Applied epidemiology of vaccine-preventable diseases in the Asia-Pacific

Thesis submitted for the degree of Masters of Philosophy (Applied Epidemiology) of the Australian National University

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Field Placement
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Declaration
I hereby declare that this submission is my own work and to the best of my knowledge it contains no materials previously published or written by another person, or substantial portions of material which have been accepted for the award of any other degree or diploma at Australian National University or any other educational institution, except where due acknowledgement is made in the thesis. The work was undertaken from March 2015 to June 2017 as part of the degree of Masters of Philosophy in Applied Epidemiology, Australian National University. This research is supported by an Australian Government Research Training Program (RTP) Scholarship.

Signed:.................................................................................................................................

1st November 2017

Date:.................................................................................................................................
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Acknowledgements
Firstly I would like to thank my supervisors, A/Prof Fiona Russell (MCRI, field) and Dr Stephanie Davis (ANU, academic). Their never ending support, guidance and most of all patience throughout my MAE has been invaluable for my learning and growth as a budding epidemiologist.

Whilst in Laos, I have been very fortunate to work with many fantastic people all with the goal of improving health outcomes for the Lao people. First of all I would like to thank Dr Anonh Xeuavongsa, head of the National Immunization Programme (NIP) in Laos, who has always supported the work we are doing. My thanks also extends to the rest of the NIP team for all their assistance in providing us the relevant approvals and data we needed for our work. My gratitude to Dr Siddhartha Datta from the WHO Laos Country Office for his guidance. Additional thanks to the Epidemiology and Surveillance team at WHO, in particular Dr Manilay Phengxay and Jennie Musto, who allowed me to join their meetings, increasing my knowledge of field surveillance. Thank you to Prof Paul Newton and Dr David Dance and the LOMWRU team for hosting us and making us a part of the LOMWRU family. My eternal thanks to my PneuCAPTIVE study team who worked tirelessly on the study, resulting in its success.

My thanks to Prof Kim Mulholland, Dr Catherine Satzke, Dr Eileen Dunne, Anne Balloch, Dr Cattram Nguyen, Dr Ruth Lim and Dr Jocelyn Chan from MCRI for their support and advice working on the various projects.

Thanks to my family and friends who have supported me throughout the program in good times and bad. Thank you also to the MAE team at NCEPH, their knowledge and guidance throughout the program was a great learning experience for me on my next career path. Lastly, thank you to my MAE cohort: Dr Alicia Arnott, Dr Amy Burroughs, Mr Anthony Draper, Dr Johanna Dups, Dr Paul Dutton, Dr Tanyth de Gooyer, Dr Tambri Housen, Ms Alex Marmor, Ms Samantha Siripol, Dr Craig Thompson, Mr Darren Westphal and Ms Cecilia Xu for their eternal friendship and support.
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Abstract
From 2015-2016 I undertook the Master of Philosophy in Applied Epidemiology (MAE) whilst under the employment of the Murdoch Childrens Research Institute (MCRI) in Melbourne as a research officer for a study based in the People’s Democratic Republic of Laos (Lao PDR). To satisfy the requirements of the MAE, I completed projects in the areas of data analysis, public health surveillance, epidemiological research and outbreak investigation.

The work I was employed for with MCRI formed the basis of my data analysis competency. The aim of this project was to determine the pneumococcal conjugate vaccine (PCV) coverage required to achieve herd immunity using pneumococcal carriage surveillance at Mahosot Hospital in Lao PDR. Beyond the analysis of these data, I was responsible for overseeing and coordinating the larger body of work for this project based in Lao PDR. This work is ongoing and a final publication will be published later in 2017.

With guidance from my field supervisor, I was responsible for establishing the epidemiology of acute gastroenteritis (AGE) in Kiribati pre- and post-rotavirus (RV) vaccine introduction. As part of this review, I established post-marketing surveillance of intussusception (IS) as part of RV vaccine introduction. The World Health Organization (WHO) recommends the surveillance of IS post-RV vaccine introduction due to experiences with a previous formulation of the vaccine. This evaluation is ongoing and will be completed in 2017.

In response to vaccine preventable disease (VPD) outbreaks in Lao PDR, the Ministry of Health, National Immunization Programme (NIP) requested information regarding evidence of serological protection of H. influenzae type b (Hib) in their population. This study was the basis of my epidemiological research for the MAE. The results from this study would provide data on Hib protection in their population to help inform NIP if changes to their current schedule were necessary.
For my outbreak investigation competency, I was involved with the team at WHO Lao PDR country office in responding to a circulating vaccine-derived poliovirus type 1 (cVDPV1) outbreak in Lao PDR from October 2015 to mid-2017. As part of this work I will contribute to the outbreak investigation section of the larger WHO report to be submitted to NIP.

This thesis presents my experience as a MAE scholar; the skills gained, knowledge learnt and the impact this body of work had on public health in the Asia-Pacific region for VPD.
# Table of Contents

**Chapter 1:** Introduction .................................................................................................................. 1  
**Chapter 2:** Using nasopharyngeal carriage surveillance in children hospitalised with acute respiratory illness to demonstrate direct and indirect effects of pneumococcal conjugate vaccine (PneuCAPTIVE Laos) ................................................................. 9  
**Chapter 3:** Kiribati rotavirus vaccine introduction; Establishment of post-marketing surveillance ........................................................................................................................................ 69  
**Chapter 4:** *Haemophilus influenzae* type b (Hib) serosurvey ............................................................ 154  
**Chapter 5:** Circulating vaccine-derived poliovirus type 1 (cVDPV1) outbreak in Laos PDR ............................................................................................................................................. 193  
**Chapter 6:** Teaching ...................................................................................................................... 231
Chapter 1
Introduction
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**Introduction**

As part of the Masters of Applied Epidemiology (MAE) program, I was lucky enough to be placed in the field in Vientiane, Laos, where I conducted the bulk of my work. Through my program I was able to experience field epidemiology throughout the Asia Pacific region in the realm of vaccine-preventable disease (VPD).

My place of employment was with the Pneumococcal Research Group at the Murdoch Childrens Research Institute (MCRI). Murdoch Childrens Research Institute was established in 1986 with a broad focus on child health research from infant to adolescent health. Their beliefs and purpose is to give all children the opportunity to live a healthy and fulfilled life. Murdoch Childrens Research Institute is the largest child health research institute in Australia, employing approximately 1500 researchers who work from basic research to translation into practice. Researchers work across 5 key areas; infection and immunity, cell biology, clinical sciences, genetics and population health\(^1\). The Pneumococcal Research Group sits under the Infection and Immunity research theme at MCRI, led by Prof. Kim Mulholland, and aims to develop, evaluate and enhance vaccination strategies worldwide. As part of the Pneumococcal Research Group, I am employed as a research officer working as an epidemiologist for the PneuCAPTIVE study (Chapter 2), primarily based in Laos, whilst providing support to the site in Goroka, Papua New Guinea at the beginning of my employment.

My primary field placement was at the Laos-Oxford-Mahosot Hospital- Wellcome Trust-Research Unit (LOMWRU) in Vientiane Capital, Laos. LOMWRU was established in 2000 as collaboration between Mahidol Oxford Tropical Medicine Research Unit (MORU) and Laos’ main internal medicine hospital, Mahosot Hospital in the capital Vientiane. The work conducted is designed to provide Lao health workers and the Lao government with key data that will allow them to make evidence-based decisions for individual patients and for health policy.

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\(^1\) Murdoch Childrens Research Institute Website. Accessed 5\(^{th}\) April 2015. Available from: [https://www.mcri.edu.au](https://www.mcri.edu.au)
LOMWRU's principal research areas are the epidemiology and treatment of malaria, typhoid, typhus, community-acquired septicaemia, meningitis and causes of acute febrile illness. Acute febrile illness is the most common medical presentation in the country. LOMWRU also work on many other tropical diseases with the aim to increase the understanding of these diseases in the country\(^2\).

The work I completed at LOMWRU contributed to 2 of my core competencies (Chapter 2 & 4) for the MAE program. The first was the PneuCAPTIVE study (Chapter 2) where I acted in a study coordinator position, investigating the use of nasopharyngeal carriage surveillance in children to measure the direct and indirect effects of pneumococcal conjugate vaccine (PCV). The second was an epidemiological study to describe the coverage by written record of *H. influenzae* type b (Hib) vaccine (given as part of DTPw-Hib-HepB) and evidence of serological protection to Hib from these same children (Chapter 4). For both of these studies I was responsible for ensuring data was collected and entered, whilst addressing issues of errors and completeness. The data collected from the PneuCAPTIVE project was presented at multiple international conferences (ISPPD 2016, ACPID 2016, TEPHINET 2016) either as a poster or an oral presentation. In addition the PneuCAPTIVE project was presented at the monthly microbiology seminars held at MORU in Bangkok to keep the larger unit abreast of the work being conducted at LOMWRU. Post-MAE, the Hib chapter results will be presented informally to the NIP team as a presentation and a short report to update them on the outcome of the work.

Early 2015, A/Prof Fiona Russell was asked to conduct an evaluation in Kiribati for rotavirus vaccine by WPRO. This was recognised as an opportunity to satisfy the surveillance core competency as part of my MAE. Kiribati had planned to introduce rotavirus vaccine mid-2015 and had no baseline data established for evaluation or safety monitoring. For the first part of the evaluation we were contracted to identify the baseline incidence of hospitalised acute gastroenteritis (AGE) and describe the characteristics of cases in the 5 years pre-vaccine introduction. As part of the introduction we were also required to establish post-marketing vaccine

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safety surveillance, monitoring intussusception (IS). The establishment of the IS surveillance made up my surveillance competency (Chapter 3). We will complete the evaluation late 2017 and present the early impact of rotavirus vaccine in the Kiribati population to WPRO for the stakeholders. This work has been presented at multiple international conferences (ACPID 2016, TEPHINET 2016) as both an oral presentation and poster. A late draft manuscript describing the incidence of AGE pre-vaccine introduction in Kiribati will be submitted for publication.

At the beginning of 2016, I was given an opportunity by both WHO and NIP to participate in the outbreak response to circulating vaccine-derived poliovirus type 1 (cVDPV1). The outbreak began in October 2015 and was spread over 4 provinces north of Vientiane Capital. Due to the complexity and inherent language barriers, I was primarily an observer, but when appropriate did assist in the investigation and response to the best of my abilities. I was very fortunate in being allowed to experience all aspects of the investigation and response effort mounted by the government and NGO’s to stop the outbreak from spreading. This was the first outbreak of polio in Laos since certification in 2000. I was given permission to use the outbreak investigation data to satisfy my outbreak investigation and response competency (Chapter 5). Post-MAE I will assist with the writing of the official report for WHO and NIP.
Summary of MAE core activity requirements

I completed the following requirements for the Master of Philosophy (Applied Epidemiology) qualification:

**Core competencies**

**Epidemiological study**
- Chapter 4 - *Haemophilus influenzae* type b (Hib) Serosurvey

**Analysis of public health data**
- Chapter 2 - Using nasopharyngeal carriage surveillance in children hospitalised with acute respiratory illness to demonstrate direct and indirect effects of pneumococcal conjugate vaccine (PneuCAPTIVE Laos)

**Establishment/Evaluation of public health surveillance system**
- Chapter 3 – Kiribati rotavirus vaccine introduction; Establishment of post-marketing surveillance

**Outbreak investigation**
- Chapter 5 – Circulating vaccine-derived poliovirus type 1 (cVDPV1) outbreak in Laos PDR

**Additional requirements**

**Public health report**
- World Health Organization mission and findings report:
  Retrospective review of acute gastroenteritis and intussusception and establishment of intussusception surveillance post-rotavirus vaccine introduction in Kiribati
  Mission and findings report submitted to WHO (WPRO) June 2015 (Chapter 3, Appendix D) and April 2016 (Chapter 3, Appendix E), respectively

**Scientific manuscript for a peer-reviewed journal**
- **Jana Lai**, Beia Tabwaia, Agnes Nikuata, Ereti Timeon, Andre Reiffer, Stephanie Davis, Kimberly Fox and Fiona Russell. **High rates of hospitalised acute gastroenteritis and severe acute malnutrition in Kiribati children prior to rotavirus vaccine introduction: a retrospective review** – late draft for submission to the Western Pacific Surveillance and Response Journal (WPSAR) (Chapter 2)
Chapter 1 - Introduction

Teaching

- LFF
- Participated in all ‘Lessons from the Field’ hosted by the group of my colleagues I was assigned to
- Group teaching of 1st year MAE 2016 colleagues (Chapter 6)

Oral presentation at a national/international conference


Other requirements

- A literature review was completed for each of the field projects to satisfy the core competencies.
- To fulfill the lay communication requirement, a poster describing the PneuCAPTIVE study (Chapter 2, Appendix B) was prepared and hung in the relevant paediatric wards to inform both the staff and patients of the purpose and preliminary results of the study. This was written in both English and Lao language.

Courseblock residentials

- I attended all three residential during 2015 and 2016
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Chapter 2
Using nasopharyngeal carriage surveillance in children hospitalised with acute respiratory illness to demonstrate direct and indirect effects of pneumococcal conjugate vaccine (PneuCAPTIVE Laos)
Contents

1. Prologue ......................................................................................................................... 15
  1.1. Role .......................................................................................................................... 15
  1.2. Lessons learnt ........................................................................................................... 16
  1.3. Public Health implications and impact ................................................................. 16
2. Abstract ......................................................................................................................... 18
3. Introduction .................................................................................................................. 20
  3.1. Pneumococcal disease ......................................................................................... 20
  3.2. Pneumococcal Conjugate Vaccine (PCV) ............................................................ 20
  3.3. Impact of PCV on invasive pneumococcal disease (IPD) ....................................... 21
  3.4. Herd immunity ......................................................................................................... 21
  3.5. Measuring direct and indirect effects of PCV on pneumococcal disease ............ 23
  3.6. PCV and pneumococcal carriage ......................................................................... 24
  3.7. Carriage surveillance and herd immunity ............................................................. 25
  3.8. Laos and PCV .......................................................................................................... 29
  3.9. Aims ........................................................................................................................ 30
4. Methods ......................................................................................................................... 31
  4.1. Study Site ................................................................................................................ 31
  4.2. Design ....................................................................................................................... 31
  4.3. Study Participants ................................................................................................... 31
  4.4. Data and swab collection ....................................................................................... 32
  4.5. Lab methods ............................................................................................................ 33
  4.6. PCV vaccination status .......................................................................................... 34
  4.7. Sample size, data management and analysis ....................................................... 35
  4.8. Ethical considerations ............................................................................................. 38
5. Results .......................................................................................................................... 40
  5.1. Characteristics of cases ......................................................................................... 40
  5.2. Pneumococcal carriage ......................................................................................... 42
  5.3. Carriage of VTs and PCV13 coverage .................................................................... 42
6. Discussion ..................................................................................................................... 45
7. Recommendations: ....................................................................................................... 50
8. References ..................................................................................................................... 52
9. Appendices .................................................................................................................... 57
Chapter 2 – PneCAPTIVE

A. Case CRF .................................................................................................................. 57
B. Lay poster – PneuCAPTIVE Study .......................................................................... 63
C. ISPPD conference poster ......................................................................................... 64
D. Conference oral presentation – Asian Congress of Pediatric Infectious Disease 2016 ................................................................................................................................. 65
List of Figures
Figure 1: Post-PCV7 introduction invasive pneumococcal disease caused by vaccine types summary rate ratios from random effects meta-analysis........22
Figure 2: Nasopharyngeal carriage prevalence of *S. pneumoniae* vaccine-type serotypes in all ages, Kilifi Kenya.................................................................25
Figure 3: Comparison of the prevalence of PCV13 serotype carriage among immune and nonimmune children, plotted with the coverage of PCV13 in children <5 years of age in the community..............................................................27
Figure 4: Three-month moving average of PCV13-specific type carriage prevalence among under-immunized Navajo and White Mountain Apache children <5 years and community PCV13 uptake and coverage .................................................28
Figure 5: Collecting a nasopharyngeal swab ................................................................33
Figure 6: Decision making flow chart of case's PCV vaccination status .................35
Figure 7: Recruitment flowchart of study up to July 2016........................................40
Figure 8: Case enrolment from Dec 2013 to July 2016............................................41
Figure 9: PCV13 vaccine serotype carriage in vaccinated and undervaccinated cases, by case PCV13 vaccination status, using 7-month rolling intervals........43
Figure 10: Rate ratio of risk of VT carriage in vaccinated and undervaccinated cases ..................................................................................................................44

List of Tables
Table 1: Classification of PCV13 vaccination status by age and number of doses...36
Table 2: Characteristics of ARI cases admitted to Mahosot Hospital, Vientiane Capital, Lao PDR from December 2013 to July 2016, stratified by vaccination status..................................................................................................................41
Table 3: Pneumococcal carriage in ARI cases admitted to Mahosot Hospital, Vientiane Capital, Lao PDR from December 2013 to July 2016, stratified by vaccination status ..................................................................................................................42
## Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>ANU</td>
<td>Australian National University</td>
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<tr>
<td>ARI</td>
<td>Acute respiratory infection</td>
</tr>
<tr>
<td>BMGF</td>
<td>Bill and Melinda Gates Foundation</td>
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<tr>
<td>CAP</td>
<td>Community-acquired pneumonia</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>Ct</td>
<td>Cycling threshold</td>
</tr>
<tr>
<td>CRF</td>
<td>Case report form</td>
</tr>
<tr>
<td>DOB</td>
<td>Date of birth</td>
</tr>
<tr>
<td>EPI</td>
<td>Expanded Programme of Immunization</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
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<tr>
<td>Gavi</td>
<td>Global Alliance for Vaccines and Immunization</td>
</tr>
<tr>
<td>HIC</td>
<td>High-income country</td>
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<tr>
<td>IMCI</td>
<td>Integrated Management of Childhood Illnesses</td>
</tr>
<tr>
<td>IPD</td>
<td>Invasive pneumococcal disease</td>
</tr>
<tr>
<td>Lao PDR</td>
<td>Lao People’s Democratic Republic</td>
</tr>
<tr>
<td>LDC</td>
<td>Least developed country</td>
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<tr>
<td>LMIC</td>
<td>Low and middle-income country</td>
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<tr>
<td>LOMWRU</td>
<td>Laos-Oxford-Mahosot Hospital-Wellcome Trust-Research Unit</td>
</tr>
<tr>
<td>MAE</td>
<td>Masters of Philosophy in Applied Epidemiology</td>
</tr>
<tr>
<td>MCH</td>
<td>Mother-child health</td>
</tr>
<tr>
<td>MCRI</td>
<td>Murdoch Childrens Research Institute</td>
</tr>
<tr>
<td>NP</td>
<td>Nasopharyngeal</td>
</tr>
<tr>
<td>NPS</td>
<td>Nasopharyngeal sample</td>
</tr>
<tr>
<td>NVT</td>
<td>Non-vaccine serotype</td>
</tr>
<tr>
<td>PCR</td>
<td>Polymerase chain reaction</td>
</tr>
<tr>
<td>PCV</td>
<td>Pneumococcal conjugate vaccine</td>
</tr>
<tr>
<td>PCV7</td>
<td>7-valent pneumococcal conjugate vaccine (Prevenar®, Wyeth)</td>
</tr>
<tr>
<td>PCV10</td>
<td>10-valent pneumococcal conjugate vaccine (Synflorix, GSK)</td>
</tr>
<tr>
<td>PCV13</td>
<td>13-valent pneumococcal conjugate vaccine (Prevenar13®, Pfizer)</td>
</tr>
<tr>
<td>qPCR</td>
<td>Quantitative real-time PCR</td>
</tr>
<tr>
<td>STGGB</td>
<td>Skim milk-tryptone-glycerol-glucose broth</td>
</tr>
<tr>
<td>US</td>
<td>United States of America</td>
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<tr>
<td>VT</td>
<td>Vaccine serotype</td>
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<td>-------</td>
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<tr>
<td>WPRO</td>
<td>Western Pacific Regional Office</td>
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1. Prologue

1.1. Role
For my Masters of Philosophy in Applied Epidemiology (MAE), I was employed to work on this project by A/Prof Fiona Russell as my supervisor through the Murdoch Childrens Research Institute (MCRI), Melbourne. The project was funded by the Bill & Melinda Gates Foundation (BMGF) to demonstrate how nasopharyngeal (NP) carriage surveillance in hospitalised children with acute respiratory illness (ARI) or pneumonia could be used to estimate the pneumococcal conjugate vaccine (PCV) coverage required to show evidence of herd immunity and monitor the vaccine’s impact on carriage. This would help inform national planners on the coverage required to gain maximum effectiveness of PCV from their respective immunisation programs. The People’s Democratic of Laos (Lao PDR) is one of 3 sites, with the other 2 being in Mongolia and Papua New Guinea. The final analysis for the project will pool together the results of all 3 sites to estimate the coverage required for herd immunity effects. The larger study will continue through to the end of 2018.

I acted in a coordinator role based in Vientiane, Lao PDR working in conjunction with Australian doctors, managing a local team. My responsibilities on the project were to oversee the day to day work, set the priorities for the project, design and implement data collection tools for PCV coverage, assist with the writing of the study analysis plan, have input and maintain the relevant study databases, participate in field work when needed, train local staff for non-clinical work, monitor and monthly reporting to investigators of the project. My role will continue on this project until the end of 2017, but for the purposes of the MAE, I will only include data up until July 2016, as this was the microbiological data that was available at the time of writing.

From this work I have presented preliminary data at 3 international conferences in both oral and poster format. I have presented informal talks regarding this study at our collaborator meetings in both Bangkok and Lao PDR. A publication will be prepared and published at the end of the study in late 2017.
1.2. Lessons learnt
The concept of the study design was challenging and took me time to grasp. Through my role I had to learn to manage a team to achieve the goals of the study, with the added complications of working in a non-English speaking environment coupled with constant staff changes. I spent time in the field to develop different survey methods for our study to estimate vaccination coverage for our cases. To do this I had to organise the relevant approvals from National Immunisation Program (NIP) and then plan with staff the schedule of district hospital/health centre visits. Through this exercise I learnt about the nuances of administrative data, how to adapt and fit a systematic method for all the different scenarios we faced when collecting data. A key part of this was formulating a list of questions we would ask district hospital/health centre staff and how to cross-check their responses with the data recorded in the immunisation registries. Health centre staff received limited training on how to record the data and frequently received different data recording tools. It was important to understand the process followed by staff at each centre with their routine immunisation. This was because each health centre, even within districts, recorded data differently. To manage the situation I kept a detailed diary of these visits including date of the visit so we could match the information given verbally to us by staff, to the photos we took of the immunisation registries at each centre. This information fed into development of the data analysis methods in conjunction with the biostatistician and epidemiologist for the project. I learnt how to conduct monitoring and the process of reporting to investigators on a regular basis. I was responsible for the preparation of the vaccination status and coverage reporting to investigators as well as hosting, running and noting the discussions each meeting. Through this I learnt how to interact with different stakeholders in the project, correct methods of note taking and how to use these data for forward project planning to meet the goals of the study, either for reporting or data analysis.

1.3. Public Health implications and impact
The purpose of this study was to test a new method to be used for determining the maximum benefit of PCV use in a population. The maximum benefit of PCV for a
population lies in the effect of herd immunity. Many countries in resource-poor settings, such as Southeast Asia, do not have robust systems to monitor invasive pneumococcal disease (IPD), pneumonia and/or community carriage, making it difficult to determine the herd immunity effects of PCV in the population. Beyond the added benefit of describing pneumococcal carriage in Lao PDR, the data from this study will add to the body of data in the PCV evaluation being prepared for the NIP, continuing the support for use of PCV in Lao PDR. The surveillance method proposed in this study can be implemented quickly in sentinel hospital sites, with an easily accessible population and isn’t dependent on pre-vaccine data, making it adaptable to other low and middle-income countries (LMICs). However determination of PCV coverage is a challenge and novel methods need to be considered. This is important as many countries are considering the introduction of PCVs in the region and face a similar situation to Lao PDR. The use of this method will provide other LMICs with a method to observe the effect of PCV in their country, supporting their use.

1.4. Acknowledgements
I would like to thank A/Prof Fiona Russell for first of all for allowing me to work on this study and subsequently guiding me through this complex body of work. Additional thanks also goes out to Dr Ruth Lim who I worked closely with at the beginning of the study to get it to the strong state it is in today. My gratitude to Dr Anonh Xeuatvongsa, Dr Siddhartha Datta and the rest of the NIP team for always supporting our work and providing the necessary knowledge and assistance to ensure the study ran smoothly. At LOMWRU I would firstly like to thank Dr David Dance and Prof Paul Newton for the unfaltering support and guidance. My thanks to the Pneumococcal Research Group at MCRI; Prof Kim Mulholland, Dr Cattram Nguyen and Dr Jocelyn Chan for support and the microbiology team for all their assistance in not only helping us process our samples but also for making sure we met our reporting deadlines. Finally, my eternal gratitude goes out to our PneuCAPTIVE team in Lao PDR who without the dedication we would not be able to present this data today.

1.5. Funding
Bill & Melinda Gates Foundation
2. Abstract

Background/aims: People's Democratic of Laos (Lao PDR) introduced 13-valent pneumococcal conjugate vaccine (PCV13) in October 2013 for children up to 12 months of age. The primary aim of this study is to determine the PCV13 coverage needed to show evidence of herd immunity using nasopharyngeal (NP) pneumococcal carriage surveillance in hospitalised children in Lao PDR. Secondary aims were to describe the epidemiology of cases and describe overall pneumococcal carriage, VT carriage and NVT carriage among vaccinated and undervaccinated cases.

Methods: Children 2-59 months of age admitted to Mahosot Hospital, Vientiane with acute respiratory infection (ARI) were prospectively enrolled from December 2013 to July 2016, and had a NP swab collected. Pneumococcal carriage status was determined using lytA real-time quantitative PCR (qPCR), with positives and equivocals serotyped by microarray. Monthly PCV13 vaccine-type (VT) carriage rates were determined in undervaccinated and vaccinated children. The PCV13 vaccination rate was calculated using 7-month rolling intervals each month by the number of cases vaccinated based on written records (mother child health (MCH) card or health centre immunisation registry) and the total number of cases enrolled each month. Herd immunity effects were determined by calculating the risk of VT carriage among vaccinated and undervaccinated children. A risk ratio equivalent to 1 was deemed as herd immunity effects being achieved in the population.

Results: From December 2013 to July 2016, 800 cases were enrolled into the study. Of those, 53% had pneumonia and the majority resided in Vientiane Capital. PCV13 vaccinated cases were significantly younger (12 months, IQR 8-17) than undervaccinated cases (21 months, IQR 8-33) (p<0.001). Cases residing in the provinces were significantly less likely to be vaccinated (p<0.001). Overall pneumococcal carriage was 40%, with vaccinated cases significantly less likely to carry a VT (p<0.001) than undervaccinated cases. Over time, VT carriage in vaccinated cases declined, whilst VT carriage in undervaccinated cases remained relatively unchanged over time. The vaccination rate in cases steadily increased.
over the study period from 16% to 70% by July 2016. The risk ratio of VT carriage in vaccinated and undervaccinated did not equal 1 over the study period.

**Summary and Conclusions:** Direct effects have occurred shown by VT carriage decreasing in vaccinated cases. However herd immunity has not, indicated by a risk ratio of VT carriage between vaccinated and undervaccinated cases greater than 1. Further analysis is required to adjust for confounding in carriage. The reasons for absent herd immunity effects are related to the case vaccination rate overestimating community coverage, lack of an active catch-up campaign and early post-PCV data (over 2 years) being shown. Surveillance will continue for 5 years and if herd immunity effects do occur, they will occur within this time period. These data are important to not only inform decision makers what PCV13 coverage is required to maximise the benefits of PCV13 but also to monitor changes to pneumococcal epidemiology due to use of the vaccine.
3. Introduction

3.1. Pneumococcal disease

In 2000, it was estimated pneumococcal infections were responsible for about 826,000 deaths in children 1-59 months of age (1). Pneumonia is the second leading cause of deaths in children under the age of 5 years globally (2), with pneumococcus being the most common cause of bacterial pneumonia (3). Almost all pneumonia-related deaths occur in low and middle-income countries (LMICs) where children are poor, timely access to health services may be difficult or even impossible and where risk factors for more frequent and severe disease are common (4). Ninety-eight percent of all pneumonia deaths in children less than 5 years of age occur in just 68 LMICs (5).

*Streptococcus pneumoniae* or pneumococcus is a Gram-positive bacterium that naturally resides in the nasopharynx of humans. Nasopharyngeal (NP) carriage is common and most carriers are healthy (6). Transmission occurs via direct contact with respiratory secretions from carriers to non-carriers (1). Acquisition and subsequent infection with pneumococcus is the precursor to disease (7, 8), with the highest pneumococcal carriage rates in children during their first 2 years of life (8). From this point, pneumococcus can be spread to others and also gain access to other sites in the body such as the lungs, which then can lead to pneumonia (8). Thus far there have been over 90 unique serotypes identified however not all serotypes cause disease. Diseases caused by pneumococcus include pneumonia, meningitis, febrile bacteraemia, otitis media, sinusitis and bronchitis (1).

3.2. Pneumococcal Conjugate Vaccine (PCV)

In 2007, WHO recommended the use of pneumococcal conjugate vaccines (PCVs) in all countries, urging the highest priority for introduction given to countries with high pneumonia and under 5 mortality rates (1). In February 2000, the United States (US) Food and Drug Administration (FDA) licenced the first PCV, 7-valent PCV (PCV7)(9). PCV7, also known as Prevenar®, contained 7 pneumococcal polysaccharides (4, 6B, 9V, 14, 18C, 19F and 23F) conjugated to a non-toxic diphtheria-toxin variant carrier protein, CRM197 (9). Because of issues with
serotype replacement and coverage of other important serotypes in LMICs, new formulation PCV's are now available, with the two currently licenced being PCV10 and PCV13, licenced in 2009 and 2010 respectively. PCV13, also known as Prevenar13®, has the same components as PCV7, with the addition of addition of 6 serotypes; 1, 3, 5, 6A, 7F and 19A.

3.3. Impact of PCV on invasive pneumococcal disease (IPD)
Evidence from high income countries (HICs) that have adopted PCVs into their National Immunization Programmes (NIPs), have shown their use can prevent much morbidity and mortality (9, 10). Since the use of PCV7, countries that adopted the use of the vaccine reported significant declines in IPD. In a review by Feikin et al. (2013), reductions in invasive pneumococcal disease (IPD) up to 7 years post-PCV7 introduction were summarised. Feikin et al. (2013) included 21 datasets for their analysis from 4 geographical regions (North America, Europe Australasia, South America). In children <5 years of age, by the first year of use, IPD caused by vaccine-types (VTs) significantly decreased from a risk ratio of 0.34 to 0.14, further decreasing after 7 years of use to 0.03 (11). Focusing on pneumococcal meningitis, Htar et al. (2013) assessed the impact of PCV7 on pneumococcal meningitis. Seventeen articles were included in this review from two continents; Western Europe and North America. Comparing pre- and post-vaccination periods, reductions ranging from 59.2% in the US to 100% in Belgium in VT pneumococcal meningitis incidence were shown in vaccine-eligible children (12).

3.4. Herd immunity
The reductions in IPD after PCV introduction were not limited to vaccinated populations, extending to unvaccinated groups, namely older children and adults. Herd immunity, or herd protection/indirect effect of vaccination, is where unvaccinated populations are also protected from disease. For PCV, the reduction in NP carriage of VTs caused by vaccine use interrupts transmission to unvaccinated contacts (9, 13). The use of PCV resulted in reductions of pneumococcal disease burden in the non-immunised adult population, where the burden in terms of mortality, morbidity and hospitalisation costs of IPD and
Community-acquired pneumonia (CAP) is larger than in children (13). In terms of cost saving, Ray et al. (2006) estimated a 15-fold increase in cost-effectiveness when herd immunity was considered in US estimates (14). In terms of actual dollar value, McIntosh et al. (2005) estimated that the direct cost of per life year gained in the UK when herd immunity was considered equated to 4,360 pounds (15). Thus to get the maximum benefit of PCV use in a population, herd immunity needs to be considered.

Figure 1 is an excerpt from Feikin et al. (2013) and illustrates the impact of PCV7 on VT IPD in HICs up to 7 years post PCV7 introduction. From Figure 1, the greatest reductions are seen in children <5 years of age, as described in the previous section, but there are also reductions in adult age groups over this 7-year period (11).

**Figure 1**: Post-PCV7 introduction invasive pneumococcal disease caused by vaccine types summary rate ratios from random effects meta-analysis. Adapted from Feikin et al. (2013)

In a recent systematic review and meta-analysis by Shiri et al. (2017), IPD due to PCV7 serotypes in countries with mature PCV programmes has been all but eliminated due to herd immunity (16). They also predicted that the residual IPD caused by the additional 6 VTs in PCV13 will be halved after a mean period of about 3 years and nearly eradicated (90% reduction) after about 9 years of PCV13 use (16). However as highlighted by Goldblatt et al. (2017) using the Shiri et al. (2017) paper, most of the data for the indirect effect of PCV are from HICs with mature surveillance systems where PCV was introduced into the infant immunisation programmes soon after licensure (16, 17). Shiri et al. (2017) used data from only 4 LMICs, with none of them from Asia, raising questions of the applicability of the data on indirect effect of PCV to LMICs (16, 17).
The extent of herd immunity is dependent on coverage and serotype distribution in the population. This becomes particularly important when considering the impact of PCV in LMICs. Tsaban et al. (2017), stated that ‘profound indirect protection can only be achieved in populations with high (>70-80%) vaccine coverage’, where extensive sustained interruption of VT transmission occurs (13). The length of time since PCV introduction also plays a role; countries with mature PCV programmes seeing a greater vaccine impact in both child and adult populations (13). However in a comment piece by Klugman and Rodgers (2017), reported IPD reduction incidence in Europe is less than that seen in the US (18). Reasons for this are the variety in vaccine coverage rates in different countries and a wider diversity of pneumococcal serotypes causing disease (19). These reasons are a concern for LMICs, which see lower coverage of PCV and greater diversity of pneumococcal serotypes causing disease (16, 18). However, the ecology of pneumococcal transmission in LMICs may be very different to what is seen in HICs (16). Thus perhaps, different levels of vaccine coverage may be adequate to achieve herd immunity. Also different formulations of pneumococcal vaccines may have a greater impact on pneumococcal disease in LMIC settings. More research is required to assess the indirect affects of PCV in these settings.

3.5. Measuring direct and indirect effects of PCV on pneumococcal disease

Determining direct and indirect effects of PCV on pneumococcal disease are difficult because of the complex nature of pneumonia and also the low sensitivity in identifying pneumococcus as the cause of invasive disease (20). Pneumonia can be caused by range viruses, bacteria or fungi, with the progression of disease also affected by a range of socioeconomic factors. In addition, as the lungs are internal, the methods for diagnosis range from invasive, such as a lung puncture to observatory such as a chest x-ray to try and determine the aetiological agent (21). Furthermore, to definitively diagnose IPD, pneumococcus must be isolated from a sterile site such as blood, cerebrospinal fluid, ascetic fluid, etc. Pneumococcus is difficult to detect in the laboratory, and newer diagnostic tests are adding to our understanding of the burden of disease. In addition to the inherent difficulties of pneumococcal isolation from patient samples, LMICs have the added
disadvantages of problems with basic microbiological culture of organisms, leading to further reductions in culture sensitivity (20, 22). Due to the limitations of current diagnostic methods and pre-diagnostic antibiotic use, pneumonia aetiology studies often underestimate the true burden of pneumococcal disease (20, 23).

The cornerstone for support of PCV introduction and continued use in NIPs is IPD surveillance (22). The recommendation for accurate vaccine assessment is consistent surveillance for a minimum 2 years pre-vaccine and 5 years post-vaccine introduction (22). The reality for most LMICs is they are unable or do not have systems in place for robust disease surveillance to show herd immunity, making it very difficult to determine if they are getting the maximum benefit of PCV in their population (6). This becomes even more crucial when assessing the value of PCV in their immunisation programs. Thus for LMICs, new methods need to be assessed such as syndromic surveillance (22) or the use of a proxy such as VT carriage to determine the impact of PCV in their population.

3.6. PCV and pneumococcal carriage

Nasopharyngeal carriage is of great interest in terms of PCV impact as it is the natural biological niche for pneumococcus, other upper respiratory pathogens and commensals (8). Pneumococcal carriage is highest in children <5 years of age with peak carriage occurring between 3-11 months, making young children the primary source of pneumococcal transmission (24, 25).

There are many studies showing the impact of PCV on VT carriage. A study in Kilifi, Kenya by Hammitt et al. (2014) illustrated this effect succinctly. Figure 2 below shows the reductions in VT carriage following PCV10 introduction. In children <5 years of age, carriage prevalence of VTs significantly decreased from 34% to 13%, 2 years after PCV10 introduction into the population. In children and adults >5 years of age, there were also significant reductions in carriage of VTs in the same period from 8% to 4%. A net total reduction in VT carriage for all ages was observed. Based on the surveillance system used, coverage of PCV10 was 67% by the second year of PCV10 introduction (26).
Carriage is becoming frequently included in PCV evaluation studies, as PCV use has seen the decrease and/or near elimination of VTs from the nasopharynx. This has led to a decrease in transmission of VTs and subsequent reductions in pneumococcal disease (18). Therefore, the PCV effect of NP carriage in healthy carriers plays a major role in the control of pneumococcal disease and may be the key to the control of pneumococcal disease in countries that are unable to achieve PCV coverage in their entire population (18). However questions remain on how the NP carriage decline of VTs can be extrapolated to declines in VT IPD and the role of NVTs in IPD, as not all serotypes carried cause disease (6).

3.7. Carriage surveillance and herd immunity
Therefore, could carriage surveillance be used to estimate the coverage required to show herd immunity in these populations? This concept has been explored thus far by Loughlin et al. (2014) and Grant et al. (2016) in populations in Boston and American Indians respectively. Both populations had used PCV7 in their routine immunisation since 2000, so the herd immunity effects were only measured in the additional 6 serotypes covered by PCV13.
Loughlin et al. (2014) investigated the PCV13 coverage required to show herd immunity in nonimmune children (children either unvaccinated or under vaccinated) <5 years of age living in Boston, Massachusetts. PCV13 was introduced into the community in July 2010, replacing PCV7 with no catch-up campaign. Prior to the study, herd immunity effects were defined \textit{a priori} as a persistent, 50% or more decline in carriage of the additional 6 PCV13 types in nonimmune children, across comparable study intervals to account for potential seasonal variation in carriage. Vaccine uptake for the community was estimated between June 2010 and July 2012 using weekly, aggregate, stratified summaries of the number of children having received none or any number of PCV13 doses from the Boston Medical Center, Primary Care Center, where the study was held. However, during analysis of the data, the definition of herd immunity effects was changed to the time point when PCV13 carriage prevalence in the immune and nonimmune groups was equivalent. Figure 3 below shows that this carriage prevalence equivalence was achieved when community vaccine coverage was approximately 67%, lower than the \textit{a priori} definition, where the decline was seen at coverage at approximately 75% (27).
Figure 3: Comparison of the prevalence of PCV13 serotype carriage among immune and nonimmune children, plotted with the coverage of PCV13 in children <5 years of age in the community.

In a similar study, Grant et al. (2016) evaluated the direct and indirect impact of PCV13 in American Indian populations in the US relative to community vaccine coverage. For Grant et al. (2016), the coverage associated with a significant decline in PCV13 type carriage was defined as when pre-PCV13 type carriage prevalence no longer overlapped with the confidence intervals for the monthly carriage prevalence thereafter. Monthly PCV13 coverage was estimated from March 2010 through March 2012 among study participants and for the full community of children <5 years of age using electronic health records for vaccination status and the US Indian Health Service User Population for the community denominator. Herd immunity for the 6 additional serotypes was achieved 11 months after PCV13 introduction when community vaccine coverage was approximately 58%, as shown in Figure 4 below. In addition, a 60% reduction in PCV13-specific type carriage among children occurred simultaneously with an 89% decline in PCV13-specific type IPD rate among children in the same age group in community during the study period (28). Thus these data support the existence of a potential reliable
relationship between VT carriage reduction and its translation to VT IPD reduction in a community.

Figure 4: Three-month moving average of PCV13-specific type carriage prevalence among under-immunized Navajo and White Mountain Apache children <5 years and community PCV13 uptake and coverage

Red line = carriage prevalence; Histograms = PCV13 coverage; Histogram bar outlined in black identifies the month when significant reduction was achieved compared to the pre-PCV13 introduction period

From the Loughlin and the Grant studies, the prospect of using pneumococcal carriage surveillance to show effects of herd immunity may prove to be a viable option for LMICs considering the use of PCV in their NIPs. Using carriage surveillance bypasses the need for robust disease surveillance and can be implemented as the vaccine is being introduced into the population with little pre-vaccine introduction. However both of these studies use community samples not samples collected from children suffering from acute respiratory illness (ARI).

