (n=4). No cases of retinopathy of prematurity were identified.

These results not only highlight the importance of hearing and vision impairment in our study population, but also the substantial resources and systems required to support collection of high-quality outcome data in these domains.
4.4 **SUMMARY OF RESULTS**

Our neonatal outcomes study in Fiji compared long-term neurodevelopmental and health outcomes for high-risk NICU patients (n=149) compared with matched term, normal birth weight neonates (n=147) discharged from Colonial War Memorial Hospital between November 2008 and April 2010. There was a higher prevalence of families from the lowest wealth quintile, with poor maternal education and residing in rural areas in the high-risk neonatal group.

At median (IQR) age 36.1 (28.3, 38.0) months we found that the prevalence of moderate to severe NDI % (95% CI, n) in high-risk and control groups was 12 (5 to 17, n=13) and 5 (2 to 12, n=5) respectively. This reflected an increased risk ratio (95% CI) of 2.7 (0.8 to 8.9).

A higher than expected prevalence of hearing impairment was observed in both high-risk and comparison groups. When we undertook a sensitivity analysis to allow for a high-prevalence of conductive hearing loss in both groups, which was thought to be most likely due to post-neonatal factors, the overall risk ratio of NDI between high-risk and control groups increased and was significant at 6.9 (0.8–54.2, p=0.003).

Among high-risk neonates, at univariate analysis, gestational age, birth weight, diagnoses of birth asphyxia, meningitis and/or respiratory distress were significantly associated with risk of NDI. At logistic regression, only gestational age and diagnoses of birth asphyxia were associated with increased risk of NDI.

High-risk neonates had poorer growth parameters and increased respiratory symptoms compared with the control group in early childhood. Children with NDI had poorer growth and increased respiratory symptoms compared with children without NDI.
In the next section, Section 5, we will further discuss the limitations, importance and future implications of this research for ongoing high-risk neonatal outcome measurement, in Fiji and other LMIC.
Section 5

NEONATAL OUTCOMES STUDY - DISCUSSION
5. **NEONATAL OUTCOMES STUDY - DISCUSSION**

5.1 **SECTION OUTLINE**

This section extends discussion of results from our neurodevelopmental outcomes study as detailed in Section 4. It begins by highlighting the significance of the study, through comparison of neurodevelopmental and health findings with previous similar studies in LMIC, emphasizing discussion points not fully covered within the scope of our published paper. Research limitations are also discussed. We then move on to consider additional important areas for considerations including; implications of the study for ongoing neonatal neurodevelopmental outcome measurement in Fiji and relevance to measurement of neurodevelopmental outcomes in other LMIC.

The discussion will also link our research in Fiji to an increasingly identified need within global child health, to measure outcomes beyond survival, including child development. This aspect of the discussion is informed not only by our neonatal outcome study, but also by several related research and programming activities that I completed, alongside this work, during candidature.

The section will close by considering ongoing and future research questions related to neonatal outcome measurement in Fiji and other LMIC before moving onto present our developmental screening accuracy study (Section 6) and implications of this body of research for follow-up care and early intervention (Section 7), research translation in Fiji (Section 8) and future research (Section 9).
5.2 **Significance**

5.2.1 **Neurodevelopmental outcomes**

Our neonatal neurodevelopmental outcome study provided the first neurodevelopmental outcome data for high-risk neonates in Fiji. At the time it was undertaken, neonatal health was in transition and there was demand to better understand long-term outcomes for this population of children. Our study responded to limitations in previous literature as identified by our systematic review, and included a control group and hearing and vision outcomes, missing from many previous similar studies in LMIC. (2)

Overall, our findings were consistent with our research hypothesis in that we found an increased overall prevalence of NDI among NICU survivors compared with control neonates. Notably though, the overall observed prevalence of NDI in our study was similar to previous studies in LMIC in which there was a higher baseline prevalence of VLBW. (2) As such, our observed prevalence of 12.8% (7.2%–20.6%) moderate to severe NDI among the high-risk neonatal group in our study was relatively high given that the population was predominantly term and NBW.

Generally, prevalence of domain specific impairments including cerebral palsy, cognitive impairment and vision impairment were in keeping with expected from review of available pre-existing literature. (2)

However, as noted in Sections 4.2-4.3, the observed prevalence of hearing impairment, for both high-risk (5.6%, n=6) and control (4.9%, n=5) groups was high compared with prevalence expected from previous literature. (136) In both groups, this was considered multifactorial, including a mix of sensorineural and conductive hearing impairment with
middle ear disease noted in 45% (n=106) of the children assessed, as noted above. (Section 4.3) In Sections 8 and 9 we discuss the relevance of this to service development in Fiji and future research, which is warranted to see if these findings are replicable and can be explained by future studies.

Also consistent with our research hypothesis, we identified several risk factors for adverse developmental outcomes among high-risk infants, consistent with pre-existing literature, including: lower gestational age, birth weight, and diagnoses of birth asphyxia, meningitis or respiratory distress as defined in Section 3.3.3. However, we did not find an association between measured social risk factors and neurodevelopmental outcomes in this study. In subsequent sections of this thesis we will consider implications of these results for more detailed measurement of intermediary outcomes in future studies (Section 5.5.4) and for targeting follow-up care (Section 7).

### 5.2.2 Health outcomes

Several aspects of health outcomes for the study population, summarised in Table 3 of our published paper, are important to note.(3)

Firstly, our study was not designed to assess post-discharge mortality. In our study, 11 children were excluded from recruitment because CMWH morgue data indicated that these children were deceased (See Figure 1 in published paper).(3) Based on discussion with local clinicians and other sources of mortality data (i.e. a recent national child health review) we expected reasonable capture of post-discharge mortality through this approach.(10)

However, while the number of available studies is small, previous studies which have prospectively assessed mortality post-discharge in LMIC have noted high rates,
Section 5: Neonatal outcomes study - discussion

especially in low-income settings.(2) For example, in a small cohort of VLBW infants in Soweto, South Africa, Copper PA et al. observed a mortality rate of over 10% by 18 months of age.(137) While, there are fewer studies of post-discharge outcomes for neonates with NE compared with VLBW neonates, those that exist suggest very high mortality in infancy and early childhood especially in low-income settings.(138, 139) For example, in their cohort study of neonates with NE in Uganda, Tann et al. observed that mortality for neonates with NE was 40.3% compared with 3.8% by 27-30 months for neonates who had not had NE.(138) This observation of increased infant mortality compared to healthy neonates has been noted even with relatively lower morbidity neonatal populations.(140) For example, in a cohort of ultrasound dated, predominantly moderate preterm infants in Malawi, Gladstone et al. observed that preterm infants had a significantly higher risk of mortality at follow-up to 24 months than term peers.(140) Thus, in spite morgue of data suggesting low post-discharge mortality in our cohort in Fiji, prospective studies are warranted to better explore infant mortality for high-risk neonates in Fiji.

Secondly, our results indicated that the high-risk neonatal group had increased health morbidity at follow-up, compared with healthy term neonatal group, which is also generally consistent with previous literature. Particularly, our observation of poorer growth parameters and increased respiratory symptoms among high-risk neonates is consistent with previous literature showing poorer childhood growth and respiratory outcomes for preterm neonates.(18)

The prevalence of seizures observed in both high-risk and control neonatal groups was high at 7% (n=11/148) and 8% (n=11/144) respectively. While the estimated prevalence
of epilepsy varies substantially across settings and ages, meta-analysis has suggested a median lifetime prevalence of 14/1000 (IQR 10-21) people.(141) Even allowing for an increased prevalence of epilepsy in children in a LMIC, our results in this domain are substantially higher.(141) Our results were in response to asking caregivers the question ‘Does your child ever have seizures, fits or convulsions?’ (See Appendix 3 General data collection form) One possibility is that this question lacked adequate specificity to differentiate between febrile convulsions and epilepsy. Nevertheless, this finding warrants further consideration in ongoing research.

Reported immunisation rates in all groups were high (See Table 3 in published paper). While this may partly reflect reliance on parental report for this outcome, it also broadly corresponds with data available on immunisations rates in Fiji at that time.(10) Specifically, in 2009 an immunisation survey in Fiji suggested that 93.9% of one year old children had completed their measles immunisation.(10)

Additionally, our findings that children with NDI also had poorer growth (i.e. increased stunting and microcephaly) and increased respiratory symptoms are consistent with published literature showing that children with disabilities generally have poorer health in early childhood compared with typically developing peers.(142) In particular, the association between cerebral palsy and a range of associated health conditions, including and respiratory and nutritional comorbidities is important and well documented. (143, 144) Limited available studies of nutrition in children with cerebral palsy in LMIC highlight poor nutrition to be a substantial health challenge for these children in these settings. (145, 146) Similarly, while not well studied in LMIC, respiratory disease is a substantial cause of morbidity and mortality in this group, known to be the
cause of death for more than half of children and young people with cerebral palsy in HIC.(147)

Notably, however, we did not observe an overall increase in hospital admissions for children with NDI compared with those without NDI in our study. However, while not captured in our published results from this study, four children within the study cohort with cerebral palsy required admission to hospital on presentation for a combination of poor nutrition, acute respiratory illness and skin sepsis. Since children with disabilities and their families may face additional barriers in accessing health services, further assessment of care seeking and access to health services among this group is warranted in future research.

5.3 LIMITATIONS

Limitations to our study (e.g. retrospective design, loss to follow-up for hearing assessments) and ways that these were managed have been previously detailed in Sections 4.2. and 4.3.

Additionally, we have briefly noted challenges with measurement of both neonatal exposure and neurodevelopmental outcome variables. In the next several sections (Section 5.4-Section 5.6) we consider these aspects in more detail, specifically, what was learned through our research experience in Fiji and several related activities during my candidature (Sections 5.6.1-5.6.3) for strengthening neonatal outcome data in Fiji and other LMIC moving forwards.
5.4 **IMPLICATIONS**

5.4.1 **Baseline data to inform improvements in neonatal care and follow-up in Fiji**

Our study provided important observational outcome data at the time it was conducted in Fiji (i.e. 2011-2014). Findings were communicated to the Fiji Ministry of Health and Medical Services and have informed neonatal child health and development policy and there have also been positive steps forward in various aspects of follow-up care for high-risk neonates. (See Section 8)

However, since the time of our study, there have also been substantial changes in neonatal care in Fiji including, for example, use of therapeutic hypothermia for neonatal encephalopathy, surfactant and parenteral nutrition for preterm neonates. Although inpatient mortality data are collected on an ongoing basis, collection of long-term neurodevelopmental outcome data has not yet been incorporated into routine health information systems. As such, there is a need to explore how to embed outcome data collection into routine health information systems to understand the impact of these and other changes in neonatal care, beyond survival, for these children.

5.4.2 **Identification of challenges to address to improve neonatal neurodevelopmental outcome measurement in LMIC**

5.4.2.1 **Outcome measurement tools**

A major noted challenge in this research was working through what neurodevelopmental outcomes to measure and how best to measure them in Fiji. What I came to appreciate through this research is that these challenges are common for researchers and programmers across diverse LMIC. In this section, I will systematically reflect on the choices we made and challenges we experienced and consider
implications for improved neurodevelopmental outcome measurement in Fiji and other LMIC moving forwards.

We chose to use the Bayley-III, the reference standard for neonatal neurodevelopmental outcomes assessment in young children, as the primary child development assessment tool in our study. As described earlier (Section 2.3.3), this choice was driven largely by systematic review of what has been measured in previous similar studies with the aim of collecting data that would be both robust and potentially comparable across settings.

However, as also noted earlier (Section 2.4.2), there is an increasing body of evidence which demonstrates that available editions of the Bayley Scales of Infant and Toddler Development over-estimate current developmental status and are poor predictors of future performance, in particular under-identifying future language and cognitive delays.\(^{(84)}\) In addition, the proprietary nature of this tool, cultural and linguistic adaptations required, financial cost, administration time and requirement for specialist administration limit its feasibility of use, even in research, in LMIC.\(^{(77)}\)

Since our neonatal outcomes study was completed, the World Bank guidance on child development assessment in LMIC has been updated.\(^{(37)}\) This guidance now provides a useful resource for tool selection for different purposes and recent review of tool feasibility and acceptability for use in LMIC can also help guide measurement choices in diverse settings.\(^{(148, 149)}\) Within the World Bank guidance, Fernald et al. recommend the use of tools that have been shown to be reliable or valid among groups of children in specific cultural contexts.\(^{(37)}\) For example, in Sub Saharan Africa tools such as the
Malawi Development Assessment Tool and the Kilifi Developmental Inventory have been extensively tested and used in research.(37, 150)

However, in the Western Pacific Region, there were not, to our knowledge any locally developed child development assessment tools which were fit for purpose. Thus, our decision to use the Bayley-III in Fiji was a pragmatic choice, not in the context of a lack of child development measurement tools per se, but in the context of a lack of tools which were feasible and appropriate for cross contextual use in our setting.

