

Applied Epidemiology: within, at the border and outside Australia

*A thesis submitted for the degree of Master of Philosophy (Applied Epidemiology)
of the Australian National University*

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ORIGINALITY STATEMENT

'I hereby declare that this submission is my own work and that to the best of my knowledge it contains no materials previously published or written by another person, or substantial proportions of material which have been accepted for the award of any other degree or diploma at the Australian National University or any other educational institution, except where due acknowledgement is made in the text. Any contribution to the research by others is explicitly acknowledge in the thesis. I also declare that the intellectual content of this thesis is the product of my own work, except to the extent that assistance from others in the project's design and conception or in style, presentation or linguistic expression is acknowledged.'



Signed:

Date: 31 October 2018

THESIS ABSTRACT

My placement was with the Immunisation and the Health Emergency Management branches in the Office of Health Protection at the Australian Government Department of Health during 2017-2018. During this time, I also had the opportunity to also work at the Australian Institute of Health and Welfare (AIHW), the Canberra Hospital and on a deployment to Fiji. I focused on the following five projects during my training.

I deployed as an epidemiologist through the World Health Organization Global Outbreak Alert and Response Network mechanism to assist in an international response to an outbreak of multi-resistant *Acinetobacter baumannii* in the neonatal intensive care unit (NICU) at the Colonial War Memorial Hospital, Suva, Fiji. Review of patient clinical variables identified several plausible risk factors, with the most significant being re-use of single-use respiratory equipment. Transmission was successfully ceased. The mission also included an evaluation of infection control practices at the three major hospitals in Fiji and was presented together with the findings of the outbreak response in a technical report.

In the first five months of 2017 the Canberra Hospital experienced its first known outbreak of vancomycin resistant enterococci (VRE) in the NICU. Multivariate analysis identified an association of colonisation with prematurity. Whole genome sequencing showed that the VRE strain was closely related to a highly successful VRE clone endemic to the Canberra Hospital, likely introduced to the NICU from other wards. The study contributed to the growing literature on these emerging VRE strains.

As part of a larger Burden of Vaccine Preventable Diseases study (BoVPD) at AIHW, I developed an incidence-based burden of disease model for invasive pneumococcal disease (IPD). A published model from the European Centres for Disease Control and Prevention was adapted to Australian conditions following a systematic literature review. I used data from national Australian databases to inform the model. IPD accounted for the second highest overall burden of all the VPDs in the study and was shown to have a high burden on both on a population and individual level.

The surveillance system for yellow fever at the Australian border is designed to identify unvaccinated travellers that may have been exposed to yellow fever and are still within the incubation period. I evaluated the surveillance system using a survey to assess the number of travellers posing a risk of yellow fever introduction, the reasons for not vaccinating, and to inform the transition to an electronic incoming passenger card (eIPC). The system was found to be inefficient due to a high number of false positives. Recommendations how this could be minimised in the eIPC were made.

The traveller with illness checklist (TIC) surveillance system is designed to identify individuals that may have a listed human disease. These are some of the most severe diseases and have the potential for pandemic spread. Review of the TICs showed that the data quality, sensitivity and positive predictive value could be improved. It was recommended to transition to an electronic application-based format of the TIC.

ACKNOWLEDGEMENTS

Firstly, I like to acknowledge the fantastic efforts of my academic supervisor Katrina Roper. Thank you for being an inspiration and a guiding star throughout the MAE journey, and for always being available for advice and discussions. I would not have been as comfortable as I was deploying to Fiji without your guiding hand on my shoulder. But also thank you for being a good friend and for providing non-MAE related advice, such as what mountain bike components to buy. I look forward to the opportunity to working together in the future.

Thank you to Masha Somi and Rhonda Owen for selecting me into the MAE in the first place and for providing a placement in your branches. You both have always had your doors open and been interested and supportive despite your enormous work commitments. I'm grateful to all the staff in the Immunisation Policy Section, and all three sections in the Health Emergency Management Branch, who all have help me navigate the processes of the public service and quietly whispered during meetings what all the acronyms mean. A thanks must also go to the epidemiologists in the Communicable Disease Epidemiology and Surveillance Section, who generously took me on as an extra MAE student and provided valuable support throughout the two years.

I'm grateful to Fadwa Al-Yaman and Tracy Dixon for the opportunity to work at the Australian Institute of Health and Welfare and to the staff in the Indigenous Modelling and Research Unit. It was a highly useful introduction to management and statistical analysis of large datasets.

Big thanks to Nicholas Coatsworth for giving me the opportunity to work at the Canberra Hospital. It has been a true pleasure to work with and learn from you. Odd how it took for us both to leave Darwin before engaging in a project together. Thanks also to Wendy Beckingham and her infection control team for their valuable contributions to the work, and to all the interested infectious diseases physicians that were involved in the work.

It was a privilege to work with some fantastic people during the deployment to Fiji. Meghan Lyman and Peta-Anne Zimmerman, thank you for being a great field team to work with and for showing me the ropes. Also thank you to Asaeli Raikabakaba and Sister Susanna for all your hard work in guiding us, both in the hospital and in Suva in general.

The staff and lecturers of the MAE program deserves a huge thanks, in particular Martyn Kirk and Tambri Housen who have provided a constant source of guidance from the very first day of the program and throughout the two years. It is exciting to see the program expand, both in number of students and staff. Of course, this journey would not have been the same without all the wonderful fellow students in the MAE2017 cohort. It is rare to meet so many likeminded and across the board utterly likable people. You have all been instrumental to the success of

these years and the MAE WhatsApp group will remain a resource for many years I'm sure! I look forward to seeing the exciting things that you all will be doing in the future.

I would like to thank my mother and father who on a weekly basis have tuned in from Sweden to excitedly hear what has gone on in the week. Your unwavering support is warming and thanks for not being worried when your 38-year-old son declared he was quitting his job and going back to school.

And most importantly, Lauren, I consider myself very lucky to have such a wonderful wife who supports me in whatever endeavour that I choose to do. Despite preparing for and sitting the gruelling physician exams you always showed interest and provided encouragement during these two years. You are an amazing human being and well deserved of the success you have had this year. The future is looking bright!