As pneumococcal carriage is a precursor to disease, it is assumed that if VT carriage declines, VT disease also declines. However there is not always a direct correlation between carriage serotypes and those isolated in invasive disease (29). Environmental factors, host factors and bacterial virulence all play a role in development of disease. What has been shown is the presence of higher carriage of pneumococcus in children with ARI or pneumonia (30). Thus those that suffer from respiratory illness are at a higher risk of disease to begin with. The isolation of pneumococcus from the NP of children hospitalised with ARI is not indicative of an aetiological cause of their admission but the lack of VTs in carriage would mean
these types are no longer circulating in the population to cause disease (20). This in conjunction with their admission to a health centre makes them an ideal population to conduct surveillance to monitor the effects of PCV in the population (20). Explicitly this is because they are at high risk of disease, they come from the population of interest and they congregate in a health facility for care.

### 3.8. Laos and PCV

Lao PDR is classified as a least developed country (LDC) and Laotians face many challenges when accessing health care, including distance, infrastructure, cost and staffing shortages. These factors as well as generally low levels of resources make disease surveillance very difficult even in the most developed parts of the country. Lao PDR, with the assistance of Gavi, introduced PCV13 into their Expanded Programme of Immunization (EPI) program in October 2013. The schedule was for PCV13 vaccination to be given to infants at 6, 10, 14 weeks and for those up to 12 months of age that came to the clinic, 3 doses were also offered.

Prior to the introduction of PCV13 into the NIP, Lao PDR had no reliable disease surveillance data on IPD or pneumonia. This included no IPD incidence estimates or pneumonia and no routine data on circulating serotypes for either disease or carriage, making it very difficult to not only measure the direct effects of PCV13 in the population but also the level of coverage to achieve herd immunity. The only study to consider IPD in Lao PDR was a hospital-based study of all patients with suspected community acquired septicaemia or meningitis from January 2003 to April 2009 (31). Of the pneumococcal culture positive samples from patients of all ages, 76% of serotypes were covered by PCV13 (31). The major limitations of the Moore et al. (2010) study were the low culture positives (0.21% and 5.4% positivity for haemocultures and cerebrospinal fluid respectively) in thousands of patients as part of larger evaluation of all-cause sepsis and/or meningitis. Thus this was not IPD surveillance and highlighted the issues with IPD surveillance when relying on culture. Using carriage surveillance could be a viable option to address the issues surrounding the paucity of robust disease surveillance to evaluate the performance of PCV13 in Lao PDR. Carriage surveillance could be used to not only observe the direct effects of PCV13 use over time but also to determine the point at which herd immunity occurs.


3.9. Aims
The primary aim of the study was to estimate the PCV13 coverage required to demonstrate maximal indirect effects of PCV13 (also known as herd immunity) among children aged 2-59 months, hospitalised with ARI or pneumonia from December 2013 to June 2016 in Lao PDR.

Secondary aims were to describe the epidemiology of cases and describe overall pneumococcal carriage, VT carriage and NVT carriage among vaccinated and undervaccinated cases.
4. Methods

4.1. Study Site
Administratively, Lao PDR is made up of 18 provinces, each consisting of districts containing numerous villages, with some more densely populated districts containing up to 70 villages. In terms of health care, villages are serviced by their designated local health centre or district hospital. If the level of care needed is not available at the health centre/district hospital, patients are referred on to the Provincial Hospital. If the level of care is not available at the provincial level then they are further referred onto the large Central Hospitals located in Vientiane Capital. Patients can also present directly at their health facility of choice without a referral. Universal free health care is currently not available in the country, but is being trialled in a few provinces. Routine immunisations are free to all eligible children.

The study was conducted at the Paediatric Department of Mahosot Hospital, the oldest hospital in Lao PDR, a tertiary referral central hospital servicing all ages and conditions. The majority of patients that seek care there are from Vientiane Capital as the hospital is located in the city centre. Patients seek care directly at the hospital or are referred from smaller district hospitals and health centres.

4.2. Design
PneuCAPTIVE was nested in a larger study on the aetiology of ARI conducted at Mahosot Hospital, in collaboration with the Lao-Oxford-Mahosot-Wellcome Trust-Research Unit (LOMWRU). PneuCAPTIVE was a prospective cohort study with patients recruited from all wards admitting children (general paediatric ward, paediatric infectious disease ward and neonatal/paediatric intensive care unit) at Mahosot Hospital from December 2013 to June 2017. Due to submission dates for this thesis the data presented are from December 2013 to July 2016 (inclusive).

4.3. Study Participants
Eligible cases were children aged 2-59 months admitted to Mahosot Hospital during the study period with ARI defined as a history of illness ≤14 days with fever
or documented tympanic fever (>38°C) and one or more of dyspnoea (as described by the patient and/or study doctor), cough, rhinitis and abnormal pulmonary auscultatory examination. Cases that did not satisfy the eligibility criteria were excluded.

Once the case was deemed eligible, study staff, using an information sheet as a guide, explained the study to the parent/guardian of the case for informed consent. The signed consent form was kept with the relevant case report form (CRF) (Appendix A) for each case. It was made clear to the parent that at any time, they could rescind consent, removing their child from the study. Enrolled cases were allocated a unique study identification number.

4.4. Data and swab collection

4.4.1. Data collection

Data were collected from eligible cases on a dedicated study CRF (Appendix A). Data of interest collected included, village, sex, ethnicity, vaccination status, clinical signs, symptoms and management. Other potential risk factors were also collected and these included if there was a smoker present in the house, how many children lived in the house under the age of 4 years, financially self-sufficient, practised hot bed after birth, breastfed and if the child attended kindergarten/day care.

4.4.2. Nasopharyngeal swab (NPS) sample collection

Study doctors, at time of recruitment, collected a single NP sample (NPS) from each case using a flocked NP paediatric swab. To sample the nasopharynx, the NPS was inserted into the child’s nostril and passed directly backwards, parallel to the base of the NP passage and kept in place for 5 seconds or rotated 180°, as shown in Figure 5 below.
**Figure 5:** Collecting a nasopharyngeal swab

The swab was then removed and immersed immediately into a 1.0ml cryovial containing sterile skim milk-tryptone-glucose-glycerol broth (STGGB) as per standard methods (32). The NPS was kept cool and transported to LOMWRU laboratories within 4 hours of collection, where it was snap frozen at \(-80^\circ\text{C}\).

**4.5. Lab methods**

Nasopharyngeal samples were shipped in batches on dry ice to the Pneumococcal Research Group laboratories in the Murdoch Childrens Research Institute (MCRI), Melbourne for microbiology and microarray analyses. At MCRI, aliquots of NPS had DNA extracted and the DNA eluent was used to detect the presence of pneumococcus in the samples using a quantitative PCR (qPCR) method targeting the \(\text{lytA}\) gene (33, 34). Samples positive for \(\text{lytA}\) or equivocal were grown on selective nutrient media to not only increase the quantity of DNA present but also to check if those equivocal have pneumococcus in the samples. Equivocals were defined as samples with at least 1 triplicate within the <40 cycling threshold (Ct) limit. Culture positive samples subsequently underwent DNA extraction and analysed using a molecular serotyping method, microarray (34). The microarray, for the purposes of this study, elucidated what serotypes were present in the sample in rank order of the most abundant. Samples that were culture negative but were positive for \(\text{lytA}\) if 2/3 triplicates gave a positive result (<40 Ct) were classified as positive for pneumococcal carriage (33, 34).
4.6. PCV vaccination status

PCV vaccination status was determined by written record from the parent-held mother child health (MCH) card or the immunisation register at the health centre. If the child’s record of vaccination was not found at the health centre and the MCH card was still not available, any child satisfying the criteria of being born 18 months prior to PCV13 introduction into their village, receiving their vaccinations in Thailand/Vietnam or their parents reported that the child had never received any vaccinations, were considered unvaccinated. Figure 6 below, details the decision-making flowchart of each case’s PCV vaccination status.

When the date of PCV vaccinations was not legible or illogical the following assumptions were made:

- Date of birth (DOB) was crosschecked with date of hepatitis B vaccination as this was given at, or shortly after birth to check if DOB was correct
- PCV dates were compared with oral polio vaccine and pentavalent vaccine dates, as these three vaccinations should have been given at the same time to check if the PCV dates were correct
- If PCV dates made logical sense, but the year was incorrect in one of the dates it was changed accordingly. For example, PCV doses were given approximately one month apart, so if the first dose was given in November 2013, the second December 2013 and the third in January 2013, then the year of the last dose was incorrect and logically January 2014.
Figure 6: Decision making flow chart of case's PCV vaccination status

MCH=mother child health; DOB=date of birth; PCV=pneumococcal conjugate vaccine

4.7. Sample size, data management and analysis

4.7.1. Data management

Data collected from each case using the dedicated CRF were first monitored for correctness and completeness before being entered into dedicated databases. Errors fixed on the CRF had the error struck through with a line and the correct information noted above with the initials of the person making the change and the date in brackets. Collected data were double data entered by study staff into a
Microsoft Access database (Microsoft, US). Data was cleaned by comparing the two entries and corrected in the data entry database with the discrepancy. Data were extracted from the database and imported into Stata 14 IC (Statcorp, US) where analysis was done.

4.7.2. Sample size
We expected there to be a 50% reduction in VT carriage in undervaccinated cases. To see this effect size, 400 cases were estimated to be required each year for 3 years. However, the NP carriage (case) population sample size was restricted to the number of patients being admitted with ARI or pneumonia over the 3-year study period. As we were capturing all ARI cases admitted to Mahosot hospital in the 2-59 month age group, we were sampling the entire population for our definition, thus we could not improve our recruitment methods for the study to attain the estimated annual 400 required.

4.7.3. Outcome variables

PCV vaccination status
The number of PCV13 doses required for a classification of being “vaccinated” depended on the child's age at the time of vaccination and is defined below in Table 1 (35). Age was calculated by the child's date of birth and the time when receiving the first dose of PCV13.

<table>
<thead>
<tr>
<th>Age</th>
<th>Vaccinated</th>
<th>Undervaccinated</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-11 months of age</td>
<td>2 PCV13 doses</td>
<td>0 or 1 PCV13 dose</td>
</tr>
<tr>
<td>≥ 12 months of age</td>
<td>1 PCV13 dose</td>
<td>0 doses PCV13</td>
</tr>
</tbody>
</table>

PCV13=13-valent pneumococcal conjugate vaccine

Pneumococcal Carriage
Pneumococcal carriage was described as total pneumococcal, VT and NVT carriage. All samples positive for pneumococcus by qPCR were counted in the total pneumococcal carriage group. Samples with PCV13 serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F) were classified as VT carriage samples. Samples
positive for serotypes not contained in PCV13 and non-typeables were classified as NVT carriage. Samples could contain both VT and NVT types.

Pneumonia

Definition of pneumonia was defined according to the 2005 WHO Integrated Management of Childhood Illness (IMCI) guidelines. Using the 2005 case definition for pneumonia, the presence of cough or difficulty breathing and tachypnoea (>50 breaths per minute for children aged 2-11 months; >40 breaths per minute for children aged 12-59 months) plus lower chest wall in-drawing or one or more general danger signs: inability to drink, persistent vomiting, convulsions, lethargy, unconsciousness, stridor when calm, severe malnutrition (as documented in the medical records), central cyanosis or the saturation of oxygen <90% in room air.

Potential risk factors

Potential risk factors and confounders for carriage rate were self-reported. The variables included in this analysis were if there was a smoker in the house, if there were children <5 years of age living in the house (including the number), if the household was financially self-sufficient, if the case was breastfed and if the child attended kindergarten/day care.

The variables were yes/no dichotomous responses, except for the number of children <5 years of age living in the house. For this variable, the presence of children <5 years of age was analysed and the number of children living in the house was grouped, with one group having 1-2 and the other greater than 2 children <5 years of age living in the house.

4.7.4. Analysis

In general, continuous variables were summarised using the number of observations, minimum and maximum, and the mean and standard deviation (or median and interquartile range for non-parametric data). Categorical variables were summarised using frequency counts and percentages.

For descriptive analysis of the cases, stratified by PCV13 vaccinated/undervaccinated, p-values using the chi-squared test and/or 95% CIs
were calculated for both vaccinated and undervaccinated cases to determine if there were any significant differences between the two groups.

To observe the direct and indirect effects of PCV coverage and monthly VT carriage rates of vaccinated/undervaccinated cases were plotted in rolling 7-month intervals, overlaid with the monthly PCV vaccination rate of all cases over the time of the study. Monthly pneumococcal carriage rates among cases was calculated by adding the number of cases carrying a VT, divided by the total number of cases carrying any pneumococcus. Monthly vaccination rate in cases was calculated by adding the number of cases deemed vaccinated as per the definition above, divided by the total number of cases enrolled for the month. Rolling intervals were used to smooth the data caused by the small numbers per month enrolled in the study. Rolling intervals were calculated by plotting the average proportion of carriage or vaccination for the month and the 3 months before and 3 months after each month. Thus producing 7 month rolling intervals for each month from December 2013 to July 2016. For both monthly carriage and vaccination rate in cases, the 95% confidence intervals were calculated. Reported carriage rates were not adjusted for potential confounders such as age and seasonality due to time constraints.

Using the unadjusted VT carriage rates, it was determined if indirect effects had occurred during the study. Maximal indirect effects were defined as the risk of VT carriage among undervaccinated children being equivalent to vaccinated children 2-59 months of age, i.e. a risk ratio of 1. This indirect effect was chosen because there is no pre-PCV data available to calculate indirect effects using more traditional methods comparing post-PCV carriage rates among undervaccinated groups with pre-PCV carriage rates.

4.8. Ethical considerations
Any identifying information collected on CRFs were kept in locked filing cabinets only accessible by study staff. This was also the case for electronic databases kept in password protected drives, accessible to study staff only. In addition, letters of approvals to visit and access data from Mahosot Hospital, District Hospitals and Health Centres were obtained from both the director of Mahosot Hospital and LOMWRU where the study is based.
Ethical approvals were granted by 5 ethical committees; National Ethics Committee for Health Research (No. 057/2013; Ministry of Health, Lao PDR), Oxford Tropical Research Ethics Committee (1050-13; LOMWRU), The Royal Children’s Hospital (33177B; MCRI), Ethics Research Committee (2013.30.LA0.2.EPI; WPRO), Human Research Ethics Committee (2015/491; ANU).
5. Results
As the study is ongoing, data shown was until the end of July 2016.

5.1. Characteristics of cases
In total 800 cases were recruited from December 2013 until July 2016. Of those 800, 1 case was ineligible, 6 cases were missing data and 10 were outside of the 2-59 month age limits. Thus 783 cases were included in the final analysis (Figure 7).

**Figure 7:** Recruitment flowchart of study up to July 2016

From December 2013 to July 2016, approximately 30 cases were enrolled each month with a large increase of cases during June-August 2014 (Figure 8).
The demographics of cases, stratified by vaccination status can be seen in Table 2 below. The median age of vaccinated cases was significantly younger than undervaccinated cases. Undervaccinated cases were more likely to be from the province, not breastfed and less likely to attend kindergarten/day care. The cases with unknown vaccination status were a mix of Vientiane Capital and Province children. They were of similar age to the vaccinated cases and generally the characteristics do not differ greatly from the known vaccination status children, except for the attendance at kindergarten/day care and their breastfed status.

**Table 2:** Characteristics of ARI cases admitted to Mahosot Hospital, Vientiane Capital, Lao PDR from December 2013 to July 2016, stratified by vaccination status

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total (n=783)</th>
<th>Vaccinated (n=331)</th>
<th>Undervaccinated (n=351)</th>
<th>Unknown (n=101)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age in months (IQR)</td>
<td>14 (8-24)</td>
<td>12 (8-17)</td>
<td>21 (8-33)</td>
<td>10 (7-18)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>446 (57)</td>
<td>197 (60)</td>
<td>193 (55)</td>
<td>56 (55)</td>
<td>0.46</td>
</tr>
<tr>
<td>Pneumonia, n (%)</td>
<td>416 (53)</td>
<td>172 (52)</td>
<td>188 (54)</td>
<td>56 (55)</td>
<td>0.81</td>
</tr>
<tr>
<td>VC, n (%)</td>
<td>646 (83)</td>
<td>302 (91)</td>
<td>290 (83)</td>
<td>54 (53)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Province, n (%)</td>
<td>137 (17)</td>
<td>29 (9)</td>
<td>61 (17)</td>
<td>46 (47)</td>
<td></td>
</tr>
<tr>
<td>Smoker in the house, n (%)</td>
<td>307 (39)</td>
<td>121 (37)</td>
<td>141 (40)</td>
<td>45 (45)</td>
<td>0.06</td>
</tr>
</tbody>
</table>
5.2. Pneumococcal carriage

Carriage samples were available for all 783 of cases included in the final analysis. Table 3 below reports the total, VT, NVT carriage in cases, stratified by vaccination status. The proportion of total pneumococcal carriage was 40%, with no significant difference in vaccinated and undervaccinated cases (p=0.35). Overall vaccinated cases were less likely to carry a VT (p<0.001) and more likely to carry a NVT than undervaccinated cases (p=0.006). The unknown vaccination cases had similar overall carriage, but when comparing VT and NVT, the proportion carried was approximately equal.

Table 3: Pneumococcal carriage in ARI cases admitted to Mahosot Hospital, Vientiane Capital, Lao PDR from December 2013 to July 2016, stratified by vaccination status

<table>
<thead>
<tr>
<th>Pneumococcal Carriage</th>
<th>Total (n=783)</th>
<th>Vaccinated (n=331)</th>
<th>Undervaccinated (n=351)</th>
<th>Unknown (n=101)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total, n (%)*</td>
<td>313 (40)</td>
<td>126 (38)</td>
<td>150 (43)</td>
<td>37 (37)</td>
<td>0.35</td>
</tr>
<tr>
<td>VT, n (%)**</td>
<td>141 (18)</td>
<td>45 (14)</td>
<td>78 (22)</td>
<td>18 (18)</td>
<td>0.001*</td>
</tr>
<tr>
<td>NVT, n (%)**</td>
<td>153 (20)</td>
<td>78 (24)</td>
<td>59 (17)</td>
<td>16 (16)</td>
<td>0.006*</td>
</tr>
</tbody>
</table>

VT = Vaccine type; NVT = non-vaccine type

*42 pneumococcal carriage positive samples did not have a serotype or non-typeable identified

**Samples can contain multiple serotypes; both VT and NVT

5.3. Carriage of VTs and PCV13 coverage

Figure 9 shows the proportion of children carrying a VT, stratified by their vaccination status, overlaid with the vaccination rate of cases during the study period. In vaccinated cases, VT carriage declined, whilst VT carriage remained relatively unchanged in undervaccinated cases.
Figure 9: PCV13 vaccine serotype carriage in vaccinated and undervaccinated cases, by case PCV13 vaccination status, using 7-month rolling intervals.

The red line is the vaccination rate; blue lines are vaccine type (VT) carriage. The shaded areas are the 95% CI surrounding carriage and vaccination rate.
Using the unadjusted VT carriage rates in vaccinated and unvaccinated cases, the risk ratio of VT carriage between the two groups was estimated. The indirect effects have not yet been seen as the risk ratio of VT carriage in the two groups is not equivalent, i.e. does not equal 1.

**Figure 10:** Rate ratio of risk of VT carriage in vaccinated and undervaccinated cases*

*July 2016 data not included in risk ratio analysis
6. Discussion

This is the first study to assess herd immunity using carriage surveillance. The observed magnitude of indirect effects due to PCV is dependent on a range of factors such as the immunisation strategy, coverage rate, the pneumococcal population epidemiology and the quality of surveillance methods to detect these effects (36). This study established robust surveillance at Mahosot Hospital, allowing for indirect effects to be observed in this population.

As per WHO recommendations, Lao PDR uses a 3+0 schedule. This schedule has been shown to have indirect effects on VT IPD when introduced nationally (37), supporting WHO recommendations for the advocacy of these lower dose schedules. However, immunisation coverage and the inclusion of a catch-up campaign play larger roles in terms of producing indirect effects. Loo et al. (2014) found only 2 studies of 21 that showed no evidence of VT IPD reductions in unimmunised groups in their systematic analysis of indirect effects of dosing schedules on pneumococcal disease and colonisation. Both of these studies came from countries that did not employ catch-up campaigns and had vaccine coverage levels that may have been inadequate to demonstrate indirect effects (37). The method by which a catch-up campaign speeds up the process of indirect effects due to PCV is through reduction of NP carriage of VTs in toddlers who are the major reservoir for VT transmission to unvaccinated and undervaccinated groups. Even though Lao PDR did include a catch-up campaign, allowing for PCV13 to be given to children up to 12 months of age, this was a passive system and relied on children being brought to the health centre who had previously completed their vaccinations. Thus uptake would have been minimal in this older age group, allowing for continual circulation of VTs in the community. The data presented here are only up to 2.5 years post-PCV introduction. If VT carriage was to be interrupted in the community it would require vaccination of 5 birth cohorts, taking at least 4 years to achieve, delaying indirect effects, which would have been created rapidly by an effective catch-up campaign.

The vaccination rate in cases increased over time to reach 70% by July 2016. Based on the studies by Grant et al. (2016) and Loughlin et al. (2014), the coverage
required to see herd immunity effects based on VT carriage in the <5 year old population sat at approximately 60-70% (27, 28). With the case vaccination rate reaching the 60-70% mark, herd immunity was not expected as yet because this was the case PCV13 vaccination rate. The case vaccination rate is not an accurate representation of the true PCV13 coverage in the population. Firstly, the vaccination rate is based on cases that have been admitted to hospital and as cases are young, they are not representative of the community coverage for total <5 year olds. Secondly, even though PCV13 was introduced into routine immunisation in October 2013, roll out of PCV13 has been gradual, with some of the further provinces not administering PCV13 until as late as 2015 (pers. comm. Provincial Health centre staff). This anecdotal evidence is supported by the undervaccinated cases significantly more likely to come from the provinces. This means that in the wider community, PCV13 has only been in use for over a year, contributing to the lack of herd immunity effects. Thus the vaccination rate in cases is likely an overestimation of the true coverage in the community.

Mature PCV programmes see a greater impact of PCV than new adopters (13). Previous studies by Loughlin et al. (2014) and Grant et al. (2016) were undertaken in settings where PCV7 had been in use for many years, so therefore the coverage they estimated for PCV herd immunity was based on the additional 6 serotypes included in PCV13, not all PCV13 VTs. As the case vaccination rate is likely an overestimation of the true community coverage, other methods of vaccine coverage were considered. A contact serosurvey was conducted and simultaneously data was collected from immunisation registers held at health centres and district hospitals around the country. For the contact serosurvey, contacts of cases were identified and their vaccination status was determined either using MCH cards or health centre immunisation registry data. In addition a subset of contacts 12-59 months of age had a blood sample collected to determine their PCV vaccination status. For the immunisation registry data, each village keeps a record of vaccination at their assigned health centre or district hospital. This data is kept in a line list format, allowing each child to be counted individually. Amalgamated with population data for each, village, the monthly vaccination rate for each village could be estimated. Immunisation registry data was collected dependent on the village the case resided in. The theory behind both methods was
that carriage was affected most by children they have contact with. Based on preliminary data from the contact serosurvey (data not shown), the vaccine coverage rate did not correspond to the preliminary data (data not shown) from the health centre immunisation registry. Therefore, it was decided the contact serosurvey did not provide an accurate estimate of community coverage and was suspended. Data collection and analysis will be pursued for the health centre immunisation registries as the primary method for estimating community coverage in the final analysis.

Vaccinated cases had significantly lower carriage of VTs than undervaccinated cases, but total pneumococcal carriage rates did not change for both groups. Pneumococcal carriage rates are affected by age, seasonality, risk factors and the presence of NVTs. Carriage rates are associated with age, with peak carriage rates in toddlers and wane over time (38-40). As cases of ARI admitted to hospital are in younger age groups, most of these will be vaccinated in comparison to the older children in the early years of PCV introduction. Over time, the percentage of older children entering the surveillance who are vaccinated will increase as multiple birth cohorts are PCV13 vaccinated. In addition, the decline in VT in early years post PCV may purely be due to the fact older children have less carriage and subsequently less likely to carry VTs. Therefore carriage rates need to be adjusted for age. Carriage is also affected by season with winter in temperate climates and dry season in tropical climates seeing peaks in pneumococcal carriage (41, 42). However, risk factors, such as age and seasonality were not accounted for in these results. For the final analysis risk factors will be identified and accounted for in both carriage and vaccination rates in cases. In addition to age, season and PCV coverage, pneumococcal carriage is also influenced by many factors such as exclusive breast-feeding, crowding, socio-demographic information, caregiver education level, smokers in household and kindergarten attendance to name a few. However, as total pneumococcal carriage did not change over the study period, these risk factors may not have changed over time and if not accounted for will not significantly change the results. Nonetheless potential confounders will be assessed in the final analysis, but due to time constraints it was not possible to include these adjustments in these results.
Replacement carriage, or serotype replacement has been seen in all populations using PCVs (43). Serotype replacement is the increase of NVTs among asymptomatic carriers following reductions in VTs and to a lesser extent invasive disease caused by NVTs (43). The potential reasons behind this increase in NVT carriage after use of PCV in a population could be due to the phenomenon of unmasking, where the reduction of VTs has made it easier to detect NVTs or the acquisition of NVTs after VTs are removed from the nasopharynx (43).

Surveillance of NVTs is important for a number of reasons, namely monitoring of NVT IPD, increasing understanding of serotype composition in a population and design of next generation PCVs. In a systematic review and meta-analysis by Balsells et al. (2017), prior to the introduction of higher valency PCVs in North America and Europe, approximately half of childhood IPD cases were due to serotypes not incorporated in current PCV formulations (44). Asia, where the largest burden of disease lies also has a great diversity of serotypes (18), which has repercussions in how effective current formulation PCVs will be. Development of next generation PCVs will require more data from LMICs regarding NVTs to create vaccine formulations that will afford greater protection.

In conclusion, less than 3 years after PCV13 introduction, herd immunity effects of PCV13 based on NP carriage surveillance in ARI cases has not yet been observed in Lao PDR. This is not unexpected, as PCV13 coverage in the community of Lao PDR is likely too low to protect the undervaccinated population. This is because the data are only up to 2.5 years post-PCV introduction. However direct effects have manifested in vaccinated cases, shown by the reduction in VTs, with no change in total pneumococcal carriage rates for all cases. The data presented has not been adjusted for confounders. Data on potential confounders have been collected and will be included in the final analysis. The data presented here shows the applicability of NP surveillance in ARI cases as a method to determine when a PCV program has achieved herd immunity effects for their population. This is crucial for LMICs like Lao PDR, who are unable to rely on typical methods of PCV evaluation. The method presented here shows that a robust surveillance system can be established quickly in a LMIC setting. These data will strengthen the use of this method in other LMICs in the region considering using PCV in their population. Lao PDR is expected to transition to a domestic funding model for their NIP and
data such as this will provide evidence to both Ministry of Health policymakers and external funders of the effectiveness of PCV13 in the program and support its continual use in the program.
7. **Recommendations:**

- Continuation of NP carriage surveillance should continue to determine the coverage required to see indirect effects. The primary aim of the study has not been achieved as yet. Once indirect effects have been observed, the corresponding coverage will set a minimum benchmark for NIP Laos to reach in order to get the maximal benefit from PCV for their population.

- Estimation of coverage was part of the primary aim for this study. During the time of the study, PCV13 coverage was not able to be included in the EPI coverage survey. In addition to calculating vaccination rates in cases, vaccine coverage was also assessed using a contact serosurvey and raw data collected from the village immunisation registers held at health centres and district hospitals throughout the country. Based on preliminary analysis, the contact serosurvey was not a good measure to estimate vaccine coverage. Therefore, it is recommended to continue collection of immunisation data from health centres and district hospitals and to use this method to estimate vaccine coverage.

- Surveillance of serotype carriage should continue to monitor the situation with NVTs. Not all serotypes cause disease but the elimination of VTs from carriage creates an opportunity for other serotypes to occupy the vacated space and potentially cause IPD. These replacement serotypes are important, as it will advise the future PCV formulations or the design of a vaccine that targets a shared antigen irrespective of serotype.

- There should be consideration given to methods to assess changes in IPD in adults. The greatest impact of PCV is in the unvaccinated adult population. Generally, indirect effects in adults are estimated using surveillance of IPD and CAP pre- and post-vaccine introduction. For Laos this is not possible, without surveillance in place prior to vaccine introduction. A possible method could be a case-control study with the vaccination status of children living with adult IPD cases being investigated. This would be difficult as the vaccine has now been in use since October 2013, with PCV effects confounding the results. In addition, pneumococcal carriage analysis is conducted in Melbourne and timely reporting of IPD serotype would not
be possible. In the current set up, assessment of IPD in adults would not be feasible.
8. References


Chapter 2 – PneCAPTIVE


9. Appendices

A. Case CRF

<table>
<thead>
<tr>
<th>ARIVI Pilot Phase Study CRF</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>I. Patient details</strong></td>
</tr>
</tbody>
</table>
| Study ID: ARIVI-1 || 1 1 1 1 1 | First Name: ........................................
| LPC: 1 1 1 1 1 1 1 1 1 | Family Name: ........................................
| Date of birth: day / month / year | Gender: □ Male □ Female |
| Home Village: ............... | District: ............... | Province: ............... |
| Ward: ......................... | Phone number 1: ............... |
| Occupation: ................... | Phone number 2: ............... |
| Ethnicity: □ Lao Loun □ Hmong □ Khmu □ Prai □ Ma Kong □ Alak □ Ngae □ Taieng □ Dak Kang □ Other (specify): ............... |

<table>
<thead>
<tr>
<th><strong>II. Professional Environment</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Mother’s highest form of education: □ Primary □ Junior High School □ High School □ University □ None □ Unknown</td>
</tr>
<tr>
<td>Does the subject write and read Lao?: □ Yes □ No</td>
</tr>
<tr>
<td>Does the subject currently study?: □ Yes □ No</td>
</tr>
<tr>
<td>If yes, in which establishment?: □ Nursery school □ Primary Education □ Junior High School □ High School □ University</td>
</tr>
<tr>
<td>Does the subject currently work?: □ Yes □ No</td>
</tr>
<tr>
<td>If he/she works, Does the work principally take place in a confined space?: □ Yes □ No</td>
</tr>
<tr>
<td>Does the work principally take place outdoor?: □ Yes □ No</td>
</tr>
<tr>
<td>Does the work involve contact with children?: □ Yes □ No</td>
</tr>
<tr>
<td>Does the work involve contact with persons who are ill?: □ Yes □ No</td>
</tr>
<tr>
<td>Date of admission: .../.../...</td>
</tr>
<tr>
<td>Admission diagnosis: □ Pneumonia □ Lobar pneumonia □ Bronchitis □ Acute respiratory infection □ Acute lower respiratory infection □ Chest infection □ Bronchiolitis □ Asthma □ Other (specify): ...............</td>
</tr>
<tr>
<td>Has the patient been admitted to Hospital (anywhere) for a similar disease in the past?: □ Yes □ No</td>
</tr>
<tr>
<td>If yes, how long ago (in weeks, months, years)?</td>
</tr>
<tr>
<td>How many times has the patient been admitted for a similar disease in his entire life?: ... time</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>III. Household environment</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Does anyone smoke in the house?: □ Yes □ No □ Unknown</td>
</tr>
<tr>
<td>Lives alone: □ Yes □ No □ Unknown</td>
</tr>
<tr>
<td>0-4 years old: ... persons</td>
</tr>
<tr>
<td>5-18 years old: ... persons</td>
</tr>
<tr>
<td>19-44 years old: ... persons</td>
</tr>
<tr>
<td>45-64 years old: ... persons</td>
</tr>
<tr>
<td>65 years old and more: ... persons</td>
</tr>
<tr>
<td>Number rooms in the house for sleeping purpose: ... rooms</td>
</tr>
</tbody>
</table>

Page 1 of 6
### Chapter 2 - PneCAPTIVE

<table>
<thead>
<tr>
<th>Source of drinking water</th>
</tr>
</thead>
<tbody>
<tr>
<td>Piped drinking water in residence</td>
</tr>
<tr>
<td>Water from unprotected well</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Type of toilet facility</th>
</tr>
</thead>
<tbody>
<tr>
<td>No toilet</td>
</tr>
<tr>
<td>Traditional pit latrine</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Source of cooking</th>
</tr>
</thead>
<tbody>
<tr>
<td>Electricity</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Where is the cooking place located?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inside living/sleeping room</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Do you make fire inside the house?</th>
</tr>
</thead>
<tbody>
<tr>
<td>yes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>If Yes, Does it have a chimney?</th>
</tr>
</thead>
<tbody>
<tr>
<td>yes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Are any of these items present in the household?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Electricity</td>
</tr>
<tr>
<td>Telephone or mobile phone</td>
</tr>
<tr>
<td>Bicycle</td>
</tr>
<tr>
<td>Electric Stove</td>
</tr>
<tr>
<td>Air Conditioner</td>
</tr>
<tr>
<td>Livestock</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>What is the family income per months?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unknown</td>
</tr>
<tr>
<td>1100000 - 3000000 Kip</td>
</tr>
<tr>
<td>&gt;5100000 Kip</td>
</tr>
<tr>
<td>Yes</td>
</tr>
</tbody>
</table>

### IV. Health status

<table>
<thead>
<tr>
<th>How would the subject describe his/her health over the past twelve months?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very good</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Does the subject suffer or have suffered from a chronic disease?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>If yes, specify</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Is he/she followed up for this/these chronic disease(s)?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Medical treatment associated to this/these disease(s)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>For women: is she pregnant?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>If yes, for how many weeks?</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Did the subject go to Thailand to seek health care over the past twelve months?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Is the subject a smoker?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
</tr>
</tbody>
</table>

| If Yes, how many cigarettes per day: | How many year does the subject smoke: |

<table>
<thead>
<tr>
<th>Does the subject drink alcohol?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
</tr>
</tbody>
</table>

| If yes, how many glasses per day: |

### V. Vaccination
Chapter 2 – PneCAPTIVE

### IV. History

<table>
<thead>
<tr>
<th>Question</th>
<th>Options</th>
<th>Yes</th>
<th>No</th>
<th>Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>Has the participant received any PCV13?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Was the MCH book seen?</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Where vaccinated:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>If Yes, Date PCV13 1 given</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Date PCV13 2 given</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Date PCV13 3 given</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>If patient child, was s/he born by</td>
<td>Vaginal delivery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caesarean</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Did you breastfeed your baby?</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>If yes (or still breastfeeding) how long did you breastfeed for?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

For children < 6 months, did you practice hot bed?                      | Yes                      |     |    |         |
| No                                                                       |                          |     |    |         |
| Unknown                                                                  |                          |     |    |         |
| If yes, how many weeks?                                                 |                          |     |    |         |

Since the same time yesterday approximately how many people kissed your child (ie last 24 hours)? | | | | Unknown |
| How many were less than 5 years old?                                    |                          |     |    |         |
| Unknown                                                                  |                          |     |    |         |

Does this child go to kindergarten/day-care?                             | Yes                      |     |    |         |
| No                                                                       |                          |     |    |         |
| Unknown                                                                  |                          |     |    |         |
| If yes, how many hours per week?                                        |                          |     |    |         |

Are the patient’s routine childhood immunisations up to date for age?   | Yes up to date           |     |    |         |
| Incomplete                                                              |                          |     |    |         |
| Never vaccinated                                                        |                          |     |    |         |
| Unknown                                                                  |                          |     |    |         |

Is the subject been vaccinated against flu in last year?                 | Yes                      |     |    |         |
| No                                                                       |                          |     |    |         |
| Unknown                                                                  |                          |     |    |         |
| If Yes, season 2011-2012?                                               | Yes                      |     |    |         |
| No                                                                       |                          |     |    |         |
| Unknown                                                                  |                          |     |    |         |
| If Yes, season 2010-2011?                                               | Yes                      |     |    |         |
| No                                                                       |                          |     |    |         |
| Unknown                                                                  |                          |     |    |         |
| If Yes, season 2009-2010?                                               | Yes                      |     |    |         |
| No                                                                       |                          |     |    |         |
| Unknown                                                                  |                          |     |    |         |

### VI. Signs and symptoms on admission

<table>
<thead>
<tr>
<th>Maximum number of day ill</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Admission weight</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birth weight</td>
<td></td>
<td></td>
<td>g</td>
</tr>
<tr>
<td>Height (cm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temperature</td>
<td></td>
<td></td>
<td>°C</td>
</tr>
<tr>
<td>Method</td>
<td>axilla</td>
<td>rectum</td>
<td></td>
</tr>
<tr>
<td>Respiratory rate</td>
<td></td>
<td></td>
<td>breaths per minute</td>
</tr>
<tr>
<td>Heart rate</td>
<td></td>
<td></td>
<td>beats per minute</td>
</tr>
<tr>
<td>Oxygen saturation</td>
<td></td>
<td>% in room air</td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>yes</td>
<td>no</td>
<td>unknown</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>yes</td>
<td>no</td>
<td>unknown</td>
</tr>
<tr>
<td>Conjunctival suffusion</td>
<td>yes</td>
<td>no</td>
<td>unknown</td>
</tr>
<tr>
<td>Headache</td>
<td>yes</td>
<td>no</td>
<td>unknown</td>
</tr>
<tr>
<td>Abnormal pulmonary auscultation</td>
<td>yes</td>
<td>no</td>
<td>unknown</td>
</tr>
<tr>
<td>Difficulty breathing</td>
<td>yes</td>
<td>no</td>
<td>unknown</td>
</tr>
<tr>
<td>Chest pain</td>
<td>yes</td>
<td>no</td>
<td>unknown</td>
</tr>
<tr>
<td>Cough</td>
<td>yes</td>
<td>no</td>
<td>unknown</td>
</tr>
<tr>
<td>Rashes</td>
<td>yes</td>
<td>no</td>
<td>unknown</td>
</tr>
<tr>
<td>Sputum</td>
<td>yes</td>
<td>no</td>
<td>unknown</td>
</tr>
<tr>
<td>Respiratory distress</td>
<td>yes</td>
<td>no</td>
<td>unknown</td>
</tr>
<tr>
<td>Cyanosis</td>
<td>yes</td>
<td>no</td>
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</tr>
<tr>
<td>Runny nose</td>
<td>yes</td>
<td>no</td>
<td>unknown</td>
</tr>
<tr>
<td>Sore throat</td>
<td>yes</td>
<td>no</td>
<td>unknown</td>
</tr>
<tr>
<td>Wheeze on admission</td>
<td>yes</td>
<td>no</td>
<td>unknown</td>
</tr>
<tr>
<td>Wheeze other days</td>
<td>yes</td>
<td>no</td>
<td>unknown</td>
</tr>
<tr>
<td>Myalgia</td>
<td>yes</td>
<td>no</td>
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</tr>
<tr>
<td>Chest indrawing</td>
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<td>no</td>
<td>unknown</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>yes</td>
<td>no</td>
<td>unknown</td>
</tr>
<tr>
<td>Stridor when calm</td>
<td>yes</td>
<td>no</td>
<td>unknown</td>
</tr>
<tr>
<td>Back pain</td>
<td>yes</td>
<td>no</td>
<td>unknown</td>
</tr>
<tr>
<td>Nasal flaring</td>
<td>yes</td>
<td>no</td>
<td>unknown</td>
</tr>
<tr>
<td>Dysuria</td>
<td>yes</td>
<td>no</td>
<td>unknown</td>
</tr>
<tr>
<td>Grunting</td>
<td>yes</td>
<td>no</td>
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</tr>
<tr>
<td>Diarrhea</td>
<td>yes</td>
<td>no</td>
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<tr>
<td>Convulsions</td>
<td>yes</td>
<td>no</td>
<td>unknown</td>
</tr>
</tbody>
</table>
### Chapter 2 – PneCAPTIVE

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Yes</th>
<th>No</th>
<th>Unknown</th>
<th>Prostration/lethargy</th>
<th>Yes</th>
<th>No</th>
<th>Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constipation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inability to drink</td>
<td>Yes</td>
<td>No</td>
<td>Unknown</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Is there anybody with fever in your home within the last two weeks?  

<table>
<thead>
<tr>
<th>Activity</th>
<th>Yes</th>
<th>No</th>
<th>Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>Did you visit rice field two weeks ago?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Did you visit forest two weeks ago?</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Why do you think you are sick?  