In the context of limited choice for reference standards, pragmatic measurement choices are common in child development research in LMIC. During the final phase of my candidature, I was part of an evaluation team for a large donor-funded multi-country child development portfolio.(151) Within that evaluation, we reviewed how child development outcomes were measured in projects (n=39) across 23 LMIC.(149) We found that, although all teams received extensive technical advice and support in line with best-practice in the field, 49% (n=18) used a screening tool to measure outcomes following an intervention.(149) When reasons for this choice were qualitatively explored, reasons typically related to lack of feasibility of using comprehensive child developmental assessment tools which were considered too time and resource intensive to be practicable.(149)

As such, there is an urgent need within child development outcomes research, for improved child development assessment tools which are feasible, appropriate and more predictive of long-term outcomes (e.g. education, function) across settings. This will require international collaboration, not only involving child development technical experts but also end-users of child development assessment tools in LMIC, to ensure
that tools developed are feasible and appropriate for use in routine services. As we will
discuss further in Section 5.6, there are international collaborative efforts underway to
develop improved, data-driven tools for monitoring child development at population
level in LMIC (e.g. Global Scales of Early Development). However, research is required
to explore whether these might be adapted to develop improved tools for measurement
of outcomes at the level of an individual child.(152)

5.4.2.2 Ensuring quality of outcome measurement

While limitations of available child development assessment tools were largely outside
of our control as a research team, undertaking this study provided valuable experience
in other aspects of outcome measurement, also important to the quality of outcome
data, which were within our control or potentially more easily modifiable. These include
factors related to test adoption and/or adaptation, the tester, environment and testing
procedures.

Within the resourcing available for this research, we largely adopted the Bayley-III
largely without modification rather than undertaking formal adaptation or developing a
new test. Although we used interpreters to ensure that instructions were provided to
children in their first language, we documented a number of items which were culturally
challenging when used in Fiji and could potentially be modified to improve test fairness
moving forwards.

For example, for some children, it appeared that items involving store-bought toys such
as blocks, toy ducks, and puzzles were novel. While our experience suggested that most
children ultimately enjoyed playing with these toys, the lack of familiarity for some
children potentially meant that they were not culturally appropriate for testing in Fiji.

Similarly, we noted that some items in the stimulus book, which provided pictorial support for test items were unfamiliar to Fijian children. For example, items including pictures of children dressed in snow clothes or large refrigerators. There were also items which were not linguistically equivalent, even with translation. For example language items which were designed in English to test pronouns or plurals with no direct equivalent in iTaukei.

Since we were not able to formally adapt the Bayley-III we acknowledge these limitations as potential biases in using the Bayley-III in our research in Fiji. However, we used a control group to minimise the impact of such potential biases on any difference observed between the high-risk and control newborn group.

Moving forwards, we hope that our documentation of potential cross-cultural issues with the current version of the Bayley-III could be a useful resource for its future adaptation or assembly of a more culturally appropriate child development assessment tool in Fiji and the Western Pacific region.

As previously noted (Section 2.4.2), the quality of test administration is also crucial to the reliability and validity of child development assessment.(37) In addition to initial staff training, we found that ongoing supervision throughout the data collection period, was important to sustaining the quality of test administration. However, there were several practical challenges to ensuring quality of test administration.

Firstly, in the middle of a busy paediatric outpatient ward, it was a challenge to find an appropriate quiet space for testing. This meant that over the course of the study the testing room changed a number of times. Pleasingly, with support of an international
non-government organisation, a dedicated room in CWMH outpatients has now been secured for ongoing child development clinics and assessments, although this has occurred since the study was completed.

Additionally, since all Bayley-III assessors were foreign to Fiji, we were aware that for some children, the novelty of tester appearance to them may have impacted on testing comfort and potentially performance. As outlined in methods we ensured that parents and primary caregivers as well as a local staff member was present. We hope that this, tester clinical experience in paediatrics and the use of a control group mitigated against potential impact of the tester on test performance or observed differences between groups in our study.

Finally, from a practical perspective, having assessments based at CWMH meant that we were able to control the testing environment but it also meant that a number of children had to travel long distances by bus or boat to attend. For young children this was especially tiring and meant that we had to learn to accommodate for rest in our testing schedule. In several instances, where children were clearly exhausted, it meant that testing had to be delayed, while families were reimbursed for costs of travel. Similarly, we provided refreshments to children and families around testing.

5.4.3 Broadening the outcome measurement lens

5.4.3.1 Moving beyond impairment for children with neurodevelopmental sequelae

In 2007, the World Health Organization released the Child and Youth version of the International Classification of Functioning, Health and Disease (ICF-CY).(36) The purpose of the ICF-CY was to provide a common framework for conceptualising health and disability that moved beyond a traditional biomedical approach to one which better
represented the multiple determinants across sectors. Rather than just focusing on body structures or functions (i.e. impairments), the ICF-CY included activities, participation and other personal and environmental factors.

Since the introduction of the ICF-CY, there has been increasing recognition in childhood disability research, of the importance of incorporating multidimensional, biopsychosocial assessment of constructs it represents as well as others such as quality of life from caregiver and where possible and appropriate, child perspective. Measurement of each of these areas has developed a substantial academic literature in its own right, which is beyond the scope of this thesis to explore. However, while our neonatal outcomes study focused on NDI for pragmatic reasons, moving forwards further consideration of personal, family and community environmental factors will be important not only to monitor impact of changes in neonatal care, but to better understand how to improve life opportunities for children who experience NDI in the setting of neonatal illness and complications.

5.4.3.2 Measurement of intermediary outcomes and the caregiving environment

Applying a framework, such as the ICF-CY to neurodevelopmental outcome measurement, is also in line with current guidance in global child development research which emphasizes an ecological approach to measurement and consideration of multiple factors on a pathway to change. Specifically, using a theory of change based approach to intervention design and evaluation is increasingly considered best practice, incorporated into the recently developed EQUATOR guidelines for early child development (ECD) implementation research in diverse settings.
Theory of change based approaches to process and outcome measurement include measurement of variables on the pathway to change. In our outcome study, we measured a number of sociodemographic family and health variables. However, there are many more factors, including potentially modifiable variables which influence child development outcomes and could be measured along a pathway to change. Such so-called intermediary outcomes include more detailed assessments of the caregiving environment, caregiver health and child-caregiver interaction which were not a focus of this neonatal outcomes study. (158) Within high-risk neonatal follow-up and outcomes research, it could be argued that consideration of these factors is especially important for caregivers of high-risk neonates since we know that these caregivers are likely to experience high-levels of stress and distress. (21) As such, collecting more detailed data to understanding care-giver well-being including mental health and the caregiving environment will be important to development of interventions to better support families to be responsive to their child’s health and developmental needs. Section 7 will outline how we are undertaking further formative research to better explore other caregiver factors (e.g. stress, mental health, home environment) in implementation research moving forwards.

5.4.4 Importance of improving child development outcome measurement in global child health

While this research focused on improving long-term outcome data in Fiji, it occurred at a time in global child health when the emphasis was shifting beyond survival with increased attention towards enabling children to thrive, or reach their developmental potential. (6)
This section provides a broad overview of the pre- and post-Sustainable Development Goal (SDG) transition and other landmarks to highlight the increasing importance of improving child development outcome measurement to accelerate action and accountability in global child health.

Within this section, I will highlight areas of research and programming related to several of these areas that I have been involved with, in the final phase of my doctoral research. Specifically, after I completed our neonatal outcomes study in Fiji, I was based at the London School of Hygiene & Tropical Medicine for 18 months (2016-17) during which time I worked as a Technical Consultant in Early Childhood Development for the WHO during the Zika epidemic (December 2016-June 2017). I also participated in several technical workshops related to early child development. (WHO Geneva January 2017, February 2017, June 2019, UNICEF New York September 2018). Developments in global newborn health and child development during this time are highlighted to emphasise points of connection between our research in Fiji and concurrent relevant developments in this area of research and programming more broadly.

5.4.4.1 The Sustainable Development Goal era: shifting from survive to thrive

Between the years 2000-2015, the so called ‘MDG era’, the predominant global goal for child health (MDG4) was to reduce the mortality rate for children under the age of five years by two-thirds. (159) This goal focused policy, programming and investment clearly towards a measurable mortality target. (160) Having a clear target that was readily measurable also provided an important accountability mechanism. (161) However, there was no MDG focused on child development or disability which were largely invisible in the agenda at global level.
Section 5: Neonatal outcomes study - discussion

In 2015, the Sustainable Development Goals (SDGs) were launched and included a much more expansive view of global child health compared with the MDGs. SDG 3 which focuses on ‘ensuring healthy lives and promoting well-being for all at all ages’ retains a focus on achieving reductions in newborn and child mortality. However, additionally, SDG 4 which centres on ‘ensuring inclusive and equitable quality education and promoting lifelong learning opportunities for all’, has specific targets and indicators for child development.(11) (Textbox 2)

Textbox 1: Sustainable Development Goal 4, targets and indicators

<table>
<thead>
<tr>
<th>Target 4.2</th>
</tr>
</thead>
<tbody>
<tr>
<td>By 2030, ensure that all girls and boys have access to quality early childhood development, care and pre-primary education so that they are ready for primary education</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Indicators 4.2.1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion of children under 5 years of age who are developmentally on track in health, learning and psychosocial well-being, by sex</td>
</tr>
</tbody>
</table>

| 4.2.2 |
| Participation rate in organized learning (one year before the official primary entry age), by sex |

The inclusion of child development in the SDGs created an opening for child development on the global agenda, but also highlighted a challenge in how to measure child development across settings. For example, although SDG 4.2.1 created a potential mechanism for tracking progress, it also highlighted the need for greater clarity in global child development measurement, for example, how to measure the proportion of children who were developmentally ‘on track’ across settings, which had not previously been well defined, especially in LMIC.
5.4.4.2 Newborn health in the SDG era: helping ‘small and sick’ neonates survive AND thrive

At global level, there has been important ongoing emphasis on reducing preventable newborn deaths, with the launch and implementation of the Every Newborn Action Plan (ENAP) (2014) which aims to reduce preventable neonatal deaths to a target of ≤10/1000 live births in all countries by 2035. (7)

Alongside this, there has also been increased emphasis on the ‘beyond survival’ agenda which was highlighted in 2012 in a major global report of preterm births and shortly thereafter through the launch of a series of papers, referenced in the early sections of this thesis. (64, 162) (Section 2.3.1) More recently the 2018 Every Newborn Action Plan Progress Report recently launched WHO and UNICEF report ‘Survive and Thrive: Transforming care for every small and sick newborn’ have clearly highlighted improving long-term neonatal developmental outcomes as an increasing focus. (1, 163)

However, while both initiatives have detailed measurement plans to drive and track progress towards mortality reduction targets, with regards to neurodevelopmental outcome data the Survive and Thrive report makes the following statement(1):

‘The greatest gap in impact data relates to small and sick survivors after inpatient care, who remain at increased nutritional and developmental risk. Research is required to define appropriate indicators for these newborns and to clarify what follow-up care is effective, and for whom, and how often it is needed. A simplified systems is urgently needed to track at-risk newborns...to avoid suboptimal early child development outcomes.’

Reference: Survive and thrive: transforming care for every small and sick newborn. WHO 2019
5.4.4.3 Global child development and launch of the Nurturing Care Framework

At the same time that the previously described developments have occurred in global newborn health, the profile of child development in global child health has also increased. In particular, either side of the launch of the SDGs, there was the release of two landmark Lancet Series related to child development. The first, ‘Early child development in developing countries’ (2011) was a call to action for the then estimated 200 million children who were considered to failing to achieve their developmental potential, on the basis of proxy measures of extreme poverty and stunting.(117, 164) Building on this and the increasing SDG emphasis on child development, a subsequent series ‘Advancing early child development: from science to scale’ (2016) focused more directly on policy and programming to promote child development in diverse LMIC.(50, 165, 166) Both series have been very important contributions to the field in their synthesis of evidence, pulling together stakeholders from multiple perspectives and advocating for prioritisation of ECD in a crowded global child health agenda in the SDG era. However, child development measurement was not a strong focus in either series and in her comment on the second series, Dr Margaret Chan, the then Director General of the WHO, made the following comment: (167)

‘Rigorous research into the delivery of interventions, and their short-term and long-term outcomes, is important for innovation. We need stronger measurement and a new consensus on robust, valid indicators to assess children’s cognitive and socioemotional development. Intensified monitoring through nationwide population based assessments...is essential for accountability and will help us stay the course.’ Chan, Margaret et al. The early years: silent emergency or unique opportunity? Lancet 2017
More recently, the momentum for child development culminated in the launch, at the United Nations General Assembly in 2018, in the launch of the ‘Nurturing care for early child development framework’ (NCF) In line with the SDGs and the Global Strategy for Women’s Children’s and Adolescents’ Health (2016-2030), the NCF provides a policy framework which aims to support strengthened action in support of children’s development worldwide. The NCF identifies monitoring of progress as a strategic priority although specific indicators for measuring child development and disability at scale, including after neonatal illness and complications remain a gap.(39)

To further highlight the importance of measuring neurodevelopmental outcomes in global child health, Textbox 2 below, discusses how this came to be a focus of international concern, during the 2015-16 Zika epidemic. The Zika crisis provides an important example of the need for strengthened neurodevelopmental outcome data across settings to understand the public health impact of neonatal conditions. During 2016-17, towards the end of the epidemic, I was seconded to work as a consultant to the WHO Zika response team, as part of a group developing a ‘toolkit’ to improve care of children affected by Zika virus disease.(168) During my time with the WHO, I was struck that many of the measurement challenges we had experienced as a research team in Fiji, were similar to those being discussed by clinicians, researchers and public health programmers tasked with the challenge of collecting data and improving surveillance systems to understand the long-term neurodevelopmental impact of Zika virus.
Textbox 2: Zika virus epidemic - a public health emergency due to neurodevelopmental impact

During the Zika virus epidemic thousands of neonates, most prominently in Brazil and other South American countries, were born with microcephaly, ultimately demonstrated to be causally associated with Zika virus. (169) Prior to the epidemic, Zika virus was a known mosquito born virus which has been identified in a number of communities around the world for decades. (170) However, 2015-16 epidemic was unprecedented and ultimately led to the World Health Organization declaration of a Public Health Emergency of International Concern, primarily because of the microcephaly and associated neurodevelopmental impairments being observed in children in high-Zika prevalence areas. (170) This was associated with substantial coverage in the international media, as well as increased investment in research and support for scaling relevant health and ancillary services in Zika affected areas.