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CHAPTER 1

Master of Applied Epidemiology (MAE) experience and Public Health at the Australian Government Department of Health

**Australian National University
Health Emergency Management Branch, Office of Health Protection**

“Age Quod Agis”

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1 MAE EXPERIENCE

My placement was with the Immunisation and the Health Emergency Management branches in the Office of Health Protection at the Australian Government Department of Health during 2017-2018. During this time I also had the opportunity to also work at the Australian Institute of Health and Welfare (AIHW), the Canberra Hospital and on a deployment to Fiji.

1.1 Coming into the MAE

Up until February 2017 my entire adult working life had been spent in the academic research sphere, with time spent on narrowly focussed projects in the field of molecular genetics. While utterly exhilarating at times, the feeling of having blinders and that the effects of the findings on the population could only be seen far off in the distance, had me itching for a change. As with many others in the program, I was introduced to the MAE by a scholar in the program, Jana Lai (MAE2015 cohort). Speaking at a party she told me about the program and encouraged me to apply.

The MAE has far exceeded my expectations. It has opened a world of seemingly endless opportunities to engage in work that make a difference in people's lives, from the individual level in halting an outbreak, to the population level in monitoring international spread of diseases or informing vaccination programs. It is a very well-designed program that efficiently builds the knowledge and confidence of the scholars through hands-on field and applied epidemiology work, true to the motto of learning-by-doing. Drawing upon an impressive battery of engaging and knowledgeable staff and lecturers creates a truly inspiring experience.

Transitioning from the academic world to the public service world of the Australian Government was always going to be a challenge. Coming from a flat organisational structure of a research group, the strict hierarchical processes of the public service felt cumbersome at first, but I have come to understand the necessity of this given the range of areas that the senior leadership has to cover. The breadth of knowledge that the staff at the Office of Health Protection (OHP) must have to conduct their work was impressive. I came to recognise that OHP is probably one of the more technical areas of the Department of Health, which made me feel much more at home. I just had to remove my blinders and quickly learn about the wider public health world of weird, wonderful and sometimes frightening infectious diseases.

1.2 Office of Health Protection, AIHW and Canberra Hospital

The Office of Health Protection is an area in the Department of Health with a main function in public health, in particular surveillance and protection against infectious disease; and

preparation and response to health disasters. As mentioned in the first lines of this chapter, my placement was split between the Immunisation Branch, which mainly deals with the planning, policy and implementation of the National Immunisation Program (NIP); and the Health Emergency Management Branch (HEMB), which has responsibility for prevention, preparedness and response activities related to national and international health emergencies and functions as the National Focal Point (NFP) for Australia under the International Health Regulations. Two of my projects (**Chapters 5 and 6**) were conducted in the Border Health Section of HEMB, which is responsible of the international and cross-border health protection and surveillance matters. The Immunisation Branch and HEMB do not have any dedicated epidemiologists, and therefore several of my projects were conducted in collaboration with other sites and with epidemiological assistance from my academic supervisor, Katrina Roper.

For my project with the Immunisation Branch (**Chapter 4**) I had the opportunity to be seconded to the Australian Institute of Health and Welfare, which is the national agency for information and statistics on Australia's health and welfare. This provided a good insight into the high-end statistics and data management conducted in the institute.

I also conducted an epidemiological study with the Infectious Diseases and Infection Control units at the Canberra Hospital (**Chapter 3**). This placement provided more of a field experience flavour as well as easy access to the medical expertise in the units and to conduct onsite visits to the clinics in the study.

Finally, I was fortunate to have exposure to a true field epidemiology experience in the form of a deployment with the World Health Organization to assist with the outbreak response at a major hospital in Fiji (**Chapter 2**). This was a fantastic experience of doing something that had immediate impact on the population in need, and one that most definitely reinforced my interest in public health and providing technical assistance in resource poor settings.

A summary of the MAE core competencies met in each of the projects are outlined in **Section 2** of this Chapter.

1.3 Public health experience at the Office of Health Protection

During my time at the OHP I have most spent time in the HEMB. The work in this branch is by nature largely reactive in response to events that occur nationally and internationally. As the NFP for Australia this section receives alert and communication relating to national and international events, and has the operational responsibility of the National Incident Room (NIR). As part of the day-to-day roles in the section I took shifts as the Watch Officer, responsible for ongoing monitoring the NIR email inbox and answering the NIR hotline between 8am and 5pm.

These duties involved receiving and disseminating information from national and international sources to the relevant Australian jurisdictions; assemble passenger information for the purpose of contact tracing in response to communicable disease alerts and inform the relevant Australian jurisdictions or NFPs in other countries; communicate information during response activities.

I was also involved in the preparation of the response to international communicable disease incidences regarding the Ebola outbreaks in the Democratic Republic of the Congo in 2018 and the Polio outbreak in Papua New Guinea 2018. In both incidences I assisted with collating up-to-date surveillance information. During the first Ebola outbreak in the DRC in 2018 I was tasked with assembling a comparison of the outbreak response activities in the current outbreak with those in the 2014 Ebola outbreak in West Africa.

MAE scholars at the Australian Government Department of Health are responsible for the collation and preparation of a fortnightly report on international communicable disease surveillance for the Communicable Disease Network Australia (CDNA) committee, and I shared this responsibility with the other MAE in the department. This provided an interesting overview of the ongoing and emerging communicable disease issues around the world.

During the Gold Coast 2018 Commonwealth Games the report was modified to provide a more detailed surveillance of communicable disease events around the world, and with a more frequent reporting schedule. This project was led by a fellow MAE Kaitlyn Vette and myself, and is detailed in **Section 3** of this chapter.

Being situated in the Australian Government Department of Health provided the opportunity to sit in on high level national meetings of committees such as: the Chief Human Biosecurity Officers; the Australian Technical Advisory Group on Immunisation; the Communicable Disease Network of Australia; the National Immunisation Committee; the Jurisdictional immunisation Coordinators; and witnessing hallmark events like the presentation of the findings of the first Joint External Evaluation of Australia.

This placement has given me a good insight into how things operate at the federal level and how the Commonwealth works with the States and Territories, as well as how Australia interacts with other countries in the world to minimise the transmission of communicable diseases. I believe these experiences will be highly valuable in my future work in public health.