<table>
<thead>
<tr>
<th>Previous medical consultation</th>
<th>Yes</th>
<th>No</th>
<th>Unknown</th>
</tr>
</thead>
</table>

Antibiotic(s) taken in last week  

<table>
<thead>
<tr>
<th>Other drug or herbal medicines taken during illness</th>
<th>Yes</th>
<th>No</th>
<th>Unknown</th>
</tr>
</thead>
</table>

### VII. Comorbidities (please select all that apply and specify details)

- Disability  
- Concurrent infection  
- Malnutrition  
- Congenital heart disease  
- Chronic lung disease  
- Cancer  
- Asthma  
- Diabetes  
- Prematurity  
- Low birth weight (<2500g)  
- Unknown  
- Don’t have  
- Other (please specify)

### VIII. Drug(s) used at hospital

<table>
<thead>
<tr>
<th>Name</th>
<th>Dose</th>
<th>Freq</th>
<th>Duration (days)</th>
<th>Adherence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Specific investigations  

<table>
<thead>
<tr>
<th>Required hospitalization</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>If Yes, how many days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>If not admitted, Why?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Required Follow-up  

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>If Yes, motivation</td>
<td></td>
</tr>
<tr>
<td>If Yes, how many days</td>
<td></td>
</tr>
<tr>
<td>If no, motivation</td>
<td></td>
</tr>
</tbody>
</table>

**Which of the following best describes the taking of the NP swab (tick one):**

- Swab inserted at least half measured distance from earlobe to anterior nostril and rotated, leaving the swab in place for 5 seconds
- Swab inserted into the nose for the length of the tip and rotated, leaving the swab in place for 5 seconds
- Swab inserted partially and briefly into the nose; swab of skin just below nose with discharge visible
- Swab of skin just below nose with no discharge visible
- Nose blowing swab (swab of nasal discharge on tissue used to blow child’s nose)

### IX. Investigations

<table>
<thead>
<tr>
<th>Was blood taken for CRP?</th>
<th>Yes</th>
<th>No</th>
<th>Unknown</th>
<th>Result</th>
</tr>
</thead>
</table>
Chapter 2 – PneCAPTIVE

<table>
<thead>
<tr>
<th>Chest X-ray as read by the treating doctor/radiologist (tick one)</th>
</tr>
</thead>
</table>
| ☐ not done | ☐ Done 
| ☐ No abnormality | X Ray code |
| Consolidation: | ☐ Alveolar | ☐ Interstitial | ☐ Not Stated |
| ☐ Pleural effusion |
| Other abnormality (please specify) |

<table>
<thead>
<tr>
<th>Organism code</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. pneumoniae</td>
</tr>
<tr>
<td>S. pyogenes</td>
</tr>
<tr>
<td>S. aureus</td>
</tr>
<tr>
<td>H. influenzae</td>
</tr>
<tr>
<td>H. influenzae type b</td>
</tr>
<tr>
<td>H. influenzae non-typeable</td>
</tr>
<tr>
<td>K. pneumoniae</td>
</tr>
<tr>
<td>P. aeruginosa</td>
</tr>
<tr>
<td>M. tuberculosis</td>
</tr>
<tr>
<td>Other organism</td>
</tr>
</tbody>
</table>

| Lung Aspiration | ☐ Done 
| No growth | ☐ Positive Organism code |
|☐ Not done |

| Pleural Aspiration | ☐ Done 
| No growth | ☐ Positive Organism code |
|☐ Not done |

| Blood Culture | ☐ Done 
| No growth | ☐ Positive Organism code |
|☐ Not done |

<table>
<thead>
<tr>
<th>Sample collection:</th>
<th>Date of sample collection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasopharyngeal swab No. for LPC</td>
<td>☐ Not done</td>
</tr>
<tr>
<td>Nasopharyngeal swab No. for ARIVI</td>
<td>☐ Not done</td>
</tr>
<tr>
<td>Nasal Swab</td>
<td>☐ Not done</td>
</tr>
<tr>
<td>Throat Swab</td>
<td>☐ Not done</td>
</tr>
<tr>
<td>Sputum</td>
<td>☐ Not done</td>
</tr>
<tr>
<td>Urine</td>
<td>☐ Not done</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>NCLE result</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>X. Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>☐ None present</td>
</tr>
<tr>
<td>☐ Lung abscess</td>
</tr>
<tr>
<td>Other complications (please specify)</td>
</tr>
</tbody>
</table>

| Admitted to ICU | ☐ yes | ☐ no | Date admitted to ICU: |
| Discharge date from ICU: |
| Ventilated | ☐ yes | ☐ no | ☐ not stated | CPAP | ☐ yes | ☐ no | ☐ not stated |

<table>
<thead>
<tr>
<th>XI. Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>☐ Oxygen used</td>
</tr>
<tr>
<td>Date oxygen was started</td>
</tr>
</tbody>
</table>

Page 5 of 6
## XII. Outcome

| Date of discharge | _ _ _ / _ _ _ / _ _ _ |
| Diagnosis of discharge: |
| ☐ Pneumonia | ☐ Lobar pneumonia | ☐ Bronchitis | ☐ Acute respiratory infection |
| ☐ Acute lower respiratory infection | ☐ Chest infection | ☐ Bronchiolitis | ☐ Asthma |
| ☐ Other (specify) | | | |
| ☐ Alive | ☐ Discharged home to die | ☐ Dead | ☐ Unknown |

If dead, link with the disease: ☐ Yes ☐ No

If Yes, specify ____________________________________________________________

Persistent signs of severe illness when discharged home (Tick this if any of the following are documented on the day of discharge or the day before. Please tick any categories that apply)

☐ A note that the child was discharged against medical advice
☐ A note that the child remained unwell/in severe condition
☐ Evidence of severe or very severe pneumonia at time of discharge
  ☐ SpO2 < 90% or still on O2 at time of discharge
  ☐ Cyanosis
  ☐ Chest indrawing
  ☐ Severe respiratory distress
  ☐ Unable to drink
☐ Lethargy or unconscious
☐ Family decide to transfer to another hospital

## XIII. Drug(s) Prescription

<table>
<thead>
<tr>
<th>Name</th>
<th>Dose</th>
<th>Freq</th>
<th>Duration (days)</th>
<th>Compliance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>_ _ _</td>
<td>☐ Yes ☐ No</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>_ _ _</td>
<td>☐ Yes ☐ No</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>_ _ _</td>
<td>☐ Yes ☐ No</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>_ _ _</td>
<td>☐ Yes ☐ No</td>
</tr>
</tbody>
</table>

## XIV. Follow-up

Follow-up of the subject at D15
If relapse, action: _________________________________________________________

If dead, link with the disease: ☐ Yes ☐ No

☐ Recovery ☐ Relapse ☐ Death

## XV. Signatures

<table>
<thead>
<tr>
<th>Study staff</th>
<th>Date _ _ _ / _ _ _ / _ _ _</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monitor</td>
<td>Date _ _ _ / _ _ _ / _ _ _</td>
</tr>
</tbody>
</table>
B. Lay poster – PneuCAPTIVE Study

Dear Doctors and Nurses of the Mahosot Paediatric Wards,

Why are we doing this study?

As you know, since December 2015 we have been doing a study in the paediatric wards of Mahosot Hospital to see what germs are carried in the nose of children with respiratory infections.

In 2006 (1), the National Immunization Programme (NIP) introduced the 13-valent pneumococcal conjugate vaccine (PCV13) into the country as part of the routine immunisation children receive in Lao PDR.

In Lao PDR, pneumococcal meningitis is the primary cause of childhood deaths (2), and it is the most common cause of death in children under five years old (3). Pneumococcal pneumonia is the commonest cause of hospitalisation for children under five years old (4). The pneumococcal vaccine is being introduced in our country to decrease the burden of pneumococcal disease.

In other countries, this vaccine prevents pneumococcal diseases, such as pneumonia, and protects both vaccinated children and unvaccinated people. The pneumococcal germ is found in the back of the nose and is spread from person to person by coughing, sneezing etc. This vaccine reduces the pneumococcal germ in the nose of vaccinated children. This prevents the spread of the germ to unvaccinated people, stopping them getting sick as well. This is called herd immunity. Other countries have found that really large herd immunity effects from the vaccine.

We want to introduce the pneumococcal vaccine to our country to reduce the number of children who have to be hospitalised and the number of deaths. We want to protect all children at risk of pneumonia.

We are doing this study because we want to know in Laos whether this vaccine has a similar effect and if it reduces the germs in the nose of both the vaccinated and unvaccinated children. This would help us to know whether herd immunity is also occurring here.

Who did we include in the study?

We included children under 2 years old with fever and respiratory symptoms (for example, cough, runny nose, difficulty breathing) from the paediatric wards at Mahosot Hospital.

In 2017, the 1044 children were recruited in the study and 102 children were vaccinated with PCV13. In the first 2 ½ years since the study started:

- Approximately half had pneumonia
- Girls and boys were equally affected
- Most came from Vientiane Capital

Vaccinated children are younger than unvaccinated children.
Unvaccinated children are more likely to live outside of Vientiane Capital.

What does this mean?

In the second year of the study, the pneumococcal (PneuCAPTIVE) study found that the pneumococcal vaccine reduced the pneumococcal germ in the children who were vaccinated. This means that they are probably protected from the disease caused by the vaccine.

Unvaccinated children were not yet benefiting from the vaccine and are not protected from the disease, so there is no herd immunity yet.

What is happening in the future?

In future, we will continue the study and designed to show when herd immunity occurs.
Chapter 2 – PneCAPTIVE

C. ISPPD conference poster

Using pneumococcal nasopharyngeal carriage in hospitalised children to determine the pneumococcal conjugate vaccine coverage required to show herd immunity in Lao PDR


Background

- Pneumococcal conjugate vaccine (PCV) use has seen reductions in disease in both vaccinated and unvaccinated age groups (herd immunity).  
- The PCV13 coverage required to achieve herd immunity in unknown.  
- Nasopharyngeal carriage of pneumococci is a precursor to disease.  
- PCV use has been shown to reduce overall carriage and vaccine-type carriage associated with disease.  
- Lao PDR introduced PCV13 into their Expanded Programme on Immunization (EPI) in October 2015, with a catch-up period of 6, 10 and 14 weeks and catch-up campaign for infants up to 12 months old.  
- The introduction of PCV13 created an opportunity to assess the PCV13 coverage required to show evidence of direct effects and herd immunity using carriage.

Aim

To determine the PCV13 coverage needed to show evidence of herd immunity using nasopharyngeal carriage surveillance in hospitalised children in Lao PDR.

Methods

Case population

- Children 2-59 months of age admitted to Mahosot Hospital. Ventilator with acute respiratory infection were prospectively enrolled from December 2015, and had a nasopharyngeal swab selected.
- Nasopharyngeal carriage status was determined using real-time quantitative PCR, with positivity defined by histology.

PCV13 coverage calculations (2 methods)

- Percentage of cases who are vaccinated each month.
- Percentage of under 5 year old cases contacts of cases who are vaccinated each month (data not shown).
- Percentage of under 5 year old children who are vaccinated and vaccine naive in each cases' vaccine age group each month (data not shown).

Results

For the first 18 months are shown:

- Case Recruitment
  - After 20 months, 76% cases have been enrolled into the study.
  - There has been minimal change in pneumococcal carriage rates in vaccinated or unvaccinated cases (Figure 1).

- There is a downward trend of PCV13-type carriage in both vaccinated and unvaccinated cases, with a more pronounced decline in the vaccinated population.

- Within 17 months of PCV13 introduction, the PCV coverage reached >50%.

- There is a downward trend of PCV13-type carriage in both vaccinated and unvaccinated cases, with a more pronounced decline in the vaccinated population.

Figure 1. Pneumococcal carriage rates and 95% CI, stratified by PCV status.

Figure 2. Carriage of PCV13 types in PCV13 vaccinated and unvaccinated cases, and percentage of all cases PCV13 vaccinated.

Conclusion

- Surveys will continue until December 2016.
- As PCV13 coverage increases, we expect PCV13-types to decline further for each vaccination group and reach a nadir.
- This study will inform decision making what PCV13 coverage is required to maximise the benefits of PCV13.

Acknowledgments

- Thanks to: Our funders, the Bill & Melinda Gates Foundation, the Department of Health, Laos PDR, THACO (South Laos PDR) Country Office and Disease Control Office for the Western Pacific and the Laos Oxford Malahit Hospital-Wellcome Trust Research Unit (LUMRU).
- Data was entered by LUMRU.
- Laboratory staff at both LUMRU and COH.
- Staff based at LUMRU.
- Immunization logistical and distribution staff at Health Centers through Lao PDR.
- Participants (cases, contacts).

REFERENCES


64
D. Conference oral presentation – Asian Congress of Pediatric Infectious Disease 2016

PneuCAPTIVE – Using nasopharyngeal carriage surveillance in children hospitalized with respiratory illness or pneumonia to demonstrate direct and indirect effects of pneumococcal conjugate vaccine

Jana Lai
Masters in Applied Epidemiology (scholar), Australian National University

Pneumococcal disease

- Pneumococcus is a major cause of morbidity and mortality in children and the elderly
- Causes a broad spectrum of bacterial infections, such as pneumonia, sepsis, otitis media
- PCV use reduced disease in both vaccinated and unvaccinated age groups (herd immunity)

Herd immunity

- Mechanism: removal of vaccine types from carriage
- PCV reduces carriage of vaccine types both vaccinated and unvaccinated groups
- Increases cost-effectiveness of PCV

Laos

Under-immunized children of 2 years of age

Chapter 2 – PneCAPTIVE

PneCAPTIVE - Aims
To determine the PCV13 coverage needed to show evidence of herd immunity using NP carriage surveillance in hospitalised children with acute respiratory infection

PneCAPTIVE - Methods
- 3 elements:
  - Case recruitment
  - Carriage ascertainment
  - Vaccination rate

Case recruitment
Inclusion criteria:
- Children 2-59 months of age
- Admitted to Mahidol Hospital, Vientiane Lab PIR between Dec 2013-Dec 2016
- Acute respiratory infection (ARI)
- History of illness ≤14 days plus:
  - History of fever or documented fever
  - AND ≥1 of the following:
    - Diarrhea
    - Cough
    - Noits
    - Acute respiratory infection

Carriage:
- DNA from NP samples extracted
- iL-A qPCR (detection)
- Microarray serotyping

Vaccination coverage:
- PCV status obtained from cases
- Proportion of cases vaccinated plotted over time

Preliminary results – Demographics

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Case (n=768)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age</td>
<td>14 months (QR 7.1-23.4)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>425 (54%)</td>
</tr>
<tr>
<td>Female</td>
<td>343 (44%)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>404 (51%)</td>
</tr>
<tr>
<td>Ventilator</td>
<td>615 (79%)</td>
</tr>
</tbody>
</table>
Chapter 2 – PneCAPTIVE

Discussion
- Decline in PCV13-type carriage 2.5 years post-introduction
- No obvious indirect effects on PCV13-type carriage
  - Low coverage
  - Impact of 3+6 schedules less than that of schedules with booster dose
  - No catch-up campaign
  - Without 3-year to see herd immunity

Conclusions
- Study will continue recruitment until mid-2017
- Larger study has 2 other sites
  - Papua New Guinea (start April 2016)
  - Mongolia (start June 2016)
- Final analysis will pool all sites

Acknowledgements
- Funders
  - Dr and Melanie Sutle Foundation
  - MCRP
  - Prof Fiona Russell
  - Prof Kim Maholtraod
  - Dr Catherine Talbot
  - Dr Einion Evans
  - Dr Ruth
  - Dr Melissa
  - Dr Calvin Nguyen
  - Pneumococcal Group
  - St Georges, University of London
  - Dr Jasmin Vind

- Malu Lao PAS
- Dr Kowsitha Nalubunga
- BP
- Health Centre staff
- WHO PAS
- Dr Bhastha Darla
- LOMIMU
- Prof Paul Newton
- Dr David Buck
- Dr Kasdimara Virdung
- ARL/PHACAPTIVE study team
- Antoine Chambrin
- LOMIMU Laboratory

All participants in the study whom without could not do this work.
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Chapter 3
Kiribati Rotavirus Vaccine
Introduction; Establishment of post-marketing safety surveillance
Chapter 3 – Kiribati Intussusception Surveillance

Contents
1. Prologue .................................................................................................................. 73
  1.1. Role .................................................................................................................. 73
  1.2 Lessons learnt .................................................................................................. 74
  1.3 Public Health implications and impact .............................................................. 76
2. Abstract ..................................................................................................................... 78
3. Introduction ............................................................................................................... 80
  3.1. Epidemiology of intussusception (IS) ............................................................... 80
  3.2. IS and Rotavirus (RV) vaccine ......................................................................... 82
  3.3. Post-marketing surveillance of IS ................................................................. 84
  3.4. RV vaccine and Kiribati .................................................................................. 85
  3.5. Aims .................................................................................................................. 86
4. Methods ..................................................................................................................... 87
  4.1. Context ............................................................................................................. 87
  4.2. Determining baseline IS incidence ................................................................ 87
  4.3. Establishing IS surveillance ............................................................................ 90
5. Results ....................................................................................................................... 93
  5.1. Baseline IS incidence ...................................................................................... 93
  5.2. IS Surveillance ............................................................................................... 93
6. Discussion .................................................................................................................. 102
7. Recommendations .................................................................................................... 105
8. References ............................................................................................................... 106
9. Appendices .............................................................................................................. 109
  A. Intussusception review data collection form ..................................................... 109
  B. Intussusception surveillance SOP .................................................................. 111
  C. Intussusception case investigation form .......................................................... 112
  D. WHO mission report .................................................................................... 115
  E. WHO findings report .................................................................................. 121
  F. Kiribati AGE & SAM WPSAR paper – final draft for submission .................. 134
  G. Oral Presentation slides for ACPID and TEPHINET Conferences (2016) ....... 151
List of Figures
Figure 1: Pictorial of anatomy of intussusception .................................................................80
Figure 2: Intussusception incidence among children <1 year of age by region........82
Figure 3: Flow of potential IS cases into Tungaru Central Hospital (TCH) and subsequent treatment and outcome options.........................................................91
Figure 4: Outline of investigation of potential intussusception cases by local surveillance coordinator ................................................................................................................96

List of Tables
Table 1: Characteristics of intussusception cases <2 years admitted to Tungaru Central Hospital (TCH), June 2010-April 2015.............................................................93
# Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGE</td>
<td>Acute gastroenteritis</td>
</tr>
<tr>
<td>CDC</td>
<td>Center for Disease Control</td>
</tr>
<tr>
<td>DBRCT</td>
<td>Double-blind randomised control trial</td>
</tr>
<tr>
<td>EPI</td>
<td>Expanded program of immunisation</td>
</tr>
<tr>
<td>IS</td>
<td>Intussusception</td>
</tr>
<tr>
<td>MAE</td>
<td>Master of Applied Epidemiology (Australian National University)</td>
</tr>
<tr>
<td>MHMS</td>
<td>Ministry of Health and Medical Services, Kiribati</td>
</tr>
<tr>
<td>NGO</td>
<td>Non-government organisation</td>
</tr>
<tr>
<td>PVP</td>
<td>Positive value predictive</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomised control trial</td>
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<tr>
<td>RV</td>
<td>Rotavirus</td>
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<tr>
<td>SAM</td>
<td>Severe acute malnutrition</td>
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<tr>
<td>SOP</td>
<td>Standard operating procedure</td>
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<tr>
<td>TCH</td>
<td>Tungaru Central Hospital</td>
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<tr>
<td>US</td>
<td>United States</td>
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<td>WHO</td>
<td>World Health Organization</td>
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<tr>
<td>WPRO</td>
<td>Western Pacific Regional Office</td>
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<td>WPSAR</td>
<td>Western Pacific Surveillance and Response Journal</td>
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1. Prologue

1.1. Role
A/Prof Fiona Russell was contracted by the World Health Organization (WHO) Western Pacific Regional Office (WPRO) to conduct an evaluation of rotavirus (RV) vaccine introduction in Kiribati. This was to support the introduction of RV vaccine into the Kiribati national expanded program of immunisation (EPI) schedule. The terms of reference for this work was to establish post-marketing surveillance of intussusception (IS) and also to establish burden measurement of acute gastroenteritis (AGE) that could be used to evaluate the impact of RV vaccine in the community.

With the assistance and guidance of A/Prof Russell, my role was to complete the terms of reference set by WHO WPRO for evaluating RV vaccine introduction into Kiribati. The evaluation consisted of 2 parts: 1) determining baseline data for AGE, IS and severe acute malnutrition (SAM) and 2) designing and establishing an IS surveillance system as part of RV vaccine post-marketing surveillance of IS. To achieve this I was responsible for:

- Drafting of a protocol to detail our methods for the evaluation before our site visit
- Preparing all data collection instruments, adapted from WHO generic protocols for RV vaccine introduction (included in Appendix A and C)
- Liaising with Ministry of Health and Medical Services (MHMS) staff to find and access the required data
- Where available, reviewing and cleaning electronic hospital admission data
- Going through hospital admission books where electronic data were not available
- Cleaning and subsequently analysing the data for reporting
- Presentation of preliminary results and methods of continual IS surveillance to MHMS and Tungaru Central Hospital (TCH) paediatric staff
- Preparation of WHO reports (mission and findings report included in appendices D and E)
Specifically for IS surveillance, I was responsible for writing the standard operating procedure (SOP), training the local coordinator and acting as the external monitor to support and monitor the surveillance. I plan to return in late 2017 to complete the evaluation and collect any missing data from the previous site visit. With the approval from WPRO and MHMS, a manuscript describing the baseline AGE and SAM incidence prior to RV vaccine introduction was prepared for submission to Western Pacific Surveillance and Response Journal (WPSAR).

In addition during my time on site, I assisted in a limited capacity with an AGE outbreak and subsequently acute respiratory infection outbreak in Tarawa. During these outbreaks I acted in an informal capacity to help staff at TCH with case reporting and I also liaised with the different departments (statistics, laboratory and environmental unit) involved to check on the progress of the outbreak investigation. This experience was my first opportunity to apply classroom skills in outbreak investigation to a real life setting. After effective public health interventions promoting hygiene practices in the community the outbreaks ceased after a few days with a limited number of cases.

1.2 Lessons learnt
This was my first experience working in a consultancy role for WHO and through this I was exposed to processes and aims that are different to my skills and experience in research. From a data perspective I learnt about the limitations of administrative data, both population and hospital records. For population data, it can be difficult to get accurate summary data and these data are not necessarily in a format that is flexible for reporting (for example the age groups are not exclusive). For hospital records, incomplete coding, variability in text variables, etc. need to be considered. For example, with diagnoses it was important to collect both the code and the written diagnosis to ensure cases were not missed as there were occasionally mismatches between what condition the patient was coded for and the true diagnoses. Data received was often in a format requiring cleaning and checking, with careful documentation of the process followed crucial, as I often had to revisit the data for additional analyses. In addition, I learnt the benefits of receiving the data in an electronic format for ease downstream of cleaning and analysis. This became obvious when I had to reanalyse the data for SAM and did
not have the most recent data available as we had collected it by hand for AGE only. I also learnt the importance of establishing a case definition that matched the aims of the project. Because RV testing is not available in Kiribati, AGE was used as a proxy to evaluate the impact of RV vaccine in the population. This meant it was important to exclude any diagnoses that were indicative of a bacterial cause or chronic conditions. Thus the case definition excluded any diagnoses of bacterial diarrhoea, bloody diarrhoea, blood in the stool or chronic gastrointestinal disease.

I learnt how to liaise with different stakeholders, both within the hospital system and other Non-government organisations (NGOs) working in the same area. Dependent on the situation, different methods of presentation/conversation had to be employed to get the message across. I found speaking to people face to face was the best form of communication as there was less room for confusion and potential disagreement. I also had to mindful of other NGO’s working in the same area and relied heavily on A/Prof Russell’s advice on the content of my conversations and who I should include in these discussions.

The key area of development for me was the design, implementation and subsequent monitoring of a surveillance system. I was able to apply my theoretical understanding of public health surveillance to this project. Firstly I had to speak to the relevant stakeholders (MHMS, Paediatric Department of TCH, Kiribati WHO Country Office) to understand how cases presented and subsequently treated. Using this knowledge I had to adapt generic protocols and data collection tools to the specific situation at TCH. I had to train the local coordinator, a senior paediatric nurse in the SOPs and ensure that I had explained the process properly so she felt confident acting in her role. Even though there was no formal evaluation of the surveillance system, it was useful to apply the surveillance framework to identify strengths and weaknesses of the system, attempting to pre-empt issues.

Separate to the evaluation, the outbreak investigation happening on site while I was there gave me a taste of the importance of process and establishing communication lines during an outbreak response.
1.3 Public Health implications and impact

Rotavirus is the most common cause of AGE in infants and children. The use of RV vaccines has reduced the burden of RV infection in both developed and developing countries. The presence of a large burden of malnutrition in the population may lead to decreased RV vaccine effectiveness. Nonetheless, through the use of RV vaccines in Kiribati, there will still be a large number of children protected from RV infection altogether or who experience reduced severity of disease.

Intussusception is a rare severe adverse event associated with RV use. As part of the post-marketing safety of RV vaccine use in any naïve population, WHO recommends IS surveillance to be done. The importance of establishing and monitoring changes in IS in a population pre- and post-RV vaccination introduction is to provide evidence that the vaccine is safe. From the work detailed in this chapter, the epidemiology of IS will be described in Kiribati, which is important not only to add to the body of evidence on IS globally but also to establish a baseline pre-RV vaccine introduction. Monitoring for IS incidence is important to ensure both vaccine safety and public faith in the vaccine. Through the review we were able to build capacity and understanding of AGE and IS in the staff working at TCH by informing them of the background of AGE/IS, what RV vaccines are, the risks associated with RV vaccine use and showing them the epidemiology of AGE and IS at TCH prior to RV vaccine introduction and how it will help reduce the AGE burden in their community.

The data presented in this chapter provides a baseline measure and surveillance system that Kiribati health policy makers and advocates can use to monitor the safety of RV use in their population. It is hoped that the data will provide reassuring information for MHMS with regards to the safety of RV vaccine and show that the benefits of RV vaccine outweigh the risks. This would give them the confidence to keep the vaccine in the national schedule, protecting their population from RV disease, thereby reducing mortality, morbidity and strains on the health systems of Kiribati.
1.4 Acknowledgements
I would like to thank Dr Kimberely Fox, Dr Beia Tabwaia, Dr Andre Reiffer and Agnes Nikuata for their support, leadership and insight on this project. My thanks also extend to Dr Nyambat for his continual assistance in this project. My gratitude to the MHMS of Kiribati for their support and assistance, from inception and throughout the review. Much thanks to the Statistics, Medical records and Paediatric Departments at TCH for their support in helping our understanding of the system and also providing us with the data we required to complete our work. Special thanks to Senior Nurse Atiri Baaka who agreed to be the local coordinator for the IS surveillance at TCH to continue this work in addition to her many duties.

1.5 Funding
The study was funded by the World Health Organization
2. Abstract

**Background and Aims:** Rotavirus (RV) is the most common cause of acute gastroenteritis (AGE) in infants and children globally. To address the high burden of AGE in Kiribati, the Ministry of Health and Medical Services (MHMS) introduced RV vaccine in August 2015. As part of RV vaccine introduction, the World Health Organization (WHO) recommends post-marketing safety surveillance of intussusception (IS). IS is a rare, but severe, adverse event shown to be associated with RV vaccine use. Thus to support the introduction of RV vaccine, baseline IS incidence and epidemiology was determined and active surveillance of IS was established to ascertain if there was a temporal relationship of IS cases to RV vaccine as part of recommended post-marketing safety monitoring.

**Methods:** To determine baseline IS incidence and epidemiology, data were collected for children <2 years admitted to Tungaru Central Hospital (TCH) from June 2010 to April 2015. Eligibility criteria for IS cases was children ≤24months with a discharge diagnosis of IS or bowel obstruction. To ensure no cases were missed, deaths associated with dysentery or bloody diarrhoea were also searched for as a common symptom of IS is red currant stools. Medical records of potential IS cases were reviewed and IS was confirmed if they satisfied Level 1 of the Brighton clinical case definition. In addition, confirmed cases had sex, age, residence, date of admission, date of discharge, discharge diagnosis, management and outcome (alive/dead), extracted from the medical records, to describe the epidemiology of cases during the study period. The 2010 Census data for Tarawa was used as the denominator to calculate IS incidence. To establish IS surveillance post-RV vaccine introduction in August 2015, cases with diagnoses indicative of bowel obstruction and admitted to TCH, were eligible for inclusion. A temporal relationship to RV vaccine was determined by an IS event occurring 1-7 days after the first dose of RV vaccine or likely related 8-21 days after the first dose of RV vaccine or 1-7 days after the second dose of RV vaccine.

**Results:** There were 2 IS cases over the 5-year pre-RV vaccine review period and the annual IS incidence was 20 per 100,000 children (95% CI 2-73) <1 year old. Both cases were female, aged 5 months old and required surgical intervention,
Chapter 3 – Kiribati Intussusception Surveillance

with no deaths. It is estimated that one additional case of IS may occur every 5-17 years. The IS surveillance system drew on existing staff and processes at TCH. The case definition used followed WHO guidelines and a local coordinator was trained to identify and subsequently report any potential IS cases in the system. Since the introduction of RV vaccine in August 2015 there has been no reported IS cases.

Summary and conclusions: The incidence rate of IS in Kiribati is low in comparison to countries in the Asia-Pacific and the global average. However the epidemiology of cases is typical of what is seen in other parts of the world. There were no deaths from IS found in the review. Intussusception is a rare event and for at least 50% of the population, surgery is available if a case occurs. The establishment of the IS surveillance system, taps into existing systems and has minimal reporting requirements, making it easy for staff responsible to report IS cases after the introduction of RV vaccine. Thirty months since the introduction of RV vaccine, there have been no reported IS cases. As IS is a rare condition and Kiribati is a small country, Kiribati would be better suited to rely on data from other countries in the region regarding RV vaccine safety.
3. Introduction

3.1. Epidemiology of intussusception (IS)

Intussusception occurs when one segment of the bowel becomes in-folded within a more distal segment, causing bowel obstruction (1, 2).

**Figure 1:** Pictorial of anatomy of intussusception (2)

If the resulting obstruction is not relieved, the blood supply to the bowel becomes impaired and, if left untreated, this condition is likely to be fatal. Clinical symptoms include vomiting, abdominal pain, red currant jelly stools and lethargy (1). Diagnosis can be determined using radiography, ultrasonography, but most commonly contrast enema. The condition can be treated using surgical or non-surgical methods (1).

Naturally occurring IS is the most common cause of bowel obstruction in young children worldwide (3). Based on a comprehensive global review by Jiang et al. (2013) of available IS studies in children, peak incidence was seen among those 4-7 months of age at 97-126 per 100,000 infant years, with no obvious patterns of seasonality. The male to female ratio is 3:1. Of those that present to hospital, mortality post-presentation was highest in Africa (9.4%) in comparison to all other regions where it was <1% (3).

Intussusception is a rare event. In the Jiang et al. (2013) review, the mean incidence was 74 per 100,000 infant years (range 9-328 per 100,00 infant years),
but as shown in the range, there were large differences between studies. Summarising 82 original articles by region, Figure 2, taken from Jiang et al. (2013) shows the incidence for children <1 years of age, country, source of data (national, regional, hospital) and if the rates had been stratified by month of age. There were many countries in the world without reports on IS epidemiology for their country, Kiribati included. Also, there was much heterogeneity both between and within regions in terms of methods for IS diagnosis, treatment of IS and sample sizes included in each of the studies. These factors, in addition to potential environmental and genetic factors unique to each country/region may explain the large discrepancies of IS incidence between countries and regions.
3.2. IS and Rotavirus (RV) vaccine

In 2009, WHO recommended that all infants be routinely immunised with RV vaccine to prevent RV disease (4). The currently licensed RV vaccines (Rotarix®, GlaxoSmithKline and RotaTeq®, Merck) have been shown to be safe and effective against RV AGE, with reductions of up to 71% of RV-hospitalisations in children <5 years of age (5). In addition, reductions in all-cause AGE admissions for children <2 years of age of 17-50% has also been shown (6).
However, the first licensed RV vaccine, RotaShield®, was withdrawn from use after an increase of IS was observed in infants following vaccination. RotaShield® was a live-attenuated, oral vaccine consisting of three rhesus-human reassortant strains was given in a 3-dose regimen (7). From early pre-licensure trials the vaccine was shown to be highly efficacious for the prevention of severe diarrhoea and hospitalisation due to RV infection (8, 9) but there were indications of a possible association of RotaShield® and IS, with a non-significant increase in vaccine recipients in comparison to controls (10). Nine months after the introduction of RotaShield® in the US in 1998, there were 15 cases of IS reported to a passive surveillance system and the vaccination program was suspended (11). By September 1999, additional cases were reported in vaccine recipients and evidence supporting a temporal link was developing, leading to the vaccine being completely withdrawal from the market in October 1999 (12). The estimated risk of IS was calculated to be 1/10,000 children vaccinated, with cases clustering mostly within 3-14 days after the first dose, with highest risk in those receiving their first dose after 3 months of age (13, 14).

Currently there are two licenced RV vaccines in the market, RotaTeq® (Merck) and Rotarix® (GlaxoSmithKline). Both licenced vaccines use a different formulation to RotaShield®, with RotaTeq® a live oral vaccine, containing five human-bovine reassortant RV strains (15) and Rotarix® a live oral vaccine, containing a single human RV strain (16). Due to the experience with RotaShield®, both vaccines had to be shown to not only be efficacious against RV but also to demonstrate safety with IS as an outcome. In a double-blind, randomised control trial (DBRCT) of over 63,000 Latin American infants randomised to receive RotaTeq® or placebo, there were 25 cases of definitive IS (16). During the entire safety surveillance period of 100 days after dose 1, IS occurred in 9 vaccine recipients and 16 placebo recipients (difference in risk -2.23 per 100,000; 95% CI -5.70-0.94; p=0.16) (16). Thus within the trial setting, the vaccine was not associated with an increased risk of IS during the 31 day period after either dose of vaccine in comparison to placebo (16). For Rotarix®, in a DBRCT of 60,000 infants from 11 countries, randomised to receive Rotarix® or placebo, IS occurred in 6 vaccine recipients and 5 placebo recipients within the 42 day period after any dose
of vaccine (multiplicity-adjusted, relative risk 1.6; 95% CI 0.4-6.2) (15). Therefore like RotaTeq®, Rotarix® in this trial setting, was not found to have a significantly increased risk of IS in vaccine recipients at any time during the study period (15).

From pre-licensure data, both vaccines were highly efficacious against many different types of RV genotypes, making them highly appealing to all countries with a high burden of RV disease. Vaccine efficacy of 84.7% and 98% against severe RV gastroenteritis was observed for RotaTeq® and Rotarix® respectively (15, 16). Thus both RV vaccines were shown to not only be efficacious against RV disease but also demonstrated safety with IS as an outcome, leading to their successful licensure.

3.3. Post-marketing surveillance of IS
From the pre-licensure RCTs, there was no association found between RV vaccine use and IS, but increased risks of IS were seen in post-marketing surveillance in Mexican, Brazilian, Australian and United States (US) infants (17-19). Using case-series and case-control methods, an increased risk of IS 1-7 days after first dose RV vaccine was reported in vaccinated Mexican and Brazilian infants of 1 per 51,000 and 1 per 68,000 respectively (17). In Australia, using self-controlled case-series and case-control methods found a small increased risk of IS of 5.6 per 100,000 vaccinated infants in the first 1-7 days after the first dose of RV vaccine and a smaller increased risk 1-7 days after the second dose RV vaccine (18). For US infants, approximately 1.5 excess cases of IS per 100,000 recipients of the first dose of RV vaccine was observed using both a self-controlled risk-interval design and a cohort design (19).

Taking into consideration the small increased risk of IS from post-marketing surveillance, studies have assessed the risk of IS versus the benefit of RV vaccine use. For the US, the summary benefit-risk ratios for RV-associated deaths and hospitalisations were 71:1 and 1093:1 respectively to IS (20). The estimated benefit-risk ratios for England were similar for RV-associated deaths but lower for hospitalisation at 375:1 (21). Benefit-risk ratio modelling in Japan had similar levels to England for hospitalisation but a much higher ratio for RV-associated deaths at 366:1 (22). Even though the benefits of RV vaccine in preventing deaths
and hospitalisations of AGE outweigh the risk of IS, WHO recommends post-marketing surveillance should be conducted for severe adverse events, with a focus on IS whenever RV vaccines are introduced into new populations (4). This has been supported by WHO with standardised guidelines on how to conduct surveillance and data collection forms to collect pre- and post-RV vaccine introduction in a given population (1).

Post-marketing surveillance of RV vaccine can be done actively, passively or using a combination of both methods. In an active system, the options include an active search for adverse reactions or active follow up of vaccine recipients for a defined period of time. The benefits of an active system are that data are collected in real-time, collected data are the most accurate and specific research questions regarding vaccine effectiveness or potential adverse events can be addressed (7). The disadvantages of an active system are that it is more labour intensive and costly. Passive systems are reliant on reporting from stakeholders in the system. The benefits of a passive system are the use of existing resources. The disadvantages of a passive system are the reliance on reporting, which encompasses, under-reporting of adverse events, incomplete data, limited or no follow up, unable to ascertain definitive diagnoses and inaccurate/lack of numerator/denominator data to be able to establish causality or incidence (7). Monitoring for a rare severe adverse event like IS can be achieved through a combination of both active and passive systems. This minimises the disadvantages in both systems.

3.4. RV vaccine and Kiribati
Acute gastroenteritis is a substantial burden in Kiribati, with diarrhoea estimated to cause 10.7% of all <5 year old deaths (23). In 2002, 11% of all hospitalisations in children <4 years old were due to AGE (24). To address this high burden of disease, Kiribati introduced RV vaccine, Rotarix® (GlaxoSmithKline) into their EPI schedule in August 2015. For Kiribati the baseline IS incidence was unknown. Thus, Kiribati needed to determine the IS epidemiology for their population prior to RV vaccine introduction and subsequently establish IS surveillance post-RV vaccine introduction, instilling confidence in the use of RV vaccine.
3.5. Aims
The aim of the study were to:

- Describe the baseline epidemiology of IS
- Determine a baseline incidence of IS pre-RV vaccine introduction in children ≤2 years of age living on Tarawa
- Establish an IS surveillance system to capture and record all IS cases in children living on Tarawa, ≤2 years of age post-RV vaccine introduction
4. Methods

4.1. Context
Kiribati is a country of 33 atolls and low-lying reefs widely scattered along the Equator in the central Pacific Ocean (24). Kiribati has a population of approximately 100,000, with 11,000 of those being children <5 years of age (24). The island of Tarawa is home to approximately 60% of the total population of Kiribati. The national economy depends primarily on I-Kiribati people working abroad, fishing licence fees, exports of sea products and foreign aid (24). Kiribati is vulnerable both internally due to depletion of limited natural resources and externally to the effects of climate change on rising sea levels and unpredictable weather (24). Kiribati has the lowest level of development in the Pacific region when accounting for mortality, morbidity and living conditions per capita GDP and also is considered a least developed country globally (24).

Each village in Kiribati has a health centre staffed by nurses who provide basic primary health care, administer vaccinations and run health promotion activities. Patients who require further care are either referred or seek care at 1 of the 2 hospitals on Tarawa: one in Betio and the other, Tungaru Central Hospital (TCH), in Bikenibeu. TCH is the main hospital for Tarawa and also the only facility that can provide management for severe cases of disease and provide surgery. TCH is also the referral hospital for the outer islands. The majority of families on Tarawa do seek health care at TCH. However it is not uncommon for children to die at home with no autopsy or death reporting available, especially for children who reside on the outer islands where access to health care is a major issue.

4.2. Determining baseline IS incidence

4.2.1. IS case definition
We used the standard WHO case definition for IS which ranks level of certainty by incorporating various criteria and can be found in Box 1. This case definition was developed by the Brighton Collaboration Intussusception Working Group to assist with the surveillance of IS post-RV vaccine introduction, and includes a case
definition for IS based solely on clinical criteria (7). Using a clinical case definition bypassed the need for access to radiological, ultrasound or surgical diagnoses, especially in regions where these facilities or expertise may not be available (7). The definition was suitable for use in a wide range of settings and provided a set of standardised clinical criteria validated in developed and developing countries (7). Quoting from WHO post-marketing safety surveillance; ‘The definition divides clinical events into a classification according to the level of evidence for diagnostic certainty, with level 1 diagnostic certainty defined as a confirmed or definite case of intussusception” (7). However, WHO also recommends capturing all clinically suspected events, regardless of satisfaction of the Brighton Collaboration case definition (7).

Potential IS cases were those aged ≤24 months old, and had a discharge diagnosis of IS or bowel obstruction. In these cases the medical records of each potential case were reviewed and determined to be a Level 1-3 case of IS as per the Brighton clinical case definition by a paediatrician (7, 25).