Early on in the epidemic, severe microcephaly, which had led to declaration of a public health emergency by the WHO, was the measurement focus. (171) Over time, congenital Zika virus syndrome (CZVS) became more clearly defined by five key features including: severe microcephaly with partial collapse of skull, specific characteristics on brain imaging, ocular abnormalities, congenital contractures and hypertonia. (172) It was also recognised that a much broader range of neurodevelopmental sequelae and severity were possible. (172)

However, since the epidemic was new, and the neurotoxicity of Zika not fully understood, there was an imperative to collect good quality neurodevelopmental outcome data to better understand the public health impact of the condition. (170) The WHO called for support with collection of follow-up data to understand long-term impact for children with severe manifestations (i.e. CZVS) and better delineate the broader spectrum of neurodevelopmental abnormalities among children exposed to Zika virus in utero but without evidence of the syndrome at birth. (170)

One of the challenges at that time was defining both exposure and outcome variables. In response to the difficulties posed by heterogeneity of outcome measurement, mechanisms were developed to promote and improve data sharing between researchers and initiatives to develop core outcomes measurement sets were emerged. (173, 174) Fortuitously, in 2016-17 the Zika epidemic subsided and to my knowledge the proposed core outcome sets have not been released. However, processes for strengthening outcome measurement in the Zika crisis have potential relevance to a diverse range of conditions in global neonatal health, including those discussed in this thesis.
Section 5: Neonatal outcomes study - discussion

5.5 **Next steps and future research**

A common thread across our research in Fiji and these broader developments in various areas of global child health is the need for feasible, accurate and more standardised measurement of child development outcomes across LMIC. Strengthened measurement of child development outcomes in global child health is needed to better understand the life-course impact of neonatal and child health conditions and to guide development of approaches that support children to reach their best developmental potential, in spite of early life adversity.

To address this measurement challenge and improve neonatal neurodevelopmental outcome data for high-risk neonates in Fiji will require better definition of common neonatal conditions including; accurate measurement of gestational age and internationally agreed definition of serious bacterial infections and neonatal encephalopathy. In addition, better measurement of outcomes for children not included in our study, including children with congenital anomalies are also needed.

Further, over time, as local capacity builds, measurement of a broader range of emotional behavioural, educational and functional outcomes will strengthen understanding of long-term impact of neonatal complications in Fiji, as it has in HIC.

However, many measurement challenges that we experienced in our neonatal outcomes study in Fiji, are common across diverse LMIC. International collaboration will be required to address this challenge, perhaps learning from experiences and the value of neonatal collaborative research networks in HIC and recent experiences in the Zika epidemic to develop core outcome sets for measurement of neurodevelopmental outcomes in LMIC.(75, 174)
Inevitably, however, there is also a need for greater investment and research into outcome tools which are more feasible, appropriate and predictive of important long-term outcomes, across contexts compared with currently used reference standards. In some settings, such as Fiji, adaptation of available reference standards may be a useful step while new outcome measurement tools are forthcoming. While tools such as the Global Scales of Early Development have primarily been developed for population-level child development tracking, investment and research to understand their use to measure child development at the level of individual children is warranted. (175) Additionally, to drive and measure changes in obstetric and neonatal care and high-risk neonatal follow-up, definition of developmental indicators that can be incorporated into routine services and health information systems are urgently needed.

The following sections of this thesis will extend questions related to measurement, returning the focus to Fiji, to our nested study of the accuracy of nurse-led developmental screening as one component of developmental monitoring for high-risk neonates in that setting. (Section 6)
Section 6
NURSE-LED DEVELOPMENTAL SCREENING ACCURACY STUDY
6. **NURSE-LED DEVELOPMENTAL SCREENING ACCURACY STUDY**

6.1 **SECTION OUTLINE**

As discussed in the initial section of this thesis (Section 1) improving early identification of developmental delay and impairment is an important challenge to improving early intervention for high-risk neonates and other children with disability in LMIC. (176) In this section, we move on from description of our neonatal outcomes study (Sections 3-5), to describe our nested study of the accuracy of nurse-led developmental screening for identification of developmental delay and impairment in the study population.

6.2 **RATIONALE**

6.2.1 **Early identification knowledge and implementation gaps in LMIC**

So far, this thesis has focused on measuring neurodevelopmental outcomes among a cohort of NICU survivors in order to provide baseline data for improving obstetric, neonatal and follow-up care including early intervention. However, in order to strengthen access to early intervention, improved systems for early identification of children with developmental delay and impairment, through routine services on an ongoing basis are needed, rather than once off measurement of outcomes in a research.

Early identification requires developmental monitoring, a longitudinal process, in which health or other professionals respond to concerns about a child’s development, obtain a developmental history, make observations and communicate concerns with caregivers and other professionals (as previously defined in Section 1.5). (38)
Developmental screening aims to identify children at increased risk for development delays, or disorders who warrant further assessment and possible intervention and can be once-off or be repeated at different ages but does not, in itself provide a diagnosis. (38) Broad band developmental screening tools are those which are designed to identify children at increased risk for global (≥2 domains) or domain specific developmental delay (as defined in Section 1.5) compared to narrow band tools which focus on measuring risk of specific diagnoses (e.g. autism spectrum disorders, attention deficit hyperactivity disorder). (37) Developmental screening tools can be based on parent report or direct observation of child skills and behaviour. (37)

Developmental assessment typically involves longer, more detailed, usually specialist testing and provides scores to describe a children’s abilities across and within developmental domains in comparison to a reference population. In addition to enabling diagnosis of developmental delays and impairment, developmental assessment provides an opportunity for early intervention and has a range of other benefits in terms of health promotion. (37, 77) There are widely accepted criteria for assessing the reliability and validity of child development assessment tools and guidance about their selection in LMIC. (37, 150) Provision of caregiver counselling regarding findings and follow-up care including intervention for identified developmental delays or impairments are considered key components of undertaking developmental assessments. (37, 150)

In high-income countries, development monitoring through routine health and education from birth and up to primary school entry, is an important pathway through which children at high-risk for developmental delays and disability access early
intervention. In these contexts, evidence suggests that
developmental monitoring is most effective for identification of developmental delays
if it includes periodic screening with appropriate, structured and validated screening
tools. In such contexts, there are also typically well-established pathways for early
intervention when developmental delays or impairment are identified.

However, one major challenge to development of feasible, acceptable and effective
approaches for early identification of children with development delay and disability in
LMIC is the lack of tools which are designed and tested within routine services in
LMIC. In these contexts, while a multitude of developmental screening and
assessment tools exist, recent systematic review has highlighted that few are feasible
and accurate for use in routine health and educational services in LMIC. In addition,
there are well recognised gaps in provision of early intervention in many LMIC.

There are thus both knowledge and implementation gaps with regards to feasible and
effective pathways for early identification of developmental delay and impairment for
high-risk neonates in LMIC.

Note that there is an emerging literature regarding early identification of sensory (i.e.
hearing and vision) and motor impairments, as highlighted in Sections 2.4.3 and
2.4.4. This is crucial, especially for high-risk neonates who, as our Fiji
outcomes study highlighted, are at high-risk of motor impairments including cerebral
palsy and sensory impairments. However, within the constraints of available resources,
these were not included within the scope of this study.
6.2.2 Existing developmental monitoring approaches for high-risk newborns in Fiji

In our neonatal neurodevelopmental outcomes study in Fiji approximately one in ten (i.e. 12% 95% CI 5-17, n=13) NICU survivors and one in twenty (i.e. 5% 95% CI 2-15, n=5) comparison control neonates had a moderate to severe NDI in early childhood. (Section 4) Within our study cohort, we used the Bayley-III and specialist medical, audiology and ophthalmology review to provide detailed developmental assessment of children although this required substantial additional resourcing, over and above that available through routine government services. Within routine services in Fiji, early identification pathways for children with developmental delay and impairment are limited. (Sections 2.2.2-2.2.4) Developmental monitoring for young children occurs through community nurse follow-up and incorporates a non-validated milestone based checklist, administered as part of routine immunisation and growth monitoring visits from 8 weeks to 24 months. Following screening using this checklist, triggers for action and referral pathways for children with identified concerns are unclear. There are limited allied health services and one early intervention centre in Suva, which has capacity to enroll 60 children aged 18 months- 8 years. (182)

Thus, our neurodevelopmental outcome data demonstrating high prevalence of developmental delay and impairment, coupled with weak systems for early identification in routine services, illuminates an urgent need for strengthened developmental monitoring to improve early identification and access to early intervention for young children in Fiji.

In line with existing evidence of family-centred practice and as an alternate approach to existing structures for early identification of developmental delay and impairment
among young children in Fiji, we piloted and evaluated the use of the Parents’ Evaluations of Developmental Status within our high-risk neonatal population in Fiji.(183, 184)

6.3 **AIM AND OBJECTIVES**

To pilot and assess the accuracy of nurse-administered developmental screening tool/s for identification of developmental delay among a cohort of high-risk newborns in Fiji.

The present study was nested within our previously described neonatal neurodevelopmental outcomes study. (Sections 3 and 4) Objectives of this study were to;

1. Select and pilot broad band developmental screening tools for use in routine follow-up of high-risk newborns in Fiji
2. Assess selected developmental screening tool accuracy compared with reference developmental assessment standard (i.e. Bayley-III) for detection of mild or greater developmental global developmental delay in this population, when administered by nurses or non-specialist health workers.

6.4 **SIGNIFICANCE OF STUDY**

This research has potential to inform improvements in developmental monitoring of high-risk newborns in Fiji in order to strengthen early identification and access early intervention among the target population.
6.5 METHODS

6.5.1 Objective 1: Screening tool selection and piloting

6.5.1.1 Literature review
A pragmatic review of published literature via Medline using the search terms was undertaken early child development/or child development/or disabled children/or developmental disability and developing countries as well as grey literature review to identify broad band developmental screening tools which could potentially be used in LMIC settings.

6.5.1.2 Consultation and piloting with government health workers
From this, several screening tools were selected for further piloting based on the following considerations which were discussed with local government health workers: demonstrated psychometric properties in other contexts; accessibility and cost; requirements for adaptation and translation; potential feasibility (e.g. health worker training, administration and referral pathways for screen positives); perceived likely acceptability to children and families.

These tools were then piloted in a convenience sample of children on the children’s ward in Colonial War Memorial Hospital (CWMH) Suva with informal feedback from this informing final selection of developmental screening tools for formal assessment of concurrent validity, compared to the reference developmental assessment standard in the local context.
6.5.1.3 Translation and adaptation

Although English is the official language in Fiji, Fijian and Fiji-Hindi are widely spoken and the preferred languages of many families. Fijian and Fijian-Hindi translations were undertaken by experienced paediatric nurses as well as a research nurse with extensive prior experience interviewing families. Discrepancies and variations between translators were settled by discussion before final back translation. Although detailed formal adaptation was not undertaken, clearly problematic or culturally inappropriate test items were adapted where possible.

6.5.2 Objective 2: Assessment of developmental screening tool validity compared with reference standard

Developmental screening of participants was completed by trained nursing staff and paediatric registrars prior to completion of the reference developmental assessments. Nursing and paediatric registrars were trained in use of the selected developmental screening tools which were administered to all participants in the retrospective NICU cohort study including NICU survivors and matched term control neonates.

Reference developmental assessments were undertaken by trained paediatric specialists (3 paediatricians, 1 speech pathologist), blinded to both developmental screening status and neonatal history.