2 SUMMARY OF MAE CORE COMPETENCIES

	Chapter 1: International communicable disease surveillance for the Gold Coast 2018 Commonwealth Games	Chapter 2: Outbreak response for <i>Acinetobacter baumannii</i> in the neonatal intensive care unit the Colonial War Memorial Hospital, Suva, Fiji	Chapter 3: Epidemiological studies of vancomycin resistant enterococci in a neonatal intensive care unit at Canberra hospital	Chapter 4: Modelling of the burden of invasive pneumococcal disease in Australia	Chapter 5: Evaluation of the surveillance system for yellow fever at the Australian border	Chapter 6: Evaluation of the traveller with illness checklist surveillance system for Listed Human Diseases at the Australian border	Chapter 7: Teaching experience
Outbreak investigation		✓					
Epidemiological study			✓				
Analyse a public dataset				✓			
Establish or evaluate a surveillance system	(✓)				✓	✓	
Literature review		✓	✓	✓			
Communication for lay-audience				✓			
Conference presentation	(✓)	✓	✓		✓		
Manuscript for peer review	✓		✓				
Lessons from the field				✓			✓
Teaching for first year MAE students							✓

Ticks in brackets mean that not all aspects of this competency were fulfilled in the specified chapter.

3 INTERNATIONAL COMMUNICABLE DISEASE SURVEILLANCE FOR THE GOLD COAST 2018 COMMONWEALTH GAMES

3.1 Introduction

Between the 4 and 15 April 2018 Gold Coast hosted the XXI Commonwealth Games (here after referred to as GC2018). This was a large mass-gathering event with 71 competing teams from 52 members of the Commonwealth of Nations, which represent a third of the World's population. With over 6,600 competing athletes and their support staff arriving from overseas and an anticipated influx of spectators for the event (estimated at 500,000), there were a number of public health concerns to manage. One of these was the introduction and spread of communicable diseases. The rapidity of air travel means that infected individuals may enter Australia well within the incubation period of many diseases. With the diversity of nations in the Commonwealth there was a risk of introduction of diseases endemic to these countries, but may be unfamiliar to health professionals in Australia and not normally be considered as differentials in the diagnosis. The medical coordination unit of the GC2018 organising committee and the public health units in Queensland needed to have visibility of international disease outbreaks that may have an effect on Australia during the games period.

In early 2017, a year before the opening of the GC2018, the Medical Director at the Communicable Diseases Branch at the Queensland Department of Health approached the Office of Health Protection (OHP) at the Australian Government Department of Health, to ask for assistance with international communicable disease monitoring leading up to and during the GC2018. This piece of work was assigned to the Emergency Preparedness and Response Section (EPRS) and the Communicable Diseases Epidemiology and Surveillance Section (CDESS) of OHP, who routinely are responsible for national and international disease monitoring. Within these sections the role for international communicable disease surveillance is traditionally given to MAE scholars that are placed with the Australian Government Department of Health. I and Kaitlyn Vette, a fellow MAE 2017 scholar, were given the task of establishing a process for reporting of international communicable disease monitoring for the GC2018.

It should be noted that Kaitlyn and I worked very closely on this project, and therefore there will be significant similarities in the content presented in our respective bound volumes, in particular the appendices included for this section.

3.2 Reporting process

The requested surveillance report differed in terms of its scope from the international communicable disease report routinely produced by the MAEs in the EPRS and CDESS for the Communicable Diseases Network Australia (CDNA) committee. We determined that a more detailed analysis was required with an emphasis on Commonwealth countries, but still maintaining the wider international view as the GC2018 event may also attract visitors from non-Commonwealth countries. Establishing the surveillance reporting system involved: defining the scope; inclusion- and exclusion-criteria for health events; ongoing record keeping; report structure; reporting schedule; and distribution lists. During the development process we had regular consultation with the stakeholders at Queensland Health to ensure that the report would suit their needs.

The reporting schedule was informed from surveillance processes at previous mass-gathering events, such as the Sydney Olympics in 2000 and the Glasgow Commonwealth Games in 2014. Reports were provided from January 2018 to the conclusion of the GC2018. The reporting schedule was monthly for January and February, weekly from end of February to mid-March, and from there on daily until 4 days following the closing ceremony.

The report was provided to: the Queensland Department of Health; local public health units; the medical coordination unit of the GC2018 organising committee; CDNA; and staff at OHP and Sports branch of the Australian Government Department of Health. The Queensland Department of Health also disseminated the report to pathologists and general practitioners throughout Queensland.

For the occasions when both Kaitlyn and I were unable to compile and distribute the report, epidemiologists in the CDESS assisted. At the end of March, two new scholars from the first year cohort of MAE2018, Celeste Marsh and Hendrik Camphor, commenced their placements with OHP and were included in the reporting workflow.

3.3 After the games

Following the completion of the games Kaitlyn and I were invited to contribute a section on the international communicable disease surveillance reporting to a summary report of the GC2018 to be published shortly. As part of a lecture series on mass gatherings and the GC2018, Kaitlyn and I had the opportunity to give a presentation on international communicable disease surveillance for the first and second year MAEs at the National Centre for Epidemiology and Population Health. We have also prepared a rapid communication manuscript for submission to the peer-reviewed Journal of Global Biosecurity. The standard operating procedure established

provides a legacy for similar engagements by the Australian Government Department of Health in the future.

3.4 Public Health Implications

The international communicable disease surveillance report provided local, state and national health departments with continuous and up-to-date information allowing them to make informed decisions and assessments of risk. The report provided reassurance that they would have visibility of any significant disease concern.

During the reporting period for the GC2018, 25 reports were assembled and distributed to stakeholders. A total of 27 communicable disease events were followed, of which the following were notable:

- The to-date largest outbreak of Lassa fever in Nigeria
- Dengue in the Pacific
- An outbreak of meningococcal disease in Fiji
- Mumps in the Pacific, with a large outbreak in Auckland, New Zealand.

3.5 Lessons learned

This was my first experience in developing a reporting system, from which I learned a number of lessons. The initial request from Queensland Health was quite vague and more probed what the Australian Government Department of Health would be able to provide. It proved to be a delicate balance to offer something useful without over-stretching the resources we had at hand. These resources were only Kaitlyn and I, and we would have to do the surveillance scanning and compilation of all the reports. With both of us having 4-5 other projects that simultaneously required attention we had to be timewise.

It also became apparent that the purpose and limits of the task had to be clearly defined, with inclusion and exclusion criteria established. From our previous experience with preparing international communicable disease surveillance reports for CDNA we knew that you can only start nailing down these criteria once you are familiar with the data. Initially there was an element of flexible stability to the criteria, which solidified after the second report and a standard operating procedure (SOP) established and documented. The SOP was critical as we had to hand the process over to other epidemiologists while we attended a MAE course block.