**Box 1: Brighton clinical case definition of intussusception**

- Level 1 - diagnosis of IS by surgical, radiological or autopsy criteria;
- Level 2 - presence of 2 major clinical criteria or 1 major and 3 minor criteria;
- Level 3 - presence of 4 or more minor clinical criteria

Major criteria were, evidence of intestinal obstruction, features of intestinal invagination and evidence of intestinal vascular compromise or venous congestion. Minor criteria were age <1 year, male, abdominal pain, vomiting, lethargy, pallor, hypovolemic shock and plain abdominal radiograph showing an abnormal but non-specific bowel gas pattern.

### 4.2.2. IS data collection

Hospital admission books (June 2010-April 2015) and electronic medical records were reviewed for potential IS cases in children <2years of age. For the electronic data, the search terms ‘IS’ and ‘bowel obstruction’ were used to find potential
cases. Using the same search terms, hospital admission books were manually searched for the time periods electronic data was not available. Data from January 2014 and February 2014 were incomplete from both sources. Both sources were in a line list format, inclusive of unique hospital number. In addition, following on from concerns of the paediatric staff of potential cases being missed with the above inclusion criteria, deaths caused by dysentery or had reported blood in the stool were also reviewed as potential IS cases. To cross-check the list of potential cases found was complete, we also asked the paediatricians and paediatric surgeon if there were any potential cases we had missed.

All potential IS cases had their medical records reviewed and data were recorded on a dedicated data collection form (Appendix A). Variables collected from the hospital records were sex, age, residence, date of admission, date of discharge, discharge diagnosis, management and outcome. Based on clinical symptoms and/or results from investigations, cases were classified as a level 1, 2, 3 using the Brighton clinical case definition by a paediatrician. All completed forms were placed in a folder held at the WHO country office.

4.2.3. Study population

For incidence calculations, the TCH catchment population was defined as children <2 years residing on Tarawa. Potential cases residing outside of Tarawa were excluded after all cases were identified. Hence, only hospitalised IS cases residing on Tarawa were included in the population-based analysis. Denominator data for rates were obtained from the most recent census, which occurred in 2010. The age groups in the 2010 census relevant for this review were <12 months and 12-23 months. A 2.2% growth rate was applied per annum to the 2010 census data to calculate the 2011-2015 <2 years population.

4.2.4. Estimation of potential IS cases attributable to RV vaccine

Based on data from post-licensure surveillance conducted in Mexico, Brazil, US and Australia, the increased risk of IS post-RV vaccination was 1 per 51,000, 1 per 68,000, 1.5 per 100,000 and 5.6 per 100,000, respectively (17-19). Using the population to be vaccinated (3000 infants per year) in Kiribati and the estimated risk (2-7 per 100,000 vaccinated) from these data, an estimated number of
additional IS cases per year potentially attributable to RV vaccination for Tarawa was calculated.

4.3. Establishing IS surveillance

4.3.1. System objectives
The objective of the IS surveillance system is to capture and record all IS cases in children ≤2 years of age living on Tarawa post-RV vaccine introduction.

4.3.2. Engaging stakeholders
The Ministry of Health and Medical Services in Kiribati asked WHO to assist with the evaluation and IS surveillance for RV vaccine introduction. Thus MHMS was engaged in the process from the outset. We had a series of meetings with the paediatricians and a TCH surgeon to explain the purpose and goals of our visit. During these meetings we discussed their clinical experience and management of IS cases and the number of IS cases seen each year. In addition the meetings were to explain the purpose of conducting IS surveillance to not only increase awareness of IS in the hospital but also to identify a suitable staff member who could conduct the surveillance.

4.3.3. Flow of information into the system
Based on discussions with the paediatric staff at TCH, the flow of potential IS cases into TCH was mapped. Figure 3 is a flowchart of how potential cases go through the system, providing the foundation for the IS surveillance system to piggyback onto.
4.3.4. Available/required resources

We considered the following resources that would be required for system operation: data collection tools, method of data storage, a local coordinator and a SOP for them to follow. Through discussions with paediatric staff, WHO country office and MHMS we considered whether employing a local coordinator from outside the hospital was feasible. However, the paediatric staff suggested it would be best to ask a senior member of staff to act in this capacity as they would be on site and also already knew the protocols at TCH.

4.3.5. Attributes

As part of my MAE, I undertook a review of the surveillance attributes of the planned system as per the Center for Disease Control (CDC) Updated Guidelines for Evaluating Public Health Surveillance Systems (26). The attributes assessed were:
Chapter 3 – Kiribati Intussusception Surveillance

- Simplicity (simple structure and ease of operation)
- Flexibility (ability to adapt to changing information needs or operating conditions with little additional time, personnel, or allocated funds)
- Data quality (completeness and validity of the data)
- Acceptability (willingness of persons and organizations)
  Sensitivity (proportion of cases of a health-related event detected)
- Positive value predictive (PVP) (proportion of reported cases that actually have the health-related event)
- Representativeness (accurately describes the occurrence of a health-related event over time and its distribution in the population by place and person)
- Timeliness (speed between steps in the system)
- Stability (ability to collect, manage, and provide data properly without failure and to be operational when it is needed)
- Usefulness (contribution to prevention and control of adverse health events, inclusive of an improved understanding of the public health implications of such events)
5. Results

5.1. Baseline IS incidence
There were 2 IS cases over the 5-year period pre-RV vaccine introduction (Table 1). Both cases were female, aged 5 months old and required surgical intervention. Case 1 fully recovered with no sequelae and Case 2 recovered with sequelae, requiring further surgery for intestinal adhesions. The annual incidence of IS was 20 per 100,000 (95% CI 2-73) children <1 years. In addition, no deaths from dysentery or reported blood in stool met the Brighton IS classification.

Approximately 3000 infants will be vaccinated in Kiribati each year. The estimated increased risk of IS due to rotavirus vaccine is 2-7 cases per 100,000 infants vaccinated. Therefore, based on the risk calculated by previous studies (17, 18), there may be one additional case of IS every 5-17 years in Kiribati, following the introduction of RV vaccine.

Table 1: Characteristics of intussusception cases <2 years admitted to Tungaru Central Hospital (TCH), June 2010-April 2015

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Case 1</th>
<th>Case 2</th>
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<tbody>
<tr>
<td>Age</td>
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<td>5 months</td>
</tr>
<tr>
<td>Sex</td>
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</tr>
<tr>
<td>Residence</td>
<td>Bikenibeu</td>
<td>Betio</td>
</tr>
<tr>
<td>Year of admission</td>
<td>2014</td>
<td>2011</td>
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<tr>
<td>Management</td>
<td>Surgery</td>
<td>Surgery</td>
</tr>
<tr>
<td>LOS</td>
<td>3 days</td>
<td>28 days</td>
</tr>
<tr>
<td>Outcome</td>
<td>Fully recovered</td>
<td>Recovered with sequelae</td>
</tr>
</tbody>
</table>

5.2. IS Surveillance

5.2.1. Results of stakeholder engagement
Informal feedback from paediatric and nursing staff indicated the meetings we held to discuss the planned IS surveillance were well received. A major concern identified from these meetings was that this surveillance system would not add substantially to their workload. As a result of this and other discussions with the
paediatric staff, WHO country office and MHMS, we decided it would be best to identify an existing staff member to act as the local coordinator for the system. The local coordinator would absorb the IS surveillance role into their pre-existing duties.

Concerns were raised by medical staff of the possibility of missed IS cases due to misdiagnosis of IS as dysentery. Thus we also included a review of any cases of death with dysentery or reported blood in stool of children in our age group to ensure these were not misdiagnosed and subsequently missed in our system. Discussions with paediatric staff at TCH also informed our understanding of the data, in that we became aware that surgical intervention is available but ultrasound reduction and air/liquid enema are not available and autopsies are not performed.

5.2.2. Case definition

The case definition used for IS was the same as the one used for review from WHO guidelines.

Causality of IS to RV vaccine will be established by reviewing the time of the IS event and date of RV vaccination. As definitive causality cannot be established for individual cases, the causality assignment, based on post-marketing surveillance of RV vaccines as discussed in the introduction (17, 18), is divided into three categories:

- Potentially vaccine related – 1-7 days after the first dose of RV vaccine
- Likely related – 8-21 days after the first dose of RV vaccine or 1-7 days after the second dose of RV vaccine
- Unrelated to vaccine – 21 days after any dose of RV vaccine

5.2.3. Flow of information into system

Prior to the visit to Kiribati, WHO, A/Prof Russell and MHMS had decided the IS surveillance system would be set up at TCH. This was because IS is severe and requires hospital and surgical treatment, thus cases would present here. TCH was chosen to host the surveillance system as it is the only tertiary health facility with the resources to treat and manage IS cases in country.
Based on the understanding how cases flowed through the TCH system, Figure 4 outlines the steps of when a case is identified by the system. Briefly, once paediatric staff identified a case, the local surveillance coordinator would either be notified by paediatric staff (nurses, paediatrician and/or paediatric surgeon) or would identify the case themselves during their time on the ward. The local coordinator would complete a case investigation form (Appendix C) using the medical records for the case and determine if the case fits the Level 1-3 case definition. For those satisfying the Level 1 case definition, the local coordinator would speak to the treating paediatrician/surgeon for the details regarding the management and clinical outcome of the case. The local coordinator would contact the clinic where the case received his or her vaccinations to determine their vaccination status, as there are no parent-held record for immunisation status. The batch and expiry date of the rotavirus vaccine would be recorded from the MHMS pharmacy records, who distribute the vaccines to the health centres. With this information, the local coordinator in consultation with paediatric staff, WHO staff, MHMS and external monitors, would decide if the IS event is potentially, likely or not related to the vaccine based on timing as detailed previously. After completion of the form and attachment of a copy of the relevant medical record, data would be entered by the local coordinator into the Epidata version 3.1 (EpiData, Denmark) database kept on the WHO country office computer, with completed paperwork of completed cases would be stored in a secure location at MHMS.
In addition, as the external monitors, we would contact the local coordinator on a regular basis (quarterly by email) to monitor the performance of the surveillance system, respond to an increase in cases and check relevant forms are being completed and stored appropriately. Suspected cases identified from the surveillance system and hospital records post-RV vaccine introduction will be reviewed by us on a subsequent annual visit within the 3 year time period to ensure all suspected cases were captured for data quality purposes.

5.2.4. **Resources required to operate the system**

We adapted existing WHO IS data collection tools from the WHO post-marketing surveillance of RV vaccine safety(7), for the situation in Tarawa. These same tools were adapted and used successfully in Fiji by A/Prof Russell and thus adapted for use in Tarawa. We designed and tested a simple Epidata database for data entry of
collection forms. We wrote an SOP for use as both training tool and surveillance protocol for the local coordinator to follow. Due to the small number of cases, paper records and photocopies of the relevant medical records will be kept at MHMS.

The deputy nurse of the paediatric ward was assigned to coordinate the IS surveillance system and as the designated local IS surveillance coordinator. The local coordinator was trained in the IS surveillance SOP (Appendix B) to undertake the surveillance at TCH.

External monitors are scheduled to return within 2 years after establishment of the system to review the data collected in the system. In the interim, external monitors were in regular contact with the local coordinator to monitor cases, help with the review of suspected cases remotely and also provide support to the local coordinator. The review post-RV vaccine introduction will be done to not only ensure no cases have been missed but also to ensure children who have died and have a discharge diagnosis of dysentery or bloody diarrhoea were correctly classified (see sensitivity below).

5.2.5. Results of the system so far
Rotavirus vaccine was introduced into Kiribati in August 2015. As of December 2016, there have been no cases of IS reported by the local coordinator and public health nurses in TCH and Kiribati respectively.

5.2.6. Attributes of the IS surveillance system

Simplicity
The surveillance system is expected to be simple as it was designed to complement the current treatment and diagnosis for suspected IS, with TCH as the only sentinel site and using existing staff in the paediatric ward. The rarity of IS pre- and post-RV vaccine introduction is not expected to add many additional cases therefore the additional workload created by the system will be minimal. In addition, the investigation form is short and the relevant medical records are easily accessible from the hospital. The data from cases will only need to be analysed when I come
for the next review. Thus there is no onus on the staff at the hospital to analyse or disseminate the data on IS incidence.

*Flexibility*

The system is expected to be flexible as there are very limited components to its function. External monitors can change forms quickly with advice from the local coordinator without affecting existing reporting or collection methods. This is also true of inclusion of other adverse events such as fever, vomiting, nausea. Intussusception is not an infectious disease and the presentation and number cases suffering from IS will not change, thus the case definition will remain the same throughout the surveillance period and thereafter. The main concern for the systems flexibility would be changing of associated health personnel. If this does happen, the external monitor will liaise with the relevant staff in WHO country office to identify suitable health personnel to take over.

*Data quality*

To address the issue of data completeness, the local coordinator will photocopy the relevant medical records held either at the bedside of the child (if they haven’t yet been discharged) or from the medical records department located at the hospital. The local coordinator will also have access to the treating paediatrician/surgeon and can discuss specific case issues and confirm a potential temporal relationship between the IS event and RV vaccination with them. For RV vaccination status, it is expected the case’s vaccination history can be located at their relevant clinic. Also the RV vaccine batch and expiry will be easily accessible from the MHMS pharmacy located at the hospital, eliminating the need to travel for this information. At the subsequent site visit, the external monitor will check all the completed forms for completeness and if there is uncertainty, consult the photocopied medical records for the case.

*Acceptability*

The request for the establishment of IS surveillance post-RV vaccine introduction was made by MHMS to WHO, to ensure RV vaccine was safe to use in their population. The system was designed in consultation with the heads of the paediatric division at TCH to ensure the establishment of the system would not increase their workload and create a barrier to the function of the system. Based
on the informal feedback from paediatric staff, they were happy to be engaged in the process and subsequent design of the system, especially as we adopted what they had deemed to be the best options in terms of how the system would fit into their daily tasks and responsibilities.

Sensitivity

This system is expected to be highly sensitive at both the level of case presentation and case diagnosis. As IS is a severe disease and causes great distress in the child, all cases will seek health care and also require admission to TCH.

A standard form for definitive diagnosis of IS was used as part of the case investigation form to provide a standardised method (7) for diagnosis of IS in infants and children. The use of a standardised case definition will improve the quality and comparability of vaccine safety data collected. For Kiribati, only a level 1 case definition was available as they do not have the facilities to satisfy the radiological criteria and do not conduct autopsies.

The key limitation of the system is missing of cases either presenting with clinical symptoms that can be mistaken for other common causes such as dysentery. The symptoms of IS are also very distinct with the distress in the child and the passing of red currant jelly stools. The passing of red currant jelly stools could be mistaken for bloody diarrhoea, leading to a misdiagnosis of dysentery. From the IS review, there were no cases missed by the medical record search and discussions with clinicians. In addition, during our review of records prior to implementation of the system there were no deaths from dysentery fitting the case definition. However to ensure that all potential cases of IS have been included post-RV vaccine introduction, the external monitor will review all hospital discharge records for any diagnoses of IS or bowel obstruction and deaths by dysentery and bloody diarrhoea during the site visit in 2017.

Predictive value positive (PVP)

Definitive diagnosis of IS for Kiribati is only possible by surgical methods and previously established clinical signs and symptoms. Even though the incidence of IS is low in the population, PVP will be high due to the methods of definitive diagnosis, unless cases die before surgery. However, even the lower levels of
classification have been shown to be highly specific (>87%) (25). To ensure reported cases are true cases, hospital records will be reviewed and assessed to ensure they fit the criteria. The case definition used for the surveillance system is based on studies done in both developed and developing country settings and agreed upon by the Brighton Collaboration, a global network of vaccine safety experts. In addition, the tools used for classifying cases have been used and tested in many countries that have introduced RV vaccine into their population. This is especially important in the first year of vaccine introduction, as there may be a risk of over reporting of cases due to the increased awareness of the disease. If cases are reported as IS but this is not supported by surgical findings or clinical criteria then they will be omitted from the reported counts.

*Representativeness*

The system is representative for Tarawa. TCH is the only hospital in Kiribati that can provide the required care and management to treat cases and is located on Tarawa. Thus all cases of IS from Tarawa will be captured here. In addition, as TCH is the referral hospital for Kiribati, children from the outer islands suffering from IS will be referred to TCH for care. With the combination of Tarawa being home to at least 50% of the population and the referral hospital in Kiribati for all IS cases, the results from the system can be extrapolated to the larger Kiribati population.

*Timeliness*

For this condition, timeliness is not an essential attribute of the system. Intussusception is a rare event that is non-communicable and not prone to outbreaks, thus if a case does occur delays in reporting would not lead to additional morbidity or mortality. It is however expected the reporting of cases will occur rapidly as the local coordinator is based in the paediatric ward where potential cases would be admitted and has daily interactions with the treating paediatrician. Rotavirus vaccination status may have more of a lag time, as it requires liaising with health centre staff. Fortunately WHO country office is very active in the community and the local coordinator would notify staff shortly after the event, as she is required to submit the paperwork to the WHO country office for storage, data entry and a response if deemed necessary.
Stability

The system is likely to be stable as it is reliant on resources already in place for IS diagnosis and management. The greatest risk for stability will be if key paediatric staff leave TCH. This is unlikely as TCH is the only tertiary hospital in Kiribati and there are no other options in terms of facilities to practice. The other main risk is as IS is a rare event, interest may wane, so regular contact between the local coordinator and external monitor will be important to ensure potential cases are being identified throughout the surveillance period. The supported surveillance will continue for 3 years post-RV introduction. Three years post RV introduction will give immunisation policy makers a good indication of the risk associated with RV use and IS in the Kiribati population. After 3 years, there will be enough evidence on the safety of the vaccine to warrant IS surveillance cessation.

Usefulness

The purpose of the IS surveillance system is to detect potential cases of IS post-RV vaccine introduction to show the vaccine is safe. This is to determine if there is a temporal relationship between the IS event and RV vaccine administration in the case. The system will serve this purpose and more importantly provide evidence there are not excess cases of IS occurring post-RV vaccine introduction. This will help to provide MHMS with the data required to show the public and policymakers the vaccine is safe.
6. Discussion

The annual incidence of IS (20/100,000 (95% CI 2-73) in children <1 year found in this review was similar to the IS incidence reported in Oceania (27-101/100,000). Reasons for the discrepancy between countries include under reporting of cases due to health seeking behaviour, inability to confirm the diagnosis and weak reporting systems. Other factors may include environmental or genetic factors, which may vary by population, highlighting the need to establish baseline IS data to assess any potential vaccine-associated risk (3). However, for Kiribati we believe that the incidence we have calculated is accurate considering Tarawa is home to more than half the population of Kiribati. In addition, TCH is accessible to all inhabitants of Tarawa for treatment and the severity of IS would force people to seek treatment. Thus few, if any, cases would be missed by TCH.

The key limitations with the IS review were the small numbers of IS cases in the 5 years preceding RV vaccine introduction. During the review period, only two cases were identified making it difficult to draw many conclusions on the baseline epidemiology of IS in Kiribati. The age of IS cases in this review reflected the naturally occurring peak found globally of 4-7 months of age (3). The sex of the cases differed from what is seen elsewhere with a male predominance in published reports, with both cases being female. For the study period, no cases were missed, cross-checked by review of the medical records, discussions with paediatric staff and also review of cases that had died of dysentery, bacterial diarrhoea or bloody diarrhoea. The latter cases of dysentery were reviewed following concerns of staff they could be misdiagnosed IS cases.

The purpose of the surveillance system is to support the introduction of RV vaccine into Kiribati and show the vaccine is safe for use in the population. The strengths of the IS surveillance system lie in the simplicity, acceptability, sensitivity and PVP of the system. The system relies heavily on the paediatric staff at TCH, therefore it was very important they were engaged, happy with the design and minimal additions to their workload. This was achieved through discussions with the key staff and presentation of the system to all the paediatric staff at the end of our visit. Due to the nature of IS and the available resources at TCH, this meant the system
had both high sensitivity and specificity to detect and diagnose cases. Intussusception is a severe condition and parents would always bring their child into TCH care if it occurred. At TCH, the only treatment available is surgery. This means all potential cases would have a definitive diagnosis of IS, a level 1 classification with near 100% specificity.

The weaknesses of the system are in the stability and data quality attributes. Because the system relies on TCH paediatric staff, if there are changes to key staff members this will undermine the system. However, there are two elements that will protect the system from instability; one being TCH is the only tertiary health facility in the country and the surveillance is only being conducted for a short period of time. The key staff involved are the paediatricians, paediatric surgeons and the senior paediatric nursing staff. Being the only tertiary health facility in the country means this is the only health facility that can house these staff and the likelihood of them moving to a different health facility is not possible, especially in the short-term. In terms of data quality, the forms are simple but data regarding RV vaccination for potential cases will need to be sought from an outside source. Thus far there have been no indications this will be an issue, but in practice it still remains to be seen.

To ensure the system is working, a post-RV vaccine introduction review will be conducted. The same methodology and case definition will be used to determine if there have been any IS cases missed. It will also be important to meet with all stakeholders to discuss how the system is functioning and if there were any issues that may inhibit the system from capturing potential cases based on the original design. A key concern in the design is the potential of missed cases from the outer islands that do not seek care in time. Whilst TCH is the referral point for Kiribati, it is possible cases from the outer islands may not be able to seek care in time and so cases may be missed this way. This shouldn't be an issue in terms of determining vaccine safety as the baseline IS data is from the same population but the system as a whole may potentially miss cases this way.

As IS is a rare adverse event, the ability to detect the expected additional case related to use of RV vaccine will be a problem if it does occur. The surveillance
system is expected to detect cases of IS post-RV vaccine introduction, but due to the small numbers, the additional case(s) will greatly increase the incidence of IS cases. Thus because the numbers are so small, an IS incidence rate post-RV vaccine introduction will not be calculated. As the population of Tarawas is small and IS is rare, one additional case occurring by chance would increase the IS incidence by 50%. Temporality of the IS case to RV vaccine receipt will provide the greatest source of evidence as to a concern in Rotarix® safety in this population. A risk assessment approach could be used, where timing of IS cases, location of IS cases and changes to access to care would be considered to determine if the IS cases were potentially related to vaccine or by chance. However, in this setting it will be very difficult to determine causality. This is because as the numbers are so small, the same assessments post-marketing in the US, Mexico and Australia will be impossible to achieve in Kiribati.

An evaluation of the surveillance system will be done in late 2017, when we return to complete the AGE evaluation. WHO recommends IS surveillance for 3 years post-RV vaccine introduction. If there were issues with vaccine safety, these would be seen within these 3 years. The data collected during this 3-year period will provide enough evidence to reassure MHMS of the vaccine’s safety. There would be no need to continue this surveillance beyond the recommended time period. In addition, based on the review, IS cases received appropriate surgical care, with no deaths. This means if a vaccine-related case were to occur the appropriate care would be available with a favourable outcome.

Intussusception is a rare but potentially fatal event and use of RV vaccine has been shown to increase the risk of IS occurring. In Kiribati, if there are additional cases related to vaccination, effective treatment is available for at least 50% of the population. The establishment of a simple but robust IS surveillance system post-RV vaccine introduction will provide the data needed to show RV vaccine is safe. To support this, a check of the data quality will be done by external monitors within the 3 year time period of RV vaccine introduction to instil the confidence that the system did not detect any IS cases post-RV vaccine introduction.
7. Recommendations

- For the next visit, the external monitor should investigate admissions and the referral process of Betio Hospital for cases of AGE and SAM. This is to ensure children were referred onto TCH. This is to ensure the AGE and SAM incidences calculated from the initial site visit accurately reflect the burden of disease in the population. If there are a substantial number of children admitted and treated at Betio Hospital, the same review process done at TCH previously should be conducted and the incidence calculations adjusted to reflect these additional cases both pre and post-RV vaccine introduction.

- On the post-RV vaccine introduction review, to ensure maximal usefulness, it is imperative that the external monitor conducts the following activities:
  
  o Meet with the local coordinator to discuss the operation of the surveillance system. This is to identify if there are issues or problems with the surveillance system.
  
  o Discuss the operation of the surveillance system with paediatric staff to check if the system is still acceptable and capturing all potential cases.
  
  o Check the medical records of IS cases detected by the surveillance system to ensure data is complete and accurate during their next site visit.
  
  o Review medical records of fatal cases of dysentery or bloody diarrhoea, to ensure these are not missed IS cases.
8. References


# 9. Appendices

## A. Intussusception review data collection form

The impact of rotavirus vaccine on hospitalised acute gastroenteritis and intussusception in Kiribati: IS review version 1.1, 26th May, 2015

<table>
<thead>
<tr>
<th>Patient Details</th>
<th>Case No.</th>
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</thead>
<tbody>
<tr>
<td>Hospital ID:</td>
<td></td>
</tr>
<tr>
<td>Age: ___ years ___ months</td>
<td></td>
</tr>
<tr>
<td>Date of admission: <strong><strong>/</strong></strong>/____</td>
<td>Date of discharge: <strong><strong>/</strong></strong>/____</td>
</tr>
</tbody>
</table>

### Discharge Diagnosis

- [ ] Intussusception
- [ ] Other: ____________________________

### Rotavirus vaccination history

<table>
<thead>
<tr>
<th>Rotavirus vaccine</th>
<th>1(^{st}) dose or [ ] Unk</th>
<th>2(^{nd}) dose or [ ] Unk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date of administration</td>
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</tbody>
</table>

### Management

- [ ] Surgery required
- [ ] Ultrasound with reduction verification
- [ ] Air/Liquid contrast enema
- [ ] Autopsy

### Outcome

- [ ] Fully recovered
- [ ] Recovered with sequelae
- [ ] Dead
- [ ] Unknown
- [ ] Pending

### Comments:

...
# Chapter 3 – Kiribati Intussusception Surveillance

The impact of rotavirus vaccine on hospitalised acute gastroenteritis and intussusception in Kiribati: IS review  

<table>
<thead>
<tr>
<th>LEVEL 1: CASE DEFINITION</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>(≥1 criterion)</td>
<td></td>
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</tbody>
</table>

- Surgery  
- Air/liquid contrast enema  
- Ultrasound with reduction verification  
- Autopsy  

<table>
<thead>
<tr>
<th>LEVEL 2: CASE DEFINITION</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>(2 major or 1 major and 2 minor criteria)</td>
<td></td>
</tr>
<tr>
<td>MAJOR CRITERIA</td>
<td></td>
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</tbody>
</table>
- Intestinal obstruction  
|  |

- Features of intestinal invagination  

- Intestinal mass  
- Rectal mass  
- Intestinal prolapse  
- Plain abdominal x-ray showing IS mass  
- CT scan showing IS mass  

- Intestinal vascular compromise of venous congestion  

- Passage of blood per rectum  
- Passage of “redcurrant jelly” stool  
- Blood on rectal examination  

<table>
<thead>
<tr>
<th>MINOR CRITERIA</th>
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</thead>
<tbody>
<tr>
<td>LEVEL 3: CASE DEFINITION</td>
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</tr>
<tr>
<td>(≥4 minor criteria)</td>
<td></td>
</tr>
</tbody>
</table>

- Age <1 year  
- Abdominal pain  
- Vomiting  
- Lethargy  
- Pallor  
- Hypovolemic shock  
- Plain x-ray: abnormal non-specific bowel gas pattern  

<table>
<thead>
<tr>
<th>OTHER SYMPTOMS</th>
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</thead>
<tbody>
<tr>
<td>Diarrhoea</td>
<td></td>
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<tr>
<td>Irritability</td>
<td></td>
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<tr>
<td>Fever – temp:</td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td></td>
</tr>
<tr>
<td>Urticaria</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>RELEVANT PAST HISTORY</th>
<th></th>
</tr>
</thead>
</table>

- Abdominal surgery:  
- Describe:  
- Allergies  
- CNS disease  
- Immunodeficiency  

- Vaccine-related adverse events  
- Prematurity  
- Medications or traditional therapies used in the last 3 weeks; describe type, dose dates

<table>
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<th></th>
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<tr>
<th>Date:</th>
<th></th>
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</thead>
</table>

Day  
Month  
Year
B. Intussusception surveillance SOP

Hospital Intussusception Surveillance Post-Rotavirus Vaccine Introduction in Kiribati

- When a case of intussusception or acute bowel obstruction is admitted to TCH the local coordinator will review the medical record of the child

- The case definition for intussusception requiring review:
  - Child ≤24 months of age
  - Bowel obstruction
  - Symptoms or investigations indicative of intussusception (see case investigation form)

- The local coordinator will complete the case investigation form using the medical records for the case

- The local coordinator will determine whether the case fits the Level 1, 2, or 3 case definition described on the case investigation form. Only those cases fitting the Level 1-3 criteria will be included.

- For those fitting the Level 1-3 criteria, the local coordinator will need to speak to the following people to complete the form:
  - Paediatrician and surgeon for the details regarding the management and clinical outcome for the case
  - Local clinic nurse where case received rotavirus vaccination to determine the date of vaccination, dose number, location of receipt of vaccination and the vaccine lot number administered. The vaccine lot number may have to be obtained from the distributing pharmacy rather than the local clinic

- The local coordinator will need to determine whether the Level 1-3 case is potentially, likely or not related to the vaccine based on the timing of administration of the rotavirus vaccines in relation to the IS event.

- After completion of the case investigation form, the local coordinator will photocopy the medical record and attach it to the case investigation form.

- Completed case investigation forms and accompanying medical records will be stored in a secure location at the Ministry of Health Office

- Cases will be reviewed annually by a visiting WHO representative (Fiona Russell – fraruss@unimelb.edu.au or Jana Lai – jana.yr.lai@gmail.com)
C. Intussusception case investigation form

The impact of rotavirus vaccine on hospitalised acute gastroenteritis and intussusception in Kiribati: IS surveillance version 3.3, 26th May, 2015

Case Investigation Form

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Clinic/Hospital Information

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<th>Hospital ID: ________________</th>
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</thead>
<tbody>
<tr>
<td>Name of person reporting: __________________</td>
<td>Position: ____________________</td>
</tr>
<tr>
<td>Name of Clinic/Hospital: __________________</td>
<td>__________________________</td>
</tr>
<tr>
<td>Telephone: __________________</td>
<td>Email: ______________________</td>
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</table>

Patient Details

<table>
<thead>
<tr>
<th>Address: ____________________</th>
<th>Village: ____________________</th>
<th>Sex: ☐ Male ☐ Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date of birth: <em>/__/</em>___</td>
<td>Age: ___ years ___ months</td>
<td></td>
</tr>
<tr>
<td>Date of admission: <em>/__/</em>___</td>
<td>Date of discharge: <em>/__/</em>___</td>
<td></td>
</tr>
<tr>
<td>Length of stay: __________ days</td>
<td>Date of onset of symptoms: <em>/__/</em>___</td>
<td></td>
</tr>
<tr>
<td>Name of Clinic where vaccines given: ____________________________</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Discharge Diagnosis

☐ Intussusception ☐ Other: ________________________________
### Rotavirus vaccination history

<table>
<thead>
<tr>
<th>Rotavirus vaccine</th>
<th>1st dose</th>
<th>2nd dose</th>
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<tbody>
<tr>
<td>Date of administration</td>
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<tr>
<td>Vaccine lot number</td>
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<tr>
<td>Vaccine expiry date</td>
<td></td>
<td></td>
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<tr>
<td>Location received</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other relevant data</td>
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</tr>
</tbody>
</table>

### Causality

- [ ] Potentially vaccine related 1- 7 days after the first dose of RV vaccine
- [ ] Likely related 8-21 days after the first dose of RV vaccine: or 1-7 days after the second dose of RV vaccine
- [ ] Unrelated to vaccine 21 days after any dose of RV vaccine

### Management

- [ ] Surgery required
- [ ] Ultrasound with reduction verification
- [ ] Air/Liquid contrast enema
- [ ] Autopsy

### Outcome

- [ ] Fully recovered
- [ ] Recovered with sequelae
- [ ] Dead
- [ ] Unknown
- [ ] Pending

### Comments:
## Chapter 3 – Kiribati Intussusception Surveillance

The impact of rotavirus vaccine on hospitalised acute gastroenteritis and intussusception in Kiribati IS surveillance

### LEVEL 1: CASE DEFINITION
(≥1 criterion)
- Surgery
- Air/liquid contrast enema
- Ultrasound with reduction verification
- Autopsy

### LEVEL 2: CASE DEFINITION
(2 major or 1 major and 2 minor criteria)
**MAJOR CRITERIA**
- Intestinal obstruction

**MINOR CRITERIA**
- Level 3: CASE DEFINITION
  (≥4 minor criteria)
- Age <1 year
- Abdominal pain
- Vomiting
- Lethargy
- Pallor
- Hypovolemic shock
- Plain x-ray: abnormal non-specific bowel gas pattern

### OTHER SYMPTOMS
- Diarrhoea
- Irritability
- Fever – temp: _____ °C
- Rash
- Urticaria

### RELEVANT PAST HISTORY
- Abdominal surgery:
  - Describe:
- Allergies
- CNS disease
- Immunodeficiency

- Vaccine-related adverse events
- Prematurity
- Medications or traditional therapies used in the last 3 weeks; describe type, dose dates

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Signature: ___________________________  Date: _____/____/____

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version 3.3, 26th May, 2015

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114
D. **WHO mission report**

**CONSULTANT’S REPORT**

*Retrospective review of acute gastroenteritis and intussusception and establishment of intussusception surveillance post-rotavirus vaccine introduction in Kiribati*

**Date:** Monday 15th June, 2015

**Contractual partner:** Centre for International Child Health (WHO Collaborating Centre for Research and Training in Child and Neonatal Health), Department of Paediatrics, The University of Melbourne, Australia

**Contact person:** A/Prof Fiona Russell, Principal Research Fellow

**Postal address:** CICH, Dept. of Paediatrics, The Royal Children’s Hospital, Flemington Rd, Parkville, 3052, Australia

**Telephone no:** +61 393454077 or +61 412109223

**Duration:**
- A/Prof Russell: 7 – 14 May 2015, 7 days in country
- Jana Lai: 7 – 21 May 2015, 14 days in country; Ms Lai spent an additional 5 working days entering and analysing data and preparing a report

**Background**

Kiribati Ministry of Health and Medical Services plans to introduce rotavirus vaccine in June 2015. To document the burden of diarrhoeal disease among young children and the impact of vaccine introduction, a retrospective review of diarrhoea admissions will be undertaken at the main hospital in Kiribati. To ensure appropriate monitoring for a rare adverse event related to rotavirus vaccine, intussusception (IS) surveillance will also be established at the main hospital.

**Purpose/Specific objective of the activity**

The contractor will:

a) collaborate with national and hospital staff to conduct retrospective data collection for up to 5 years for diarrhoeal hospitalisations among children under 5 years old and for IS at the main hospital in Kiribati;

b) develop simple hospital-based system for syndromic IS surveillance to monitor cases prospectively for 3 years;

c) plan for annual retrospective collection of data on diarrhoeal hospitalisations among children under 5 years old; and

d) advise national and hospital authorities on key measures to monitor IS surveillance.

**Description of activities carried out**

The contractors wrote the protocol (Annex 1), and subsequently collected and reviewed hospital data for diarrhoea and acute gastroenteritis (referred to as AGE henceforth),
all-cause hospitalisation and IS for children <5 years of age admitted to Tungaru Central Hospital (TCH). This data was sought from both electronic hospital records and medical records. To calculate hospitalisation incidence, both by month and by age, Census data were sought from the Health Information Unit (HIU) to ascertain the population of Tarawa from 2010 to 2015.

In addition the contractors trained a local staff member to conduct IS surveillance post-introduction of rotavirus vaccination in Kiribati. This included training in the attached SOP (Annex 2) and use of the IS case investigation form (Annex 3).

Method to carry out the activity

Prior to the visit in May 2015, the protocol and forms for data collection and IS surveillance (Annexes 1 – 6) were prepared and printed ready for data collection in May 2015. Forms used included tally sheets for all-cause admissions of children <5 years of age (Annex 4), and specific data collection forms for AGE admissions (Annex 5), the IS review (Annex 6) and an IS case investigation form (Annex 3). An SOP for the IS surveillance was developed (Annex 2) for the local IS surveillance coordinator.

Description of the tasks/process involved in carrying out the activity

The contractors:

a) Met with hospital, statistics and WHO staff to organise collection of data from hospital admissions, medical records and census surveys;
b) Reviewed records and documented the cases of AGE and all-cause admissions for children <5 years of age from Jun 2010-Apr 2015;
c) Reviewed records to find and review cases of IS ≤2 years of age from Jun 2010-Apr 2015;
d) Identified and trained a local coordinator to oversee the surveillance of IS post-rotavirus vaccine introduction;
e) Spoke with Ministry of Health and Medical Services paediatricians, surgeon, junior doctors and nurses, and WHO and UNICEF staff about rotavirus infection, rotavirus vaccine, IS, and the evaluation; and
f) Provided a brief report of preliminary data and the future work schedule to the Ministry of Health and Medical Services, WHO and UNICEF.

Report

Evaluation site

Tarawa is home to approximately 60% of the total population of Kiribati. Each village has a health centre staffed by nurses who provide basic primary health care, administer vaccinations and run health promotion activities. Patients who require further care are
either referred or seek care at one of the two hospitals on Tarawa: one in Betio and the other, TCH, in Nawerewere. TCH is the main hospital for Tarawa and also the only facility that can provide management of severe cases of disease and cases of IS. TCH is also the referral hospital for the outer islands. Some serious cases of AGE do not present to the hospital, as it is not uncommon for children to die at home with no autopsy or death reporting available, especially for children who reside on the outer islands where access to health care is a major issue. However the majority of families on Tarawa, do seek health care at TCH. Hence most hospitalised AGE cases, IS cases, and deaths in children occur at TCH.

**Immunisation records**

DTP3 coverage is relatively high and estimated to be 86% in the lowest performing area in Kiribati. Immunisations are recorded for each child in each administering health centre. Immunisation records for each child are held at the relevant health facility with a copy given to the parents. To determine the vaccination status of an individual child, a search could potentially be done by searching the registers held in each health centre if the clinic where the vaccines were administered was known, made easier if the month of administration was known.

**AGE data collection**

Meetings with staff from the HIU88, medical records, laboratory staff, and the paediatricians of TCH were conducted to determine the source of relevant data. Stool samples from AGE cases are not routinely collected or tested to determine the aetiology of diarrhoea. However for diarrhoea outbreaks, the TCH laboratory is able to perform a rapid test for rotavirus, culture (not Campylobacter), microscopy for parasites, and E.coli 157 testing. Information on previous outbreaks of diarrhoeal disease were sought from WHO and the WHO Rotavirus Regional Reference laboratory. In the past 5 years there have been 2 major outbreaks recorded in Kiribati, both with laboratory confirmation of rotavirus. The 2013 outbreak investigation was caused by rotavirus strain type G3P[8]. There was no further data available from the 2014 outbreak.

Hospitalised AGE cases <5 years old were collated from two sources. Data from June 2010 to 2014 was provided from the electronic hospital discharge database by the medical records department. As the 2014 electronic data was incomplete, the 2014 data was instead collated from the paper-based hospital paediatric admission book from March 2014 to May 2015, with data from January 2014 and early February 2014 missing from both sources. AGE cases were determined to be any diagnosis of diarrhoea (viral and bacterial), gastroenteritis (viral and bacterial). As rotavirus diarrhoea is an acute watery, non-bloody diarrhoea, cases of chronic or persistent diarrhoea, bloody diarrhoea and dysentery were excluded.
For incidence calculations, the TCH catchment population was defined as the < 5 year olds residing on Tarawa. Hence, only hospitalised AGE cases residing on Tarawa were included in the population based analysis. The annual population calculations were extrapolated from the official 2010 census data. The age groups in the 2010 census relevant for our review were <12 months, 12-23 months and 2-5 years. To calculate the number of children between 24-59 months, 75% of the total 2-5 years population was used from the 2010 Census. The population for the other years (2011 - 2015) was extrapolated from the 2010 Census data by applying 2.2% increases for the <5 year old population.

IS review

Meetings with the paediatricians and a TCH surgeon were held to determine their clinical experience and management of IS cases, and the number of IS cases seen each year. Concerns were raised by medical staff of the possibility of missed IS cases due to misdiagnosis of IS as dysentery. Abdominal x-rays and ultrasound are available to assist diagnosis. For treatment, surgical intervention is available but ultrasound reduction and air/liquid enema are not available. There are no autopsies performed in Kiribati.

Potential IS cases were identified using a search criteria of IS or bowel obstruction in any child ≤2 years of age from the electronic hospital discharge database from TCH, June 2010-April 2015. Medical records of potential IS cases were reviewed and determined to be IS based on whether they fitted the IS case definition (based on the Brighton clinical case definition for IS, see Annex 3). Two IS cases were found—both were Level 1 IS cases. Both cases were confirmed by surgery and had favourable outcomes. To search for any potential missed cases, the electronic hospital discharge database was reviewed over the same time period for any child ≤2 years of age who had died from dysentery, bloody diarrhoea or bacterial diarrhoea. No additional cases were found.