Given the age of children at the time of assessment as noted in Sections 3 and 4, the Bayley Scales of Infant and Toddler Development Third Edition (Bayley-III) was used as the reference developmental assessment standard although noting that this had not previously been translated, adapted or normed in Fiji. Local nursing staff assisted with translation into the child’s first language where needed.
Corrected ages were used for interpretation of both developmental screening and assessment test scoring and interpretation in accordance with international guidance for developmental assessment of preterm children in early childhood.\(^{(185, 186)}\)

Definitions used for global developmental delay were the same as those used in our neurodevelopmental outcome study and included:

Score in \(\geq 2\) of cognitive, language AND/OR motor composite scales of \(\geq 70\) and \(<85\) (mild) OR \(<70\) (moderate-severe), using standardised reference means on the Bayley Scales of Infant and Toddler Development Third Edition\(^{\circ}\) (Bayley-III). Note that references means were used for comparison in the neonatal outcome study since we had a control group to enable local comparison.

For both developmental screening and assessments, although inter-rater reliability was not formally measured, all staff were formally trained and fully-supervised until their test administration, scoring and interpretation were consistent and considered reliable by the supervising paediatrician (KM or SW). Intermittent direct supervision of testing was continued throughout the data collection period to ensure that established developmental screening and assessment standards were maintained.

### 6.6 INFORMED CONSENT AND ETHICS APPROVAL

Informed consent was obtained from children’s parents/guardians prior to recruitment. Caregivers were reimbursed for costs of travel to CWMH as needed. Approval was obtained from the Fiji National Health Research, Fiji National Research Ethics Review and University of Melbourne Human Research Ethics Committees.
6.7 DATA ANALYSIS

Data were entered into EpiData Version 3.1, cleaned and exported to Stata IC Version 14 for analysis. Baseline data for the study population were described according to mean (SD) and median (IQR) with use of paired t-tests or chi-squared statistic as indicated. Screening cut-points for increased risk of developmental delay using developmental screening tools were compared to Bayley-III results for mild and/or moderate-severe global developmental delay. Sensitivity, specificity (PPV and NPV) of developmental screening tools compared to the reference standard for detection of mild and moderate-severe global developmental delay were described.

6.8 RESULTS

6.8.1 Selection and piloting of developmental screening tools (Table 5)

A broad Medline search was undertaken using the MeSH terms and key words; child development/or disabled children/or developmental disabilities and developing countries. Grey literature was also reviewed via World Health Organization, UNICEF, World Bank and other international non-government organisation websites. From this, the most comprehensive document identified to guide developmental screening tool selection within this study was the World Bank review ‘Examining early child development in low-income countries: a toolkit for the assessment of children in the first five years of life’. (78)

This document, provided detailed review of all published (n >300) and/or copyrighted child development measurement tools used outside the USA at that time (i.e. 2009). (78) It also provided guidance about how to select tools for specific purposes across LMIC in
particular it recommended that tools be; psychometrically robust (i.e. valid and reliable), balanced with numbers of items across age bands, enjoyable, easy to adapt and use in LMIC, accessible, inexpensive and able to be used across a broad age range.\(^7\)\

Using this broad guidance we selected several developmental screening tools for further piloting. (Table 5) These included the Ages and Stages Questionnaire (ASQ), Rapid Neurodevelopmental Assessment (RNDA), Parents’ Evaluation of Developmental Status (PEDS), Parents’ Evaluation of Developmental Status: Developmental Milestones (PEDS:DM) and Brigance Early Childhood Screens (Brigance).\(^135, 187-189\)
Table 5: Developmental screening and assessment tool characteristics

<table>
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<tr>
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<tbody>
<tr>
<td>Age range (yr.mths)</td>
<td>0-8</td>
<td>0-8</td>
<td>0-5</td>
<td>0.1-5.5</td>
<td>0-5</td>
<td>0.1-3.5</td>
</tr>
<tr>
<td>Domains measured</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cognition</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Language (receptive and expressive)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Motor (fine and gross)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Socio-emotional development</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes (as additional questionnaire)</td>
</tr>
<tr>
<td>Mode of testing</td>
<td>Parental report</td>
<td>Parental report</td>
<td>Direct observed performance</td>
<td>Parental report</td>
<td>Performance and parent report</td>
<td>Directly observed performance</td>
</tr>
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</table>
### Section 6: Nurse-led developmental screening accuracy study

<table>
<thead>
<tr>
<th>Test duration (reported, min)</th>
<th>5-10</th>
<th>15-20</th>
<th>10-15</th>
<th>10-20</th>
<th>30</th>
<th>30-90</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Level of training required</strong></td>
<td>Minimal</td>
<td>Minimal</td>
<td>Minimal</td>
<td>Minimal</td>
<td>Moderate</td>
<td>Specialist</td>
</tr>
<tr>
<td>**Psychometric properties (i.e. validity, reliability, cultural adaptability) *</td>
<td>Robust in initial validation populations (USA)</td>
<td>Robust in initial validation populations (USA)</td>
<td>Not published</td>
<td>Robust in initial validation populations (USA)</td>
<td>Adequate in initial validation population (Bangladesh)</td>
<td>Robust in initial validation sample (USA) but poor cultural adaptability</td>
</tr>
<tr>
<td><strong>Cost to purchase and use the tool, accessibility</strong></td>
<td>$36, Copyright by PEDStest.com, no charge for use in research</td>
<td>$275, Copyright by PEDStest.com, no charge for use in research</td>
<td>$385 for standard kit, Copyright Hawker Brownlow Education</td>
<td>$275 for photocopiable starter kit, Copyright by Brookes Publishing.</td>
<td>Not known</td>
<td>$1200 for comprehensive kit including 25 tests, Copyright by Pearson</td>
</tr>
</tbody>
</table>

Reference: Adapted from review by Boggs et al rating of early child development measurement tool feasibility and acceptability in routine services in LMIC.(77)
Selected developmental screening tools were introduced to local paediatric staff and informally piloted between January and February 2011 by paediatric registrars (n=3) and nurses (n=1) on the Children’s Ward at CWMH. Health staff reported that for feasible implementation, important considerations were; ease of and time required for training, administration and scoring; cost and minimal equipment requirements.

Staff reported that greater emphasis, within the RNDA, on prevalent health conditions relevant to child development in resource limited settings (e.g. undiagnosed sensory impairments, seizures, malnutrition) was potentially advantageous but given the lesser time and equipment requirements of the other tools, these were considered more practical for an initial developmental screening test.

Based on feedback from health staff during piloting, the PEDS was selected for further evaluation because of perceived simplicity including ease and rapidity of administration and interpretation. (Textbox 3) Other tools were excluded primarily because of the need for multiple questionnaires (ASQ) and a perceived emphasis on formal pre/academic skills (Brigance) which were less directly applicable in the local context.
Textbox 3: Parents’ Evaluation of Developmental Status Tests

Parents’ Evaluation of Developmental Status (PEDS) and related Parents’ Evaluation of Developmental Status: Developmental Milestones (PEDS:DM) developmental screening tools identify children at risk for developmental delay by eliciting parental concerns in a range of developmental domains including language (expressive and receptive), motor (fine and gross), behaviour, social and self-help skill development. (135) Based on responses, children are then classified as being at high, moderate, low or no risk of developmental delay with corresponding guidance about follow-up requirements provided. (135)

Since the PEDS tests are brief, require minimal (i.e. several hours) training and can be administered by non-specialist professionals, they present a potentially feasible tool for use in developmental monitoring in health services and have already been used in many LMIC. (77, 183) However, while previous validation testing from the USA demonstrated robust psychometric properties for identification of children at high and/or moderate risk of developmental delay (i.e. Sensitivity 91-97%, Specificity 73-86%), its validity in LMIC such as Fiji, has not been established. (135, 148)

Due to low anticipated parent literacy, the PEDS and PEDS: DM were administered as parent interviews. Tests were scored according to developer guidelines with the PEDS providing several ‘pathways’ for prediction of developmental delay (e.g. ‘Path A’ = two or more predictive concerns, ‘Path B’ = one predictive concern).
6.8.2 Translation and adaptation

Developmental screening tools were translated and back translated. A particular issue which arose for translation of the PEDS was difficulty translating the word ‘concerns’ for which there was no clear equivalent word in either Fijian or Fijian Hindi.

Specific items in both the PEDS and PEDS: DM which were identified as potentially needing adaptation, included; items which focused on pre-academic skills, use of store bought toys, dressing, particular linguistic concepts (e.g. plurals and pronouns) or types of play. Where possible, these were managed at translation stage (e.g. substituting asking about drawing with a ‘crayon’ for drawing with a ‘pen’ or ‘stick’ or substituting ‘blocks’ with ‘small objects’).

Within the scope of this research project it was not feasible to translate, formally adapt or norm the Bayley-III.

6.8.3 Developmental screening and assessment flow within neonatal cohort (Figure 3)

The overall process of developmental screening and assessment within the neonatal cohort study is summarised in Figure 3. Note that completion rates for both developmental screening and assessment for study participants were high (i.e. >95%).
6.8.4 Description of study population, developmental screening and assessment results (Tables 6 and 7)

The study population consisted of a diagnostically mixed high-risk group of NICU graduates who were predominantly term, although with a large range of gestational age and birth weight. Approximately 2/3 were Itaukei and 1/3 Indo-Fijian. The comparison group were term and normal birth weight. The high-risk group were also more socioeconomically disadvantaged on measured indices (place of residence, maternal...
education, and income) compared with the control group at baseline. Further description of the sample population is also provided in Section 4.

When the PEDS was administered verbally to parents in their preferred language, the majority of parents for children in both high-risk and control newborn groups reported no concerns. However 27% (n=40) of the high-risk newborn and 14% (n=20) of the control group had PEDS results which were categorised as either moderate or high risk of global developmental delay. A minority of children in both groups had PEDS results that were categorised as high-risk for global developmental delay (i.e. 8% in high risk newborn and 2% for control newborn group respectively. Overall, including both the high-risk and comparison neonatal groups (n=292), 5% (n=15/292) and 15% (n=45/292) of the study population were categorised as being at high or moderate risk of global developmental delay based on parental responses to the PEDS test.

On formal developmental assessment using the reference standard (i.e. Bayley-III) nine children (6% of all participants) had test results indicating moderate to severe and 22 children (15% of all participants) mild global developmental delay.
### Table 6: Description of study population, developmental screening and assessment results

<table>
<thead>
<tr>
<th>Population characteristics</th>
<th>High-risk group (n=149)</th>
<th>Control group (n=147)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex Female, %</strong></td>
<td>42</td>
<td>40</td>
</tr>
<tr>
<td><strong>Birth weight, g, median (IQR)</strong></td>
<td>2610 (1750-3500)</td>
<td>3350 (3000-3650)</td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indo-Fijian, n (%)</td>
<td>50 (34)</td>
<td>48 (33)</td>
</tr>
<tr>
<td>Itaukei, n (%)</td>
<td>96 (62)</td>
<td>93 (64)</td>
</tr>
<tr>
<td><strong>Maternal age, yr, median (IQR)</strong></td>
<td>26 (18-41)</td>
<td>26 (19-37)</td>
</tr>
<tr>
<td><strong>Residence at birth, rural, %</strong></td>
<td>35</td>
<td>19</td>
</tr>
<tr>
<td><strong>Maternal education, primary school only, %</strong></td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td><strong>Family income &lt;100FJD per week combined, %</strong></td>
<td>20</td>
<td>11</td>
</tr>
</tbody>
</table>

#### Parents’ Evaluation of Developmental Status Results

<table>
<thead>
<tr>
<th>Screening test completed</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>n=146</td>
<td>n=146</td>
<td></td>
</tr>
<tr>
<td>No concerns, % (n)</td>
<td>73 (106)</td>
<td>86 (126)</td>
</tr>
<tr>
<td>Moderate risk (i.e. 1 predictive concern), % (n)</td>
<td>19 (28)</td>
<td>12 (17)</td>
</tr>
<tr>
<td>High risk (≥2 predictive concerns), % (n)</td>
<td>8 (12)</td>
<td>2 (3)</td>
</tr>
</tbody>
</table>
### Bayley Scales of Infant & Toddler Development (3rd Edition) Results

<table>
<thead>
<tr>
<th></th>
<th>Reference test completed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=149</td>
</tr>
<tr>
<td>Moderate to severe global developmental delay (i.e. composite score &lt;70 in ≥ 2 domains, % (n))</td>
<td>5 (7)</td>
</tr>
<tr>
<td>Composite score ≥70 and &lt;85 in ≥ 2 domains, % (n)</td>
<td>8 (12)</td>
</tr>
<tr>
<td>Cognitive composite score, mean ± SD</td>
<td>90 (11)</td>
</tr>
<tr>
<td>Language composite score, mean ± SD</td>
<td>92 (13)</td>
</tr>
<tr>
<td>Motor composite score, mean ± SD</td>
<td>98 (16)</td>
</tr>
</tbody>
</table>
6.8.5 Concurrent validity of PEDS compared with Bayley-III for detection of global developmental delay (Table 7)