The lessons learned were to define clear goals and expectations from all stakeholders, and keep these goals in mind during the process of the project.

3.6 Acknowledgements

I would like to extend my appreciation to Kaitlyn for a very successful collaboration on the project, for good discussions, sharing the workload and generally making the work much more enjoyable. A big thanks also goes to Celeste and Hendrik for “volunteering” to help out with the reporting, and the epidemiologists in the CDESS who covered for us while we were at course block. I would like to acknowledge the support from the branch heads of the EPRS and CDESS, Rhonda Owen and Sarah Norris, and the contributions that those sections made to the project. Finally, I would like to thank the Gold Coast Public Health Unit and the Queensland Department of Health for their input in the development process.

APPENDIX 1A – Standard Operating Procedure protocol for international communicable disease surveillance for the Gold Coast 2018 Commonwealth Games

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International Reporting Guidelines

Objective of the report

To provide relevant information about international communicable disease outbreaks and trends which have specific relevance to public health and emergency response relevant to the Gold Coast 2018 Commonwealth Games (GC2018) to the Queensland Public Health Authorities and the game organisers.

The GC2018 will run over the time period of 4-15 April 2018. There will be 70 teams competing from the 52 members of the Commonwealth of Nations. An increase in travel associated with the GC2018 is expected, both with respect to competing athletes and their families, as well as spectators of the games. This means there is a heightened risk of communicable disease transmission over the period surrounding the GC2018. The Commonwealth Department of Health will be providing enhanced rumour surveillance reports to the Queensland Department of Health, with a particular attention to public health events in Commonwealth countries. The enhanced reporting will be operational only for a limited time covering the GC2018 games, with a reporting schedule as set out later in this SOP. During this time period, the enhanced information will be used for the fortnightly CDNA report, and replacing the regular international report section. At the end of the GC2018 enhanced reporting period (last report due 2 May), the international section for the fortnightly CDNA report will return to its regular format.

Inclusion criteria

Important considerations:

1. Does the event have potential to be imported to Australia by international travellers?
 - For example: a communicable disease or infectious agent – human only.
2. Is the affected population likely to be travelling to the games?
 - For example: if transmission is primarily in a disadvantaged population, are they likely to be travelling to the games.
3. Does it have potential to continue transmission if imported?
 - For example: a disease without a competent vector or a food/water-borne disease is unlikely to continue spreading.

These may include:

1. Communicable disease outbreaks or a higher than normal incidence within Commonwealth countries;
2. Communicable disease outbreaks of significance internationally;
3. Higher than normal incidence of a communicable disease of significance to Australia;
4. Only new issues or significant updates (e.g. increase in case numbers or deaths) are to be included in the report.

Exclusion Criteria

Events should be excluded if they meet one or more of the following criteria:

1. Routine reports of communicable diseases such as global reports;
2. Potential threats or situations based on research outcomes alone; or

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3. Issues provided in previous reports - unless significant new information is available. If unsure, please check with the relevant epidemiologist.

Sources of information

- WHO EIS and situational reports - <http://apps.who.int/ihr/eventinformation/>
- WHO Disease Outbreak News - <http://www.who.int/csr/don/en/>
- WHO SEARO surveillance and outbreak - http://www.searo.who.int/entity/emerging_diseases/en/index.html
- WHO WPRO surveillance and outbreak- http://www.wpro.who.int/outbreaks_emergencies/en/index.html
- WHO AFRO surveillance and outbreak – <http://www.afro.who.int/health-topics/disease-outbreaks/outbreaks-and-other-emergencies-updates>
- ECDC - <http://www.ecdc.europa.eu/en/press/news/Pages/News.aspx>
- CDC - <http://www.cdc.gov/>
- CIDRAP - <http://www.cidrap.umn.edu/>
- UK HPA - <http://www.hpa.org.uk/>
- ProMED mail - <http://www.promedmail.org/>
- ProMED Mekong basin: <http://www.promedmail.org/mbds>
- GPHIN (see “Email lists” section below for instructions on how to access this)
- PacNET: <http://www.spc.int/phd/epidemics/>

Sources for additional information about known event or threat:

- Reuters alert net - <http://www.trust.org/?show=alertnethumanitarian>
- FLUTRACKERS - <http://www.flutrackers.com/forum/>
- HealthMap - <http://healthmap.org/en/>
- Reliefweb: <http://reliefweb.int/>

Email lists

- PACNET
 - To be added to PACNET send an email to join-pacnet@lyris.spc.int. They will email you back asking why you want to join.
- CIDRAP Newsletter – Go to <http://www.cidrap.umn.edu/newsletter> and add your email details
- GPHIN alerts can be read in the Health ops inbox (access to Health ops inbox provided to Watch Officers (WO) – please contact WOs if you require information about GPHIN alerts)

Interpretation of information

When using sources such as Reuters or ProMed ensure you check where the information has originated from and reference the original source as well as ProMed itself. These websites act as repository of information, so it is important to check the sources these websites reference to ensure the information is accurate and plausible. Some media articles are recycled. You should always check the date from the original source and cross-reference with a known credible source such as a government website or UN agency website where possible. For the purposes of Commonwealth Games surveillance, including information without an official source is acceptable if it is of interest.

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Report structure

The Surveillance Issues Log will be used as the depository for the surveillance information collected. The columns and expected content is described below. Once updated, the filters are used to generate a view specific to the Commonwealth Games report and exported to an Excel format.