Establishment of IS surveillance

Briefings were held with paediatric and nursing staff to discuss the IS surveillance to be commenced at the same time rotavirus vaccine is introduced. The deputy nurse, Atiri Baaka, of the paediatric ward was assigned to coordinate the IS surveillance system. Sister Baaka was trained in the SOP (see Annex 2) to undertake the surveillance. To determine the vaccination status of each IS cases, she will need to contact the clinic where the case received their vaccinations, as there is no parent held record which records immunisation status. The batch and expiry date of the rotavirus vaccine can be recorded from the Ministry of Health and Medical Services pharmacy records which distributes the vaccines to the health centres. Jana Lai will contact Sister Baaka regularly to monitor the surveillance system and the forms and cases will be reviewed on her subsequent visits.
Other notes

During the visit there was an outbreak of diarrhoeal disease on Tarawa. The contractors provided guidance during the outbreak and liaised with staff from the laboratory and statistics department to advise on the public health response and monitoring of cases. Initially the cause was thought to be viral, potentially rotavirus, due to the age of the cases affected, but later on there were increasing reports of dysentery (bloody diarrhoea) in up to 17% of the ~300 cases. Some stool samples were sent to the laboratory and at the time of departure, the stools tested were rotavirus negative. An environmental assessment was also undertaken. Summaries and available reports on the outbreak were sent to WHO.

Severe acute malnutrition (SAM) is common in Kiribati, as such the effectiveness of rotavirus vaccine is likely to be less (50-75%). Hospital admissions with SAM as the primary cause of admission, are captured in the same electronic hospital database of all TCH admissions.

Recommendations and future work

- The results of the AGE and IS review will be submitted on 15th June 2015.
- As this evaluation is part of a broader UNICEF Child Survival package with many interventions, any decline in AGE incidence post-rotavirus vaccine introduction is unlikely to be due to rotavirus vaccine alone. To provide further evidence that rotavirus vaccine is effective in Kiribati, we would recommend that for any future outbreaks on Tarawa, samples are collected and tested locally and overseas to determine the aetiology of each outbreak.
- As the efficacy of rotavirus vaccine is potentially reduced by malnutrition, the rotavirus vaccine effectiveness is likely to be 50-75% in Kiribati. It is recommended that the rates of hospitalised severe acute malnutrition (SAM) are also established throughout the same time frame (June 2010 to April 2018). This could be done using the same database provided for the AGE review.
- Jana Lai will return to South Tarawa mid 2016 and 2018 to review the hospital records for May 2015-May 2016 (time period during vaccine introduction) and if funding permits, June 2016-May 2018 (time period post-vaccine introduction) to evaluate the impact of rotavirus vaccine in Kiribati.
- At each subsequent visit, IS cases reported through the surveillance system post-rotavirus vaccine introduction will be reviewed. Jana Lai will also keep in regular contact with the IS surveillance co-ordinator to monitor implementation.
Financial report

One economy airfare Melbourne-Tarawa (Fiona Russell)
One economy airfare Vientiane-Tarawa (Jana Lai)
Accommodation receipts: Bangkok (Jana Lai) and Nadi (Fiona Russell) and Tarawa (both)

Fiona Russell
The University of Melbourne

Stakeholders consulted

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Tebiria Kabiriera, Officer in Charge, H1U
Tabuanaba Baraniko, Statistical Officer, HIU
Tebau Bantarawa, Senior Medical Records Officer, Hospital Medical Records
Gretta Tauma, Deputy Head, Laboratory Department
Bineta Ruia, Microbiologist, Laboratory Department
Tebikau Tibwe, Ag Chief Health Inspector, Environmental Health Services

Paediatric Department
Dr. Peter Asuo, Head of Paediatrics and Training
Dr. Kabiri Tuneti, Head of Paediatric Surgery
Atiri Baaka, Second in Charge, Paediatric Nurse

WHO Kiribati Office
Agnes B. Nikuata, Maternal and Child Health, WHO Kiribati

UNICEF
Dr. Patrick Byarungha
Dr. Nahad Sadr-Azodi
E. WHO findings report

CONSULTANT’S REPORT

Retrospective review of acute gastroenteritis and intussusception and establishment of intussusception surveillance post-rotavirus vaccine introduction in Kiribati

Date: 27th April, 2016

Contractual partner: Centre for International Child Health (WHO Collaborating Centre for Research and Training in Child and Neonatal Health), Department of Paediatrics, The University of Melbourne, Australia

Contact person: A/Prof Fiona Russell, Principal Research Fellow

Postal address: CICH, Dept. of Paediatrics, The Royal Children’s Hospital, Flemington Rd, Parkville, 3052, Australia

Telephone no: +61 393454077 or +61 412109223

EXECUTIVE SUMMARY

Background and Aims: Kiribati Ministry of Health and Medical Services will introduce rotavirus vaccine in June 2015. To document the burden of acute gastroenteritis (AGE) and severe acute malnutrition (SAM) among young children and the impact of vaccine introduction, a retrospective review of hospitalised AGE, SAM and intussusception (IS) was undertaken at the main hospital in Kiribati. To ensure appropriate monitoring for IS, a rare adverse event potentially related to rotavirus vaccine, IS surveillance was also established.

Methods: Data were collected for children <5 years admitted to Tungaru Central Hospital (TCH) from June 2010 to April 2015 for all-cause, AGE, SAM and IS admissions. The 2010 Census data for Tarawa was used to calculate the AGE, SAM and IS incidence.

Results: The median age of AGE cases was 13.4 months (IQR 9.4-20.3) and the highest proportion of AGE cases (43%) occurred in children 12-23 months old. The majority of cases were male (59%) and the case fatality ratio was 7%. AGE contributed to 12% of all <5 years admissions and 16% of all-cause mortality in hospitalised children <5 years. The annual incidence of hospitalised AGE was 1,266 per 100,000 (95% CI 1,161-1,377) children <5 years old. Children <24 months had the highest incidence of hospitalised AGE. The AGE pattern in Kiribati is consistent with other tropical countries where marked seasonality is not displayed. AGE outbreaks occurred in 2013 and 2014, which were both laboratory confirmed for rotavirus. The 2013 outbreak was caused by rotavirus strain G3P[8]. The annual IS incidence was 20 per 100,000 children (95% CI 2-73) <1 years. The annual incidence of SAM was 453 per 100,000 children (95% CI 381.2-534.1) with a case fatality ratio of 21%. SAM contributed to 16% of all-cause mortality in hospitalised children <5 years.

Summary and conclusions: AGE causes a large burden of disease for children in Kiribati. Consistent with other countries, rotavirus infection is likely to contribute to a substantial proportion (~40%) of AGE and contributed to two recent AGE outbreaks. A considerable proportion of all childhood deaths are due to AGE. The incidence rates of hospitalised AGE before and after the introduction of rotavirus vaccine will be compared in 2017. The effectiveness of rotavirus vaccine may be affected by the high rates of malnutrition in Kiribati. Nevertheless, the burden of AGE caused by rotavirus in
Kiribati is likely to be reduced by 50-75%. As rotavirus vaccine introduction is part of a number of interventions to improve child health in Kiribati, any reduction in AGE admissions post rotavirus vaccine introduction will still be partially due to rotavirus vaccine. It is recommended that for any future outbreak of AGE, that the aetiology of the outbreak is established, including rotavirus testing. Following national introduction of rotavirus vaccine in Kiribati, one additional case of IS may occur every 5-17 years.

**ABBREVIATIONS**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>AGE</td>
<td>acute gastroenteritis</td>
</tr>
<tr>
<td>SAM</td>
<td>severe acute malnutrition</td>
</tr>
<tr>
<td>IS</td>
<td>intussusception</td>
</tr>
<tr>
<td>TCH</td>
<td>Tungaru Central Hospital</td>
</tr>
<tr>
<td>IQR</td>
<td>inter-quartile range</td>
</tr>
<tr>
<td>SAM</td>
<td>severe acute malnutrition</td>
</tr>
<tr>
<td>CI</td>
<td>confidence interval</td>
</tr>
<tr>
<td>USA</td>
<td>United States of America</td>
</tr>
<tr>
<td>UNICEF</td>
<td>United Nations Children’s Fund</td>
</tr>
</tbody>
</table>
BACKGROUND AND AIMS

The aims of the consultation were to:

a) collaborate with national and hospital staff to conduct retrospective data collection for up to 5 years for AGE and SAM hospitalisations among children <5 years and for IS at the main hospital in Kiribati;

b) develop a simple hospital-based system for syndromic IS surveillance to monitor cases prospectively for 3 years;

c) plan for annual retrospective collection of data on AGE and SAM hospitalisations among children <5 years; and

d) advise national and hospital authorities on key measures to monitor IS surveillance.

This findings report documents the findings from the first site visit to document the hospitalised AGE and SAM burden prior to rotavirus vaccine introduction and review IS cases in the past 5 years to establish a baseline case number of IS prior to vaccine introduction. Prospective IS surveillance was also established during this site visit, so that in the future the number of IS cases can be compared before and after the introduction of rotavirus vaccine. For more details on the IS surveillance please refer to the mission report.

METHODS

Tarawa is home to approximately 60% of the total population of Kiribati. Each village has a health centre staffed by nurses who provide basic primary health care, administer vaccinations and run health promotion activities. Patients who require further care are either referred or seek care at one of the two hospitals on Tarawa: one in Betio and the other, TCH, in Bikenibeu. TCH is the main hospital for Tarawa and also the only facility that can provide management of severe cases of disease and cases of IS. TCH is also the referral hospital for the outer islands. Some serious cases of AGE do not present to the hospital, as it is not uncommon for children to die at home with no autopsy or death reporting available, especially for children who reside on the outer islands where access to health care is a major issue. However the majority of families on Tarawa, do seek health care at TCH. Hence most hospitalised AGE cases, IS cases, and deaths in children occur at TCH.

AGE data for all children <5 years admitted to TCH were collected from the hospital admission books (February 2014- April 2015) and the electronic medical records (June 2010- Dec 2013). Data from January and February 2014 were incomplete from both sources. An AGE case was any child <5 years with a discharge diagnosis of diarrhoea (viral and bacterial), and gastroenteritis (viral and bacterial). As rotavirus diarrhoea is acute, watery, non-bloody diarrhoea, cases of chronic or persistent diarrhoea, bloody diarrhoea and dysentery were excluded. Laboratory confirmation of rotavirus is not routinely available. In previous outbreaks, rotavirus testing has been done overseas. This information was sourced from WHO, C. Kirkwood and also from a paper by Tabunga et al. (2014) detailing testing of stool samples in Australia from the outbreak in 2013 (1). The 2014 outbreak was also caused by rotavirus (pers comm. WPPO WHO), but there we do not have access to any additional data to confirm this information. In recent years, rapid testing has been available at TCH for diarrhoea outbreak confirmation.
SAM, as the primary cause of admission to TCH, for all children <5 years old admitted were collected from the hospital electronic medical records (Jun 2010 – Dec 2013). The electronic data for 2014 and 2015 was incomplete and thus not included in this analysis. A SAM case was defined as any child <5 years with a discharge diagnosis of severe malnutrition, malnutrition, failure to thrive, very low weight, marasmus or kwashiorkor.

For incidence calculations, the TCH catchment population was defined as children <5 years residing on Tarawa. Hence, only hospitalised AGE and SAM cases residing on Tarawa were included in the population-based analysis. The population data was obtained from the official 2010 census. The age groups in the 2010 census relevant for this review were <12 months, 12-23 months and 2-5 years. We used 75% of the 2-5 year old population as the number of children aged 24-59 months old. A 2.2% growth rate was applied per annum to the 2010 census data to calculate the 2011-2015 <5 years population.

Both hospital and medical records over the same time period as stated above, were reviewed to identify potential cases of IS. Potential IS cases were those aged ≤24 months old, and had a diagnosis of IS, bowel obstruction, or other diagnoses that may indicate some form of bowel obstruction. To identify any potential missed cases, medical records were also reviewed if a child had died from dysentery or bacterial diarrhoeal disease. The medical records of each potential case were reviewed and determined to be a Level 1-3 case of IS as per the Brighton clinical case definition (2).

FINDINGS

AGE review

Table 1 shows the characteristics of the 554 hospitalised <5 years hospitalised AGE cases from June 2010 to April 2015. AGE contributed to 12% of all-cause hospital admissions and 16% of all-cause hospital deaths in <5 years children. There were significantly more males than females (59% vs. 40%, p-value <0.0001). AGE was most common in the 12-23 month old age group (Fig 1). The AGE case fatality ratio was 7%. The AGE mortality incidence was 92 per 100,000 (95% CI 65.4-125.7) children aged <5 years. There were more males in the AGE mortality group than females but this was not statistically significant (p-value <0.14). The majority of cases came from the most populous areas of Tarawa: Bikenibeu, Betio, Temwaiku and North Tarawa (Fig 2).

Table 1: Characteristics of AGE hospitalisations in children <5 years at Tungaru Central Hospital (TCH) from June 2010-April 2015 (n=554)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>N=554</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age in months</td>
<td>13.4 (IQR 9.4-20.3)</td>
</tr>
<tr>
<td>Sex*</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>329 (59%)</td>
</tr>
<tr>
<td>Female</td>
<td>224 (40%)</td>
</tr>
<tr>
<td>Case fatality ratio (n=39)</td>
<td>7%</td>
</tr>
<tr>
<td>Proportion of all-cause admissions in &lt;5yo due to AGE</td>
<td>554/4474 (12%)</td>
</tr>
<tr>
<td>Proportion of all-cause mortality in &lt;5yo due to AGE**</td>
<td>38/244 (16%)</td>
</tr>
</tbody>
</table>
### Chapter 3 - Kiribati Intussusception Surveillance

#### Table 1: Sex of deaths

<table>
<thead>
<tr>
<th>Sex</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>24/38</td>
<td>63%</td>
</tr>
<tr>
<td>Female</td>
<td>14/38</td>
<td>37%</td>
</tr>
</tbody>
</table>

*Sex unknown for 1 case
**Data only available for June 2010-December 2014; only includes deaths occurring in TCH

#### Figure 1: Age distribution of children <5 years hospitalised with AGE at Tungaru Central Hospital, June 2010-April 2015 (n=551)*

- 0-5: 5% ± 1% (95% CI: 3.5 - 6.5)
- 6-11: 30% ± 3% (95% CI: 26.5 - 33.5)
- 12-23: 40% ± 4% (95% CI: 36.5 - 43.5)
- 24-59: 25% ± 2% (95% CI: 22.5 - 27.5)

*An additional 3 cases were not included in this analysis, as their age in months was not known.

#### Figure 2: Proportion of AGE hospitalisations to TCH in children aged <5 years, by residence on Tarawa, June 2010-April 2015 (n=554)

- Tengaru: 0.6%
- Antenon: 0.7%
- Unknown: 0.9%
- Nanikai: 1.7%
- Bairiki: 2.8%
- Teorsereke: 5.2%
- Bonriki: 7.9%
- Eita: 8.8%
- Banraeaba: 8.8%
- North Tarawa: 14.0%
- Temwaku: 14.4%
- Betio: 15.5%
- Bikenibeu: 19.1%
The average annual incidence of AGE hospitalisation was 1,266 per 100,000 (95% CI 1,161-1,377) children aged <5 years. Children aged <24 months had the highest incidence for AGE hospitalisation (Fig 3). The average monthly incidence of AGE hospitalisation was 116 per 100,000 (95% CI 52-216) children <5 years (Fig 4). In the past 5 years, there were 2-3 diarrhoeal outbreaks causing an increase in hospitalisation. The 2013 and 2014 outbreaks occurred between June and October. The outbreaks in 2013 and 2014 were both laboratory confirmed for rotavirus (1, pers. comm. WPRO WHO). The 2013 outbreak was caused by rotavirus strain type G3P[8] (1, pers. comm. C. Kirkwood). No further data was available from the 2014 outbreak.

Figure 3: Average annual incidence of AGE hospitalisation in children <5 years per 100,000 by age group (n=534)

*3 cases were not included, as their age in months was not known

Figure 4: Monthly hospitalisation incidence of AGE hospitalisations per 100,000 children <5 years from June 2010-April 2015*(n=537)

*There is no data for January 2014 and incomplete data for February 2014
Table 2 shows the characteristics of the 143 children aged <5 years hospitalised with SAM. SAM contributed to 5% of all-cause hospitalisations and 16% of all-cause mortality in <5 years hospitalised children during this time period. There were no sex differences found in SAM admissions (p>0.05). Children aged 6-23 months were most commonly admitted for SAM (Fig 5). The SAM case fatality ratio was 21%. The hospitalised SAM mortality incidence rate was 96 per 100,000 (95% CI 64.6-136.7) children aged <5 years old.

Table 2: Characteristics of SAM hospitalisations (n=143) in children <5 years at Tungaru Central Hospital (TCH) from June 2010-December 2013

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>N=143</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age in months</td>
<td>12.8 (IQR 8.7-17.6)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>68 (48%)</td>
</tr>
<tr>
<td>Female</td>
<td>75 (52%)</td>
</tr>
<tr>
<td>Case fatality ratio (n=30)*</td>
<td>21%</td>
</tr>
<tr>
<td>Proportion of all-cause admissions in &lt;5yo due to SAM</td>
<td>143/3024 (5%)</td>
</tr>
<tr>
<td>Proportion of all-cause mortality in &lt;5yo due to SAM**</td>
<td>30/192 (16%)</td>
</tr>
<tr>
<td>Sex of deaths</td>
<td>N=30</td>
</tr>
<tr>
<td>Male</td>
<td>15/30 (50%)</td>
</tr>
<tr>
<td>Female</td>
<td>15/30 (50%)</td>
</tr>
</tbody>
</table>

*Outcome of 1 case unknown
**Only includes deaths occurring in TCH

Figure 5: Age distribution of children <5 years hospitalised with SAM at Tungaru Central Hospital, June 2010-December 2013 (n=142)
The annual incidence of hospitalised SAM was 453 per 100,000 (95% CI 381.7-534.1) children aged <5 years. Children aged <24 months had the highest incidence for SAM hospitalisation (Fig 6).

Figure 6: Average annual incidence of SAM hospitalisation in children <5 years per 100,000 by age group (n=142)

<table>
<thead>
<tr>
<th>Age group (months)</th>
<th>Annual hospitalisation per 100,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-11</td>
<td>1200</td>
</tr>
<tr>
<td>12-23</td>
<td>1200</td>
</tr>
<tr>
<td>24-59</td>
<td>200</td>
</tr>
</tbody>
</table>

**IS review**

There were 2 IS cases over the 5-year period (Table 3). Both cases were female, aged 5 months old and required surgical intervention. Case 1 fully recovered with no sequelae and Case 2 recovered with sequelae, requiring further surgery for intestinal adhesions. The annual incidence of IS was 20 per 100,000 (95% CI 2-73) children <1 years.

Approximately 3000 infants will be vaccinated in Kiribati each year. The estimated increased risk of IS due to rotavirus vaccine is 2-7 cases per 100,000 infants vaccinated. Therefore there may be one additional case of IS every 5-17 years in Kiribati.

**Table 3: Characteristics of intussusception cases ≤2 years admitted to Tungaru Central Hospital, June 2010-April 2015**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Case 1</th>
<th>Case 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>5 months</td>
<td>5 months</td>
</tr>
<tr>
<td>Sex</td>
<td>Female</td>
<td>Female</td>
</tr>
<tr>
<td>Residence</td>
<td>Bikenibeu</td>
<td>Beito</td>
</tr>
<tr>
<td>Year of admission</td>
<td>2014</td>
<td>2011</td>
</tr>
<tr>
<td>Management</td>
<td>Surgery</td>
<td>Surgery</td>
</tr>
<tr>
<td>LOS</td>
<td>3 days</td>
<td>28 days</td>
</tr>
<tr>
<td>Outcome</td>
<td>Fully recovered</td>
<td>Recovered with sequelae</td>
</tr>
</tbody>
</table>
Chapter 3 – Kiribati Intussusception Surveillance

DISCUSSION

Kiribati has a large burden of hospitalised AGE in children aged <5 years. The annual AGE incidence for children <5 years was 1,266 per 100,000 (95% CI 1,161-1,377). The incidence rate in Kiribati is similar to those reported in Fiji (3), but much higher than those reported in Australia (4), prior to rotavirus vaccine introduction. Globally, AGE hospitalisation incidence ranges from 625 to 2,700 per 100,000 in children <5 years (5). Differences in incidence rates between countries are likely to be due to differences in health seeking behaviour, access to health care, admission criteria, and environmental factors leading to increased burden of AGE in the community.

The median age of AGE (13.4 months) was comparable with other countries, where the peak incidence of diarrhoea is in children <2 years and more specifically at 6-11 months of age (6). More males than females were 59% were affected, fitting the epidemiological pattern seen in other countries (7). The AGE pattern in Kiribati is consistent with other tropical countries, such as Fiji, where marked seasonality is not displayed (3, 5). This is contrast to countries in temperature climates whereby rotavirus diarrhoea usually peaks each year during the cooler months (5).

Although there is no routine laboratory confirmation in Kiribati, there were two outbreaks in the last 5 years due to rotavirus. Data was available on the 2013 outbreak through personal communication from C. Kirkwood and the paper by Tabunga et al. (2014). From Tabunga et al. (2014), of the 20 specimens collected, 16 returned a result with 13 (81%) positive for rotavirus (1). Eight rotavirus positive specimens were further subject to genotyping and found to be strain G3P[8] (1, pers comm. C. Kirkwood). This is higher than the global review by Tate et al. (2012), which estimated rotavirus infection caused 40% (95% CI 36-44) of all diarrhoeal hospitalisations in children <5 years (8). AGE contributed to 12% of all-cause admissions at TCH in this age group. Therefore if it is assumed that rotavirus infection contributes to 40% of all AGE admissions at TCH, rotavirus infection would cause ~5% of all TCH admissions in this age group.

The AGE case fatality ratio was 7%, with an AGE mortality incidence of 92 per 100,000 (95% CI 65.4-125.7) children aged <5 years. Even though rotavirus-specific mortality cannot be calculated in Kiribati, a global review estimated that 37% (95% CI 34-40%) of AGE-related deaths were associated with rotavirus (8). Our results showed that AGE-related childhood deaths occurring in TCH were higher (16%) than a 2013 global review, which estimated that AGE caused 10.7%, 5.7 %, and 9% of all deaths in children <5 years in Kiribati, the Western Pacific region, and worldwide, respectively (7). Kiribati has the highest <5 years mortality rate in the Pacific Island region (9) and has substantial challenges regarding improved access to clean drinking water and sanitation (10), which may explain why AGE contributes to such a high proportion of all childhood deaths. Health seeking practices and the quality of medical care may also contribute but were not explored in this review. However it should be noted that our results only included deaths occurring at TCH and did not include all deaths in the country.

Following rotavirus vaccine introduction, a 50-87% reduction of rotavirus hospitalisations in children <2 years has been reported from high, middle, and low-income countries (11). In addition, the reduction in all-cause AGE admissions for children <2 years of age was 17-50% (11). The USA has
found a 31-55% and 63-94% reduction in all-cause AGE hospitalisations rates and specific rotavirus coded hospitalisations in children <5 years respectively, following the implementation of rotavirus vaccine in 2006 (12). Mexico found that rotavirus vaccine prevented one-third of AGE deaths in children <5 years (13). Rotavirus vaccine efficacy seems to correlate with economic level (14). The efficacy of rotavirus vaccine is reduced by poor immunological responses, which may be affected by malnutrition (14). For these reasons, it is likely that rotavirus vaccine in Kiribati may be less effective and range between 50-75% (14), and SAM rates may assist in interpreting the impact of rotavirus vaccine in years to come.

WHO defines SAM as a very low weight-for-height (below -3z scores of the median WHO growth standards), visible severe wasting, or the presence of nutritional oedema (15). It is considered a public health emergency when ≥10% of children <5 years suffer wasting (16). Oceania (excluding Australia and New Zealand), Southeast Asia and Western Africa are approaching this nutritional public health emergency status (16). In this hospital based study in Kiribati, SAM contributed to 5% of all-cause admissions in <5year olds to TCH and contributed to 16% of all-cause mortality at TCH. This study may have underestimated SAM for a number of reasons. Firstly, we only included SAM cases appearing as a primary cause of admission, and it is known that SAM is often a co-morbidity identified on admission. Secondly, it is unclear how many children with SAM may be have been identified and treated at a community level. However, the SAM case definition used in this review also included failure to thrive and very low weight, which may not have fulfilled the WHO case definition. However these two conditions contributed very few additional SAM cases (n=7, 5%). Hence, we believe our SAM results are a conservative estimate of the true burden of SAM in Kiribati.

There are no available incidence rates for hospitalised SAM in the literature to compare to. Reporting of SAM as a prevalence or percentage of hospital admissions is common practice. Studies from Africa, have found 15-26.9% of hospital admissions were due to SAM (17-20). A retrospective review of health centres in an urban Bangladeshi slum, found 4% of all children 6-59 months of age seeking care were due to SAM (21). A hospital-based study in Sri Lanka found 8.7% of childhood admissions were due to SAM (22). Kiribati results (5% of all-cause admissions) is probably an underestimated for aforementioned reasons.

Hospitalised SAM in Kiribati had a CFR of 21% and is similar to the CFR of malnutrition of child inpatients in Uganda, Malawi and South Africa (23). However, malnutrition is a risk for mortality for a number of infectious diseases and it has been estimated that malnutrition contributes to 45% of all-cause <5 year old mortality (24). It is possible that many of the AGE deaths also had SAM, as the presence of SAM has been shown to increase the odds of mortality in children suffering diarrhoea as a primary diagnosis (17-18,23,25). In this review, there was insufficient time to review individual medical records to ascertain this to be the case in Kiribati.

Rotavirus vaccine introduction in Kiribati is one component of an integrated UNICEF Child Survival package with many interventions, which target the protection, prevention, treatment of children against pneumonia and diarrhoea. Any decline in AGE incidence post-rotavirus vaccine introduction is unlikely to be due to rotavirus vaccine alone, and will likely be due to a combination of these interventions. Moreover as laboratory confirmation of rotavirus is not available, vaccine effectiveness will not be able to be calculated in Kiribati. An alternative approach to determining vaccine effectiveness is the use of a case-control design in the early phase of rotavirus vaccine
introduction or during an AGE outbreak. However this approach is probably not feasible in Kiribati without substantial additional resources, due to the lack of rotavirus laboratory confirmation of AGE making it difficult to define cases and controls, difficulty in ascertaining the vaccination status of cases and controls, and the expected high coverage of rotavirus vaccine on the island of Tarawa. In an outbreak situation, a control group would be difficult to define given the nature of the epidemiology of AGE, as there may be near universal infection during a rotavirus outbreak, and for other reasons outlined previously. However, it is recommended for future AGE outbreaks on Tarawa, the aetiology of diarrhoea is ascertained to provide further evidence of vaccine effectiveness.

The annual incidence of IS was 20 per 100,000 (95% CI 2-73) children aged <1 year. An IS review in 2013 found the IS incidence ranged from 9-328 per 100,000 one year olds in the Asia-Pacific region (26). IS incidence calculated for this review was lower than that reported in Oceania (27-101 per 100,000) and similar to some countries in Asia (Malaysia – 18; India – 18). Possible reasons for the large differences in reported IS rates might be related to under reporting of cases due to health seeking behaviour, the inability to confirm the diagnosis, and weak reporting systems. Other factors may include environmental or genetic factors, which may vary by population highlighting the need to establish baseline IS data to assess any potential vaccine-associated risk (26).

Naturally occurring IS peaks between 4 and 7 months of age (26). Both IS cases from this review were 5 months of age. There is a male predominance for IS cases in published reports (26), however both cases in Kiribati were female. The numbers are so small in this study that it is difficult to draw any further epidemiological conclusions from the data. Based on data from post-marketing surveillance, there is an increased risk (approximately 1 per 51,000-68,000 infants vaccinated) of IS one to 7 days after the first dose of rotavirus vaccine in Mexican and Brazilian infants with the risk being smaller in the latter group (27). In Australia, it has been estimated there are an additional 5.6 cases per 100,000 vaccinated infants (28). Based on these numbers, Kiribati may see an additional IS case every 5-17 years.

RECOMMENDATIONS

- To complete the rotavirus vaccine impact evaluation, Jana Lai will return to South Tarawa mid 2016 and 2018 to review the hospital records for May 2015-May 2016 (time period during vaccine introduction) and if funding permits, June 2016-June 2017 (time period post-vaccine introduction) to evaluate the impact of rotavirus vaccine in Kiribati. The hospitalised AGE and SAM incidence rate will be compared before and after the introduction of rotavirus vaccine.

- It is recommended that a site visit to Betio Hospital be conducted with the next visit to ensure that no hospitalised AGE cases on Tarawa are missed. If AGE cases were admitted to Betio Hospital, we would recommend the hospital data be reviewed over the same time period to ensure the data is complete for Tarawa.

- It is recommended for future outbreaks on Tarawa, the aetiology of diarrhoea be ascertained to provide further evidence of vaccine effectiveness.

- It is recommended that a review of the quality of care of childhood diarrhoea and health seeking behaviour is undertaken to understand the higher than expected childhood mortality due to AGE.

- SAM is common and it recommended that further health promotion, prevention, and treatment programs are supported, if they have not already been developed.

- At each subsequent visit, IS cases reported through the surveillance system post-rotavirus vaccine introduction will be reviewed. Jana Lai will also keep in regular contact with the IS surveillance co-ordinator to monitor implementation.
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F. Kiribati AGE & SAM WPSAR paper – final draft for submission

High rates of hospitalised acute gastroenteritis and severe acute malnutrition in Kiribati children prior to rotavirus vaccine introduction: a retrospective review

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Abstract:

Objectives: To describe the epidemiology of children hospitalised in Kiribati with acute gastroenteritis (AGE) and severe acute malnutrition (SAM), pre-rotavirus vaccine introduction.

Methods: In a retrospective review, children aged <5 years old, admitted to Tungaru Central Hospital (TCH), Tarawa from June 2010 - April 2015 with a discharge diagnosis of all-cause AGE and SAM were extracted from hospital electronic databases. Chronic or persistent diarrhoea, bloody diarrhoea and dysentery were excluded. Incidence rates of AGE and SAM were calculated.

Results: There were 554 and 143 cases of AGE and SAM, respectively. The median age for AGE was 13.4 months (IQR 9.4-20.3), with the majority (59%) being male. AGE had a case fatality ratio of 7% and contributed to 12% of all admissions for children <5 years old. AGE accounted for 16% of hospitalised all-cause mortality in this age group. The annual incidence of hospitalised AGE was 1,266 per 100,000 (95% CI 1,161-1,377) children <5 years old. The annual incidence of SAM was 453 per 100,000 children (95% CI 381.2-534.1), with a case fatality ratio of 21%.
Conclusions: The incidence of hospitalised AGE is high and SAM is common. Rotavirus vaccine is likely to reduce the AGE burden by 15-30%, despite high rates of SAM.

Introduction
Rotavirus (RV) is the most common cause of severe diarrhoeal disease in children worldwide. There were more than 500,000 deaths per year in the <5 year old age group in 2004\(^1\). Almost all children will have experienced one or more RV diarrhoeal episodes regardless of their living conditions by the age of 5\(^2\). Diarrhoeal disease is the second leading cause of death in children <5 years of age and is estimated to kill around 760,000 children in this age group each year\(^3\). Rotavirus is associated with about one third to one half of hospitalised cases of diarrhoeal illness in children <5 years of age, with peak incidence in the 6-24 month age group\(^4\). In temperate climates, RV diarrhoea occurs in seasonal peaks during cooler months, while in tropical climates RV diarrhoea is constant throughout the year with a moderate peak in the cooler dry months\(^4\).

In 2009, WHO recommended that all infants be routinely immunised with RV vaccine to prevent RV disease\(^5\). The currently licenced RV vaccines (Rotarix®, GSK and RotaTeq®, Merck) have been shown to be safe and effective against rotavirus AGE in large-scale clinical trials\(^6\). In the pre-licensure trials, the efficacy of Rotarix® (GSK) against severe RV gastroenteritis, RV-associated hospitalisations and all-cause diarrhoea was 85, 100 and 42% respectively\(^6\). RotaTeq® (Merck), also showed similar
results, with reductions in severe RV gastroenteritis and RV-associated gastroenteritis of 74 and 98% respectively. Post-licensure, RV vaccines have been effective with reports of declines of 71 and 38% of RV coded-hospitalisations and non-RV coded AGE hospitalisations respectively.

However, the efficacy of RV vaccine in gastroenteritis-related hospitalisations appeared to be lower in low income countries, at around 50% than high income countries seeing closer to 98% efficacy/effectiveness. A reason for this discrepancy is thought to be due to poorer immunological responses possibly affected by malnutrition in the population. Recent data from Malawi found that stunted children had lower vaccine effectiveness than their well-nourished counterparts, but this distinction was not statistically significant. Therefore it is advisable to also review the levels of malnutrition prevalent in the population when introducing RV vaccine.

Kiribati has one of the highest child mortality rates in the Pacific and has substantial challenges with the provision of safe drinking water and effective sanitation. In Kiribati, AGE is estimated to cause 10.7% of all deaths in those aged 5 and under in Kiribati. In 2002, 11% of all hospitalisations in children under 4 years old were due to AGE. While there are little data available, due to lack of availability for laboratory testing, it is likely that a large proportion of AGE cases are due to RV. To address this high burden of AGE, Kiribati introduced RV vaccine into their national immunisation schedule in August 2015. As one of the measures to measure impact of RV vaccine in this population, the incidence of hospitalised AGE in children <5 years of age...
before and after the introduction of RV vaccine will be compared. The aim of this study was to establish a baseline of both AGE incidence and characteristics of children admitted with AGE 5 years prior to RV vaccine introduction. As malnutrition may reduce RV vaccine effectiveness, severe acute malnutrition (SAM) hospitalisation rates were also calculated to understand the potential impact this may have on RV vaccine effectiveness in the population.

**Methods**

**Study location**

Kiribati is a country of 33 atolls and low lying reefs widely scattered along the Equator in the central Pacific Ocean with a population of approximately 100,000, with about 11,000 children <5 years of age\(^{11}\). In the Pacific region, Kiribati has the lowest level of development in regards to mortality, morbidity and living conditions per capita GDP and is considered a least developed country\(^{11}\). The island of Tarawa, where this study was undertaken, is home to approximately 60% of the total population of Kiribati. There are two hospitals on Tarawa: one in Betio and the other Tungaru Central Hospital (TCH). Tungaru Central Hospital is the only referral hospital in Kiribati with referrals of patients from both Tarawa and the outer islands admitted there. This is inclusive of patients that require admission to hospital from Betio Hospital. In addition, the majority of families on Tarawa, seek health care at TCH. Hospitalised AGE cases and deaths in children would occur at TCH and thus TCH was chosen as the site to conduct the review.
Study population

An AGE case was defined as any child <5 years old with a primary discharge diagnosis of acute, diarrhoea or gastroenteritis admitted to TCH from June 2010 to April 2015. As RV diarrhoea is acute, watery, non-bloody diarrhoea, cases of chronic or persistent diarrhoea, bloody diarrhoea and dysentery, as recorded on the discharge diagnosis were excluded.

A SAM case was defined as any child <5 years with a primary discharge diagnosis of severe malnutrition, malnutrition, failure to thrive, very low weight, marasmus or Kwashiorkor.

Data collection

Data for all children <5 years admitted to TCH were collected from two sources; hospital admission books (February 2014- April 2015) and the electronic medical records (June 2010- Dec 2013). Data from January, February and March 2014 were incomplete from both admission books and electronic medical records. AGE and SAM cases were identified based on the recorded primary discharge diagnosis in both sources of data. Variables collected from both admission books and electronic medical records were date of birth, date of admission, age, sex, village and outcome (dead/alive). Laboratory confirmation of RV is not routinely available, and for the time period presented here, RV testing was only performed on a limited number of samples as confirmation in diarrhoeal outbreaks.
Data analysis

Continuous data were analysed using median and interquartile ranges (IQR). Categorical data were analysed using frequency and proportions with a binomial t-test used to test for significant differences.

For incidence calculations, only those cases residing on Tarawa were included. The number of cases for both AGE and SAM were divided by the <5 year population for the relevant study period, with the omission of 2 months of the population to account for the missing data of January-February 2014. The TCH catchment population was defined as children <5 years residing on Tarawa. Population data were obtained from the 2010 census and was adjusted for growth at 2.2% per annum. The age categories used for this study were <12, 12-23 and 24-59 months. We used 75% of the 1-5 year old population as the number of children aged 24-59 months old.

Results

Table 1 shows the characteristics of the 554 hospitalised AGE cases <5 years during the study period. AGE contributed to 12% of all-cause hospital admissions and 16% of all-cause hospital deaths in <5 years children. There were significantly more males than females hospitalised with AGE (59% vs 40%, p-value <0.0001). AGE was most common in 12-23 month old children. The AGE case fatality ratio was 7%, with a mortality incidence of 92 per 100,000 (95% CI 65.4-125.7) children aged <5 years. There were more male children who died from AGE compared with female children but this was not statistically significant (p-value <0.14). The majority of cases came from the
most populous areas of Tarawa; Bikenibeu, Betio, Temwaiku and North Tarawa.

Table 1. Characteristics of AGE hospitalisations in children <5 years at Tungaru Central Hospital, Tarawa, Kiribati, June 2010-April 2015 (n=554)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>N=554</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in months, median (IQR)</td>
<td>13.4 (9.4-20.3)</td>
</tr>
<tr>
<td>Sex*, n (%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>329 (59%)</td>
</tr>
<tr>
<td>Female</td>
<td>224 (40%)</td>
</tr>
<tr>
<td>AGE case fatality ratio (n=39)</td>
<td>7%</td>
</tr>
<tr>
<td>All-cause admissions in &lt;5yo due to AGE, n (%)</td>
<td>554/4474 (12%)</td>
</tr>
<tr>
<td>All-cause mortality in &lt;5yo due to AGE**, n (%)</td>
<td>38/244 (16%)</td>
</tr>
<tr>
<td>Deaths, n (%)</td>
<td>N=38</td>
</tr>
<tr>
<td>Male</td>
<td>24 (63%)</td>
</tr>
</tbody>
</table>

*Sex unknown for 1 case
**Data only available for June 2010-December 2014

The average annual incidence of AGE hospitalisation was 1,266 per 100,000 (95%CI 1,161-1,377) children aged <5 years. Children aged <24 months had the highest incidence for AGE hospitalisation at 2,368 per 100,000 (95% CI 2,156.7-2,593.4) in the <5 year age group. The average monthly incidence of AGE hospitalisation was 116 per 100,000 (95% CI 52-216) children <5 years (Fig 1). There were no patterns of seasonality, only 2-3 diarrhoeal outbreaks causing an increase in hospitalisation (Fig 1). The outbreaks in 2013 and 2014 were both laboratory confirmed for RV (pers. comm. WPRO WHO).
Table 2 shows the characteristics of the 143 children aged <5 years hospitalised with SAM. SAM contributed to 5% of all-cause hospitalisations and 16% of all-cause mortality in <5 years hospitalised children during this time period. There were no sex differences found in SAM admissions (p>0.05). The highest proportions in this age group of hospitalised SAM cases were children aged 6-23 months. The SAM case fatality ratio was 21%. Of those hospitalised with SAM, the mortality incidence rate was 96 per 100,000 (95% CI 64.6-136.7) children aged <5 years old.
Table 2. Characteristics of SAM hospitalisations (n=143) in children <5 years at Tungaru Central Hospital (TCH), Tarawa, Kiribati, from June 2010-December 2013

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>N=143</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in months, median (IQR)</td>
<td>12.8 (8.7-17.6)</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>68 (48%)</td>
</tr>
<tr>
<td>Female</td>
<td>75 (52%)</td>
</tr>
<tr>
<td>SAM case fatality ratio (n=30)*</td>
<td>21%</td>
</tr>
<tr>
<td>All-cause admissions in &lt;5yo due to SAM, n (%)</td>
<td>143/3024 (5%)</td>
</tr>
<tr>
<td>All-cause mortality in &lt;5yo due to SAM, n (%)</td>
<td>30/192 (15%)</td>
</tr>
<tr>
<td>Deaths, n (%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>15/30 (50%)</td>
</tr>
</tbody>
</table>

*Outcome of 1 case unknown

The annual incidence of hospitalised SAM was 453 per 100,000 (95% CI 381.7-534.1) children aged <5 years. Children aged <24 months had the highest incidence for SAM hospitalisation at 943 per 100,00 (95% CI 790.3-1,116.8).