Performance characteristics of the PEDS test when compared with the Bayley for detection of mild and moderate-severe global developmental delay are outlined in Table 7. The validity of both high-risk and moderate risk categorisation (i.e. pathways A and B) using the PEDS tests were assessed. Sensitivity of the PEDS for detection of both mild and moderate-severe global developmental delay using the reference standard was poor across both risk categories, although confidence intervals were broad. Correspondingly, positive predictive value (PPV) was also poor. By contrast, specificity and negative predictive value were strong when compared with the reference standard.
### Table 7: Concurrent validity of PEDS compared with Bayley-III for detection of global developmental delay

**Moderate to severe global developmental delay* (n=9)**

<table>
<thead>
<tr>
<th>PEDS test result</th>
<th>Sensitivity % (95% CI)</th>
<th>Specificity % (95% CI)</th>
<th>PPV¶ (95% CI)</th>
<th>NPV** (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High risk‡</td>
<td>44 (14,79)</td>
<td>96 (93,98)</td>
<td>27 (8,66)</td>
<td>98 (96,99)</td>
</tr>
<tr>
<td>Moderate risk§</td>
<td>56 (21,86)</td>
<td>86 (81,90)</td>
<td>11 (4,24)</td>
<td>98 (96,100)</td>
</tr>
</tbody>
</table>

**Mild global developmental delay† (n=22)**

<table>
<thead>
<tr>
<th>PEDS test result</th>
<th>Sensitivity % (95% CI)</th>
<th>Specificity % (95% CI)</th>
<th>PPV¶ (95% CI)</th>
<th>NPV** (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High risk‡</td>
<td>30 (12,54)</td>
<td>97 (94,99)</td>
<td>40 (16,68)</td>
<td>95 (92,97)</td>
</tr>
<tr>
<td>Moderate risk§</td>
<td>50 (27,73)</td>
<td>87 (83,91)</td>
<td>22 (11,37)</td>
<td>96 (93,98)</td>
</tr>
</tbody>
</table>

**KEY**

*Bayley-III score of <-70 in ≥ 2 domains
†Bayley-III score of <-70 and <85 in ≥ 2 domains
‡High risk = PEDS pathway A = 2 predictive concerns
§Moderate risk = PEDS pathway B = 1 predictive concern
¶PPV = positive predictive value
**NPV = negative predictive value
6.9 DISCUSSION

This study provided the first assessment of nurse-led developmental screening as a potential approach to improving developmental monitoring for high risk neonates in Fiji, a middle-income setting. However, while a parent-report screening tool was attractive for its potential feasibility for use in routine health services, our study findings suggest that the PEDS psychometric properties were inadequate for detection of global developmental delay or impairment in this context. Specifically, the consistently low observed sensitivity of the test, when compared with reference standard, suggests that its application in neonatal follow-up care in this setting could result in missed opportunities for early identification.

Limitations of this study are acknowledged. Firstly, as noted earlier, formal measurement of inter-rater reliability was not undertaken, partly due to logistical challenges of arranging for all assessors, several of whom travelled internationally to undertake assessments, to be on site together across time and space. However, as noted earlier we made rigorous efforts to ensure assessment quality through initial and ongoing training and supervision to ensure assessor performance.

Secondly, we note that our assessment of screening test accuracy was cross-sectional. As the creators of the PEDS test emphasise, and consistent with internationally recognised guidance, developmental screening tools should be used within a longitudinal developmental monitoring process, in the context of a long-term professional relationship with children and families to allow more meaningful interpretation of development over time.
Thirdly, we noted difficulties with adequate translation of the word ‘concerns’ in our translation and back translation of the PEDS test that may have affected assessment of tool performance in our study. In particular, the English translation of the iTaukei (i.e. sega na leqa) word in our translation of the PEDS test was closer to no problem rather than no concern. Glascoe et al. have highlighted the importance of nuanced language in eliciting parental concerns about child development and it is possible that our translations were too coarse to be sensitive, in spite of our best efforts in local consultation for translation and back-translation. (190)

It is also possible that there were cultural barriers to reporting and that in this context, more directed rather than open questions of parents may elicit greater reporting. Further qualitative research is required to explore these possibilities and guide different potential health service responses to under-reporting (e.g. health worker education, further participatory adaptation of tools, use of alternate screening tools).

Nevertheless, our results suggest poor accuracy of the PEDS within our study, for detection of global developmental delay or impairment in this high-risk neonatal population. Overall parental reporting of concerns in both high-risk and control neonatal groups in this study, was relatively low compared with the broader literature. In their systematic review of the prevalence of parental concerns measured by the PEDS, Woolfenden et al. reviewed results from a total of 210,242 subjects across 37 studies conducted in both high and LMIC.(183) Overall Woolfenden et al. reported 13.8% (95% CI 10.9-16.8) of PEDS results being categorised as indicating children with high-risk and 19.8% (95% CI 16.7-22.9) with moderate risk of global developmental delay.(183) By contrast, in this study, only 5% (n=15/292) and 15% (n=45/292) of children were
categorised at high or moderate risk of developmental delay on the basis of their PEDS test results. This is in spite of the reference standard assessment with the Bayley-III indicating lower or comparable overall mean Bayley-III scores for all cognitive, language and motor domains compared with reference populations. Thus based on developmental assessment performance, relatively higher rates of concerns on accurate screening test would be expected.

Findings of this study are consistent with recent reviews in the field more broadly which reflect that while there are an abundance of child development measurement tools, relatively few are effective and appropriate for use in developmental surveillance within routine health services in LMIC. Specifically, in review of 2016 World Bank Early Child Development Measurement Inventory, which included 147 tools, Boggs et al identified only 25 tools which were considered potentially fit for purpose in term of both psychometric properties and feasibility in terms of accessibility, training requirements and linkage to referral pathways.

We also previously noted literature which highlights important limitations of the reference standard itself in terms of both predictive validity and under recognition of developmental delay with the Bayley-III. (Section 5.4.2)

Thus, in spite of several limitations, this study highlights challenges in cross-contextual administration of brief developmental screening measures and established reference standards for early identification of developmental delay and impairment in high-risk neonates in LMIC.
6.10 NEXT STEPS AND FUTURE RESEARCH

In order to develop improved approaches to developmental monitoring and assessment that are feasible and accurate in LMIC, international collaboration and longitudinal research, embedded in routine health and education services is needed.

One example of such research is a multi-country newborn follow-up study that I am involved in through the London School of Hygiene & Tropical Medicine as a Co-Investigator. Our research project is called EN-SMILING (Every Newborn Simplified Measurement Integrating Longitudinal Neurodevelopment & Growth) and builds on an-existing observational birth cohort study of > 20,000 births in health facilities in Bangladesh, Nepal and Tanzania. EN-SMILING is a mixed methods follow-up study, which will link to several international initiatives to improve child development measurement in LMIC and develop and test the feasibility, acceptability and accuracy of several approaches to monitoring child development compared with measured cognitive outcomes aged three to five years.

Investment in such research, linked to early intervention is needed to ensure that children identified as have increased risk of developmental delay or impairment are crucially also supported to reach their best developmental potential.

6.11 CONCLUSION

In this research we have piloted a range of developmental screening tools and assessed the cross-sectional validity of a brief developmental screening tool/s for identification of developmental delay among a cohort of high-risk newborns in Fiji. The results, show inadequate psychometric performance of a commonly used parent-report measure, compared to reference developmental assessment standard, in this context. As such,
Section 6: Nurse-led developmental screening accuracy study

this study does not provide direct answers to the clinical questions of which developmental screening tools to use, when and how, to improve follow-up care for high-risk neonates in this middle-income setting. To better answer these questions, relevant to many child health systems in transition, international collaboration to improve the reference standard and longitudinal interdisciplinary research to explore the performance of systems of developmental monitoring which are contextually appropriate are needed, rather than an increasing abundance of tools.
Section 7
PRACTICAL EXPERIENCES AND FUTURE DIRECTIONS – FOLLOW-UP CARE AND EARLY-INTERVENTION
7. FOLLOW-UP CARE AND EARLY-INTERVENTION – PRACTICAL EXPERIENCE AND FUTURE DIRECTIONS

7.1 SECTION OUTLINE

A major driver for this research was to inform improvements in follow-up care including early intervention, for high-risk neonates in Fiji. Through the process of undertaking this research we gained useful firsthand experience of practical challenges encountered in challenges in providing follow-up care for young children in the Fiji, even within a research context. Reflections on these challenges including communication, referral pathways, transport and responding to identified developmental delay and impairment are discussed here. (Sections 7.2 and 7.3)

In addition, while our research was observational and did not therefore assess models of follow-up care and early-intervention, in coming towards the end of this thesis I draw on broader understanding of current literature to consider key elements of care including health care, hearing and vision follow-up. (Sections 7.2-7.6) We will also consider what is known about early intervention in LMIC and future research priorities, including ongoing implementation research piloting parent support early interventions for young children with cerebral palsy in Fiji. (Section 7.4.3)

7.2 COMMUNICATION, TRANSPORT AND REFERRAL PATHWAYS

7.2.1 Establishing and maintaining contact with families

We anticipated and experienced substantial challenges in establishing contact with families even within the controlled, relatively well resourced construct of a research
study. As indicated in our neonatal neurodevelopmental outcomes paper there were many potentially eligible children who we were unable to contact or locate. (See Figure 1 in neonatal outcomes paper, Section 4.2) This reflected multiple issues including challenges with medical records (e.g. inaccessibility of maternal records, recording of temporary rather than permanent maternal contact details), families moving and problems with mobile phone connectivity. While we had no control over health information systems within the remit of this research, we learned to always record multiple contact numbers and requested that parents contact health services when their address changed. Apart from hearing assessments, once children were recruited, we had very good follow-up rates with all other aspects of our study.

Additionally, we found it invaluable to have an experienced local research nurse who was able to locate and provide a central point of contact for families. Our Research Nurse Coordinator (LK) who had several decades of maternal, neonatal and child health experience and was local to Fiji was both persistent and resourceful with ways to find families. As an example, on one occasion when there were difficulties locating a child who lived in an isolated village a long distance from Suva, she went to the main market on the day she suspected that the family would be selling produce and was able to make contact.

Once children were recruited to the study, LK provided a central point of contact for families, readily accessible by mobile phone. Our impression, based on informal feedback from families, was that this was well received.
7.2.2 Transport

Transport was also reported by families and local health staff to be a major practical barrier to attendance at hospital clinics in Fiji. As such, within our research study we reimbursed families for the cost of travel. Without reimbursement clinic attendance for some families, especially over a sustained period of time, was thought likely to be unfeasible. While this was possible within our research, from a programming perspective, this would need to be addressed with consideration for sustainability in the long-term. For example, if reimbursement is considered unfeasible from a health systems perspective, outreach or community based models of care may warrant consideration as alternatives.

For children with disabilities, additional consideration needs to be given to mobility requirements. Our observation was that in Fiji young children with disabilities were typically carried to clinic due to lack of access to mobility devices and/or limitations of available devices in the local setting (e.g. lack of footpaths, wheelchair inaccessibility of transport and buildings). Moving forwards these practical barriers that limit accessibility of follow-up care for children with disabilities warrant further consideration in research and programming.

7.2.3 Strengthening referral pathways

Although not formally assessed, our experience as a research team in following-up children in our research cohort was that lack of clear referral pathways and communication between various service providers, especially between health and education, was a major practical challenge to providing follow-up care of high-risk neonates in Fiji. For example, at the start of this research allied health staff at special
developmental schools nearby to the hospital were not routinely allowed to attend in-service training at the hospital and although many children at the early intervention centre within easy walking distance of the hospital required medical review, I found that the majority of junior medical staff I spoke to were initially unaware of its existence.

As a team, we considered that working within government services to strengthen existing referral pathways, rather than working in parallel to existing services, was important to the feasibility of ongoing research and service development endeavors related to our work.

We had a presence at CWMH over a number of years and by keeping local service providers updated about our research progress, we aimed informally to facilitate strengthening of referral pathways, although this was not a specific research objective.

While there are ongoing challenges, our perception as a team, supported by referral data is that there have been increased referral linkages between health and education services for young children with developmental delay and impairments in Suva over a number of years. The main early intervention service provider in Suva, the Frank Hilton Organization and the Child Development Clinics at CWMH, which started around the same time as this research, have both seen a progressive increase in referrals over the past 8-10 years. (Personal communication) There are likely to be multiple contributory factors to referral patterns which were not explored in this research. However we note that this research occurred in the context of strong local paediatric leadership in neonatal care and child development, increased investment in inclusion in the education sector and support for capacity building in child development monitoring, assessment and early intervention. (See Section 8)
7.3 RESPONDING TO IDENTIFIED NEEDS IN RESEARCH

One particular issue challenge for our team was balancing the procedural ethics involved in a research programme with the ethics in practice of providing ancillary care in the context of poorly resourced government services.