Heading	Description and format
Issue/Incident Title	"Disease – Country"
Date of update	The day that you made this entry
Date first reported or first aware	The first date of reporting if reported previously (check the log for previous entries).
Disease	Full name of the disease
Countries/regions/areas affected	Can be "country", "continent+countries", "country+specific areas"
Source of information/data	State the source and provide a link
Case numbers	Number of suspected and confirmed cases only. Details should be provided elsewhere.
Affected population	In broad terms (e.g. general population, young people, Indigenous people, urban/rural, occupation-specific)
Background description	Summarise important background information. Any important contextual information for internal record keeping and decision making should be in here.
Summary description	Summarise the most important information. Should be as concise as possible and contain only relevant information pertaining to time, place, and person.
Serious health impact	Does the health event result in a serious health impact, can be significant event if only having local affects. Some sources (such as EIS) will have a risk assessment that can be used. Otherwise look at the assessment from previous instances of similar health events in the surveillance issues log, or ask an epidemiologist in the relevant area.
Unusual or unexpected	Is this health event unusual or unexpected, or is it endemic to the country or has a seasonal recurrence. Some sources (such as EIS) will have an assessment that can be used. Otherwise look at the assessment from previous instances of similar health events in the surveillance issues log, or ask an epidemiologist in the relevant area.
International disease spread	Is the health event likely to result in transmission to neighbouring countries (for instance when borders are porous, conflict zones, affecting displaced populations), or even further international spread (through air travel). Some sources (such as EIS) will have an assessment that can be used. Otherwise look at the assessment from previous instances of similar health events in the surveillance issues log, or ask an epidemiologist in the relevant area.
Likelihood of impacts for Australia	Is the health event is likely to have an effect on Australia (for instance through importation and local transmission, Australian residents travelling overseas). Revisit the key considerations at the beginning of this document.
Include in reports	Tick if the information should be included in the Commonwealth Games report or CDNA report. If it is a Commonwealth country and the other considerations of inclusion are met, it should be included. Even if it is a major health event in a non-Commonwealth country, it could be of relevance for the Commonwealth report as there may still be significant numbers of visitors from this country and risk of onward transmission. All commonwealth games surveillance should be included in the CDNA report, however there may be additional events that are necessary for the CDNA report that are not necessary for the Commonwealth games report (eg non-Commonwealth

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Heading	Description and format
	countries with outbreaks that are unlikely to be imported, but more likely for Australians to visit that country).
Current actions, related reports, documents	Mainly used by the CDESS.
Additional actions that might be required	Mainly used by the CDESS.
Smarttraveller updated	Mainly used by the HPPB Surveillance sections. Check Smarttraveller website to see if there is advice about the disease and note that.
Current/superseded/closed	Indicate the state of the entry. Please check if there are previous entries about the same disease, ensure to 'supercede these' and make yours current. Ensure to update and close entries (especially your own) when they are no longer active.
Logged by initials	Put in your initials

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**APPENDIX 1B – Sample of international communicable disease report for the
Gold Coast 2018 Commonwealth Games**

Commonwealth Games international disease surveillance report Reporting period: 17 April 2018									
Issue/Incident Title	Date of update	Date first reported or first aware	Disease	Affected source populations	Case numbers	Commonwealth country affected?	Summary description	Countries/regions/areas affected	Source of information/data
Lassa fever - Nigeria	18/04/2018	26/01/2018	Lassa fever	Two thirds of the cases are male and the people predominantly affected are between 30 and 50 years.	413 confirmed, 9 probable, 5 awaiting laboratory results	Yes	The Lassa fever outbreak in Nigeria continues however new cases reported over the past week (9-15 April) and the epidemic curve indicate that the peak number of cases nationally has passed. However, the Lassa fever period can be expected to continue for another 1-2 months, into June 2018. This is the largest outbreak of Lassa fever ever reported in Nigeria. In the reporting week 15 (9-15 April 2018), 5 new confirmed cases were recorded from 4 States. Between 1 January -15 April 2018, a total of 1849 suspected cases have been reported from 21 states. Of these, 413 were confirmed positive, 9 are probable, 1422 are negative (not a case) and 5 are awaiting laboratory results (pending). Since the start of the 2018 outbreak, there have been 105 deaths in confirmed cases. Case fatality rate in confirmed cases is 25.4 %.	Nigeria	Nigeria Centre for Disease Control week 13: 1 April 2018 http://www.ncdc.gov.ng/diseases/sitreps
Hepatitis A virus - New Zealand	18/04/2018	18/04/2018	Hepatitis A	Children associated with one kindergarten	6	Yes	Following diagnosis of 3 children from 2 families associated with a kindergarten in Oamaru last week (reported 7 April), 3 more cases have been confirmed through blood testing of the centre's children and staff. Vaccinations for those at the kindergarten were completed on 13 April 2018. Although the origin of the virus had not been identified, it was thought to be from outside the country.	New Zealand	http://www.promedmail.org/ Archive Number: 20180417.5751276 Otago Daily Times: https://www.odt.co.nz/regions/north-otago/3-more-hepatitis-cases
Measles - Europe	17/04/2018	2/07/2017	Measles	Unvaccinated general population	14,813 cases including 13 deaths	Yes	New information: There is an ongoing measles outbreak in Europe with 14,813 cases reported across 30 countries between 1 March 2017 and 28 February 2018. Outbreaks of measles are ongoing in France, Greece, Ireland, Italy, Portugal and Romania. As of 14 April 2018, Romania has had the most cases with 1,709 cases so far this year, followed by Greece (1,463), France (1,346), and Italy (411). Most concerning are the case counts in France and Italy, which have almost tripled and more than doubled, respectively, in the last month. Of these cases, where age was known, 35% were in children under five and 47% were in those 15 years or older. Where vaccination status was known, 86% were unvaccinated. Outside of the European Union, Ukraine has continued to experience the largest outbreak, with almost 10,000 cases reported year to date in 2018, including seven deaths. Ongoing outbreaks are also being reported in Albania, Belarus, Georgia, Serbia, and Turkey. Over 500 cases are reported from Russia, which will host country of FIFA 2018 during the 2018 European summer.	European countries	https://ecdc.europa.eu/sites/portal/files/documents/Communicable-disease-threats-report-14-apr-2018.pdf PHE https://www.gov.uk/government/publications/notifiable-diseases-weekly-reports-for-2018
Typhoid fever - Pakistan	16/04/2018	24/01/2018	Typhoid fever - multi drug resistance	Children aged 2-10 years	>850 cases in 14 districts, including at least 4 deaths	Yes	New information: The first known epidemic of extensively drug-resistant (XDR) typhoid is spreading through Pakistan, infecting at least 850 people in 14 districts since November 2016, according to the National Institute of Health Islamabad. The typhoid strain, resistant to 5 types of antimicrobial agents including ceftriaxone, the antibiotic previously used to treat MDR strains of typhoid, is expected to disseminate globally, replacing weaker strains where they are endemic. Experts have identified only one remaining oral effective antibiotic - azithromycin. Only 4 isolated cases of extensively drug-resistant (XDR) typhoid had previously been reported worldwide. Background: Antibiotic resistance is a major problem in <i>Salmonella enterica</i> serovar Typhi, the causative agent of typhoid. Multidrug-resistant (MDR) isolates are prevalent in parts of Asia and Africa and are often associated with the dominant H58 haplotype.	Pakistan	PromedArchive Number: 20180415.5747027 https://www.nytimes.com/2018/04/13/health/drug-resistant-typhoid-epidemic.html ProMED: https://www.thereports.com.pk/print/27217-hyderabad-facing-worlds-first-outbreak-of-drug-resistant-typhoid-aku http://www.coalitionagainsttyphoid.org/the-perfect-storm-in-pakistan-unsafe-drinking-water-and-drug-resistant-typhoid/