Discussion

Kiribati has a large burden of hospitalised AGE in children aged <5 years. The AGE incidence rate found in this study is similar to those reported in other countries in the region prior to RV introduction such as Fiji (1251 per 100,000)\(^{13}\) and Australia (1419 per 100,000)(8), prior to RV vaccine introduction. Incidence rates are often difficult to compare between countries as rates are likely to vary due to differences in surveillance, health seeking behaviour, access to health care, admission criteria, and environmental factors leading to increased burden of AGE in the community.
The median age of AGE was comparable with other countries, where the peak incidence of diarrhoea is in children <2 years and more specifically at 6-11 months of age\textsuperscript{14}. More males than females were affected, fitting the epidemiological pattern seen in other countries\textsuperscript{15}. The AGE pattern in Kiribati is consistent with other tropical countries, such as Fiji, where marked seasonality is not displayed\textsuperscript{13}. This is in contrast to countries in temperate climates whereby RV diarrhoea usually peaks each year during the cooler months\textsuperscript{15}.

Although there is no routine laboratory confirmation in Kiribati, there were two outbreaks in the last 5 years due to rotavirus. Data was available on the 2013 outbreak through personal communication from C. Kirkwood and the paper by Tabunga et al. (2014). From Tabunga et al. (2014), of the 20 specimens collected, 16 returned a result with 13 (81\%) positive for RV\textsuperscript{16}. Eight RV positive specimens were further subject to genotyping and found to be strain G3P[8] (1, pers comm. C. Kirkwood). This is higher than the global review by Tate et al. (2012), which estimated RV infection caused 40\% (95\%CI 36-44) of all diarrhoeal hospitalisations in children <5 years\textsuperscript{17}. Acute gastroenteritis contributed to 12\% of all-cause admissions at TCH in this age group. Therefore if it is assumed that RV infection contributes to 40\% of all AGE admissions at TCH, RV infection would cause ~5\% of all TCH admissions in this age group.

Our results showed that the proportion of AGE-related childhood deaths occurring were higher (16\%) than a 2013 global review, which estimated that
AGE caused 10.7%, 5.7%, and 9% of all deaths in children <5 years in Kiribati, the Western Pacific region, and worldwide, respectively\textsuperscript{12,18}. As this is a hospital-based study, it did not capture deaths in the community as a whole, thus our rate may be higher than what would be expected in Kiribati, if all community deaths were also included. However the high number of AGE-related deaths in hospitalised AGE cases requires further review of health seeking practices and the medical care given. Kiribati has the highest <5 years mortality rate in the Pacific Island region\textsuperscript{12,18} and has substantial challenges regarding improved access to clean drinking water and sanitation\textsuperscript{11}, which may explain why AGE contributes to such a high proportion of all childhood deaths. Rotavirus-specific mortality cannot be calculated in Kiribati, however this is likely to be an important pathogen given that a global review estimated that 37% (95% CI 34–40%) of AGE-related deaths were associated with rotavirus\textsuperscript{17}.

This study found that SAM was common and contributed to 16% of all <5 year old mortality in TCH. Globally WHO estimates that SAM contributes directly or indirectly to 35% of all childhood deaths\textsuperscript{19}. We were unable to find other studies that report incidence rates of SAM among hospitalised children that we could compare to, however reporting of SAM as proportion of hospital admissions is common practice. A retrospective review of health centres in an urban Bangladeshi slum, found 4% of all children 6-59 months of age seeking care were due to SAM\textsuperscript{20}. A hospital-based study in Sri Lanka found 8.7% of childhood admissions were due to SAM\textsuperscript{21}. The reported proportion of SAM cases of all hospital admission in Kiribati is more likely an underestimation of
the true burden of SAM as the review only counted SAM cases if it was a primary diagnosis, not if it was a co-morbidity and it is unclear how many children with SAM were treated at the community level. In addition, hospitalised SAM in Kiribati had a CFR similar to the CFR from malnutrition of child inpatients in Uganda, Malawi and South Africa\textsuperscript{22}. These data show SAM as a major contributor to morbidity and mortality in Kiribati and needs greater attention to address the issue.

Following RV vaccine introduction, a 50-87\% reduction of RV hospitalisations in children <2 years has been reported from high, middle, and low-income countries\textsuperscript{23}. In addition, the reduction in all-cause AGE admissions for children <2 years of age globally was 17-50\%\textsuperscript{23}. However the high rates of SAM found in the Kiribati may have implications for the effectiveness of RV vaccine. For these reasons, it is likely that RV vaccine in Kiribati may be less effective and sit in the range observed in middle to low-income countries. Ongoing review of SAM rates may assist in interpreting the impact of rotavirus vaccine in years to come.

Limitations exist in our study for both AGE and SAM rates reported. Missing data for January 2014 and incomplete data for February/March 2014, could have contributed to underestimation of AGE incidence in the population. Future evaluations will extract and include these data in the comparison analysis of AGE incidence pre- and post-RV vaccine introduction. There is the risk that cases have been missed from the outer islands due to the large distances required for travel to reach TCH, with more a concern for deaths
rather than cases, diminishing the AGE CFR estimation. However, even though the incidence calculations did not include those from islands outside of Tarawa, there were cases admitted from these outer islands, suggesting the referral system for Kiribati is followed. In this study we did not review the medical records for AGE deaths to look for SAM, but this would be recommended in subsequent evaluations post-RV vaccine introduction to investigate why the AGE mortality rates are very high. The presence of SAM has been shown to increase the odds of mortality in children suffering diarrhoea as a primary diagnosis\textsuperscript{22,24-26}.

It is likely that our rate of SAM is an underestimation of the true burden of SAM. WHO defines SAM as a very low weight-for-height (below -3z scores of the median WHO growth standards), visible severe wasting, or the presence of nutritional oedema\textsuperscript{19}. The SAM case definition in this study also included failure to thrive and very low weight, which may not have fulfilled this WHO case definition. However these two conditions accounted for 7 out of 142 (5\%) admissions for SAM included in the study, meaning that this would have minimal effect on our results. In addition, we only included SAM cases appearing as a primary cause of admission, and as malnutrition contributes to 45\% of all-cause <5 year old mortality\textsuperscript{27} and it is unclear how many children with SAM may be have been identified and treated at a community level and not presented to hospital. Thus it is likely the hospitalised SAM rate is underestimated. Nevertheless SAM is a significant problem in Kiribati.
For both AGE and SAM, cases could have been missed as we used administrative data and were reliant on clinician diagnosis. The potential for coding errors in hospital admission records and the potential for misdiagnosis, as the criteria for inclusion in the study was dependent on clinician discretion rather than a strict case definition with objective measures. Both of these scenarios contribute to an underestimation of AGE and SAM incidence during this review period.

In Kiribati, AGE and SAM are major causes of hospitalisation and mortality. The routine use of RV will prevent many hospitalisations due to AGE in Kiribati. However, the effectiveness of RV in Kiribati may be less than that seen in high-income countries due to the presence of high levels of malnutrition, as indicated by the high levels of hospitalised SAM cases. However to support the use of RV vaccine in the population, it is recommended that for future outbreaks of diarrhoeal disease on Tarawa, the aetiology of diarrhoea should be ascertained to provide evidence of vaccine effectiveness. The high CFR rates for both AGE and SAM are concerning. For AGE deaths, it is recommended to review the individual medical records to determine if there was a co-morbidity present such as AGE and to better understand the characteristics of these cases and the care they received. This review highlighted the frequency of SAM in the population and it would be recommended to support health promotion, prevention and treatment programs addressing this issue if they have not already been developed. A review will be conducted in the 3 years post-RV introduction to compare the AGE and SAM rates to these baseline data.
Chapter 3 - Kiribati Intussusception Surveillance

Conflicts of interest

None to report

Funding

WPRO funding

Acknowledgements

We would like to thank the staff at TCH who assisted us with the finding of data for our review and also spending valuable time helping us understand the healthcare, hospital system and patient care facilities in Kiribati.

References


G. Oral Presentation slides for ACPID and TEPHINET Conferences (2016)

High rates of hospitalised acute gastroenteritis and severe acute malnutrition in Kiribati children prior to Rotavirus vaccine introduction: A retrospective review

James L, et al
Masters of Applied Epidemiology Scholar: Australian National University and Murdoch Childrens Research Institute, Melbourne

Rotavirus vaccine impact
- Varies by setting
  - Developed setting (US/Finland): 75-85% vaccine effectiveness against severe rotavirus gastroenteritis
  - Developing settings (Africa/SE Asia): 50-70% vaccine effectiveness against severe rotavirus gastroenteritis
  - Improved immunity
  - Other Intestinal pathogens
  - Malnutrition

Rotavirus vaccine-preventable
- Vaccine effectiveness of acute gastroenteritis (AGE) 17-65%
- Vaccine effectiveness rotavirus hospitalisation 45-60%

Kiribati and Rotavirus Vaccine
- Diarrhoea estimated to cause 11% all US deaths
- In 2002, 11% all hospitalisation in US due to AGE
- UNICEF implementing integrated Global Action Plan for Prevention and Control of Pneumonia and Diarrhoea (GAPPID) to address burden
- Rotavirus vaccine (Rotarix) introduced into national immunisation program mid 2016

Aims
- Overarching aim is to conduct a pre- and post-rotavirus vaccine incidence rate ratio (IRR) of AGE in Kiribati
- For this review aims were to:
  - Determine the incidence of acute gastroenteritis (AGE) pre-vaccine introduction as a baseline
  - Determine severe acute malnutrition (SAM) burden pre-vaccine to understand potential effect on vaccine effectiveness
  - Describe the epidemiology of hospitalised AGE and SAM pre-vaccine introduction
Methods

- Tungaru Central Hospital electronic database/hospital admission records
- June 2010-April 2015 (AGE)
- June 2010-Dec 2013 (SAM)
- Children aged ≥6yo admitted with primary diagnosis of AGE/SAM
- 2010 Census data

Results

AGE hospitalisations in children <5 years at Tungaru Central Hospital from June 2010 – April 2015

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>N=54</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age in months</td>
<td>13.4 (IQR 6-20.3)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>32 (59.3%)</td>
</tr>
<tr>
<td>Female</td>
<td>22 (40.7%)</td>
</tr>
<tr>
<td>Case fatality rate</td>
<td>39/54 (72.2%)</td>
</tr>
<tr>
<td>Proportion of acute SAM admissions</td>
<td>55/64 (86.3%)</td>
</tr>
<tr>
<td>Proportion of acute SAM mortality</td>
<td>38/54 (69.6%)</td>
</tr>
<tr>
<td>Average annual incidence</td>
<td>1,266 per 100,000 (95%CI 1,185-1,377)</td>
</tr>
</tbody>
</table>

SAM hospitalisations in children <5 years at Tungaru Central Hospital from June 2010 – Dec 2013

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>N=43</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age in months</td>
<td>13.0 (IQR 6-17.4)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>29 (67.4%)</td>
</tr>
<tr>
<td>Female</td>
<td>14 (32.6%)</td>
</tr>
<tr>
<td>Case fatality rate</td>
<td>50/341 (14.7%)</td>
</tr>
<tr>
<td>Proportion of acute SAM admissions</td>
<td>143/761 (18.8%)</td>
</tr>
<tr>
<td>Proportion of acute SAM mortality</td>
<td>50/341 (14.7%)</td>
</tr>
<tr>
<td>Average annual incidence</td>
<td>463 per 100,000 (95%CI 381.7-624.1)</td>
</tr>
</tbody>
</table>

Discussion/Limitations

- Hospitalised AGE incidence is high and comparable to countries in the region like Fiji prior to vaccine introduction
- High rates of hospitalised SAM
  - Similar to reports from Bangladesh and Sri Lanka
  - High mortality in AGE cases
- Under estimation of true AGE burden in the community
  - Excluded outer islands
  - Only hospitalised cases

Conclusions

- Expect that rotavirus vaccine effectiveness reduced by high rates of SAM
  - Against hospitalised rotavirus diarrhoea <50-70%
  - Against hospitalised rotavirus <15-30%
- In 2017, incidence of AGE will be determined, to compare pre- vs post-vaccine introduction rates

Recommendations

- For future AGE outbreaks, pathfinding to be defined to support vaccine effectiveness
- Review of large AGE cases to determine comorbidities at next evaluation visit
- Attention still needed to address WASH (Water, sanitation, and hygiene) issues

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- Nufi
  - Data Room
  - WHO
- TCI4
  - Dr Endi Timoe
  - Hospital records
  - Hospital records
- ANLI
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Chapter 4

*Haemophilus influenzae* type b (Hib) Serosurvey
Chapter 4 – Hib Serosurvey

Contents

1. Prologue ......................................................................................................................... 158
   1.1. Role ....................................................................................................................... 158
   1.2. Lessons learnt ........................................................................................................ 158
   1.3. Public Health implications and impact ................................................................. 159
2. Abstract .......................................................................................................................... 161
3. Introduction ...................................................................................................................... 163
   3.1. Haemophilus influenzae type b (Hib) ................................................................. 163
   3.2. Monitoring of vaccine coverage .......................................................................... 163
   3.3. Serological evidence of Hib immunity .............................................................. 167
   3.4. Vaccine preventable disease outbreaks (VPD) – situation in Lao PDR .......... 169
   3.5. Aims and objectives ............................................................................................. 170
4. Methods .......................................................................................................................... 171
   4.1. Context .................................................................................................................. 171
   4.2. Recruitment and data collection ........................................................................... 172
   4.3. Laboratory methods ............................................................................................. 172
   4.4. Outcomes measures ............................................................................................... 173
      4.4.1. Written record ............................................................................................... 173
      4.4.2. Serological evidence of Hib antibody protection ......................................... 173
   4.5. Statistical consideration ....................................................................................... 173
      4.5.1. Written record coverage .............................................................................. 173
      4.5.2. Evidence of serological protection ............................................................... 174
   4.6. Ethical consideration ............................................................................................. 174
5. Results .................................................................................................................................. 175
   5.1. Hib vaccination coverage ...................................................................................... 176
   5.2. Serological evidence ............................................................................................. 177
   5.3. Unvaccinated participants ...................................................................................... 177
6. Discussion .......................................................................................................................... 178
7. Recommendations ........................................................................................................... 182
8. References ........................................................................................................................ 183
9. Appendices ....................................................................................................................... 187
   A. Contact information sheet ....................................................................................... 187
   B. Contact data collection form ..................................................................................... 191
List of Figures

Figure 1: Strengths and weaknesses of different methodologies for assessing vaccination coverage................................................................. 165

Figure 2: Flowchart of participant recruitment into the written record and serological evidence survey, from May 2015 to February 2017......................... 175

Figure 3: Hib vaccine coverage by written record in participants by age group... 176

Figure 4: Proportion of samples with short- and long-term antibodies for *H. influenzae* type b (Hib) by age................................................................. 177

List of Tables

Table 1: Written record of vaccination sample size calculations with differing levels of intra-cluster correlation (ICC) at 5% precision, 95% confidence in comparison to nationally reported vaccination coverage of 77% in the 12-23 month age group ................................................................. 174

Table 2: Evidence of long-term antibodies to *H. influenzae* type b (Hib) sample size calculations with differing levels of intra-cluster (ICC) at 5% precision, 95% confidence in comparison to the range 19-83% reported in the literature... 174

Table 3: Characteristics of participants, stratified by vaccination status as determined by written record........................................................................... 176
Abbreviations

BCG  Bacillus-Calmette-Guerin vaccine  
DTP  Diphtheria-tetanus-pertussis vaccine  
DTP-HepB  Diphtheria-tetanus-pertussis-hepatitis B vaccine  
DTPw-Hib-HepB  Diphtheria-tetanus-whole cell pertussis-Hib-hepatitis B vaccine  
ELISA  Enzyme-linked immunosorbent assay  
EPI  Expanded Programme of Immunization  
HepB  Hepatitis B  
Hib  *Haemophilus influenzae* type b  
HIC  High-income country  
ICC  Intra-cluster correlation  
IgG  Immunoglobulin G  
Lao PDR  People's Democratic Republic of Laos  
LDC  Least developed country  
LMIC  Low-middle income country  
LOMWRU  Lao PDR-Oxford-Mahosot Hospital-Wellcome Trust-Research Unit  
MAE  Master of Philosophy in Applied Epidemiology (ANU)  
MCH  Mother-child health  
MCRI  Murdoch Childrens Research Institute  
MoH  Ministry of Health  
NIP  National Immunization Programme  
PRP  Polyribosyl-ribitol-phosphate  
SIA  Supplementary immunisation activity  
UK  United Kingdom  
ULT  Ultra low temperature  
VPD  Vaccine preventable disease  
WPRO  Western Pacific Regional Office, WHO
1. Prologue

1.1. Role
Over the past couple of years, there have been a number of vaccine-preventable disease (VPD) outbreaks in rural People's Democratic Republic of Laos (Lao PDR). This has led health authorities to have an increased interest in VPD immunity, and consequently Dr Anonh Xeuatvongsa head of the National Immunization Programme (NIP) Lao PDR, requested a serosurvey of *Haemophilus influenzae* type b (Hib) antibodies to assess the immunity to Hib in the population. As our PneuCAPTIVE study (detailed in Chapter 2) was already collecting immunisation data and sera from children living in Vientiane Capital in a contact serosurvey for pneumococcus, we were also able to use the same sera for detection of Hib antibodies.

The Hib serosurvey detailed in this chapter was the work required to satisfy the epidemiological component of my Masters of Philosophy in Applied Epidemiology (MAE). My responsibilities on the project included the design of the study, preparation of the documents and forms needed, overseeing the day-to-day work for the contact serosurvey, setting priorities for the project, participation in field work when required, maintenance of the study databases, training of local staff and regular reporting to investigators. From this work, I will prepare a report to present to NIP and if permitted, a manuscript to be published in a peer-reviewed journal post-MAE.

1.2. Lessons learnt
The lessons I learnt on this study were broad, ranging from epidemiological concepts to logistical skills. One of the first lessons I learnt through this work was in regards to sampling methodology. I learnt about the different sampling methods and the limitations of each, in particular the commonly used Expanded Programme of Immunization (EPI) survey method. The EPI survey method was important for me to understand because this was the survey method used in Lao PDR to estimate vaccine coverage in the country. Following on from sampling I came to a greater understanding of the concepts of internal and external validity.
As the design of the study used convenience sampling, I learnt about the impact this had on statistical considerations for the results. I learnt how to calculate sample sizes of varying precision for different levels of clustering. In addition, I had to consider the potential effect measurement bias played in my results due to cross-reactivity of other bacteria to the Hib assay.

1.3. Public Health implications and impact
Since the development and widespread use of Hib vaccines, incidence of Hib disease has significantly decreased. However, in more recent times, some countries have seen an increase in Hib incidence and also breakthrough disease. This data contributes to the knowledge of Hib in the region. This is the first Hib serosurvey done in the region and provides an example of the situation in Southeast Asia and supports the recommendation for continued surveillance of Hib disease to ensure there is no increase post-Hib vaccine introduction.

Based on recent serosurveys for hepatitis B (HepB) and measles conducted in various Lao PDR, coupled with VPD outbreaks, there are concerns between what is recorded either on the mother-child health (MCH) card or immunisation registers and the serological immunity in the population. This has flowed into Hib disease, where there are concerns children in the wider population are not protected. The results from this study attempt to address these questions by describing both the vaccination status by written record and serological immunity in the same sample population. Currently there is no booster dose in the schedule and based on the results for this work there is no recommendation to add a booster dose into the schedule. However, the written record vaccine coverage from this study was similar to the NIP estimates for Vientiane Capital. However these estimates are lower than both the regional and global estimates of DTP-Hib-HepB vaccine, giving NIP further impetus to continue improving vaccine coverage through both old and alternative vaccination efforts.

1.4. Acknowledgements
I would like to thank A/Prof Fiona Russell, Dr Stephanie Davis and Anne Balloch for their support, expertise and patience with me for this project. My gratitude to Dr Anonh Xeuatvongsa for always supporting our work with NIP. My thanks to Dr
Chapter 4 – Hib Serosurvey

Cattram Nguyen for helping me understand the statistical intricacies of my study. Special thanks to the PneuCAPTIVE team in Vientiane who were responsible for conducting the fieldwork and to Dr Ruth Lim who provided the training needed for blood collection. Finally, thanks to all participants and their families, who without their support we could not do this study.
2. Abstract

**Background/aims:** People’s Democratic Republic of Laos (Lao PDR) has suffered in recent times from outbreaks of vaccine-preventable disease (VPD), leading to an increase in concerns the population was not protected from other VPDs such as *H. influenzae* type b (Hib). The aim of the study in Vientiane Capital was to report the vaccination coverage by written record in children <5 years of age and describe evidence of serological protection to Hib from these same children.

**Methods:** A convenience sample of children <5 years of age living in Vientiane Capital was used to determine coverage by written record for Hib vaccine (given as part of DTPw-Hib-HepB vaccine). A subset of these children aged 12-59 months had a blood sample taken to test for IgG antibody levels to Hib capsular polysaccharide, polyribosylribitol phosphate (PRP). Vaccination status was defined as children having received 3 doses of Hib vaccine. Written record was defined as either the parent-held mother child handbook (MCH) containing the record of vaccination or via immunisation registers held at the child’s health centre. Evidence of serological protection was defined as short and long-term with cut-offs being ≥0.15μg/ml and ≥1.0μg/ml, respectively. Chi-squared tests and 95% confidence intervals were used to compare groups.

**Results:** In total, 559 and 262 participants were included in the analysis for written record vaccination coverage and serological evidence of Hib protection, respectively. Overall, 62% of children were Hib vaccinated based on written record, with the highest coverage (74%) in children 12-23 months old. Unvaccinated children were more likely to be from an ethnic minority than Lao Loum (p<0.001) and seek care from a local health centre rather than a tertiary hospital (p<0.001). Vaccinated children were more likely to seek care at a tertiary hospital (p<0.001) rather than a local health centre. Of those with a blood sample all had serological evidence of short-term immunity and 60% had serological evidence of long-term immunity, with no significant difference between age groups for evidence of long-term immunity (p=0.492). Of the children with serological results available, 34% were unvaccinated by written record. All unvaccinated
children by written record had serological evidence of short-term immunity and 23% had evidence of long-term immunity.

*Summary and Conclusions:* Vaccination coverage in this population by written record was similar to the reported coverage for Vientiane Capital by the National Immunization Programme (NIP). However, the Hib vaccine (given as part of DTPw-Hib-HepB vaccine) coverage estimates by written record in Lao PDR are lower than both regional and global estimates. All children with serological results have evidence of short-term protection to Hib irrespective of written vaccination status. In addition, a large proportion of unvaccinated children showed serological evidence of long-term immunity to Hib. Possible reasons for this discrepancy are recording errors, cross-reactivity of other pathogens with the Hib assay or ongoing exposure to Hib in the population creating an environment of natural protection. Based on these data, changes to the current immunisation schedule cannot be recommended without adequate Hib disease data. *H. influenzae* type b disease surveillance is recommended to continue to monitor for any changes.
3. Introduction

3.1. *Haemophilus influenzae* type b (Hib)

*H. influenzae* is a Gram-negative coccobacillus, of both capsulated and non-encapsulated types. *H. influenzae* type b (Hib) is the most pathogenic, accounting for >90% of systemic infections. *H. influenzae* type b primarily causes pneumonia and meningitis almost exclusively in children <5 years of age. In 2000, Hib was estimated to have caused approximately 2-3 million cases of serious disease and 386,000 deaths in young children worldwide, with peak incidence in those younger than 6 months of age. Transmission occurs through infectious respiratory droplets (1).

The best method of Hib disease prevention is through the use of Hib conjugate vaccines. *H. influenzae* type b vaccines have been available since the 1980s, however widespread vaccination did not occur until the 2000s. With widespread routine vaccination, Hib meningitis has largely been eliminated from high-income countries (HICs) and low- and middle-income countries (LMICs) that have introduced Hib vaccines into their population (1). Hib vaccine is available in a monovalent form or in combination vaccines containing diphtheria (DTP), reducing the number of injections needed to cover infants from common childhood diseases (2).

3.2. Monitoring of vaccine coverage

Vaccination coverage is defined as the number of persons in a defined population vaccinated against a certain disease over the total target population (3). The purpose of monitoring vaccine coverage in a population is to ensure the population remains protected from disease, through both the identification of gaps and maintenance of herd immunity. Monitoring of vaccine coverage in a national program helps identify areas of low coverage, where the population is susceptible. This is important as there is a need to design and implement custom interventions to ensure the susceptible population are protected. Herd immunity effects are where unvaccinated populations are also protected from disease and when considered, the maximum value a vaccine has in a vaccination program is realised.

In addition to these functional purposes, reporting of vaccination coverage acts as
a good indicator for setting targets for health programs at local, national and international levels (3).

In general, the determination of vaccine coverage is reliant on record and recall-based sources of data such as administrative data, surveys, immunisation registries and parent recall. Each of these sources of data have pros and cons, which are summarised in Figure 1, from a review by Lopalco and Santisteve, 2014 (3).
Figure 1: Strengths and weaknesses of different methodologies for assessing vaccination coverage. Taken from Lopalco and Santistevé et al. (2014)(3).

<table>
<thead>
<tr>
<th>Method</th>
<th>Strengths</th>
<th>Weaknesses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Administrative</td>
<td>Based on routine collection, provide robust series of data.</td>
<td>Can be severely affected by inaccurate numerator and/or denominator.</td>
</tr>
<tr>
<td>methods</td>
<td>Integrated in the vaccination programme, do not require ad hoc implementation.</td>
<td>Do not provide individual data if only number of administered doses is reported.</td>
</tr>
<tr>
<td></td>
<td>Not expensive.</td>
<td></td>
</tr>
<tr>
<td>Surveys</td>
<td>Useful to assess data collected through administrative methods.</td>
<td>Require ad hoc implementation.</td>
</tr>
<tr>
<td></td>
<td>Are the only source of information if administrative systems are not in place.</td>
<td>Require ad hoc resources.</td>
</tr>
<tr>
<td></td>
<td>Can provide additional information, i.e. on reasons for missed vaccination.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Can be integrated into surveys with broader scope (nutrition, child health, education, etc.).</td>
<td></td>
</tr>
<tr>
<td>Seroprevalence</td>
<td>Can provide information on the actual level of immunity in the target population.</td>
<td>Impossible to distinguish between vaccination-acquired and naturally acquired immunity.</td>
</tr>
<tr>
<td>surveys</td>
<td>Extremely useful in population subgroups that are likely to be missed by administrative methods (hard-to-reach).</td>
<td>Are suitable only when a clear serological correlate of protection is available.</td>
</tr>
<tr>
<td>Immunization</td>
<td>Can provide very precise, individual information on immunization status.</td>
<td>Are designed for improving service delivery (reminder systems, schedule compliance, etc.) more than providing vaccine coverage data.</td>
</tr>
<tr>
<td>registries</td>
<td>Can be linked to other health data sources for assessing other aspects of vaccination programme (safety, effectiveness, impact, etc.).</td>
<td>Estimates are strongly affected by the coverage of the registry. Are implemented at national level in few countries so far.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

In general, the major issue with these methods is the reliability of the numerator and/or denominator data and the method of data collection. This is particularly noticeable in LMIC settings where these data may either not exist or be severely over/underestimated for a range of reasons. In addition, these methods may not be ideal for the assessment of long-term protection in a population, due to waning antibody levels over time and changes in the biology of the pathogens that may affect the protection afforded by these vaccines in the population.
Administrative data, when collected and reported correctly, gives a robust estimate of vaccine coverage and is the primary source for vaccine coverage estimates in HICs. However, use of administrative data in LMICs is particularly problematic, with concerns surrounding the reliability of the numerator and denominator data. For denominator data, accurate estimates of the population are difficult to obtain due to the lack of clear administrative boundaries to count population numbers, registries of births, deaths and migration. Numerator data are affected by accurate record keeping, missing data, differences in reporting (i.e. only the number of doses given and not the actual number of children vaccinated in their population) and also the logistics of getting this data to the relevant administrative bodies to be included in the coverage estimates.

Due to the issues surrounding the reliability of administrative data, surveys have been used in LMICs to provide an additional source of vaccine coverage estimates. One well-known example is the Expanded Programme of Immunization (EPI) coverage surveys, which use a cluster survey design. The World Health Organization (WHO) and the United Nations Childrens Fund (UNICEF) developed the EPI survey method in response to a need for a rapid and cost-effective method to assess the immunisation coverage at a national level (4). In brief, after the selection of 30 clusters, 7 households are randomly selected within each cluster and children 12-23 months are surveyed (4). This method theoretically gives a total sample size of 210 children 12-23 months of age, providing an estimate within 10% of the population immunisation rate (4). However this method is prone to selection bias and applicability to measure other health outcomes is limited (5). The selection of households is a major factor to the introduction of selection bias into the results. In many LMIC settings, there are no up to date household lists, making it difficult to choose a representative sample. Thus the training of surveyors and supervisors is important to ensure households are chosen at random.

Another method to determine the immunity in a population is through the use of serosurveys. The benefits of using serosurveys are that they provide an objective measure of the actual level of immunity in a population. This is important for
identification of factors that may predict low coverage and also waning immunity in a population (3). Serosurveys rely on the collection of samples, most commonly blood or related fluids, to test for the prevalence of antibodies in individuals from a population (6). Serosurveys can include serum collected for other purposes or specifically to address a research question. The key limitations are the potential high costs associated with conducting a serosurvey, selection process and if a reliable correlate of protection exists. Serosurveys can be prone to selection bias, especially if they rely on serum collected for a different purpose. If there is no clear correlate of protection, they cannot distinguish between vaccination and naturally acquired immunity (3). In LMIC settings, specimen collection, reliable laboratory assays and appropriate statistical analysis have been a hindrance to their use (6). However, serosurveys can be very useful to help design and monitor vaccination programs (6).

3.3. Serological evidence of Hib immunity
Hib immunity is determined by measuring antibody production against a component of its capsule, a repeating polymer of ribosyl and ribitol phosphate (polyribosyl-ribitol-phosphate, PRP), which is essential for its pathogenicity but also the immunogenic component of Hib conjugate vaccines (7). Through animal studies, studies of passive immunisation, analysis of natural immunity and early Hib polysaccharide vaccine efficacy trials, short-term and long-term protection anti-PRP antibody thresholds of ≥0.15μg/ml and ≥1.0μg/ml, respectively, were established (7). A month after a primary series of Hib vaccine, >95% of vaccine recipients had both short and long-term immunity (8-11) as determined by the antibody cutoffs detailed above.

However persistence of immunity is a concern, as documented in the United Kingdom (UK). In 1992, Hib vaccine was introduced into the UK routine infant immunisation schedule as a 3-dose regimen, given at 2, 3 and 4 months of age, and no booster (12). Simultaneously, a catch-up campaign was also introduced to give a single dose to children 6 months to 4 years of age to reduce Hib disease rapidly (12). At first, the incidence of disease rapidly decreased in children <5 years of age from 22.9 in 1990 to 0.65 per 100,000 in 1998 (13). By 2000, not only had Hib disease incidence increased (14), but there were also reports of vaccine failures
(15), even with maintenance of high vaccine coverage (13). Potential reasons for this included lower vaccine effectiveness in infants compared to older children vaccinated in the catch-up campaign (13), loss of natural boosting to Hib due to reduced Hib carriage exposure in the community (16), waning of herd immunity (17) and use of lower efficacy combination vaccines (acellular pertussis formulation rather than whole-cell) (18-20). Thus it was unknown whether protection persisted. Serosurveys were employed to investigate long-term persistence of antibody and immunological memory in older children who had received infant Hib vaccination.

In studies conducted in HICs, Hib antibody levels were measured in children 2-5 years of age, who in infancy had been fully Hib vaccinated. Approximately 75% of these children had Hib antibody levels ≥0.15μg/ml and approximately 40% had Hib antibody levels ≥1.0μg/ml (12, 19, 21-23). Specifically in the UK, children who received vaccine in infancy had lower antibody concentrations than those who received vaccine during a catch-up campaign (17). In English adults, median Hib antibody concentrations fell from 1.29μg/ml to 0.7μg/ml from 1991 to 1994, with no significant change in antibody concentrations up to 2003 (24). The outcome from these studies suggested a decline in natural boosting due to less exposure to Hib and also supported the proposal for an additional booster to be included for older children.

The long-term persistence of Hib immunity in LMICs is unclear. Studies conducted in children <6 years of age, in LMICs found that antibody levels for both the short and long-term protection were slightly higher than those in HICs, approximately 92% and 78%, respectively (20, 25, 26). The children included in these studies were not all fully vaccinated, with approximately 15% overall being unvaccinated. Looking at specific LMICs, the experience of long-term protection against Hib disease post-Hib vaccine introduction is mixed. In a longitudinal surveillance study based in Kenya investigating the effect of Hib vaccine on disease, carriage and population immunity, 79% of children 4-35 months of age had evidence of long-term protective antibodies, 8 years after Hib vaccine introduction into the community (27). In the Kenyan setting, this level of seroprotection kept Hib disease under control with no need for a booster dose, but continued surveillance
was recommended (27). In contrast, using the same infant schedule as Kenya (3 doses with no booster), the Gambia has seen a gradual increase in Hib disease incidence in children 2-59 months of age in the post-Hib vaccine era (28). Seventy per cent of children 5-6 years of age had evidence of long-term protective antibodies in the Gambia (28). However, there is no recommendation to introduce a booster dose as questions remain of necessity, age and also what factors may influence resurgence of Hib disease in LMIC settings. Regardless, ongoing surveillance is important in order to detect changes in Hib disease after vaccine introduction and is recommended by all studies.

3.4. **Vaccine preventable disease outbreaks (VPD) – situation in Lao PDR**

In the past a small number of serosurveys have been conducted in Lao PDR, with the focus on VPD, namely diphtheria and hepatitis B (HepB). Black et al. (2014) conducted a cross-sectional serosurvey in Lao PDR of HepB serology in the population. From their results, Black et al. (2014) found vaccination coverage was suboptimal (65.6%) even in the urban populations with best access to care (29). In addition, only 17% of pre-school children with 3 documented HepB vaccinations were serologically protected (black 2014). However it is well documented with HepB vaccination, immunological memory persists even though circulating antibody may be low (30). Thus circulating antibodies is not an accurate representation of true immunological protection against HepB in the population.

Nanthavong et al. (2015) investigated diphtheria immunity in rural Lao PDR where there had been diphtheria outbreaks in the past. Using a cluster sampling design, Nanthavong et al. (2015) reported only 83.6% of children with written evidence of receiving 3 doses of diphtheria containing vaccine had protective levels of diphtheria antibodies (31). Both of these studies highlight the discrepancy between the documented vaccination coverage versus the serological immunity in the population. However as evidenced with HepB, low levels of antibody does not necessarily mean absence of protection.

Since 2015, in Lao PDR there have been multiple outbreaks of VPDs including measles, diphtheria and polio. This has raised concerns in regards to the documented coverage versus the serological immunity in the population, leading
to a request by National Immunization Programme (NIP) to investigate. Thus far, there has been a measles serosurvey conducted with the results pending. To add to this, an assessment was requested by NIP to investigate the immunity of Hib in the population as a proxy for DTPw-Hib-HepB vaccine coverage.

3.5. Aims and objectives

The aims of this study were to determine in children <5 years of age living in Vientiane Capital:

1. The percentage of children vaccinated with Hib vaccine, based on written immunisation records;
2. The percentage of children aged 12-59 months with serological evidence of Hib protection; and
3. What percentage of the unvaccinated children have serological evidence of Hib protection.

To achieve the study aims, the following objectives from a convenient sample of children <5 years of age living in Vientiane Capital, Lao PDR were to calculate the:

- Coverage of Hib vaccine from written immunisation record (parent-held card or health centre immunisation register), by age group and sex;
- Serological evidence of Hib short-term (≥0.15ug/ml) and long term (≥1.0ug/ml) immunity by measuring the IgG antibody levels to Hib capsular PRP, by age group and sex; and
- Percentage of unvaccinated children that have serological evidence of Hib short-term immunity (≥0.15ug/ml) and long term immunity (≥1.0ug/ml) by measuring the IgG antibody levels to Hib capsular PRP, by age group.
4. Methods

4.1. Context
Lao PDR is classified as a least developed country (LDC) globally and is made up of 18 provinces, each consisting of districts containing numerous villages. Eighty percent of the population lives in a rural setting, whilst 20% live in an urban setting, predominantly in Vientiane Capital. Vientiane Capital is located on the banks of the Mekong River overlooking Thailand. Vientiane Capital consists of 9 districts and has a population of approximately 820,940, with a <5 year old population of approximately 98,000 and under 5 mortality rate of 86 per 1000 live births (32).

Pentavac (Serum Institute of India and Quinvaxem, Berna Biotech, Korea) containing diphtheria, HepB, tetanus, pertussis and Hib, was introduced into the Lao PDR NIP in 2009, replacing DTP-HepB vaccine. This vaccine is administered at 6, 10 and 14 weeks of age along with 13-valent pneumococcal conjugate vaccine and oral polio vaccine. According to NIP data, 2016 coverage of the third dose of DTPw-Hib-HepB vaccine in children 12-23 months is approximately 77% in Vientiane Capital.

Five major central hospitals, 9 district hospitals and approximately 30 health centres service Vientiane Capital. Parents/caregivers can access routine immunisation services at any one of these health facilities free of charge for their children. In addition to DTPw-Hib-HepB vaccine, vaccines included in the NIP are birth dose HepB, BCG, oral polio vaccine, pneumococcal conjugate vaccine, measles and rubella. Generally, routine immunisation is a passive program with mothers bringing their children to the clinic, however limited outreach programs do operate, depending on the health centre and their available resources. During an outbreak situation, district hospitals and health centres are required to conduct supplementary immunisation activities (SIAs) as requested by NIP, a recent example being the polio campaigns for the polio outbreak in Lao PDR in 2015 (see chapter 5).
4.2. Recruitment and data collection
A convenience sample of children <5 years of age living in Vientiane Capital were recruited from contacts of children hospitalised with acute respiratory infection (refer to Chapter 2 for details regarding the recruitment of these cases) as part of another ongoing study.

After consent had been sought from cases to conduct the contact serosurvey, a list of all contacts were identified from the case’s parent/guardian and listed in the screening book, with each contact given a unique study identification number. Parents of contacts were contacted either by phone or in person and had the study explained to them with the use of an information sheet (Appendix A).

Consent was obtained from parents in two stages. First they were asked to give consent to be part of the written record survey, which included viewing and recording their child’s vaccination status from their MCH card or to find their record at the health centre. The second stage of consent was for the serosurvey. If the child was >12 months old, parents were asked to give consent for a blood sample to be taken. If consent was given for the blood sample, up to 1ml was collected, using aseptic technique by finger prick. Blood samples were then transported to the LOMWRU laboratory in a cool box on the day of collection.

For both the written record and serosurvey, basic demographic data were collected on a dedicated data collection form (Appendix B). Data collected included date of birth/age, sex, ethnicity and where they seek medical care for their child.

4.3. Laboratory methods
Blood collected in serum tubes were centrifuged to separate the serum from the other blood components by laboratory technicians at the LOMWRU laboratories. The serum was then aliquotted into microtubes for storage at -80°C in ultra low temperature (ULT) freezers on site. Serum samples stored in the LOMWRU laboratory were shipped in batches on dry ice to the immunology group at MCRI in Melbourne, Australia for serological testing. Each shipment of serum samples had a sample list included to ensure the receiving laboratory could account for all
samples in the shipment. Once all serum samples had arrived at the immunology lab they were stored in ULT freezers until they were processed.

4.4. Outcomes measures

4.4.1. Written record
Using either the MCH card or health centre immunisation registry, participants that had received 3 doses of vaccine were considered fully vaccinated. Participants receiving 2 doses or less were considered undervaccinated.

4.4.2. Serological evidence of Hib antibody protection
For determining Hib antibody levels in serum samples, ELISAs measuring IgG anti-PRP levels were performed with samples containing ≥0.15μg/ml and ≥1.0μg/ml considered evidence of short and long-term immunity, respectively.

4.5. Statistical consideration
Continuous variables such as age were summarised using median and interquartile range. Discrete variables including sex, ethnicity and health seeking behaviours, were summarised using frequency counts and percentages. P-values were calculated using chi-squared tests. Ninety-five percent confidence intervals were reported for proportion calculations of written record coverage and antibody levels. All statistical tests were considered significant at the 0.05% level.