Procedural ethics has been defined as ethics related to the norms, standards and procedures for ethical planning and conduct of research and responsibilities of researchers. As outlined in Section 3.8, with regards to procedural ethics, approvals were gained from the Fiji National Health Research, Fiji National Research Ethics Review and University of Melbourne Human Research Ethics Committees before this study and the study was undertaken in compliance with requirements of these governing bodies.

From a procedural ethics perspective, we had an approved research protocol which outlined the care that we had committed to providing children who were identified with health problems, developmental delay or impairment, or other difficulties, during the course of our research. This was typically broadly defined as best available care within local services. I was also fortunate, as a doctoral researcher conducting this research in Fiji to be part of a well-established, well-governed research group where I consider that broader principles of ethical practice in LMIC including responsivity to local needs, benefit sharing, research capacity building and provision of ancillary care were embedded in practice.

By contrast, ethics in practice has been defined as ‘ethical issues that arise in the everyday activities of carrying out a research project and the interactions of researchers with participants, and other people within and around the research process’. The related concept of ancillary care has been defined as ‘care needed by research
participants but not necessary to ensure scientific validity, prevent study-related harms or address study related injuries’ (194)

From an ethics in practice perspective, we identified a dilemma between what our research team could support short term with what was likely to be sustainable long-term, after our research study had ended. This was often experienced as a tension between supporting best care for individual children in our research study, with ensuring that we did not create expectations of services that could not be sustained after the study had ended.

For example, during the time we completed data collection for this study, there were no government services able to provide audiology follow-up, hearing aids or early intervention for young children with hearing impairment in Fiji. As such, referral to government services alone would have left those identified with hearing impairment without follow-up. Instead, during our study we partnered with an overseas NGO, the Carabez Alliance, to provide follow-up care of children identified with hearing concerns during initial tested. This involved arranging follow-up reviews by visiting audiologists who travelled from Australia for repeat testing, fitting and ongoing adjustment of hearing aids as well as limited early intervention for young children identified with hearing impairment, 6% (n=6/107) of high-risk and 5% (n=5/102) of control children respectively. (Section 4.3) This required substantial time and financial investment for both research and NGO staff, beyond what was required for study data collection, but from our perspective as a research team, was imperative to ensure our practical ethical obligations were met.
In the short-term, our approach also potentially raised expectations of local services. Certainly, during the course of our hearing clinics the Carabez Alliance received additional referrals for children and family members who had heard by about the clinic, through our study, and this service, which was supported by an international NGO, is now no longer functioning. However, since our study ended, as discussed below, there has also been a strengthening of government audiology services which we hope has mitigated against this over time (Section 8.2)

Nevertheless, moving forwards as emphasis on global child development and disability research in LMIC increases, guidance to support researchers in navigating practical ethical issues around provision of ancillary and follow-up care are warranted, especially in low income settings where these tensions may be even more pronounced that in middle income countries such as Fiji.(195)

### 7.4 Strengthening follow-up health care including hearing and vision

As noted throughout this thesis, a major driver for this research, increasingly recognized globally, is the need to develop simplified, evidence-informed guidance for follow-up of high-risk neonates in routine services LMIC.(1)

#### 7.4.1 Health care

In Section 5.2.2 we have discussed how existing prospective cohort studies in LMIC have demonstrated increased risk of neonatal mortality post-discharge compared to term, healthy peers.(2) In that section we also discussed predictable causes of morbidity and potentially mortality for high-risk neonates in these settings and also observed in our Fiji outcomes study in including increased prevalence of nutritional difficulties, respiratory
disease and seizures. We also noted how, based on our study and previous literature, we know that children with identified with developmental delay or impairment (i.e. those with disabilities) are at especially high-risk from the dual disadvantage of increased morbidity and poorer access to care. (56)

As such, an important aspect of high-risk neonatal follow-up is increased early health surveillance with additional support, especially early post discharge for predictable morbidity. In particular extra support for feeding and counselling around care-seeking for respiratory tract infections, seizures and other acute illnesses will be important. Pleasingly, although our study showed high immunisation rates in both high-risk and comparison groups in Fiji, ensuring access to routine immunisation remains crucial for this group, especially in settings such as Fiji where the burden of infectious diseases remains higher than in HIC such as Australia.(10, 43)

Further, given results of this and other studies discussed in Section 7.4 which highlight adverse nutritional outcomes often experienced by high risk neonates and the importance of nutrition for optimising health and development, ensuring additional feeding support including support for breast feeding, micronutrient supplements where recommended and complementary feeding strategies are needed. Health workers require additional focused training on how to support mothers of high risk neonates who may be particularly challenging to feed, especially those who have developmental disabilities.

Our research has also highlighted the importance of embedding systems to prevent, identify and manage hearing and vision impairment within neonatal care and follow-up
in Fiji and other LMIC. While it is beyond the scope of this thesis to discuss approaches in detail, as we have already highlighted, there are substantial bodies of research and increasingly programmes at scale related to prevention and management of both retinopathy of prematurity and hearing impairment in high-risk neonates in LMIC.(87)

Our research and previous literature also indicate that it may be appropriate to target follow-up to sub-groups of neonates and children who are known to be at highest-risk for health morbidity. In particular, children with NE, increasing prematurity and identified developmental delay and impairment, have been demonstrated in our research, to potentially warrant more intensive follow-up even compared with other NICU patients in Fiji.

However, as has recently been highlighted in the WHO *Survive and Thrive Report* much more research is required across LMIC to not only define the content and frequency of follow-up, driven by local data, but also to develop and test implementation of child and family focused models of care which are feasible and sustainable in routine services in resource limited settings. (1)

### 7.4.2 Early identification and intervention in LMIC

In Sections 6.8 and 6.9 we discussed the significance and implications of our developmental screening study for developmental monitoring of high-risk neonates in Fiji. In particular, we highlighted the need for further longitudinal research to develop evidence based approaches to support early identification of developmental delay and impairment in ways that are feasible and sustainable within routine services.
Another major knowledge and implementation gap relates to provision of early intervention for high-risk neonates. As defined in Section 1.5, early intervention is a broad concept which includes:

‘...a systematic and planned effort to promote development through a series of manipulations of environmental or experiential factors, initiated during the first five years of life which involves strategies which aim to intervene early in the life of a problem and provide individually tailored solutions. It typically focuses on populations at a higher risk of developing problems, or on families that are experiencing problems that have not yet become well established or entrenched.’ (4,38)

While it is well beyond the scope of this research to systematically review early intervention literature, we have already highlighted a well-recognised gap related to which interventions will improve what outcomes for high-risk neonates and children with developmental delay and impairment within diverse LMIC. (38, 39, 180)

To address this gap, international, inter-disciplinary collaboration and intervention research embedded within local government services is needed to not only understand what works but how, over time, it might be scaled, to support more high-risk neonates to survive and thrive.

If Fiji, building on this doctoral research, we have recently developed another project, to adapt and pilot the feasibility and acceptability of a parent support programme for young children with cerebral palsy, funded through the Murdoch Children’s Research Institute and in collaboration with the Fiji Ministries of Health and Education. This ongoing research, which I am leading, builds on similar work by colleagues in Uganda, Ghana and Brazil, using a programme called ‘Getting to Know Cerebral Palsy’. (196, 197)
While our pilot study only involves a small number of children and families (n=30), we hope that this formative research will inform ongoing efforts to improve follow-up care of children who experience development sequelae as a result of neonatal illness and complications in Fiji.

In summary, while the overall goal of this research was to provide quality local outcome data, rather than being interventional or implementation research, it has highlighted important ongoing knowledge and implementation gaps related to models of follow-up health care, developmental monitoring and early intervention for high-risk neonates in Fiji and other LMIC.
Section 8

RESEARCH TRANSLATION IN FIJI
8. **Research translation in Fiji**

8.1 **Neonatal and child development policy**
Results of our research were communicated to the Fiji Ministry of Health and Medical Services and other local stakeholders in Fiji over a series of presentations in 2014-15. Our findings informed development of relevant sections of 2012-2015 Child Health Policy and Strategy and the 2016 Draft Child Health Review and Strategy. Relevant sections of the Draft Strategy were workshopped with key stakeholders within the MoHMIs in early 2016 including recommendations for high-risk neonatal follow-up, child development monitoring and early intervention, although this strategy has not yet been endorsed. *(Personal communication, Dr Ilisapeci Tuibeqa, CWMH)*

8.2 **Service development**
As noted previously, there have been substantial advances in neonatal intensive care, even since we undertook this research. In terms of ancillary care, the ophthalmology screening protocol for NICU patients at CWMH has not changed but high-risk neonatal hearing screening commenced in 2016. This includes automated auditory brainstem responses and otoacoustic emissions testing is supported by an Australian trained audiologist who visits several times a year and a Fijian audiometrist working with the Frank Hilton Organization nearby to the hospital. In 2015, an Australian trained paediatric physiotherapist resided in Fiji and worked with local physiotherapists to strengthen neuromotor monitoring and assessments of NICU patients. However, while implemented for a time, these monitoring systems have not been sustained since her return to Australia. NICU follow-up clinics are now held jointly by a paediatric registrar and CWMH hospital physiotherapists. As described previously in Section 7 further
development of early intervention services, including related implementation research are ongoing. (Personal communication, Dr Ilisapeci Tuibeqa, CWMH and Ms Sureni Perera, Frank Hilton Organization)

8.3 LEADERSHIP DEVELOPMENT IN CHILD DEVELOPMENT AND DISABILITY

At the start of this research paediatric registrars received very little undergraduate or postgraduate training in child development. We were delighted that three paediatric registrars who acted as study doctors and a number of nurses were also involved in this research. As noted above, alongside this study, twice yearly child development assessment clinics have been established and basic training in child development and common neurodevelopmental disorders has been incorporated into undergraduate and postgraduate paediatric training. This work was led and made possible by co-investigator and Australian paediatric colleague Dr Susan Woolfenden in collaboration with the CWMH Team. Two paediatric registrars also working with the research team for our current early intervention pilot.

While these aspects of the research were not formally evaluated, in retrospect I perceive these to be some of the most important aspects of this research in terms of ongoing contribution to services and sustainability of change in Fiji.

In summary, through the process of undertaking this neonatal outcomes research over a number of years in collaboration with colleagues in the Fiji Ministry of Health and Medical Services, we have been able to develop long-term working relationships and knowledge sharing which has enabled research translation beyond the direct scope of my initial doctoral research aims. We have been able to establish partnerships and
begun to translate findings of this research into action in multiple domains to further address the needs of high-risk neonates and their families moving forwards.
Section 9

CONCLUSION
9. **CONCLUSION**

This doctoral research has responded to an identified clinical need in Fiji and provided the first neonatal neurodevelopmental and long-term health outcomes data to inform ongoing improvements in neonatal care and follow-up in that setting. Informed by background systematic review of previous high-risk neonatal outcome studies in LMIC, our neonatal outcomes study in Fiji provided multi-domain developmental outcome data including hearing and vision outcomes for both high-risk and a comparison term, healthy neonatal control group. Results demonstrated that approximately one in ten NICU graduates in our cohort experienced moderate to severe NDI in early childhood, with several identifiable risk factors. Unexpectedly, one in twenty control neonates also developed moderate to severe NDI, mostly related to hearing impairment.

Further research to explore unexpected findings as well as longer term outcomes beyond impairment are needed to better understand the neurodevelopmental impact of a diverse range of neonatal conditions in Fiji and other LMIC where neonatal health is in transition. Investment in research and international collaboration is also required to address substantial measurement challenges including an urgent need for more standardised measurement of outcomes which can be embedded in routine health information systems to monitor efforts to improve quality of care.

Our nurse-led developmental screening study, designed to begin to explore models of developmental monitoring which might be feasible in context, demonstrated poor psychometric performance of a commonly used parent-report measure, compared to reference developmental assessment standard. Additionally, the process of
undertaking this research provided practical experience in the challenges in provision of follow-up care in the local context.

Longitudinal research embedded in routine health and education services is needed to develop and test approaches to early identification of developmental delay and impairment which are feasible, appropriate and sustainable in routine services, also linking with systems of hearing and vision surveillance for high-risk neonates.

Finally, it is crucial that ongoing efforts include implementation research to support development of contextually appropriate models of early intervention which support all high-risk neonates, including those who experience NDI, to reach their best developmental potential, enabling their fullest participation in family and community life.
10. REFERENCES


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Section 11
APPENDICES
11. APPENDICES
APPENDIX 1 PLAIN LANGUAGE STATEMENT AND THIRD PARTY CONSENT FORM
Fiji Newborn Integrated Care Initiative:

Plain Language Statement

Organizations involved:  Fiji Ministry of Health

University of Melbourne, Centre for International Child Health, Melbourne Australia

UNICEF Pacific

Carabez Audiology Clinic

Principal Investigator: Prof Trevor Duke

Co-investigators:  Dr Joseph Kado

Dr Kate Milner

Dr Gehan Roberts

Dr Andrew Steer

Dr Susan Woolfenden
Introduction

Your child is invited to participate in a study that is being organized by the groups listed above.