Scarlet fever - UK	16/04/2018	5/03/2018	Group A Streptococcus - Scarlet fever	89% of cases are children under 10 years - The age distribution of cases is similar to previous years.	17 103 cases reported in 2018 (to week 14 - ending 8 April)	Yes	There has been an unusually high level of scarlet fever circulating in the UK. In the 14 weeks ending 8 April 2018, 17,103 suspected cases of scarlet fever were reported to Public Health England (PHE) across England and Wales. The number of reports to date (8 April) in 2018 is more than double the 2017 figure and much higher than over the same period in the previous 8 years. There were 7,050 cases reported in 2017, compared to 8,360 in 2016, and 1,016 in 2011.	England, Wales	Promed/Archive Number: 20180408.5732644 Public Health England NODs Weekly Report - Week 11 ending 18 March 2018 https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/692810/NODs-weekly-report-week11-2018.pdf
Measles - New Zealand	13/04/2018	10/04/2018	Measles	Unvaccinated general population	5 confirmed, up from 3 confirmed, 1 probable previously	Yes	As of April 11, an additional 2 new confirmed cases have been reported in Nelson and Christchurch, in addition to three previous cases in Queenstown, Wanaka, and Christchurch, bringing the total to 5 confirmed cases in the South Island, with age range 13 months to 46 years old. Investigations are continuing and close contacts are being identified for follow up.	New Zealand	Promed/Archive Number: 20180409.5734358 Canterbury Health http://www.scoop.co.nz/stories/CE1804/S00008/three-cases-of-measles-confirmed-in-south-island.htm
Dengue - Malaysia (Sabah State)	12/04/2018	12/04/2018	Dengue virus	General population	958 cases of dengue, including 10 deaths, this year up to March 31	Yes	According to the Sabah Department of Health, all districts in the state of Sabah have registered an increase in the number of dengue cases in the first quarter of 2018. Sabah has recorded 958 cases of dengue, including 10 deaths up to Sat 31 Mar, 2018. Malaysia as a whole has a similar dengue incidence trend for 2018 (until March 29) compared to previous years according to the WHO WPRO Dengue Situation Update.	Sabah state, Malaysia	ProMED-IMBDS: Mekong Basin/Archive Number: 20180407.5730876 WHO WPRO: http://www.wpro.who.int/emerg_diseases/dengue_biweekly_report_20180329.pdf?ua=1
Dengue - Pacific	11/04/2018	11/12/2016	Dengue	General population	Approximately 2,000 suspected cases	Yes	New information: New Caledonia: As of 6 April 2018, 528 confirmed cases since 1 January 2018; with co-circulation of dengue serotypes 1 and 2, of which 79.5% is serotype 2. One imported confirmed case of serotype 4 in the capital Noumea. Background: As at 25 March 2018, there are ongoing dengue serotype-2 outbreaks in Fiji, New Caledonia, Samoa and Vanuatu. The weekly number of cases (dengue serotype-2) reported is decreasing in Tonga. Tonga: As at 19 March 2018, there was an increasing number of dengue cases of dengue serotype-2. Vanuatu: As at 22 March, the outbreak of dengue serotype-2 was ongoing. As at 20 March there were 329 suspected cases reported. 52 of these were confirmed with rapid diagnostic test. Age range is 1-85 years old, 42% are children below 14 years of age and 55% are male. Fiji: As at 23 March, there is an ongoing outbreak of dengue serotype-2. There were 426 cases reported in January 2018 alone. American Samoa: As at 18 March, cases of dengue serotype-2 had peaked and are decreasing in number. Wallis and Futuna: As at 20 March, the outbreak of dengue serotype-1 has reportedly slowed. As at 22 January, 31 cases had been reported, 9 of which were confirmed, of which 8 are dengue serotype-1. There have been 5 hospitalised cases and no 1 new case of wild poliovirus type 1 (WPV1) has been confirmed as at the 3 April, 2018. The case occurred in Dikik district, Balochistan province, with onset of paralysis on 8 March 2018. This is the 1st case reported in Pakistan in 2018. The total number of officially reported WPV1 cases in Pakistan in 2017 was 8. The next set of supplementary immunization days are planned for 9 April 2018, during which vaccinators will aim to vaccinate children across 8 provinces using bivalent oral polio vaccine (bOPV).	Pacific Islands New Caledonia PacNET Dengue Vanuatu Sit. Rep #3, 20 March 2018 PacNET Syndromic Surveillance Report week 10 11 March 2018	
Polio - Pakistan	9/04/2018	7/09/2017	Wild polio virus	Children	8 (2017), 1 (2018)	Yes	As of 5 April 2018, there has been a total of 38 cases of meningococcal disease including 4 deaths. Of these, 22 cases are laboratory confirmed, and 16 are either suspected or probable cases. There has been an average of 2.5 cases per week in the last 4 weeks. The majority of the cases are from the Central division and all cases are less than 19 years of age. This outbreak is caused by serogroup C, with isolates sent to the WHO reference lab for molecular typing reported to be resistant to penicillin and ciprofloxacin.	Pakistan	GEPI - Polio now - 03/04/2018 http://polioeradication.org/polio-now/polio-now/this-week/
Meningococcal - Fiji	9/04/2018	22/03/2018	Meningococcal (serogroup C)	Children and young adults (<19 years)	38 cases including four deaths.	Yes	As of 5 April 2018, there has been a total of 38 cases of meningococcal disease including 4 deaths. Of these, 22 cases are laboratory confirmed, and 16 are either suspected or probable cases. There has been an average of 2.5 cases per week in the last 4 weeks. The majority of the cases are from the Central division and all cases are less than 19 years of age. This outbreak is caused by serogroup C, with isolates sent to the WHO reference lab for molecular typing reported to be resistant to penicillin and ciprofloxacin.	Fiji	Fiji Meningococcal C Outbreak Situation Report Update: 5th April 2018

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APPENDIX 1C – Presentation on international communicable disease surveillance reporting during the Gold Coast 2018 Commonwealth Games.