4.5.1. Written record coverage
Using the estimated national coverage (77%) and considering the effect of clustering due to the sample collection method, the required sample size was calculated for this study. As the size of the clusters were not the same, sample size was calculated with the following formula:

\[
\text{Overall sample size} = n_1 * k(1-\text{ICC})/(k- n_1*\text{ICC})
\]

Where: 
- \(n_1\) was the sample size under individual randomisation
- \(k\) was the number of clusters
- ICC was the intra-cluster correlation
Thus for the primary aim of vaccine coverage by written record, prevalence was estimated in the sample to be within 5 of the estimated coverage of 77%. In the sample there were 168 clusters, with cluster size ranging from 1-20. Taking into consideration the effect of the ICC the sample size required for the following ICC values are shown in Table 1:

<table>
<thead>
<tr>
<th>ICC value</th>
<th>0.01</th>
<th>0.02</th>
<th>0.03</th>
<th>0.05</th>
<th>0.1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample size (5% precision)</td>
<td>274.7</td>
<td>276.5</td>
<td>278.4</td>
<td>282.3</td>
<td>293.4</td>
</tr>
</tbody>
</table>

### 4.5.2. Evidence of serological protection

Based on the literature, the proportion of vaccinated children 2-5 years of age showing evidence for short and long-term immunity ranged 77-100% and 19-83%, respectively (19-23, 25). However, because the children in this study received their last vaccinations at 14 weeks of age, only evidence of long-term immunity was relevant for the purposes of sample size calculations.

In the sample there were 49 clusters ranging in size from 1-10. Taking into consideration the effect of the ICC, the sample size required for the following ICC values are shown in Table 2 for long-term immunity:

<table>
<thead>
<tr>
<th>ICC value</th>
<th>0.01</th>
<th>0.02</th>
<th>0.03</th>
<th>0.05</th>
<th>0.1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample size (5% confidence)</td>
<td>224.8-246.6</td>
<td>233.3-257.1</td>
<td>242.7-268.9</td>
<td>264.8-297.0</td>
<td>350.5-413.1</td>
</tr>
</tbody>
</table>

### 4.6. Ethical consideration

Ethics approval was gained from the Royal Children’s Hospital (RCH) Human Research Ethics Committee (33177B; MCRI), Oxford Tropical Research Ethics Committee (1050-13; LOMWRU), WPRO Ethics Research Committee (2013.30.LAO.2.EPI) and the Human Research Ethics Committee (2016/770; ANU).
5. Results

From the 1st of May 2015 until the 28th of February 2017, there were 935 contacts screened for both written record and serological evidence for Hib vaccination. For the written record and serological evidence a total of 559 and 262 were included in the study, respectively. The flowchart for the inclusion of contacts for both surveys can be seen in Figure 2.

**Figure 2:** Flowchart of participant recruitment into the written record and serological evidence survey, from May 2015 to February 2017

<table>
<thead>
<tr>
<th>Written record survey</th>
<th>Serological survey</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total screened</strong> (n=935)</td>
<td><strong>Total screened</strong> (n=935)</td>
</tr>
<tr>
<td>Ineligible (n=207)</td>
<td>Ineligible (n=382)</td>
</tr>
<tr>
<td><strong>Total eligible</strong> (n=728)</td>
<td><strong>Total eligible</strong> (n=553)</td>
</tr>
<tr>
<td>No consent (n=81)</td>
<td>No consent (n=231)</td>
</tr>
<tr>
<td>Unable to locate (n=71)</td>
<td>Consent (n=322)</td>
</tr>
<tr>
<td>Consent (n=626)</td>
<td>Blood sample taken (n=322)</td>
</tr>
<tr>
<td>Unable to find written record (n=65)</td>
<td>Insufficient sample (n=56)</td>
</tr>
<tr>
<td>Data not available (n=2)</td>
<td>Tested 266</td>
</tr>
<tr>
<td><strong>Included in analysis</strong> (n=559)</td>
<td>Testing failure (n=4)</td>
</tr>
<tr>
<td></td>
<td><strong>Included in analysis</strong> (n=262)</td>
</tr>
</tbody>
</table>

Children were ineligible for the written record if they were >59 months of age. Children were ineligible for the serological survey if they were <12 months of age or >59 months of age.

The characteristics of contacts, stratified by Hib vaccination status based on written record is shown in Table 3. Undervaccinated contacts were significantly more likely to be of an ethnicity other than Lao Loum. Regarding health seeking behaviour, vaccinated contacts were significantly more likely to visit a tertiary hospital for care, whilst undervaccinated contacts were significantly more likely to seek care at their local health centre. Contacts with unknown vaccination status were older, but this was not statistically significantly. However, contacts with unknown vaccination status were significantly more likely to seek care at a pharmacy.
### Table 3: Characteristics of contacts, stratified by vaccination status as determined by written record (n=624)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total (n=624)</th>
<th>Vaccinated (n=348)</th>
<th>Undervaccinated (n=211)</th>
<th>Unknown (n=65)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median age in months, (IQR)</strong></td>
<td>24 (IQR 11-37)</td>
<td>22 (IQR 11-33)</td>
<td>28 (IQR 11-43)</td>
<td>32 (IQR 24-41)</td>
<td>0.32</td>
</tr>
<tr>
<td><strong>Male, n (%)</strong></td>
<td>340 (54)</td>
<td>183 (53)</td>
<td>119 (56)</td>
<td>38 (58)</td>
<td>0.54</td>
</tr>
<tr>
<td><strong>Ethnicity, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lao Loum</td>
<td>534 (86)</td>
<td>316 (91)</td>
<td>166 (79)</td>
<td>52 (80)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Other</td>
<td>90 (14)</td>
<td>32 (9)</td>
<td>45 (21)</td>
<td>13 (20)</td>
<td></td>
</tr>
<tr>
<td><strong>Healthcare, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tertiary hospital</td>
<td>490 (79)</td>
<td>304 (87)</td>
<td>140 (66)</td>
<td>46 (71)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Local Health Centre</td>
<td>164 (26)</td>
<td>68 (20)</td>
<td>73 (35)</td>
<td>23 (35)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Private Clinic</td>
<td>367 (59)</td>
<td>206 (59)</td>
<td>122 (58)</td>
<td>39 (60)</td>
<td>0.93</td>
</tr>
<tr>
<td>Pharmacy</td>
<td>327 (52)</td>
<td>167 (48)</td>
<td>115 (55)</td>
<td>45 (69)</td>
<td>0.005*</td>
</tr>
</tbody>
</table>

#### 5.1. Hib vaccination coverage

The total coverage of Hib vaccine (given as part of DTPw-Hib-HepB vaccine) by written record was 62% (348/559). Vaccination status was unknown for 65 cases. Contacts 12-23 months of age had significantly higher coverage than other age groups at 74% (p<0.001). Coverage of different age groups can be seen in Figure 3.

**Figure 3:** Hib vaccine (given as part of DTPw-Hib-HepB vaccine) coverage by written record in participants by age group (bars indicate 95% CIs)
5.2. Serological evidence
Of the 553 contacts eligible for the serosurvey, 322 provided consent. Of those, 262 blood samples were included in the final analysis (Figure 2). All contacts tested had serological evidence of short-term protection. Sixty percent (95% CI 54-66%) of contacts tested had serological evidence of long-term protection. There was no significant difference between age groups (p=0.492) (Figure 4) or sex (p=0.482) for long-term seroprotective levels.

![Figure 4: Proportion of samples with short- and long-term antibodies for *H. influenzae* type b (Hib) by age (bars indicate 95% CI)](image)

Samples with antibodies >0.15μg/ml are positive for short-term immunity. Samples with antibodies >1.0μg/ml are positive for long-term immunity.

5.3. Unvaccinated contacts
Of the 262 contacts with a blood sample tested, 34% were unvaccinated based on the written record. Of those unvaccinated by written record with a blood sample available, all had serological evidence of short-term protection and 61% had serological evidence of long-term protection.
6. Discussion

The written coverage of Hib vaccine reported from this study is similar to the latest coverage estimates for Vientiane Capital (77%) from NIP. However, the nationally reported coverage estimates for Lao PDR are lower (86%) than those reported globally for Hib vaccine (given as part of DTPw-Hib-HepB vaccine) third dose (33). In addition, the nationally reported coverage estimates in comparison to the region (94%) are even lower (33). The nationally reported coverage estimates for Lao PDR could be an underestimation of the true coverage due to the limitations of the surveying methods and use of administrative data. The WHO EPI survey method is used by many LMICs, inclusive of Lao PDR to estimate vaccine coverage in their respective countries. As highlighted in the introduction, the EPI method is prone to selection bias caused by out-dated household lists, presence of transient populations, particularly in the rural area and general logistical issues, where the population is spread over large areas of difficult terrain. These are all problems common for Lao PDR when conducting EPI surveys.

All children in the study showed evidence of short-term immunity and 60% showed evidence of long-term immunity irrespective of written record vaccination status. Of particular interest are the high antibody levels in children marked as unvaccinated. A community serosurvey in Mali prior to the introduction of Hib vaccine found 1.5% of 6-7 month old infants had Hib antibodies ≥0.15 μg/ml suggesting naturally acquired Hib antibody levels infants in this population and age group are low (26). Therefore in this study in Lao PDR, we would expect a negligible proportion of unvaccinated children to have Hib seroprotective levels. Possible reasons for the high levels of Hib immunity are recording errors, cross-reactivity of other pathogens with the Hib assay or ongoing exposure to Hib in the population (19, 34). It is possible, unvaccinated children by written record did in fact receive vaccination but did not have it recorded either in their MCH card or in the health centre registries by staff. Irrespective of the administrative data issues, the level of vaccine coverage reported may protect the population from Hib disease but may not be sufficient to eliminate Hib carriage. This is supported by our colleagues in Lao PDR conducting an aetiological study of acute respiratory infection (ARI) in hospitalised children (unpublished data, pers. Comm. A. Dubot-
Chapter 4 – Hib Serosurvey

Peres & H. Nguyen) who found Hib in their carriage samples. This provides opportunities for natural boosting of Hib in the population, maintaining high levels of circulating Hib antibody. There is also uncertainty as to the specificity of the Hib assay, which may also explain the high level of short and long-term immunity observed in the unvaccinated children. Exposure to organisms such as E. coli that share common antigenic structures with the Hib capsule, create antibodies with the capabilities to cross-react with assays that target Hib antibodies (34, 35), thereby reducing the specificity of this assay to detect Hib antibodies. This brings into question the use of this Hib assay as a measure of Hib protection in the community; is the high proportions of children with evidence of serological immunity through natural exposure, vaccination or via cross-reactivity with other organisms? The most likely explanation for the discrepancy between written record and serological evidence is a combination of all these factors. Therefore it is unknown if measuring circulating Hib antibody is a good correlate of protection.

In comparison to other studies both from HICs and LMICs, the proportion of children in this Lao PDR study with serological evidence of short and long-term immunity are higher than countries from both these settings. The discrepancy of serological evidence of Hib immunity between HICs and LMICs are most likely due to vaccine coverage levels and length of time since vaccine introduction. Studies from the UK, Kenya and the Gambia, report high vaccine coverage levels post-vaccine introduction (13, 27, 28), with the UK having introduced the Hib vaccine into their schedule the earliest. With the maintenance of higher levels of coverage for an extended length of time, this has meant Hib carriage has been all but eliminated along with Hib disease, reducing the opportunities for natural boosting in the population (19). Coupled with the effect of waning antibody in vaccinated children and less immunogenic combination vaccine formulations, the levels of circulating Hib antibody in the older age groups of the population is reduced (19). This has meant, as seen in the UK, increases in Hib disease incidence. Thus in response additional doses of vaccine have been or are being considered to be added into the routine immunisation schedules. The identification of this change in Hib disease epidemiology has been attributed to robust disease surveillance, highlighting the importance of post-vaccine introduction surveillance to monitor
the effectiveness of the vaccine. In all studies investigating the issue of Hib disease protection, surveillance is a key recommendation.

The key limitation to the study is the use of a convenience sampling method. This was because participants were chosen based on exposure to cases admitted to Mahosot Hospital with ARI as part of an ongoing study (Chapter 2). Convenience sampling is non-probabilistic and is affected by selection bias therefore the external validity needs to be considered when discussing the results. The use of a non-probabilistic population is likely to diminish the results from being generalised to the actual population, as not all people in the population have an equal chance to be selected. In addition, because the participants were contacts of cases, clustering was a concern. Clustering reduces the overall number of the sample, as participants from the same cluster are likely to have similar characteristics. To address this issue, the effect of clustering was taken into account when calculating the sample size as detailed in the methods. The number of participants exceeded the calculated sample size, thus the results are reliable for this sample population. Another factor to consider for these data are the participants are all from Vientiane Capital and not representative of Lao PDR as a whole. Vientiane Capital is weighted towards an urban population, when the actual distribution of the country as a whole is primarily rural/remote. In addition, access to health services is easier in the capital, leading to an overestimation of vaccine coverage if extended to the whole country. Nevertheless, the Hib coverage calculated in this survey were similar to the official rates suggesting our data are representative of Hib coverage in Vientiane Capital.

The coverage levels reported by NIP for Vientiane Capital and our data may be enough to allow for protection against Hib disease but not eliminate carriage of Hib, providing opportunities for natural boosting to occur. In addition, the discrepancy between written record and serological evidence may also be attributed to recording errors, with vaccinated children not being marked as such. We cannot say from these results if a booster dose is required, especially as it is not supported with Hib disease data. Continuation of surveillance is recommended to monitor the post-vaccine situation in Lao PDR to identify increases in disease and potential breakthrough disease attributed to vaccine failures not only for Hib
but other VPDs. The prevention of VPDs in Lao PDR is through the increased uptake of vaccines, subsequently increasing vaccine coverage in the population. Improvements in vaccine coverage are the major focus area for NIP and development of new methods to improve the protection in the population need to be considered.
7. Recommendations

- Given the levels of Hib vaccine found in the study were lower than both regional and global estimates, ongoing efforts by NIP and WHO to boost vaccination rates should be supported. These may include outreach programs, both education and mobile vaccination units. Considering the resources available, the education component could be supported by village health volunteers and for the mobile vaccination units, these could be deployed on dedicated days.

- Hib surveillance is already conducted at sentinel sites such as Mahosot Hospital. However the number of cerebrospinal and blood samples is low. Ways to improve this could be through increasing clinician awareness of the importance of Hib surveillance and financial support for testing. Considering the available resources, this is achievable with the support of senior paediatric staff.

- Surveillance is limited to monitor Hib disease in Lao PDR, making it difficult to investigate the association of antibody levels to risk of disease. Due to resource constraints and logistical difficulties, rather than investigating the antibody levels required for protection against Hib disease, it is recommended that NIP take its advice from other countries in a similar situation on changes they want to make on their current policies for routine immunisation.
8. References


9. Appendices

A. Contact information sheet

**Acute Respiratory Infections in Vientiane Pilot study, OXTRC No. 1050-13**

Information sheet for Consent Form for Parents of Contact Children 3 March 2015 v1

---

**Introduction**

My name is ............. (phone number xxxxx), and I am working at the Microbiology Laboratory at Mahosot Hospital. In 2013 the Laos Ministry of Health introduced the pneumococcal vaccine for all babies in Laos to prevent the commonest cause of pneumonia and meningitis, from the germ called pneumococcus. This germ commonly lives in the nose of well people. The pneumococcal vaccine can stop this germ from living in the nose and thereby prevent vaccinated people from getting the disease. This also prevents the germ from spreading in the community, so unvaccinated people may also be protected. The aim of this study is to determine the pneumococcal vaccination level needed in the community to show a decline in the carriage of pneumococcal germs in the nose, and hence show evidence of protection from the disease.

We are inviting the contacts of [add case’s name] who was recently sick in hospital to take part in this study. I am going to give you information and invite you to consent to have your child participate in this study. Before you decide whether you want your child to participate, you can talk to anyone you feel comfortable with. There may be some words that you do not understand. Please ask me to stop as we go through the information, and I will take time to explain. If you have questions later, you can ask the study doctor, the staff or me.

**The Study**

The study we are conducting will give information to the Ministry of Health, Government of Laos, about the level of pneumococcal vaccine they need to achieve in the community before most people can benefit from the immunisation program.

Today, we would like to:

- See your child’s immunisation record and record what vaccines have been given
- Take a finger prick blood test and take up to 1.5ml of blood

The blood sample will be sent to laboratories in other countries for analysis that cannot be performed in Laos. It will look for levels of protection from the common vaccine preventable diseases in Laos.
Potential Benefits
The blood sample will not help the care of your child but we hope that the information will help provide information for the Lao Ministry of Health to improve their immunisation service.

Potential Risks
Taking the blood sample will be uncomfortable for your child but we will have trained study staff to perform the test and will aim to do it as quickly as possible. Your child’s finger may be a little bruised but this will go away after a few days.

Alternatives
Your decision to have your child participate in this study is entirely voluntary. If you choose not to consent, all the services your child receives normally will continue as usual. Even if you agree now but decide to change your mind and withdraw later, the services your child normally receives will continue.

Confidentiality
All your child’s details will remain confidential and will only be known to the health staff looking after your child and the research team.

Costs
There will be no extra costs to either yourself or the hospital.

Questions
If you have any concerns or would like to ask any questions now or in the future please ask the ward doctor or any of the staff involved in the research.
Chapter 4 – Hib Serosurvey

Acute Respiratory Infections in Vientiane Pilot study. OXTREC No. 1050-13

Consent Form for Parents of Contact Children - 3 March 2015 v1
Study: Acute Respiratory Infection in Vientiane - Pilot study
You will be given a copy of the consent form and the information sheet.

Certificate of consent
The child I am responsible for has been invited to participate in a study to determine the pneumococcal vaccination level needed in the community to show a decline in the carriage of the pneumococcal germ in the nose, and hence show protection from the disease in Vientiane, Lao P.D.R.

I have read the information sheet, or it has been read to me. I have had the opportunity to ask questions, and any questions that I have asked have been answered to my satisfaction. I consent voluntarily to my or my child’s participation in this study.

Print name of child: __________________________
Print name of parent or guardian: __________________________
Signature of parent or guardian: __________________________
Date: __________________________
(dd/mmm/yyyy)

Witness’ signature: (A witness’ signature and the thumbprint of the participant’s parent or guardian are required only if the parent or guardian is illiterate. In this case, a literate witness must sign. If possible, this person should be selected by the participant’s parent or guardian and should have no connection with the study team).

I have witnessed the accurate reading of the consent form to the potential participant’s parent or guardian, who has had the opportunity to ask questions. I confirm that the participant’s parent or guardian has given consent freely.

Print name of witness: __________________________
Signature of witness: __________________________
Date: __________________________
(dd/mmm/yyyy)
Investigator’s signature:

I have accurately read or witnessed the accurate reading of the consent form to the potential participant’s parent or guardian, who has had the opportunity to ask questions. I confirm that the participant’s parent or guardian has given consent freely.

Print name of investigator: ______________________

Signature of investigator: ______________________

Date: ______________________

(dd/mmm/yyyy)

A copy of this informed consent form has been provided to the patient or the participant’s parent or guardian. _____ (initials of the principal investigator/assistant).
## B. Contact data collection form

### Contact Details

<table>
<thead>
<tr>
<th>Case LPC ID Number</th>
<th>LPC Case date of admission: (dd/mm/yy)</th>
<th>Contact ID Number</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Eligible for blood?**  
☐ Yes  ☐ No  
**Date of blood taking:** (dd/mm/yy)  
[ ] [ ] [ ] [ ] [ ] [ ] [ ] [ ] [ ]

**Date of Birth:** (dd/mm/yy)  
[ ] [ ] [ ] [ ] [ ] [ ] [ ] [ ] [ ]

**Age:**  [ ] years  [ ] months

**Gender:**  ☐ Male  ☐ Female

**Ethnicity:**  
☐ Lao Loum  ☐ Hmong  ☐ Khmu  ☐ Pral  ☐ Ma Kong  ☐ Alak  
☐ Ngae  ☐ Taiileung  ☐ Dak Kang  ☐ Other (specify) ..................

**Relation to case:**

☐ Does the contact live in the same house as the case?  
☐ Yes  ☐ No

☐ How frequently does your child see the case?  
☐ Every day  ☐ Every week  
☐ Once a month  ☐ Other:

**Vaccination status:**

☐ Has the child been vaccinated?  
☐ Yes  ☐ No

☐ Photo of book taken?  
☐ Yes  ☐ No  
If no, why? __________________________

☐ Record of PCV vaccination found at health centre (HC)?  
☐ Yes  ☐ No

**PCV vaccination:**  
☐ Yes  ☐ No  
Source:  ☐ Book  ☐ Verbal  ☐ Health Centre

If Yes, Date (dd/mm/yy) PCV13 1 given  [ ] [ ] [ ] [ ] [ ] [ ] [ ] [ ] [ ]

If Yes, Date (dd/mm/yy) PCV13 2 given  [ ] [ ] [ ] [ ] [ ] [ ] [ ] [ ] [ ]

If Yes, Date (dd/mm/yy) PCV13 3 given  [ ] [ ] [ ] [ ] [ ] [ ] [ ] [ ] [ ]

**Measles vaccination:**  
☐ Yes  ☐ No  
Source:  ☐ Book  ☐ Verbal

If Yes, Date (dd/mm/yy) Measles 1 given  [ ] [ ] [ ] [ ] [ ] [ ] [ ] [ ] [ ]

If Yes, Date (dd/mm/yy) Measles 2 given  [ ] [ ] [ ] [ ] [ ] [ ] [ ] [ ] [ ]

**Pentavalent (DTP-Hib-HepB) vaccination:**  
☐ Yes  ☐ No  
Source:  ☐ Book  ☐ Verbal

If Yes, Date (dd/mm/yy) Pentavalent 1 given  [ ] [ ] [ ] [ ] [ ] [ ] [ ] [ ] [ ]

If Yes, Date (dd/mm/yy) Pentavalent 2 given  [ ] [ ] [ ] [ ] [ ] [ ] [ ] [ ] [ ]

If Yes, Date (dd/mm/yy) Pentavalent 3 given  [ ] [ ] [ ] [ ] [ ] [ ] [ ] [ ] [ ]

**General health:**

☐ Has your child ever had a fever and rash illness (measles or rubella)?  
☐ Yes  ☐ No

If Yes, when:  [ ] [ ] [ ] [ ] [ ] [ ] [ ] [ ] [ ] [ ]

If your child was sick and needed to go to the hospital, which hospital would you attend?

☐ Mahosot Hospital  ☐ Setthathirath Hospital

☐ National Children’s Hospital  ☐ Mother and Child Hospital

☐ 103 Hospital  ☐ April 5th Hospital

☐ Private Clinic  ☐ Health Centre

☐ Other: __________________________

**Other Comments:**

---

Research Assistant:  
[ ] Monitor:  
[ ] Date:  

---
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Chapter 5
Circulating vaccine-derived poliovirus type 1 (cVDPV1) outbreak in Lao PDR
This chapter was removed due to the data and information presented from an ongoing outbreak at the time of writing. Therefore the data and information had not been formally vetted and assessed by the custodians of the data.

The custodians of the data (National Immunisation Program of Lao PDR, National Centre of Laboratory and Epidemiology of Lao PDR and the World Health Organization Lao PDR Country office, whom act as secretariat to the Ministry of Health Lao PDR) have requested for the data and information presented in this chapter to be restricted indefinitely.

There will be formal reports and publications prepared and disseminated to the public once the outbreak is completed and formally assessed.
Chapter 6
Teaching
Contents
1. Prologue.................................................................................................................................................. 233
   1.1. Role and lessons learned.................................................................................................................. 233
2. Appendices .............................................................................................................................................. 236
   A. Lessons from the Field (LFF)........................................................................................................... 236
   B. MAE Courseblock 2016 .................................................................................................................... 256
   C. LOMWRU bias and confounding presentation.................................................................................. 276
1. Prologue

1.1. Role and lessons learned

The Master of Applied Epidemiology (MAE) program included 2 teaching requirements:

1. Lessons from the field (LFF) – a teaching exercise based on a real-life situation encountered on the field delivered as a teleconference session; and

2. Teaching session for first-year MAE cohort – group work based on a timeframe of a 3 hour teaching session on a chosen topic

In addition to the MAE requirements, I assisted in the teaching sessions for the journal club program at the Laos-Oxford-Mahosot Hospital-Wellcome Trust-Research Unit (LOMWRU), People’s Democratic Republic of (Lao PDR) Field Epidemiology Training Program cohort 8 (FETP8) and was responsible for teaching staff employed for the PneuCAPTIVE project (Chapter 2).

One of the most challenging aspects of my work was calculating vaccine coverage. Thus for my LFF I decided to run a session on vaccine coverage and the difficulties that can be faced when working with administrative data in a low-resource setting. As the MAE cohort of 2015 was large and had 2 international MAEs, for the sake of ease (the group was spread over many different timezones) and also as both Dr Tambri Housen, based in Medecins Sans Frontier (MSF) India, and myself had planned to cover similar topics based on our placements we decided to combine our LFF session. Thus our LFF was titled “Vaccine coverage – Select, wait and ??” (Appendix A). The aim of the LFF was to walk our MAE LFF group on the process of sampling and common methods related to vaccine coverage estimation and then using real data, how to extract information and consideration of other methods of vaccine coverage estimation. My role in the LFF was to prepare and present the introduction section dealing with the theoretical concepts of sampling and different methods of calculating vaccine coverage. I was then responsible for walking the group through the real data I had collected in the field.
The teaching session for the first years was developed in collaboration with a group of my colleagues from my cohort (Dr Tanyth de Gooyer, Dr Tambri Housen, Dr Craig Thompson, Anthony Draper, Dr Alicia Arnott) on the topic of ‘Administering questionnaires when conducting an outbreak investigation’ (Appendix B). We developed the session based on our experiences in the field and theoretical training from the MAE program. The aims of the session were to introduce some of the considerations (and pitfalls) associated with conducting interviews as part of outbreak investigations and to provide a practical experience of interviewing. The preparation of the session was difficult as we were spread both in Australia and internationally. The session was structured with an introduction, practice interviews and reflections on the session. From the evaluation, the session was very successful with the overall session receiving 4.7/5 by the MAE 2016 cohort.

Being based in Lao PDR, there were many opportunities to assist in training of local staff on epidemiological concepts. I helped with training of local staff both at LOMWRU and the FETP managed jointly by the World Health Organization (WHO) Laos PDR country office and the National Centre for Laboratory and Epidemiology (NCLE) in the Ministry of Health (MoH). For the training at LOMWRU, it was identified that staff attending the regular journal club session each month had limited training in epidemiological concepts, making it difficult to critically appraise journals each month. To improve the understanding and encourage more engagement of local staff with the journal club, a series of lectures addressing study design, sampling, statistical analyses and limitations were presented to local staff to improve their epidemiological knowledge. I was asked to present the session on bias and confounding. The slides used are in Appendix C. During my time interacting with the surveillance team at WHO, I offered to help out with the FETP cohort in 2016. I assisted in their data analysis sessions held at NCLE.

As part of my employment I acted in a coordinator position for the PneuCAPTIVE study (Chapter 2) based in Lao PDR. In this role I was responsible for a team of staff working on the non-clinical aspects of the study. This meant that I was responsible for all the training of our staff for the contact serosurvey and health centre immunisation register data collection. For the contact serosurvey staff had
to be trained on the identification and consent process of contacts, subsequent data collection on dedicated forms and entry of data into the relevant databases. For the health centre immunisation register data collection staff had to be trained on the process of understanding the data contained in the registries, as each health centre recorded the data differently, how to collect the data contained in the registries and finally the data entry process. The data for both the serosurvey and health centre registries were double data entered into Epidata databases.
2. Appendices

A. **Lessons from the Field (LFF)**

**Vaccine coverage – Select, wait and ??**

**Lesson from the Field Overview**

Using vaccine coverage as a basis, this lesson will take you through how to select a representative sample from a target population in a remote area of a resource limited country using complex sampling methods. In addition you will also be shown how to weight your sample prior to data analysis and be exposed to the various methods of vaccine coverage estimation.

This lesson is split into two parts; Part A focuses on sampling and common methods related to vaccine coverage estimation, whilst Part B works through an example of collating/extracting data from real field sources and other methods for vaccine coverage estimation.

**Learning objectives:**

By the end of this LFF you should be able to:

- List various methods of estimating vaccination coverage
- Explain terms associated with sampling; target population, sampling population, enumeration areas, primary sampling unit, secondary sampling unit, sampling frame.
- Understand what is meant by complex sampling methods and be able to explain the single-stage cluster design in detail.
- Construct a simple random sample using probability proportional to size
- Calculate sampling weights from survey data
- Conduct a sensitivity analysis of survey prevalence estimates and interpret the findings
- Understand the complexities of collating and extracting field epidemiological data in resource limited settings
Chapter 6 - Teaching

Part A
The Scenario

You are an MAE student placed with Médecins Sans Frontières in a remote area of Laos and have been asked to conduct a household survey to determine vaccine coverage in the district you are based.

Vaccine coverage is an estimate of the proportion of the population who have been vaccinated.

While the government established an Expanded Program of Immunisation (EPI) in 2013 with the aim of vaccinating all children under 5 years of age according to the national immunization schedule, repeated outbreaks of pertussis and measles in the district has led to concern that the nationally published immunisation coverage figures are over-estimated.

Furthermore, during a measles outbreak response that you led in the district as part of your MAE you found out that the population in remote villages of the district have some strong cultural beliefs that my affect immunization uptake. One such belief is that measles is a normal childhood illness and all children should get measles in order to strengthen their body against other illness and ensure they grow strong and resilient.

The medical coordinator (MedCo) has asked you to conduct a vaccine coverage survey as your epi project to fulfill your MAE requirements and provide them with much needed accurate estimates of vaccine coverage.

You start by conducting a quick literature scan on how to conduct a vaccine coverage survey and realize that one of the main issues is going to be sampling. You understand the importance of a representative sample and start thinking of some of the biases that you must consider when designing your sampling frame and method.
Chapter 6 – Teaching

As a refresher, here is a list of various the forms of sampling related bias with a brief description of how they are introduced.

<table>
<thead>
<tr>
<th>Sampling error</th>
</tr>
</thead>
<tbody>
<tr>
<td>- inappropriate number or cluster size is chosen for the population</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Selection bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Sampling frame – if there are differences in vaccine uptake in individuals included in the sample and those excluded from the sample</td>
</tr>
<tr>
<td>- Sampling procedures – non-probability sampling can introduce bias</td>
</tr>
<tr>
<td>- Poor sampling procedures at field level</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Information bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Missing data and the inappropriate handling of missing data</td>
</tr>
<tr>
<td>- Inaccurate reporting by participants</td>
</tr>
<tr>
<td>- Inaccurate recording by survey enumerators</td>
</tr>
</tbody>
</table>

Your field supervisor has referred you to the WHO manual for EPI, chapter 7 of which discuss in detail how to conduct an EPI coverage survey.

**Suggested reading**


[http://www.who.int/immunization/monitoring_surveillance/Vaccination_coverage_cluster_survey_with_annexes.pdf?ua=1](http://www.who.int/immunization/monitoring_surveillance/Vaccination_coverage_cluster_survey_with_annexes.pdf?ua=1)

- Pages 3-8 provides some good background info on measuring vaccine coverage
- The impact of bias highlighted in Task 1 coverage estimates is described on page 9

LFF_MAE_Sampling_Vaccine Coverage
Task 1: From the reading list some of the different ways of calculating vaccine coverage and provide a brief explanation of where the data comes from for each method. Think about which method you would feel most appropriate for estimating vaccine coverage in a district in Laos.

After gaining some understanding of the different methods used in estimating vaccine coverage you understand that conducting a household coverage survey is the most appropriate method for you to use in this remote area of Laos.
Chapter 6 – Teaching

After discussion with the MedCo and your epi supervisor you have established the following

**Primary research question**
Are survey results of vaccine coverage in Feuang District, Vientiane Province, Lao PDR consistent with administrative coverage estimates?

**Specific objectives**
- To estimate vaccine coverage of all children aged 6-59 months for all vaccines included in the national EPI using household survey method
  - Stratified by rural/urban
- To estimate vaccine coverage of all children aged 6-59 months for all vaccines included in the national EPI using administrative methods
  - Stratified by rural/urban

You now consider the study design required in order to meet these goals.

You define your **target population** as:
- All children aged 6-59 months in Feuang District, Vientiane Province, Lao PDR

The Feuang District population is 589,127, with the ≤5 years of age estimated at 8% of the total population. You visit the district health office and review the administrative immunisation coverage estimates for June 2016. Below is a table of data collected from administrative reports of the number of children ≤5 years of age vaccinated for measles and the total ≤5 year old population in each village.

<table>
<thead>
<tr>
<th>Village</th>
<th>Children vaccinated</th>
<th>Population Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anou</td>
<td>1250</td>
<td>1406</td>
</tr>
<tr>
<td>Sikhai</td>
<td>5120</td>
<td>5368</td>
</tr>
<tr>
<td>Bor O</td>
<td>2221</td>
<td>1883</td>
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<tr>
<td>Tardthong</td>
<td>5390</td>
<td>5932</td>
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<td>Mai</td>
<td>4170</td>
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<td>7179</td>
<td>7472</td>
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<td>Kaoliao</td>
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<td>5577</td>
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<tr>
<td>Nongniew</td>
<td>4240</td>
<td>4779</td>
</tr>
<tr>
<td>Sisavath</td>
<td>5279</td>
<td>5652</td>
</tr>
<tr>
<td>Vungma</td>
<td>4398</td>
<td>4301</td>
</tr>
<tr>
<td><strong>Total:</strong></td>
<td><strong>44546</strong></td>
<td><strong>47130</strong></td>
</tr>
</tbody>
</table>

LFE_MAE_Sampling_Vaccine Coverage
Chapter 6 - Teaching

Task 2: What is the vaccine coverage of measles in Feueng District using administrative data?

Suggested reading

Here we list some different sampling designs for vaccine coverage surveys in resource-limited settings.

- **Non-probability sampling**
  - Choose a starting point and select households until the desired quota (7 households per cluster) is obtained.

- **Probability based sampling**
  - The probability of each child being selected is quantifiable.
  - Cluster sampling -
  - Systematic random sampling – first unit is selected randomly and the rest selected according to a predesigned pattern

- **Lot quality assurance sampling**
  - A lot is defined as a population area assigned to a health unit, a health centre or health records within a health centre. The sample is drawn from the lot. This method is not recommended for use in a one-off survey but rather when repeat surveys are required.
Task 3: Define the following terms

1. Sampling Frame:

2. Cluster:

3. Enumeration Area:

4. Primary Sampling Unit:

5. Secondary Sampling Unit:

6. Sampling Interval:

7. Strata

8. Design Effect

9. Non-response inflation factor
Your sample size

**Recommended readings** (not necessary reading for this exercise - I give you the sample size. Good reference material should you have to ever do this).

http://www.who.int/immunization/monitoring_surveillance/Vaccination_coverage_cluster_survey_with_annexes.pdf?ua=1

- Specifically for EPI surveys you can refer to page B1-2 thru to C-2

Dalisay, S et al. 2013. Developing a master sample design for household surveys in developing countries: A case study from Bangladesh in Survey methods: Insights from the field.
http://surveyinsights.org/?p=2151

You have the help of an external statistician and after establishing your desired inferential goals she calculates the sample size for you.

The inferential goals you set include:
- Precision of 0.05, expressed as 95% confidence intervals (CI)
- The probability of making a type I error\(^2\), expressed as \(\alpha\) (alpha) is set at 5%
- The probability of making a type II error\(^3\), expressed as \(\beta\) (beta) is set at 80%
- Non-response is calculated at the standard 10%
- Administrative EPI coverage is reported at 85% for this district

Your sample size estimation is 980 children aged 6-59 months. Within the 10 villages we decide to select 40 clusters of 33 households. You will approach all children in your cluster. An estimated 1320 households will be interviewed in order to capture 980 children

**Sampling Frame**
You are fortunate to have national census data from 2012. The census was conducted with funding from the World Bank enabling the GPS mapping of survey enumeration areas. You therefore have a list of all villages, their Aldeia (smaller administrative units) and urban centres with corresponding populations. You decide to use this census as your sampling frame.

---

\(^2\) Probability of a Type I error refers to the probability that the hypothesis test will declare the difference to be statistically significant when in truth there is no underlying difference. (WHO, 2015)

\(^3\) Probability of a Type II error refers to the probability that the hypothesis test will declare the difference to be not statistically significant when in truth there is a significant difference. This is also known as the statistical power of the classifier (WHO, 2015)
### Chapter 6 – Teaching

<table>
<thead>
<tr>
<th>District</th>
<th>Name</th>
<th>Type</th>
<th>Number of Households</th>
<th>Cumulative number of Households</th>
<th>Total Population</th>
<th>Population under 5 yrs of age</th>
</tr>
</thead>
<tbody>
<tr>
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<td>64</td>
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<td>841</td>
<td>841</td>
<td>841</td>
</tr>
</tbody>
</table>
Chapter 6 - Teaching

Task 4: List some limitations associated with using the 2012 census data as your sampling frame.

You assess the context and note there has been no reported population displacement or substantial in-migration or out-migration in the district. The area is politically stable so you feel the census, although dated- offers the best sampling frame you will find short of conducting your own census, which MSF does not have the resources for.

Suggested reading
You return to your WHO manual and read pages 41 – 42 on using cluster sampling and Annex D – pages D1-D7 an example of systematic random cluster selection using probability proportional to size http://www.who.int/immunization/monitoring_surveillance/Vaccination_coverage_cluster_survey_with_annexes.pdf?ua=1

Task 5: Open the file: CensusData.xlsx and following the steps highlighted in the reading and using population proportional to size randomly select 40 census enumeration areas as clusters for your survey. For the purposes of this exercise Do not worry about stratifying for rural/urban or combining and dividing EAs, just select the clusters using the census list as it is.

Write the names of the first 5 villages you selected in this box

These are your randomly selected Primary Sampling Units that you will visit to conduct the survey.

LFF_MAF_Sampling_Vaccine Coverage
Chapter 6 – Teaching

All goes well with the survey and you have a long list of lessons learnt for your bound volume. Now it is time to analyse the data. You have collected your data on tablets so have immediate access to a nice complete dataset. It is now time to refer to your previously constructed data analysis plan.

On conducting the initial descriptive analysis (after cleaning and coding your data) you now must weight your data in order to calculate representative vaccine coverage estimates for the target population.

You note that your urban/rural distribution is different from that in the census and so you weight your sample accordingly in order ensure that it is representative.

**Suggested reading**
You return to your WHO manual and read pages 73 on calculating weights for analysis

http://www.who.int/immunization/monitoring_surveillance/Vaccination_coverage_cluster_survey_with_annexes.pdf?ua=1

and


The *sampling weight* is the inverse of the probability of selection.

\[
1 \div (\text{number of individuals in the sample} \div \text{the population size})
\]

The *stratification weight* is the inverse of the probability of the probability of selection by strata

\[
\frac{\text{Population proportion}}{\text{sample proportion}}
\]
Chapter 6 – Teaching

Task 6: Follow the steps highlighted in the reading to calculate sampling weights based on the given population and sample data

Table: Sampling weights by stratum, Vaccination Coverage Survey, Feuang District, Vientiane Province, Lao PDR

<table>
<thead>
<tr>
<th>Stratum</th>
<th>Total number of ≤ 5 years of age in the population</th>
<th>Population Prop$^a$</th>
<th>Number of children ≤ 5 years of age in the sample</th>
<th>Sample Prop$^a$</th>
<th>Sampling weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rural</td>
<td>71010</td>
<td></td>
<td>842</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urban</td>
<td>28842</td>
<td></td>
<td>198</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>99852</td>
<td></td>
<td>1040</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Prop$^a$ = proportion

A sensitivity analysis can be conducted by calculating the vaccine coverage estimates with and without weighting. This will show you the impact weighting has on your estimates or if your sample was self-weighted due to the sampling design.

Below is an example of a sensitivity analysis of weighted and un-weighted results. I have included additional weighting including weights for cluster selection.

Cluster weight is the inverse of the probability of each cluster being selected

\[ = \frac{1}{(\text{number of households in the cluster} \times \text{the number of clusters} \div \text{total number of households})} \]

Table: Proportion of fully vaccinated children, allowing for the weights, stratification and clustering, Vaccination Coverage Survey, Feuang District, Vientiane Province, Lao PDR

<table>
<thead>
<tr>
<th>Fully vaccinated children</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simple proportion</td>
<td>60.44</td>
</tr>
<tr>
<td>+sampling weight</td>
<td>62.32</td>
</tr>
<tr>
<td>+sampling weight +clustering</td>
<td>62.32</td>
</tr>
<tr>
<td>+sampling weight +clustering + stratification</td>
<td>65.96</td>
</tr>
</tbody>
</table>

CI = confidence interval
Task 7: Make a statement on the impact weighting has had on vaccine coverage estimates.

Your estimates for vaccine coverage showed that indeed the administration figures are over-inflated. Your team decides to use the results of the survey as an advocacy tool for improved EPI implementation in this district in order to decrease morbidity and mortality from preventable outbreaks. A discussion on community sensitization and health education programs is also commenced in collaboration with the MoH service providers with the aim of improving vaccine uptake.