This purpose of this study is to look at the health and development of toddlers who were admitted to the Colonial War Memorial Hospital when they were babies. This study will include a group of children who required admission the Newborn Intensive Care Unit at the Colonial War Memorial Hospital as well as a group of children who did not have any complications as newborns but are similar in other ways.

The main aim of this research is to improve understanding of the long-term effects of newborn complications on children’s health and development, so that we can improve the care and support provided to young babies and their families, when they leave hospital.

How did you get my child’s name?

The Ministry of Health has given us permission to approach parents or guardians of newborn babies who were admitted to Colonial War Memorial Hospital between January
and June 2009. We have also been given permission to approach parents or guardians of newborn babies who were born at the Colonial War Memorial Hospital during this period and did not require Intensive Care but are similar in other ways. This project has been approved by the ethics committees of the Fiji Ministry of Health and the University of Melbourne.

**What will happen if my child participates in the study?**

If you agree for your child to participate in this study they will be asked to attend two follow-up appointments at CWMH or your local hospital or health centre and an additional appointment at a children’s hearing clinic in Suva.

At the follow-up appointments your child will be reviewed by a nurse and children’s doctor who will undertake a detailed assessment your child’s growth, nutrition and physical health as well as their learning and development. Each appointment will take about 2-3 hours in total, allowing time for some time for your child to rest and have something to eat during the appointment.

Review appointments will involve answering questions about your child’s health and development as well as physical examination of your child. Your child’s development will
then be assessed through a series of questions and observation of how your child undertakes a series of tasks which explore their motor skills (how your child uses their arms, legs, hands and feet to don things), speech, understanding, social and self-help skills, hearing and vision.

Hearing will be assessed through an appointment arranged at the Carabez Audiology Clinic in Suva for detailed testing on a separate date.

Your child will also have a finger-prick blood test to see if they have anaemia ('weak blood'). This takes a few minutes. Staff will be well trained in doing this test and it is has minimal risk for your child.

If there are any concerns regarding your child’s growth, nutrition, physical health or development we will discuss these concerns with you and arrange follow-up care through Colonial War Memorial Hospital and other local health services. You will be provided with a written summary of your child’s review.

How will this project help?
The project will help us to understand problems that babies who have been ill as newborns may experience as they grow such as nutritional problems, slow growth and development, hearing and vision problems. It will also help us improve ways of monitoring and caring for these children after they leave hospital.

**Will this project help my child?**

This project will provide your child with the opportunity for a comprehensive medical review. If this raises any concerns about your child’s health or development we will discuss these with you and make arrangements for referral for ongoing care. We will also provide you with a written report summarizing your child’s health and development.

**Does my child have to take part in the study?**

Your child’s participation in this research study is completely voluntary. If you decide that you do not want your child to participate in this research, this decision will not affect your child’s medical care in the future.

**Are there any risks for my child?**
We do not anticipate any risks to your child from participating in this study. In the extremely unlikely circumstance that your child is injured as a result of taking part in this study, medical treatment will be provided.

**Will the privacy of my child be protected?**

Yes. The information we collect about your child’s health will be recorded and kept strictly confidential. It will be entered into in a computer. Access to information about your child’s health will be restricted to those people employed by the project. With your consent, we will also provide a copy of the written report of your child’s health and development to your child’s General Practitioner if they have one.

All personal information will be kept in a locked filing cabinet and only study staff will have access to this information. Data will be stored indefinitely with your permission. Your child’s name will not appear in any reports, as each child will be given a number. Confidentiality will be maintained. However, if there are unforeseen legal requirements then access to this personal information may be required.
The results of the study will be published in scientific journals and presented at conferences. Dr Kate Milner will also use the results of this study as part of her PhD thesis. However, your child’s name will not be identified in any of these reports. Any information that may be published will be released in such a way that an individual’s identity will not be disclosed. Only persons directly related to the project or officers of the Ethics Committee may have access to the information you provide us.

If I decide for my child to participate, what should I do?

You do not need to do much. You will be asked to sign the consent form that is attached to this document. We will then arrange an appointment for us to review your child at your local health centre or hospital.

Who approved this project?

This study has been approved by the Fiji School of Medicine Ethics Committee and the University of Melbourne Human Research Ethics Committee. These ethics committees make sure that the study is being done in the best and safest way.

Who is funding this project?
This project is being funded by AusAID.

How can I get more information?

If you would like more information about the project, or if you have any questions, either now or in the future, do not hesitate to ask one of the project staff. You can call the study nurse or Dr Kate Milner at CWMH on telephone number 3317670 for more information.

If you would like to speak with someone not directly involved with the study you are welcome to contact a representative of the Ethics Committees Executive Officer, Human Research Ethics, the University of Melbourne. Ph: 0061 3 8344 2073
Fiji Newborn Integrated Care Initiative:

Third Party Consent Form

(To be used for participants who cannot consent for themselves)

Principal Investigator: Prof Trevor Duke
Co-investigators: Dr Joseph Kado, Dr Kate Milner, Dr Gehan Roberts, Dr Andrew Steer, Dr Susan Woolfenden

I have read, or have had read to me in my first language, and I understand the Plain Language Statement. I give my permission for_________________________________

to participate in the Fiji Newborn Integrated Care Initiative project according to the conditions in the Plain Language Statement.

I understand that participation in this project is voluntary and that I can withdraw my child from the study at any time.
I understand that this project is for the purposes of research.

I understand that my child’s participation or a later decision to withdraw won’t affect my child’s future medical treatment.

Confidentiality of data will be maintained at all times except when there is a legal requirement otherwise.

The researcher has agreed not to reveal the participant’s identity and personal details when this project is published or presented in any public forum.

I have a copy of the Plain Language Statement and the Consent Form to keep.

This form will be retained by the research team.

Participant’s Name *(printed)* .................................................................

Name of Person giving Consent *(printed)*: ..............................................

Signature: ...............................................................Date: .... / ....... / .......

Category *(circle that which is applicable)*: Parent Next of Kin

Researcher’s Name *(printed)*: ..............................................................

Signature: ...............................................................Date: .... / ....... / .......
APPENDIX 2 BASELINE PERINATAL DATA COLLECTION FORM
FIJI NEWBORN INTEGRATED CARE INITIATIVE FORM 3:
PERINATAL DATA COLLECTION

INFANT NATIONAL HOSPITAL RECORD NUMBER

DATE OF BIRTH: yyyy/mm/dd

CHRONOLOGICAL AGE: mm/dd

PREMATURITY: mm/dd

ADJUSTED CHRONOLOGICAL AGE: mm/dd

PLACE OF BIRTH

☐ CWMH  ☐ other

GENDER

☐ Male  ☐ Female

BIRTHWEIGHT grams

LENGTH cm
HEAD CIRCUMFERENCE

NUMBER OF FETUSES

BIRTH ORDER

MATERNAL AGE

MATERNAL RESIDENCE AT TIME OF BIRTH
STUDY ID: ———  Date: ———/——/———

Antenatal clinic attended?
☐ Yes

If yes,
☐ CWMH
☐ Elsewhere

Appointments attended;
☐ 1-2
☐ 2-5
☐ >5
☐ Unknown
☐ No

Antenatal ultrasound?
☐ Yes

If yes,
☐ Normal
☐ Abnormal
☐ EDD__________________________
Complications of pregnancy

- [ ] Pregnancy induced hypertension
- [ ] Diabetes
- [ ] Bleeding
- [ ] Infection
- [ ] Premature labour

  Antenatal steroids: [ ] yes [ ] no

- [ ] Isoimmunisation
- [ ] Anaemia
- [ ] VDRL positive
- [ ] Rubella
- [ ] Ultrasound abnormalities
- [ ] Medication
- [ ] Other, please describe: ____________________________________________
Mode of Delivery

- [ ] vaginal
- [ ] caesarean
<table>
<thead>
<tr>
<th>Diagnoses</th>
</tr>
</thead>
<tbody>
<tr>
<td>☐ Low birth weight</td>
</tr>
<tr>
<td>☐ Prematurity</td>
</tr>
<tr>
<td>☐ Asphyxia</td>
</tr>
<tr>
<td>☐ Sepsis</td>
</tr>
<tr>
<td>☐ Meningitis</td>
</tr>
<tr>
<td>☐ Respiratory distress -pneumonia (including either HMD, RDS or MAS)</td>
</tr>
<tr>
<td>☐ Respiratory distress -HMD</td>
</tr>
<tr>
<td>☐ Respiratory distress –MAS</td>
</tr>
<tr>
<td>☐ Respiratory distress – unspecified or indeterminate cause</td>
</tr>
<tr>
<td>☐ Severe jaundice</td>
</tr>
</tbody>
</table>
Surgery

☐ Other, please
describe____________________________________________________

Treatment

☐ Antibiotics

☐ Phototherapy

☐ Respiratory support
  ☐ Nasal prong oxygen
  ☐ CPAP
  ☐ Ventilation

☐ Blood transfusion

☐ Stoids (postnatal)

☐ Other, please
describe____________________________________________________

Complications

☐ Nosocomial infections ☐ No

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NICI_Form3_perinatal_DCF_V2_24032011
Yes

☐ Other complications ☐ No

☐ Yes, please

describe___________________________
STUDY ID: ————  Date: ——/——/———

Screening

Cranial US performed

☐ No

☐ Yes  If yes, date   ____________ dd/mm/yyyy

☐ Normal

☐ Abnormal

If abnormal, please describe_______________________________________

ROP screening performed

☐ No

☐ Yes  Normal

☐ Abnormal

If abnormal, please describe findings

___________________________________________
Ophthalmology referral

- [ ] No
- [ ] Yes

Ophthalmology follow-up attended

- [ ] No
- [ ] Yes

Audiology referral

- [ ] No
- [ ] Yes

DISCHARGE FINDINGS AND ARRANGEMENTS

Mode of feeding

- [ ] Exclusive breast feeding
- [ ] Cup feeding (breast milk only)
- [ ] Gastric tube feeding (breast milk only)
- [ ] Breast and formula
Formula only

Prescribed discharge medications

☐ No

☐ Yes

If yes,

☐ Haematinics

☐ Multivitamin

☐ Anticonvulsants

☐ Other, please list

Place of discharge

☐ Home

☐ Other, please list

_____________________________
Follow-up

- [ ] Outpatients at CWMH
- [ ] Other, please
  describe
- [ ] Not arranged

Readmissions (since discharge CWMH)

- [ ] No
- [ ] Yes

Please list readmission dates and diagnoses

________________________________________________________________________________
________________________________________________________________________________
______
APPENDIX 3 GENERAL FOLLOW-UP DATA COLLECTION FORM
FIJI NEWBORN INTEGRATED CARE INITIATIVE: DATA COLLECTION FORM 4: FOLLOW-UP ASSESSMENT

Do you have any concerns about your child's health?

a)  [ ] Yes  [ ] No

b) If yes, please describe:

_________________________________________________________________________
_________________________________________________________________________
_________________________________________________________________________
_________________________________________________________________________

3. Does your child have cough or difficulty breathing?  [ ] Yes  [ ] No

4. Does your child have diarrhoea?  [ ] Yes  [ ] No

5. Does your child have fever?  [ ] Yes  [ ] No

6. Does your child have an ear problem?  [ ] Yes  [ ] No

7. Does your child have a skin problem?  [ ] Yes  [ ] No

8. Does your child ever have seizures/fits/convulsions?

a)  [ ] No

[ ] Yes
b) If yes, please define;

- Single typical febrile convolution

  Brief (< 10 min) generalised (involving both sides of body) fit in a child who has a fever with full spontaneous recovery.

- Recurrent febrile convulsions or any atypical febrile or unprovoked convulsions

  This includes, multiple febrile fits, febrile fits that are prolonged or involve specific parts of the body only or where recovery is prolonged or requires medical intervention OR fits that occur in absence of fever or head trauma.

- Recurrent atypical febrile or unprovoked convulsions

  Recurrent febrile fits that are prolonged or involve specific parts of the body only or where recovery is prolonged or requires medical intervention OR fits that occur in absence of fever or head trauma.

- Unable to define

Health service utilisation

9. Since birth, has your child had any admissions to hospital?

a) Yes No

b) If yes, please list estimated date/s and reason for admission/s:

_________________________________________________________________________
_________________________________________________________________________
_________________________________________________________________________
STUDY ID: ———  Date: ———/——/————

_________________________________________________________________________

_________________________________________________________________________

(Code frequency, reason)

10. Has your child been seen in hospital outpatients?

a)  □ No
    □ 1-2 times
    □ 2-5 times
    □ > 5 times

b) If yes, please describe in which department/s (tick any that apply);
    □ Paediatrics
    □ Orthopaedics
    □ Eye department
    □ Emergency (not admitted)
    □ Other
11. Apart from clinic days (i.e. appointments for immunisations), how many times would you estimate that your child has attended a MCH clinic or local health centre?