COMMONWEALTH GAMES INTERNATIONAL SURVEILLANCE REPORT

Patiyan Andersson
Kaitlyn Vette

March 2018
National Center for Epidemiology and Population Health



Purpose of the report

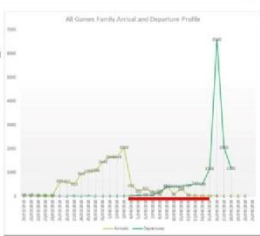
- Commonwealth Games on the Gold Coast from 4 - 15 April 2018
- 52 countries, 70 competing teams
- Commonwealth's role
- International communicable disease outbreaks and trends





Surveillance period

- **Monthly:** January and February
- **Weekly:** End of Feb to mid March
- **Daily:** Mid March to mid April
- **Weekly:** Until beginning of May





Surveillance sources

- WHO EIS
- WHO disease outbreak news
- WHO SEARO
- WHO WPRO
- ECDC
- CDC
- CIDRAP
- UK HPA
- ProMED
- GPHIN
- PacNET





What to include

Scope

- Major events
- Commonwealth countries

Inclusion criteria

- Outbreaks and higher than normal incidence
- Likelihood of affected population travelling
- Likelihood of ongoing transmission





Report structure

- Incident Title
- Date of update
- Date first reported or first aware
- Disease
- Affected source populations
- Case numbers
- Commonwealth country affected?
- Countries/regions/areas affected
- Source of information/data
- Description





Report dissemination

- Internal staff
- Key epidemiologists in QLD Health
- Public health units in QLD
- Health section of Commonwealth Games organisers
- National Incident Room
- Commonwealth Department of Health sport area



Key lessons

- Great opportunity
- Coordination
- Coverage
- A lot more commonwealth countries than we knew about
- Beneficial to work as a team

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CHAPTER 2

International outbreak response to a multi-resistant *Acinetobacter baumannii* in the NICU at the Colonial War Memorial Hospital in Suva, Fiji

**The Colonial War Memorial Hospital
Suva, Fiji**

GOARN deployment

“If it looks like a duck, and quacks like a duck, we have at least to consider the possibility that we have a small aquatic bird of the family Anatidae on our hands.”

Douglas Adams

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ABBREVIATIONS

CPAP	continuous positive airway pressure
CWMH	Colonial War Memorial Hospital
EIS	Epidemic Intelligence Service
ELBW	extremely low birth weight (<1000 grams)
FPBS	Fiji Pharmaceutical and Biomedical Services
GOARN	Global Outbreak Alert and Response Network
ICU	intensive care unit
IPC	infection prevention and control
LBW	low birth weight (≥ 1500 grams to <2500 grams)
MAE	M.Phil. Applied Epidemiology
MOHMS	Ministry of Health and Medical Services
MRO	multi-resistant organism
NICU	neonatal intensive care unit
PICU	paediatric intensive care unit
SNP	single nucleotide polymorphism
ST	sequence type
VLBW	very low birth weight (≥ 1000 grams to <1500 grams)
WHO	World Health Organization
WGS	whole genome sequencing

ABSTRACT

Background: Between December and June 2017, the Colonial War memorial Hospital (CWMH) in Suva, Fiji, had 12 neonatal intensive care patients with *Acinetobacter baumannii* resistant to all tested antibiotics isolated from blood or cerebrospinal fluid specimen. All 12 patients died. With the outbreak still ongoing, the Fiji Ministry of Health and Medical Services requested international assistance from the WHO. An outbreak response team was assembled and deployed from the Global Outbreak Alert and Response Network (GOARN). I was deployed as an epidemiologist, together with another epidemiologist and an infection control expert. The terms of reference were to conduct an outbreak investigation at CWMH and an evaluation of the infection control practices at the three major hospitals in Fiji.

Methods: Log-books of multi-resistant organisms were reviewed back to January 2015 to establish the baseline presence of *A. baumannii*. A descriptive study was conducted using clinical and demographic data from medical records. The evaluation of infection control practices was conducted using an assessment tool developed at Griffith University.

Results: The epidemiological investigation revealed a long-term presence of a highly resistant *A. baumannii* strain in the neonatal intensive care unit (NICU), but with a steep increase in infections and deaths from December 2016. A total of 34 patients were identified, 14 patients with highly invasive disease (positive blood or cerebrospinal specimens) and 20 patients with positive specimens from other sites. Twenty-three of the 34 patients died from their infections. The descriptive analysis identified a universal use of respiratory support equipment among the infected infants. Whole genome sequencing of 14 specimen from 11 patients, showed an *A. baumannii* sequence type 2, with a phylogenetic tight clustering characteristic of an outbreak and with signs of microevolution consistent with the timeline.

The evaluation of the infection control practices indicated systemic infrastructure issues not conducive to support effective and consistent infection control, including unreliable supply of: single use respiratory equipment leading the inappropriate and unsafe reprocessing of items; personal protective equipment; intravenous fluids and medication; hand hygiene equipment and supplies.

Conclusion: The outbreak of a highly resistant *A. baumannii* in the NICU was successfully halted. The investigation revealed multiple possible sources of transmission, most notably involving the reuse of single-use respiratory equipment without adequate sterilisation between patients. There were critical infection control concerns identified, which stemmed from significant medical supply issues.

EXTENDED PROLOGUE

This prologue will be more extensive compared to other prologues in this thesis in order to provide context for the technical report from the mission included as **Appendix 2A** in this chapter. The report describes the detailed findings from the mission, and in the prologue I will provide information on the deployment, the work conducted and my role in the mission. The report was written by the outbreak response team on behalf of the WHO and provided to the Fiji Ministry of Health and Medical Services (MOHMS). The enclosed version is the one approved (for release) by the WHO and MOHMS.

GOARN outbreak response mission

In early July 2017 the Ministry of Health and Medical Services (MOHMS) of Fiji submitted a formal request to the World Health Organization (WHO) for international assistance with outbreaks of multi-resistant *Acinetobacter baumannii* in the neonatal intensive care unit (NICU) at the Colonial War Memorial Hospital (CWMH) in Suva (**Figure 1**). The CWMH had been battling two consecutive outbreaks of the bacterium in the NICU since the beginning of 2017. At the time of the request for assistance the outbreaks had resulted in a significant number of deaths of neonates and had overwhelmed the in-country capacity. There was intense media interest and a growing perception in the wider community that the hospital was no longer safe to go to.