I have added a do file on sample weighting for your reference and files in case you find yourself doing a household survey one day :-)}
Chapter 6 – Teaching

Part B
After completing your household survey, a new vaccine (PCV13) has just been introduced and the information on coverage of this vaccine has not been collected due to various logistical constraints.

To get the best estimate with your limited resources, you plan to find this data administratively. Luckily, one of your Lao colleagues worked previously in district health centres and informs you of the possibility there may be village immunisation registries with the data you require held at health centres. So you organise to go to a nearby health centre to have a look.

Upon arriving at the health centre, you find that there is indeed village immunisation registries recording PCV13, in a line list format.

Task 8: What questions would you ask staff to find out more about this data?

Talking to staff you find out that there are multiple books for each village as they received a few new books in the past few years. This is a problem as PCV13 was only introduced in 2013 and during this time there have been at least two versions of the immunisation registry distributed to health centres and no clear instructions were given. Also, you find out PCV13 started nationally in October 2013, but not all health centres started using it in October 2013.

Task 9: What additional questions would you like to know about the data contained in the registries?
Now you take a look at the registries. Additional information, PCV13 is given at 4, 6 and 14 weeks, but commonly it is given at 2, 3 and 4 months to match Pentavalent vaccine. A catch up campaign was also conducted for children <12 months of age when the vaccine was started.

You have access to pictures of 3 types of books, oldest (Attachment A), old (Attachment B) and new (Attachment C) book.

**Task 10:** Circle the data that you are unsure about and also write down any other questions that you may have for staff after you have seen the books, either to verify what they have told you or additional new questions.

So now you have worked out what the health centre is doing with their immunisation data, you can amalgamate it with the population data you have for each village by <5 year olds. The criteria for whether a child is considered vaccinated or not are:

<table>
<thead>
<tr>
<th>Age</th>
<th>Vaccinated</th>
<th>Unvaccinated</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;11 months of age</td>
<td>2 PCV13 doses</td>
<td>0 or 1 PCV13 dose</td>
</tr>
<tr>
<td>≥ 12 months of age</td>
<td>1 PCV13 dose</td>
<td>0 doses PCV13</td>
</tr>
</tbody>
</table>
Chapter 6 – Teaching

Below is a line list of 20 children for children from a village in your district. The population data for the village is children <5 years of age = 100.

<table>
<thead>
<tr>
<th>Village</th>
<th>District</th>
<th>Sex</th>
<th>DOB</th>
<th>PCV1</th>
<th>PCV2</th>
<th>PCV3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kaoliew</td>
<td>Feuang</td>
<td>M</td>
<td>28/10/2013</td>
<td>17/12/2013</td>
<td>31/01/2014</td>
<td></td>
</tr>
<tr>
<td>Kaoliew</td>
<td>Feuang</td>
<td>F</td>
<td>31/08/2013</td>
<td>17/10/2013</td>
<td>25/11/2013</td>
<td>20/01/2014</td>
</tr>
<tr>
<td>Kaoliew</td>
<td>Feuang</td>
<td>M</td>
<td>3/12/2013</td>
<td>20/01/2014</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kaoliew</td>
<td>Feuang</td>
<td>F</td>
<td>6/01/2014</td>
<td>21/02/2014</td>
<td>11/04/2014</td>
<td>10/06/2014</td>
</tr>
<tr>
<td>Kaoliew</td>
<td>Feuang</td>
<td>M</td>
<td>23/10/2012</td>
<td>23/01/2014</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kaoliew</td>
<td>Feuang</td>
<td>M</td>
<td>3/01/2014</td>
<td>20/03/2014</td>
<td>21/05/2014</td>
<td></td>
</tr>
<tr>
<td>Kaoliew</td>
<td>Feuang</td>
<td>F</td>
<td>23/01/2014</td>
<td>6/01/2014</td>
<td>8/02/2014</td>
<td></td>
</tr>
<tr>
<td>Kaoliew</td>
<td>Feuang</td>
<td>F</td>
<td>3/03/2014</td>
<td>22/04/2014</td>
<td>22/05/2014</td>
<td>23/06/2014</td>
</tr>
<tr>
<td>Kaoliew</td>
<td>Feuang</td>
<td>M</td>
<td>18/09/2013</td>
<td>8/05/2014</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kaoliew</td>
<td>Feuang</td>
<td>F</td>
<td>20/09/2013</td>
<td>4/11/2013</td>
<td>12/12/2013</td>
<td>20/01/2014</td>
</tr>
<tr>
<td>Kaoliew</td>
<td>Feuang</td>
<td>F</td>
<td>10/12/2013</td>
<td>4/02/2014</td>
<td>5/03/2014</td>
<td>30/05/2014</td>
</tr>
<tr>
<td>Kaoliew</td>
<td>Feuang</td>
<td>M</td>
<td>26/04/2014</td>
<td>12/06/2014</td>
<td>17/07/2014</td>
<td></td>
</tr>
<tr>
<td>Kaoliew</td>
<td>Feuang</td>
<td>M</td>
<td>30/07/2014</td>
<td>15/09/2014</td>
<td>15/10/2014</td>
<td></td>
</tr>
<tr>
<td>Kaoliew</td>
<td>Feuang</td>
<td>M</td>
<td>16/06/2014</td>
<td>1/08/2014</td>
<td>1/09/2014</td>
<td></td>
</tr>
<tr>
<td>Kaoliew</td>
<td>Feuang</td>
<td>F</td>
<td>2/07/2014</td>
<td>18/08/2014</td>
<td>18/09/2014</td>
<td>20/10/2014</td>
</tr>
<tr>
<td>Kaoliew</td>
<td>Feuang</td>
<td>M</td>
<td>30/06/2014</td>
<td>25/08/2014</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kaoliew</td>
<td>Feuang</td>
<td>M</td>
<td>11/12/2014</td>
<td>30/01/2015</td>
<td>1/03/2015</td>
<td></td>
</tr>
<tr>
<td>Kaoliew</td>
<td>Feuang</td>
<td>F</td>
<td>13/01/2015</td>
<td>2/03/2015</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Task 11: What is the PCV13 coverage in that village in May 2014 and October 2014 for children <5 years of age?

After leaving the health centre, you reflect on your discussions with staff and the routine immunisation process.

LFF_MAE_Sampling_Vaccine Coverage
Task 12: Can you also foresee any issues when analysing the data?
Chapter 6 – Teaching

<table>
<thead>
<tr>
<th>Column 1</th>
<th>Column 2</th>
<th>Column 3</th>
<th>Column 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Data 1</td>
<td>Data 2</td>
<td>Data 3</td>
<td>Data 4</td>
</tr>
<tr>
<td>Data 5</td>
<td>Data 6</td>
<td>Data 7</td>
<td>Data 8</td>
</tr>
<tr>
<td>Data 9</td>
<td>Data 10</td>
<td>Data 11</td>
<td>Data 12</td>
</tr>
<tr>
<td>Data 13</td>
<td>Data 14</td>
<td>Data 15</td>
<td>Data 16</td>
</tr>
<tr>
<td>Data 17</td>
<td>Data 18</td>
<td>Data 19</td>
<td>Data 20</td>
</tr>
</tbody>
</table>

Note: The table contains numerical data and is too detailed to provide a meaningful summary without further context.
<table>
<thead>
<tr>
<th>Date</th>
<th>Time</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>02/11/2015</td>
<td>14:24</td>
<td>Class 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Class 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Class 3</td>
</tr>
</tbody>
</table>

Chapter 6 – Teaching
### B. MAE Courseblock 2016

**Teaching exercise: Administering questionnaires when conducting an outbreak investigation**

**Overall purpose of session:**

1. To introduce some of the considerations (and challenges) associated with conducting interviews as part of outbreak investigations
2. To provide a practical exercise to give an experience of interviewing (especially for those who are more green among the group) and to illustrate strategies to overcome challenges we have identified.

**Objectives**

By the end of this session, MAE2016 will be introduced to, and be given practical experience of:

- how to deal with interviewees who are concerned about the privacy of their information collected as part of the interview process
- Some of the techniques you can use to maximise interviewee recall of information
- How keep an interview on track while also managing additional information about the investigation which interviewees may disclose as part of an open ended question

MAE2016 will also be introduced to:

- The importance of building rapport with an interviewee, while still keeping the interview on track
- Ways to ask personal questions of interviewees
- Managing disclosure of information about the investigation to ensure that bias is minimised (from an epidemiological perspective eg. how many others were ill, possible sources of illness), and that confidentiality is not breached (implicating a food supplier, who may not turn out to be the supplier of the source food)

<table>
<thead>
<tr>
<th>General actions:</th>
<th>Responsibility and timeframe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decide how these points we are trying to convey will fit into the three scenarios, realising that we may need to exclude some from the scenarios, and perhaps only mention them in the introductory or conclusion slides</td>
<td>All, prior to course block Outcome: a-c will be introduced via the video at the start and practiced during part 2 of the session. One or two slides will be prepared (Alicia and Tambri) to cover points d-e. We are introducing these as things to be aware of and perhaps suggesting resources, in the essence of time this will be short. Input from group.</td>
</tr>
<tr>
<td>Allocate an overall “MC” for the teaching exercise</td>
<td>Alicia indicated would be happy to do this. Jana – timekeeper.</td>
</tr>
<tr>
<td>Agree on roles and responsibilities for preparation and facilitation of session parts</td>
<td>All, at course block.</td>
</tr>
</tbody>
</table>

*MORE GENERALLY I THINK WE NEED TO have some agreed "principles" as to how we will organise and facilitate this session – I think we will be very tight for time and so the session needs to be slick and specific.*

| | All, at course block |
| | |
Session structure:

As I understand our group has an hour allocated to our session, so the structure below takes that into account.

**Part 1. Introduction (15 mins)**

1. Introductions of MAE2015 presenting session (If not complete elsewhere)
   *(1 Slide with our names and MAE placements)*

2. Presentation of our motivation for designing session, objectives of session, and overview of how we will run it
   *(2-3 slides showing purpose and objectives – very brief, mention why we felt this would be a useful adjunct to outbreak investigation session (where we understand only collecting food history information was practiced). Will also need to note that one of us is going to be the timekeeper for the session, so will need to listen out for a bell or the like)*

3. Ascertaining knowledge/experience level of MAE2016 cohort in conducting interviews
   *(This is a show of hands: “who has conducted interviews as part of an outbreak investigation, other than at the courseblock”; if yes, have them very briefly explain what their experience is)*

4. Showing video that highlights all pitfalls
   [https://www.youtube.com/watch?v=O6gKLOpEkfY](https://www.youtube.com/watch?v=O6gKLOpEkfY) show all of video – 9mins

5. Presenting a few slides to cover off on the points we want to make which aren’t included in the video
   *(This is brief, and included so to introduce them as important things not covered by video)*

<table>
<thead>
<tr>
<th><strong>Actions (Part 1)</strong></th>
<th><strong>Responsibility and timeframe</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Agree on content for introductory slides including:</td>
<td>Outcome: show all of video</td>
</tr>
<tr>
<td>- length of video to include</td>
<td>Outcome: Intro pres content: one slide at the beginning (us and our placements: MC to read names, we all wave), then 2-3 slides on the purpose of the session, the video and then 3 slides with points d–e. We will need to refine timing.</td>
</tr>
<tr>
<td>- how to incorporate additional information outside of scenarios</td>
<td></td>
</tr>
<tr>
<td>Prepare the introductory presentation slides (for Part 1 only)</td>
<td>Alicia, Tambri, Jana – complete at courseblock</td>
</tr>
<tr>
<td>Deliver the introductory presentation</td>
<td>Alicia, Tambri (TBC)</td>
</tr>
</tbody>
</table>
Part 2. Practical exercise (25-30 mins)

Overview

1. We will introduce a mock outbreak situation for a condition with a long incubation period, where an hypothesis generating/enhanced surveillance information questionnaire will need to be administered to obtain more information from a number of cases.

2. As supporting information, our group will have developed information of three "types" of interview situations to illustrate the challenges which may arise (drawing from dot points in objectives), along with details of how cases being interviewed may behave or respond to the interviewer.

3. In a 10-15 minute break out exercise, each person in the MAE cohort 2016 will each have the opportunity to conduct a 1:1 interview one of these "types" of cases. Our cases (interviewees) will be the 2015 MAE cohort (probably all).

Structure

1. Introduce an outbreak situation

2. Provide a some background to the disease and hypothesis generating questionnaire to MAE2016 and let them read over it before they start (5 mins)

   *We will mention that we’re happy to field questions if anyone is confused, but if this info is fairly straightforward and brief, reckon letting them read it themselves should be ok.

   *Questionnaire will have approximately 5 exposure questions, plus collection of supporting demographics. Interviewers may need to work out possible acquisition period that they will need to ask questions about.

   *Exercise will include directions toward intro statement ie: State who you are, where you are calling from and why you are calling and also suggest to have a prompt for the interviewer to thank interviewee for their time, and ask if more information was required could they be contacted again.

   *We will provide MAE2016 with a calendar.

3. Interviews
   - MAE 2016 cohort will each interview 1 MAE2015 who will have been prepped that they will be one of 3 “types” of interviewees (guidance information about this will be provided)
   - Will give MAE2016 some cheat notes to help them with their type of interviewee – ie/ give privacy text/calendar/a few words as to how to avoid a certain situation
   - Allow for 10-15 mins of interview time

   *In the essence of time, as there are 13 in each cohort – we will pre-allocate groups of interviewers and interviewees and will need to provide them with corresponding documents.

   *Interviewers will receive a generic questionnaire and a mock pathology form for the person they will be interviewing. Interviewees will receive some background to their illness, and suggested responses to possible exposure questions as well as guidance to some of the other interview behaviours we are trying to emphasise (concerns about privacy/oversharing and waffling/vague).
<table>
<thead>
<tr>
<th>Actions (Part 2)</th>
<th>Responsibility and timeframe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decide on and develop mock outbreak situation. Suggest that we provide info on the pathogen of interest, an epi curve and a potential exposure period.</td>
<td>Outcome: Hepatitis A - have observed an increased number of cases want to find out possible common sources of infection. Berries are going to be likely source. It might be worth really briefly reminding them about surveillance of notifiable conditions and the follow up of cases/cluster. It is less about the disease, more about having a hypothesis generating questionnaire to administer to a variety of interviewees.</td>
</tr>
<tr>
<td>Agree on 3 scenarios to align with a.-c.</td>
<td>Outcome: Agreed on A. privacy concerns, B. someone who has difficulties with recall, C. someone who is a waffler but who in the course of the interviewing actually incidentally provides valuable information.</td>
</tr>
<tr>
<td>Develop interviewer information</td>
<td>To be prepared by Anthony, Craig and Tanyth, with Anthony leading this (see email attachments) May need to also develop handouts, with disease background and scenario. Complete this at course block – Alicia to lead and bring draft to course block.</td>
</tr>
<tr>
<td>Develop interviewee information – these will be specific for each of the scenarios</td>
<td>Anthony has developed questionnaire and interviewee briefs – refine at course block</td>
</tr>
<tr>
<td>Find out the size of MAE2016 cohort (to work out number of interviewees required)</td>
<td>Outcome: There are 13 in MAE2016</td>
</tr>
<tr>
<td>Get agreement from other members MAE2015 to act as interviewees</td>
<td>Alicia to do prior to courseblock.</td>
</tr>
<tr>
<td>Prepare briefing information and conduct a briefing for 2015MAE which will involve introducing the purpose of the exercise, what our expectations are and providing them with a short</td>
<td>All. During courseblock</td>
</tr>
<tr>
<td>Prepare a couple of slides to introduce the practical exercises – ie generic information about the “outbreak”</td>
<td>Outcome: 1 slide to introduce exercise, other background in notes provided to MAE 2016. Prepare this at course block.</td>
</tr>
</tbody>
</table>
Chapter 6 – Teaching

Part 3. Interactive feedback/reflection (20 mins)
MAE2016 will be asked to reflect back their experiences to each other of interviewing person A, B, or C then we will come back together as a larger group.
Structure may involve:

1. Determining which MAE2016 was interviewing which "type" of interviewee, and have them come together in small groups
2. In small groups for 5-8 mins briefly discuss each person “type”: key points/tips/pitfalls which were identified, maybe we need to encourage the group to come up with tips as to what worked, what didn’t work. It might be useful to have some guiding questions to keep the discussion on track. What were the features of the interview with that person? How did they behave? How did you respond? How successful was the interview? What would you do differently if you encountered this situation again?
3. MAE2016 to report back to group as a whole about each person type.

<table>
<thead>
<tr>
<th>Actions (Part 3)</th>
<th>Responsibility and timeframe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agree on and develop structure for feedback session</td>
<td>Outcome: Will break out into small groups before coming back together</td>
</tr>
<tr>
<td>Decide whether summary slides need to be prepared</td>
<td>Outcome: Unlikely to have time maybe handout is better with top tips. Confirm at courseblock</td>
</tr>
<tr>
<td>Prepare additional slides for this session</td>
<td>Outcome: Unlikely to have time maybe handout is better with top tips. Confirm at courseblock</td>
</tr>
<tr>
<td>Determine whether we are required to obtain feedback on our teaching session from the MAE2016 cohort</td>
<td>Confirm at courseblock, develop small questionnaire if necessary. Jana to co-ordinate.</td>
</tr>
</tbody>
</table>
MAE TEACHING EXERCISE – 4 March 2016

Scenario
You have just arrived at the Victorian Department of Health to take up a post as an epidemiologist. Your new manager – Dr Bilirubin – asks you to investigate a possible outbreak of Hepatitis A amongst the local population.

Dr Bilirubin provides you with the names, contact telephone numbers and laboratory results that have just arrived for three individuals with laboratory confirmed Hepatitis A, as well as a questionnaire used by the public health unit to investigate outbreaks. Your task is to contact one of these cases and using the information provided to you, conduct an interview in an attempt to try and identify the possible source of infection. Dr Bilirubin also suggests you have a calendar handy when you call, and mentions as she walks away: “Interviews are like a box of chocolates – you never know what you’re gonna get.”

Important Information about Hepatitis A - Occurrence and transmission
The Hepatitis A virus replicates in the liver, is excreted in bile and shed in the stool. As such, transmission occurs predominantly via the faecal-oral route and the incidence of disease is higher in countries where hygiene and environmental sanitation are poor. Worldwide, most infection results from exposure to contaminated food or water.

In industrialised countries such as Australia, infection with Hepatitis A is more likely to occur:
- amongst household and sexual contacts of an acute case
- in childcare centres with children in nappies
- following overseas travel to countries with endemic Hepatitis A (Asia, Africa, South-Pacific, Central and South America)
- amongst injecting drug users
- from outbreaks

Although infrequent, foodborne outbreaks of Hepatitis A have occurred in Australia, including large outbreaks associated with consumption of contaminated raw oysters (1997) and semidried tomatoes (2009), and more recently, associated with frozen berries (2015).

Incubation period and clinical illness
The average incubation period is 28-30 days (range 14-50 days, or approx 2-7 weeks). The disease can vary from an asymptomatic illness lasting 1 – 2 weeks to a severely disabling disease that can persist for several months. Approximately 10% - 50% of infected infants and children (< five years of age), and 70% - 95% of infected adults have recognisable clinical symptoms that initially include: fever, malaise, anorexia, nausea and abdominal pain, followed by jaundice, dark urine and pale-coloured stools.

Testing of serum samples can provide serological evidence of recent Hepatitis A infection.

During case follow up, the date of onset of jaundice is often used to determine the incubation (and exposure) period.
Chapter 6 – Teaching

Surviving the Outbreak Interview

Alicia Arndt, Anthony Draper, Craig Thompson, Tanya de Gooyer, Tambri House and Jana Lai

The Team
- Anthony - OzFoodNet NT
- Alicia – Department of Health and Human Services (Communicable Disease) and Victorian Infectious Disease Reference Laboratory (VIDRL)
- Craig – National Centre for Immunization Research and Surveillance (NCIRS)
- Tanya – Department of Health and Human Services (Environmental Health Unit / Water Program)
- Tambri – Muresse Sans Frontières, India
- Jana – Murdoch Children’s Research Institute, Lao PDR

Objectives of the Session
By the end of this session you will be able to;
- Understand and apply some key principles to enhance interviews as part of an outbreak investigation
- Create strategies to overcome three common challenges faced when interviewing cases

Key Learning
- You will be provided the opportunity to gain practical experience to identify strategies for:
  - maximising interviewee recall
  - keeping interviewees on topic
  - handling interviewees’ privacy concerns raised during outbreak interviews

https://www.youtube.com/watch?v=O5gKLQpCXTY

10 key principles
- Practice
- Find a quiet space
- Be non-judgmental
- Avoid leading the interviewee
- Accurately record responses
- Ensure confidentiality
- Gently re-direct
- Prove
- Use interpreters if required
- Thank the interviewee and explain how the information will be used

The Scenario
- You are an epidemiologist placed in the Victorian Department of Health.
  - There have been a number of hepatitis A cases notified over the past few months.
  - You have been asked to undertake a hypothesis generating questionnaire to determine possible exposure sources
Chapter 6 – Teaching

You check Heymanns

- Hepatitis A – long incubation period with an average of 28-30 days (range 14-50 days)
- Faecal/oral transmission
- Signs and symptoms
  - Diarrhoea
  - Abdominal discomfort
  - Jaundice
  - Fever
  - Nausea/loss of appetite


We will give you…

- Outbreak brief
- Pathology result
- Calendar
- Screenshot from CoFoodNet
- Interview questionnaire
  - Symptoms
  - Exposure information

Discussion Questions

- What were the features of the person that you interviewed?
- How did they behave?
- How did you respond?
- What would you do differently if you encountered this person again?

Objectives of the Session

Recap
- Understand and apply some key principles to enhance interviews as part of an outbreak investigation
- Create strategies to overcome three common challenges faced when interviewing cases
## Chapter 6 – Teaching

### Outbreak Questionnaire:

#### Hepatitis A

#### Illness Summary

**Name:**

**DOB:**

**Gender:** M F

**Address:**

**Suburb:**

**Postcode:**

**Phone Number:**

#### Illness Summary

**Onset Date:** / /  

**Time of onset:**

**Date of Specimen collection:** / /

**Type of specimen:** Faeces/ blood/ urine/ other

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Onset Date of Symptom</th>
<th>History of illness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhoea</td>
<td>Yes □ No □ Unknown</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Duration(days): .......</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>Yes □ No □ Unknown</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>Yes □ No □ Unknown</td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>Yes □ No □ Unknown</td>
<td></td>
</tr>
<tr>
<td>Jaundice</td>
<td>Yes □ No □ Unknown</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>Yes □ No □ Unknown</td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>Yes □ No □ Unknown</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>Describe...............</td>
<td></td>
</tr>
</tbody>
</table>

#### INTERVIEWER USE

**Acquisition date:**

Jaundice date is regarded as onset date for calculating acquisition/exposure period. Hepatitis A incubation period is 14 – 50 days (approx 2-7 weeks) before the onset of jaundice occurs. Based on the information above the likely period of acquisition is between;

**Earliest possible acquisition date:**

**Latest Possible acquisition date:**

**Privacy statement read? Y / N**

**Privacy factsheet requested? Y / N**
### Chapter 6 - Teaching

#### Exposures

During the person’s acquisition period [Date 1 (___/___/_____)] to [Date 2 (___/___/_____)] measure the following outbreak exposures.

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Details</th>
<th>Date(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Did you travel overseas during your acquisition period?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>[ ] Yes [ ] No [ ] Unknown</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Did you attend any restaurant during your acquisition period?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>[ ] Yes [ ] No [ ] Unknown</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Did you attend any major sporting events during your acquisition period?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>[ ] Yes [ ] No [ ] Unknown</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Did you consume any foods containing frozen berries during your acquisition period?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>[ ] Yes [ ] No [ ] Unknown</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Did you consume any raw seafood/shellfish during your acquisition period?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>[ ] Yes [ ] No [ ] Unknown</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Signature

Name of interviewer (please print clearly)

Signature

Date / / How long did this questionnaire take to complete? ________

#### Investigation notes

------------------------------------------------------------------------

------------------------------------------------------------------------

------------------------------------------------------------------------

------------------------------------------------------------------------

------------------------------------------------------------------------
### Scenario A – prompting memory recall

You are the interviewee, India Pina, aged 32 (DOB: 25 June 1983), resident of Melbourne. You were born in Australia but are of Indian heritage (your parents are Indian).

You are very busy and have a poor memory. Your first response to every question is that “I really can’t remember”, and emphasize that “it was a long time ago”.

Mainly use the ‘history of illness’ and ‘details’ columns to guide your responses.

Hopefully the interviewer will use a calendar, to remind you of weekend activities, public holidays or major events and prompt your recall.

It is important that you disclose/confirm that you got jaundice on 14 February 2016. You may need to assist the MAE in determining the acquisition period (14-50 days prior to jaundice onset: 29 Dec 15 to 1 Feb 16)

If the MAE says any ‘unusual’ terms (jaundice, acquisition period) ask for clarification. Please make sure that you allow the MAE to complete the interview in the allocated time.

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Onset Date of Symptom</th>
<th>History of Illness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhoea</td>
<td>Yes</td>
<td>10/2/2016 (continued for 3 days)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diarrhoea on the day after Indian Independence Day lunch (January 26) but you put that down to spicy Indian food you ate at the lunch</td>
</tr>
<tr>
<td>Nausea</td>
<td>Yes</td>
<td>10/2/2016</td>
</tr>
<tr>
<td>Vomiting</td>
<td>Yes</td>
<td>10/2/2016</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>Yes</td>
<td>10/2/2016</td>
</tr>
<tr>
<td>Jaundice</td>
<td>Yes</td>
<td>14/2/2016</td>
</tr>
<tr>
<td>Headache</td>
<td>Yes</td>
<td>10/2/2016</td>
</tr>
<tr>
<td>Fever</td>
<td>Yes</td>
<td>11/2/2016</td>
</tr>
<tr>
<td>Other</td>
<td>Nil</td>
<td></td>
</tr>
<tr>
<td>Exposure</td>
<td>Details</td>
<td>Date(s)</td>
</tr>
<tr>
<td>-------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>-------------</td>
</tr>
<tr>
<td>Did you travel overseas during your acquisition period?</td>
<td>Last time you were overseas was in January 2008 to Mumbai.</td>
<td>2008</td>
</tr>
<tr>
<td><strong>Yes</strong></td>
<td><strong>There was an Indian independence Day luncheon at a restaurant you went to (on Tuesday 26 January). You think the restaurant was called Bombay by Night.</strong>&lt;br&gt;<strong>(Only disclose the following if the interviewer prompts your recall...</strong> You went to breakfast with friends at the Top Paddock Café in Richmond and you had hot cakes with friends that had berries and fresh cream. You remember this because it because it tasted so good, especially as you tasted some of your friend’s Eggs Benedict and the sauce on the top tasted a bit strange...it was on the weekend before the Independence Day lunch because your friends were visiting all week from interstate).**</td>
<td>26/1/2016</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(23/1/2016)</td>
</tr>
<tr>
<td>Did you attend any major sporting events during your incubation period where you ate take-away food?</td>
<td><strong>You went to the 1 day cricket one weekend in January at the MCG with your dad and watched the cricket which was Australia and India.</strong>&lt;br&gt;<strong>(When prompted: Sunday January 17, and ate chips only.)</strong>&lt;br&gt;(You also went to the Australian Open on Saturday 30 Jan, but only remember this when asked the question below)</td>
<td>17/1/2016</td>
</tr>
<tr>
<td><strong>Yes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Did you consume any foods containing frozen berries during your incubation period?</td>
<td><strong>Mention you ate berries and cream “at the tennis”</strong>.</td>
<td>30/1/2015</td>
</tr>
<tr>
<td><strong>Yes</strong></td>
<td><strong>(If the interviewer prompts you, say it was a Saturday and you saw the women’s final – a friend had a spare ticket...confirm it was 30 Jan if asked)</strong></td>
<td></td>
</tr>
<tr>
<td>Did you consume any raw seafood/shellfish during your incubation period?</td>
<td><strong>Vegetarian</strong></td>
<td></td>
</tr>
</tbody>
</table>
# Chapter 6 – Teaching

## MAE Laboratories

### PATHOLOGY RESULTS

<table>
<thead>
<tr>
<th>Patient Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name: Indra Pina</td>
</tr>
<tr>
<td>Address: 7 Chifley St</td>
</tr>
<tr>
<td>Postcode: 3001</td>
</tr>
<tr>
<td>Phone Number: 040000069678</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Testing Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Request Date: 15/2/2016</td>
</tr>
<tr>
<td>Type of specimen: Serum</td>
</tr>
</tbody>
</table>

### Results

- **Hepatitis A Virus IgG by Chemiluminescent Microparticle Immunoassay (Serum)**
  - HAVAb-IgG (CMIA): Not detected

- **Hepatitis A Virus IgM by Chemiluminescent Microparticle Immunoassay (Serum)**
  - HAVAb-IgM (CMIA): DETECTED

  *Sorological evidence of recent Hepatitis A infection.*

  *THIS IS A NOTIFIABLE DISEASE*

  *A copy of this report will be forwarded to Victorian Department of Health.*

### Clinical comments:

Presented with jaundice; onset date 16/2/2016

**Authorised by: Dr Dehease (Pathologist)** 16/2/2016
Scenario B – Concerns about privacy

You are the interviewee, Tony Fratelli, aged 54 (DOB: 28/9/61), resident of Melbourne. You are a businessman who lives in Melbourne CBD.

You are VERY concerned about why you are being contacted: how did you get my details? I thought this was between me and my doctor? What is this information going to be used for?

You even ask for the name of the interviewer and their position and phone number. You are reluctant at each question and continually seek assurance re: privacy and confidentiality.

Mainly use the ‘history of illness’ and ‘details’ columns to guide your responses.

Hopefully the interviewer will use a calendar, to remind you of weekend activities, public holidays or major events and prompt your recall.

It is important that you disclose/confirm that you got jaundice on 14 February 2016. You may need to assist the MAE in determining the acquisition period (14-50 days prior to jaundice onset: 29 Dec 15 to 1 Feb 16)

If the MAE says any ‘unusual’ terms (jaundice, acquisition period) ask for clarification. Please make sure that you allow the MAE16 to complete the interview in the allocated time.

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Onset Date of Symptom</th>
<th>History of illness</th>
</tr>
</thead>
</table>
| Diarrhoea    | Yes                                    | 10/2/2016 (3 days duration)
|              |                                        | (Express some concern about the personal nature of this information that you are disclosing) |
| Nausea       | Yes                                    | 10/2/2016                                                                          |
| Vomiting     | No                                     |                                                                                   |
| Abdominal pain | Yes                                  | 10/2/2016                                                                          |
| Jaundice     | Yes                                    | 14/2/2016                                                                          |
| Headache     | Yes                                    | 10/2/2016                                                                          |
| Fever        | Yes                                    | 11/2/2016                                                                          |
| Other        | Nil                                    |                                                                                   |
### MAE Laboratories

#### PATHOLOGY RESULTS

<table>
<thead>
<tr>
<th>Patient Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Name:</strong> Anthony Fratelli</td>
</tr>
<tr>
<td><strong>Address:</strong> 33/165 Bourke St</td>
</tr>
<tr>
<td><strong>Postcode:</strong> 3000</td>
</tr>
<tr>
<td><strong>Phone Number:</strong> 0400 058 651</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Testing Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Request Date:</strong> 18/2/2016</td>
</tr>
<tr>
<td><strong>Type of specimen:</strong> Serum</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hepatitis A Virus IgG by Chemiluminescent Microparticle Immunocassay (Serum)</strong></td>
</tr>
<tr>
<td>HAVAb-IgG (CMIA): Not detected</td>
</tr>
<tr>
<td><strong>Hepatitis A Virus IgM by Chemiluminescent Microparticle Immunocassay (Serum)</strong></td>
</tr>
<tr>
<td>HAVAb-IgM (CMIA): DETECTED</td>
</tr>
</tbody>
</table>

Serological evidence of recent Hepatitis A infection.

**THIS IS A NOTIFIABLE DISEASE**

A copy of this report will be forwarded to Victorian Department of Health.

<table>
<thead>
<tr>
<th>Clinical comments:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presented with jaundice, onset date 14/02/2016</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Authorised by: Dr Dohoo (Pathologist)</th>
<th>18/2/2016</th>
</tr>
</thead>
</table>
Scenario C – Off topic interviewee

You are the interviewee, Wendy de Waffler, aged 25 (DOB 29 Jan 1991), who is a young single mother from Ballarat. You have an opinion on just about everything and are easily side tracked.

You love a chat and will easily stray away from the questions you are asked. You will not initially respond yes or no but will embark on wild and elaborate stories. Waffle on a bit but the responses you need to provide are below.

Mainly use the ‘history of illness’ and ‘details’ columns to guide your responses.

Hopefully the interviewer will use a calendar, to remind you of weekend activities, public holidays or major events and prompt your recall.

It is important that you disclose/confirm that you got jaundice on 14 February 2016. You may need to assist the MAE in determining the acquisition period (14-50 days prior to jaundice onset: 29 Dec 15 to 1 Feb 16)

If the MAE says any ‘unusual’ terms (jaundice, acquisition period) ask for clarification. Although we encourage you to free style a bit, please make sure that you get the key food items and exposure dates across and allow the MAE to complete the interview in the allocated time.

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Onset Date of Symptom</th>
<th>History of illness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhoea</td>
<td>Yes</td>
<td>10/2/2016 (3 days duration)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diarrhoea on Wednesday 10th February. Remember watching My Kitchen Rules and having to run to the toilet. Had a headache that day, but didn’t think it was unusual – always have a headache (the kids drive you crazy!)</td>
</tr>
<tr>
<td>Nausea</td>
<td>Yes</td>
<td>Always feels nauseous</td>
</tr>
<tr>
<td>Vomiting</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>Yes</td>
<td>10/2/2016</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Woke up on the Sunday morning and you boyfriend told you that you looked yellow. Remember it was Sunday morning of 14/2/2014 because it was Valentines Day. Went to the Dr on the 15/2/2016 and got tested because that was the day that the free bulk billing Dr was open so you waited until then.</td>
</tr>
<tr>
<td>Jaundice</td>
<td>Yes</td>
<td>14/2/2016</td>
</tr>
<tr>
<td>Headache</td>
<td>Yes</td>
<td>10/2/2016</td>
</tr>
<tr>
<td>Fever</td>
<td>Yes</td>
<td>11/2/2016</td>
</tr>
<tr>
<td>Other</td>
<td>Yes – go nuts and mention whatever you like</td>
<td>(You also had a headache on 30 Jan – you'd been out the night before for your birthday).</td>
</tr>
<tr>
<td>Exposure</td>
<td>Details</td>
<td>Date(s)</td>
</tr>
<tr>
<td>-------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>----------</td>
</tr>
<tr>
<td>Did you attend travel overseas during your incubation period?</td>
<td>Never been overseas – feel free to waffle on about how she always wanted to go somewhere but then you had kids.</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Did you attend any restaurants during your incubation period?</td>
<td>Went to Sizzler on Friday January 29th because it was your birthday. Waffle on about what you ate, you ate from the salad bar and had loads of soft serve for dessert. Went to a pub afterwards.</td>
<td>29/1/2016</td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Did you attend any major sporting events during your incubation period</td>
<td>You took the train to Melbourne and went to the Australian Open for the women's final (the last Saturday in January) and ate about 10 cups of berries and cream. You go every year and get a ground pass and eat the berries and cream, except this year your boyfriend took you as a surprise for your birthday to Rod Laver Arena.</td>
<td>30/1/2016</td>
</tr>
<tr>
<td>where you ate take-away food?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Did you consume any foods containing frozen berries during your</td>
<td>Berries and cream at the Australian Open. Before you went to the tennis your boyfriend made you a smoothie at home on 30 January because you were hungover after your birthday – you are pretty sure the smoothie had frozen</td>
<td>30/1/2016</td>
</tr>
<tr>
<td>incubation period?</td>
<td>berries (dunno how long they had been in the freezer), but he did make you a fried egg (eggs are doday, right?).</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Did you consume any raw seafood/shellfish during your incubation</td>
<td>Went with the whole family to the beach on New Years Eve in Portland Victoria and ate raw oysters. Your brother bought them from Coles in Portland, they could have been a bit off because they tasted a bit slimy.</td>
<td>31/12/2016</td>
</tr>
<tr>
<td>period?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
# Chapter 6 - Teaching

## MAE Laboratories

### PATHOLOGY RESULTS

<table>
<thead>
<tr>
<th>Patient Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Name:</strong> Wendy de Waffler</td>
</tr>
<tr>
<td><strong>DOB:</strong> 25/8/1991</td>
</tr>
<tr>
<td><strong>Gender:</strong> Female</td>
</tr>
<tr>
<td><strong>Address:</strong> 7 Main St</td>
</tr>
<tr>
<td><strong>Suburb:</strong> Ballarat</td>
</tr>
<tr>
<td><strong>Postcode:</strong> 3090</td>
</tr>
<tr>
<td><strong>Phone Number:</strong> 040000069721</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Testing Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Request Date:</strong> 15/2/2016</td>
</tr>
<tr>
<td><strong>Requesting Dr.:</strong> C. Bumpkin</td>
</tr>
<tr>
<td><strong>Date of Specimen collection:</strong> 15/2/2016</td>
</tr>
<tr>
<td><strong>Type of specimen:</strong> Serum</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hepatitis A Virus IgG by Chemiluminescent Microparticle Immunoassay (Serum)</strong></td>
</tr>
<tr>
<td><strong>HAVAb-IgG (CMIIA): Not detected</strong></td>
</tr>
<tr>
<td><strong>Hepatitis A Virus IgM by Chemiluminescent Microparticle Immunoassay (Serum)</strong></td>
</tr>
<tr>
<td><strong>HAVAb-IgM (CMIIA): DETECTED</strong></td>
</tr>
</tbody>
</table>

**Serological evidence of recent Hepatitis A infection.**

**THIS IS A NOTIFIABLE DISEASE**

A copy of this report will be forwarded to Victorian Department of Health.

<table>
<thead>
<tr>
<th>Clinical comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presented with jaundice; onset date 14/2/2016</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Authorised by: Dr Doneapa (Pathologist)</th>
</tr>
</thead>
<tbody>
<tr>
<td>17/2/2016</td>
</tr>
</tbody>
</table>

274
## Evaluation Form – MAE Cohort 2015 Teaching sessions

For each session, please indicate below the extent to which you agree with the following statements:

### Session 1 -

<table>
<thead>
<tr>
<th>Statement</th>
<th>Strongly Disagree</th>
<th>Disagree</th>
<th>No Opinion</th>
<th>Agree</th>
<th>Strongly Agree</th>
</tr>
</thead>
<tbody>
<tr>
<td>The session content was informative</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>The instructor presented the material clearly</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>The methods used for delivering the topic were appropriate</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
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<tr>
<td>The session allowed me to engage with the content</td>
<td>□</td>
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<td>I felt comfortable to ask questions when I didn’t understand something</td>
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**How do you think this session could be improved? Any other comments?**

### Session 2 -

<table>
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<tr>
<th>Statement</th>
<th>Strongly Disagree</th>
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<th>No Opinion</th>
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<tr>
<td>The session content was informative</td>
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<td>The methods used for delivering the topic were appropriate</td>
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**How do you think this session could be improved? Any other comments?**

### Session 3 -

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**How do you think this session could be improved? Any other comments?**

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### Data

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**Additional comments:**

- A little bit more about the other personality types
- This was awesome, a great introduction to the topic
- A good interactive session
- More interactive sessions, interactive questions, skills transfer in the worksheets
- A good section, great ideas to present people with experience!
C. LOMWRU bias and confounding presentation
Chapter 6 – Teaching

Selection Bias
- Error introduced when the study population does not represent the target population
  - The study does not reveal the truth because of the way participants were recruited

Examples of selection bias
- Berkson’s bias
- Diagnost/treatment access bias
- Exclusion/inclusion bias
- Losses/withdrawals to follow up

Measurement Bias
- Error arising from inaccurate measurements of subjects on study variable(s)
  - The study does not reveal the truth because of the way information was collected

Examples of measurement bias
- Observer/interviewer bias
- Recall bias
- Reporting bias
- Surrogate bias

What is Confounding?
- The distortion of a measure of the effect of an exposure on an outcome due to the association of the exposure with other factors that influence the outcome.
Chapter 6 – Teaching

Potential confounders
- Age
- Sex
- Socioeconomic status

Where to find biases/confounders in a journal article
- Bias
  - Methods
    - Study population
    - Sample collection of data
  - Results
  - Discussion
- Confounders
  - Results
  - Discussion

For further resources on Bias and Confounding go to:
http://www.teacherp.org/resources/biases.htm

ANY QUESTIONS?