- [ ] < 2 times
- [ ] 2-5 times
- [ ] >5 times

12. Has your child attended any non-government health services?

a) [ ] No
   [ ] Yes

b) If yes, please define;

- [ ] Private practitioner
- [ ] Medical
- [ ] Non-medical
- [ ] Traditional health practitioner
- [ ] Other

**Nutritional history**

13. a) Has **(NAME)** ever been breastfed?
b) If yes, how long was \textbf{(NAME)} exclusively breast fed for?

\[\square \text{months}\]

14. Was \textbf{(NAME)} breastfed yesterday during the day or at night?

\[\square \text{Yes}\]
\[\square \text{No}\]
\[\square \text{Don’t know}\]

15. Next I would like to ask you about some liquids that \textbf{(NAME)} may have had yesterday during the day or at night. Did \textbf{(NAME)} have any;

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
<th>Unknown</th>
<th>If yes, how many times?</th>
</tr>
</thead>
<tbody>
<tr>
<td>A Plain water?</td>
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<tr>
<td>B</td>
<td>Infant formula?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>Milk such as tinned, powdered, or fresh animal milk?</td>
<td>Yes</td>
<td>No</td>
<td>Unknown</td>
</tr>
<tr>
<td>D</td>
<td>Juice or juice drinks including coconut juice?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E</td>
<td>Clear broth?</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>F</td>
<td>Yogurt?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G</td>
<td>Thin porridge?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H</td>
<td>Any other liquids?</td>
<td></td>
<td></td>
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</table>

16. Please describe everything that **NAME** ate yesterday during the day or night, whether at home or outside the home?

Think about when **NAME** first woke up yesterday morning. Did **NAME** eat anything at that time? If YES: please tell me everything that **NAME** ate at that time? PROBE: anything else? If NO continue to question b).
What did (NAME) do after that? Did (NAME) eat anything at that time? If YES: please tell me everything that (NAME) ate at that time? If NO repeat question b) until respondent says child went to sleep until the next day.

If respondent mentions mixed dishes like porridge or stew ask what was in that dish?

As respondent recalls foods, underline the corresponding food and circle 1 in the column next to the food group.

<table>
<thead>
<tr>
<th>Food type</th>
<th>Yes</th>
<th>No</th>
<th>Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>A Porridge, bread, rice, noodles, or other foods made from grains</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B Pumpkin, carrots, squash or sweet potatoes that are yellow or orange inside</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C While potatoes, white yams, cassava, dalo/taro, breadfruit or any other foods made from roots</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any dark green leafy vegetables</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D Ripe mangoes, ripe pawpaw</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E Any other fruits or vegetables</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F Liver, kidney, heart or other organ meats</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>G Any meat, such as beef, pork, lamb, goat, chicken, duck</td>
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</tr>
<tr>
<td><strong>H</strong></td>
<td>Eggs</td>
<td></td>
<td></td>
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<tr>
<td><strong>I</strong></td>
<td>Fresh or dried fish, shellfish or seafood</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>J</strong></td>
<td>Any foods made from beans, peas, lentils, nuts or seeds</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>K</strong></td>
<td>Cheese, yoghurt or other milk products</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>L</strong></td>
<td>Any oil, fats or butter or foods made with any of these</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>M</strong></td>
<td>Any sugary foods such as chocolates, sweets, candies, pastries, cakes or biscuits</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>N</strong></td>
<td>Condiments for flavour such as chillies, spices, herbs or fish powder</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>O</strong></td>
<td>Foods made with red palm oil, red palm nut, or red palm nut sauce</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

17. How meals or snacks did **NAME** eat yesterday during the day or night? (This includes solid, semi-solid, or soft foods other than liquids)

- [ ] times
- [ ] Unknown

**Medications**

18. Does your child take any medications, vitamins or traditional medicines?
STUDY ID: ——                                Date: ——/——/———

a)      ☐ Yes  ☐ No

b) If yes, please describe: ____________________________________________

19. Immunisation status

Birth (BCG, OPV1, HBV1)  ☐ Yes  ☐ No  ☐ Unknown

2 month DPT1, OPV2, HBV2)  ☐ Yes  ☐ No  ☐ Unknown

3 month (DPT2, OPV3)  ☐ Yes  ☐ No  ☐ Unknown

4 month (DPT3, OPV4)  ☐ Yes  ☐ No  ☐ Unknown

8 month (HBV3)  ☐ Yes  ☐ No  ☐ Unknown

9 month (measles)  ☐ Yes  ☐ No  ☐ Unknown

Social/demographic details:

20. Please describe the highest level of education that you [Child’s mother] have completed?

☐ Primary school

☐ Secondary school, form ☐

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21. What is your (Child's mother) current employment status?

a) i) □ Employed □ Unemployed

ii) Please describe ____________________________

b) If employed, which of the following categories best describes your employment:

□ Self-employed

□ Private sector employed

□ Government

□ Other (specify)

22. Please describe the highest level of education that your child's father has completed?

□ Primary school

□ Secondary school, form □
STUDY ID: ———   Date: ———/——/———

☐ Training college

☐ University

23. What is your child’s father’s current employment status?

a) i) ☐ Employed ☐ Unemployed

ii) Please describe ____________________________

b) If employed, which of the following categories best describes employment:

☐ Self-employed

☐ Private sector employed

☐ Government

☐ Other (specify)

24. In which of the following categories does the weekly household income fall? (read out categories)

☐ < 100

☐ 100-199

☐ 200-299
STUDY ID: ———                                Date: ——/——/————

☐ 300-399
☐ 400-499
☐ >500

Physical examination

Growth parameters:

25. Height/length  ☐ ☐ ☐  •  ☐ cm
(NB. Subtract 0.7cm from length to estimate height)

26. Weight  ☐ ☐  •  ☐ kg

27. Head circumference  ☐  •  ☐ cm

28. Weight for age

a) Z score  + / -  ☐  •  ☐ SD

b) Weight classification

Normal or overweight (> -1SD)  ☐
Mild underweight (-1 to -2 SD)  ☐

HREC No:1033185.1 NICI_Form4_follow-
STUDY ID: ———                                Date: ——/——/———

Moderate underweight (-2 to -3 SD)

Severe underweight ( <-3SD)

29. Weight-for-height

a) Z score  + / -  □ □ SD

b) Wasting classification
   None ( > -1 SD)
   Mild (-1 to -2 SD)
   Moderate (-2 to -3SD)
   Severe (<=3SD)

30. Height for age

a) Z-score  + / -  □ □ SD

b) Stunting classification
   None ( > -1 SD)
   Mild (-1 to -2 SD)
   Moderate (-2 to -3SD)
   Severe (<=3 SD)

31. Head circumference percentile □ □ centile
32. Hearing

a) Parental concerns

Yes

No

b) Clinical concerns (e.g. language delay)

Yes

No

34. Vision

a) Fix and follow (H-shape each eye separately with dull pen-torch at 30cm)

Normal

Abnormal

Right

Left

Both

b) Squint

Yes

No

c) Parental concerns

Yes

No

35. Haemoglobin

\[ \text{g/dL} \]

Physical examination
36. Skin
   a) [ ] Normal  [ ] Abnormal
   b) If abnormal, please describe:

37. ENT
   a) [ ] Normal  [ ] Abnormal
   b) If abnormal, please describe:

38. Cardiovascular:
   a) [ ] Normal  [ ] Abnormal
   b) If abnormal, please describe:

39. Respiratory:
   a) [ ] Normal  [ ] Abnormal
   b) If abnormal, please describe:
40. Gastrointestinal:

a) □ Normal □ Abnormal

b) If abnormal, please describe:

_________________________________________________________________________

_________________________________________________________________________

41. Neurological:

<table>
<thead>
<tr>
<th>Upper limb</th>
<th>Left</th>
<th>Right</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<thead>
<tr>
<th>Lower Limb</th>
<th>Left</th>
<th>Right</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Tone

Power

Reflexes
42. Is examination consistent with cerebral palsy?

☐ Yes
☐ No
☐ Unsure

43. If yes, please classify syndrome:

☐ Spastic, please define further;
  ☐ Diplegic
  ☐ Hemiplegic ☐ Right ☐ Left
  ☐ Quadraplegic

☐ Dyskinetic
☐ Ataxic

44. If clinical picture suggests cerebral palsy, please tick appropriate Gross Motor Function Classification System Level (NB. If adjusted chronological age is < 2 years please see Standard Operating Procedures for further details of levels)

Gross Motor Function Classification System levels for 2-4 year olds:
<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
<th>Tick box as applies</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Children floor sit with both hands free to manipulate objects. Movements in and out of floor sitting and standing are performed without adult assistance. <strong>Walking without the use of an assistive device as preferred mode of mobility.</strong></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>Children <strong>floor sit</strong> but may have difficulty with balance when both hands are free. Adult assistance is required to move in and out of sitting. Children pull to stand on a stable surface. Children crawl with reciprocal hand and need movement, cruise onto furniture and <strong>walk using an assistive mobility device.</strong></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>Children maintain floor sitting often by “W” sitting and may require adult assistance to assume sitting. Children creep on their stomach or crawl on hands and knees (often without reciprocal arm and knee movement) as their primary means of mobility</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>Children floor sit when placed but are unable to maintain alignment and balance without using their hands for support. Children often require equipment to support sitting and standing. <strong>Self-mobility for short distances</strong> (within a room) is achieved by rolling, creeping or crawling on hands and</td>
<td></td>
</tr>
</tbody>
</table>
**Key problems/Diagnoses:**

<table>
<thead>
<tr>
<th>STUDY ID: ———</th>
<th>Date: ———/——/————</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>V</strong></td>
<td>knees without reciprocal leg movement.</td>
</tr>
<tr>
<td></td>
<td>Limited voluntary control of movement and restricted ability to maintain antigravity head and trunk postures. <strong>No means of independent movement</strong> and are transported.</td>
</tr>
</tbody>
</table>

44. PEDS

45. PEDS:DM

46. Bayley

47. Key problems/Diagnoses:

General health:

Growth and nutrition:

Immunisation:

Hearing:

Vision:

Physical examination/diagnoses:

Development:

HREC No:1033185.1 NICI_Form4_follow-upDCF_V2_240311
STUDY ID: ————  Date: ——/——/———

48. **Suggested investigations and management:**

_________________________________________________________________________
_________________________________________________________________________
_________________________________________________________________________
_________________________________________________________________________
_________________________________________________________________________

49. **Follow-up plan:**

_________________________________________________________________________
_________________________________________________________________________
_________________________________________________________________________
_________________________________________________________________________
_________________________________________________________________________

50. **Name of doctor/healthworker to receive report:**
Child’s Name:  

Mother’s Name:  

Date of Birth:  

NHN:  

Phone:  

Gestational Age: /40 weeks  

Corrected Age:  

Date of assessment:  

Place of assessment: Colonial War Memorial Hospital Children’s Outpatients  

Review Team: Dr Kate Milner, Dr Anne Miller (Paediatrician), Dr Rakei Kaarira (Paediatric Registrar), Lanieta Koyamaibole (Research Nurse)  

Summary:  

_________ is a_____month old (corrected age) who was reviewed from a general medical and developmental perspective as part of the Fiji Newborn Integrated Care Initiative research project.  

Current issues: (please list all medical and developmental diagnoses/concerns)  

________________________________________________________________________________  

________________________________________________________________________________
Physical examination:

Weight:Height: Head circumference: Weight/Height Z score:

Screening Haemoglobin:

Other key findings were

________________________________________________________________________________

________________________________________________________________________________

________________________________________________________________________________

________________________________________________________________________________

________________________________________________________________________________

________________________________________________________________________________

________________________________________________________________________________

Recommendations:

________________________________________________________________________________

________________________________________________________________________________

________________________________________________________________________________

________________________________________________________________________________

________________________________________________________________________________

Follow-up plan:

________________________________________________________________________________

________________________________________________________________________________

________________________________________________________________________________

________________________________________________________________________________

________________________________________________________________________________
**Developmental assessment:**

A Bayley Scale of Infant and Development Assessment (3rd edition) was undertaken. This explores cognitive (thinking), expressive and receptive language (talking and understanding), and fine and gross motor skills (use of finger/hands and arms and legs).

_______’s performance and skills in each of the above areas were as follows:

**Cognitive** (thinking & problem-solving)

________________________________________________________________________________
________________________________________________________________________________
________________________________________________________________________________
________________________________________________________________________________
________________________________________________________________________________

**Language** (talking & understanding)

________________________________________________________________________________
________________________________________________________________________________
________________________________________________________________________________
________________________________________________________________________________
________________________________________________________________________________

Motor (use of fingers/hands and arms and legs)

________________________________________________________________________________
________________________________________________________________________________
________________________________________________________________________________
________________________________________________________________________________
________________________________________________________________________________
________________________________________________________________________________

Please do not hesitate to contact us if there are further concerns or any queries regarding this report.

Kind regards,

Phone: 9203597 (Study Nurse Phone)/3317670 (Research Office CWM Hospital)
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Author/s:
Milner, Kate MacKinnon

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