WHO assembled and deployed an outbreak response team from the Global Outbreak Alert and Response Network (GOARN). This is a network of emergency management resources (including field epidemiologists) around the world, from which WHO can deploy experts to provide assistance in response to requests. The Terms of Reference for the mission were to provide emergency outbreak response and to conduct a formal evaluation of the infection control practices at the three major hospitals in Fiji. The team deployed was composed of two epidemiologists tasked with the outbreak response and an infection prevention and control (IPC) expert. I was suggested as a suitable candidate for the mission by the ARM network, the GOARN focal point for Australia, and was selected to be deployed as an epidemiologist with laboratory expertise. The other epidemiologist was Dr Meghan Lyman, a medically trained Epidemic Intelligence Service (EIS) officer from the Centers for Disease Control and Prevention in Atlanta, USA; and the IPC expert was Dr Peta-Anne Zimmerman, from the Griffith University, Gold Coast, Australia.

I was deployed for a four-week period and arrived in Suva, Fiji on the 12th of July 2017, one day after Dr Lyman. Together we commenced the outbreak investigation at the CWMH. Concurrently, Dr Zimmerman was conducting evaluations of the infection control practices at the hospitals in Lautoka and Labasa. In the second week Dr Zimmerman arrived in Suva, and as

the CWMH was the largest hospital, Dr Lyman and I assisted in the evaluation and the compilation of the evaluation findings. During the second week Dr Lyman and I also continued with the outbreak investigation. In the third week we concluded the outbreak investigation and commenced drafting of the final report. Dr Lyman and I presented the final mission findings to the Permanent Secretary of the MOHMS, Executives and senior medical staff from the Lautoka, Labasa and CWM Hospitals and Executives from the Fiji Pharmaceutical and Biomedical Services (FPBS) (**Appendix 2B**). Dr Lyman returned to the US at the end of this week. I remained in-country for yet another week where I followed up on and confirmed data, and liaised with the Fiji WHO office to finalise the technical report. The team worked every day during the mission, with the exception of one. The time constraints of the mission allowed only a descriptive study to be conducted instead of an analytical study.



Figure 1 Neonatal intensive care unit at the Colonial War Memorial Hospital, the level 3 care facility (highest level of care) on the left and level 2 care facility on the right.

Outbreak overview

The outbreak response commenced with trying to establish a picture of the outbreak in the context of what was considered a baseline level and pattern of infections at the CWMH. It quickly became apparent that ongoing surveillance was non-existing. Each multi-resistant organism (MRO) was recorded in books (**Figure 2**), but the data was not used for ongoing analysis. To establish a baseline of the presence of *Acinetobacter baumannii* in the NICU we reviewed the MRO books from January 2015 onwards. We also included the paediatric ICU

(PICU) as there was significant staff and equipment movement between the two units. Two patterns emerged, with the NICU dominated by a highly multi-resistant (resistance to 3rd generation cephalosporins and carbapenemases) *Acinetobacter baumannii* clone (hereafter referred to as the AB investigation strain) and the PICU dominated by an *Acinetobacter baumannii* clone sensitive to 3rd generation cephalosporins and carbapenemases. The review also highlighted that the presence of the AB investigation strain in a wide range of specimens, whereas up to this point the CWMH IPC team and NICU doctors only considered positive bacterial cultures from blood and cerebrospinal fluid specimens as part of the outbreak. When expanding the case definition, it became evident that the two outbreaks observed, were in fact one sustained outbreak, where the transmission of the bacterium had never been interrupted.



Figure 2 Handwritten, loose leaf paper-based patient medical charts and the MRO books.

Descriptive analysis of risk factors

A total of 40 patients were thought to be part of the outbreak, but medical charts could only be located from 34 patients. Twenty-three (67%) of these infants died from their infections. The clinical notes in the medical charts formed the basis of the information used for assessment of risk factors for infection with the AB investigation strain. The medical charts were all handwritten with papers only loosely bound, and inevitably there were missing documents and incomplete information for some patients (**Figure 2**).

The descriptive analysis of the clinical variables found a near universal (33/34 patients) exposure to mechanical ventilation prior to the first positive specimen. Blood transfusions prior to first positive specimen was also common (28/34 patients). It should be noted that this patient group is critically ill with significant comorbidities, and that much of the procedures were routine treatments for premature infants. Therefore, without an analytical study format it was very difficult to establish a statistical association between a risk factor and infection.

The demographic and clinical variable data for the patients was supplemented with information gathered from interviews with doctors and nurses in the NICU and the IPC team, and supporting

units at the hospital. The interviews provided insight into the operation of the NICU and the hospital and were conducted with clinical and auxiliary staff (such as cleaners) in the NICU and PICU; scientists in the microbiology laboratory; the IPC team; the consumables store manager; pharmacists and representatives from the FPBS; and the antimicrobial stewardship unit.

The interviews revealed significant long-standing supply issues at the hospital, the reasons for which were multifaceted. The wards expressed a difficulty in obtaining sufficient consumables from the hospital stores for the operation of the units, but also could not define what their monthly consumption was likely to be as they had operated at deficit levels for a prolonged time. The hospital consumables stores manager claimed that they were not aware of how much stock was available at the FPBS and only requested supplies to maintain the store's levels. The FPBS in turn stated they were bound by the available budget and, without a statement of need from the hospital, were unable to advocate for an adjustment of the budget. The result was that the hospital worked with a frustratingly consistent deficit of supplies, ranging from simple items such as hand sanitizer of sufficient strength to advanced equipment such as single-use ventilator tubing. This undersupply led to dangerous practices such as the re-use of single-use ventilator and oxygen tubing (**Figure 3**). As these items were meant for single use, they were not able to be cleaned or sterilized appropriately, and were only rinsed in tap water and air dried.

The observation regarding the re-use of respiratory equipment supported the observation of near universal use of respiratory equipment among the infected patients. The lack of small volume vials of consumables such as sterile saline, led to large 1L vials being accessed multiple times, and sometimes for multiple patients. The evaluation of infection control practices revealed that these issues were common to all wards at CWMH, and also to the hospitals in Lautoka and Labasa.



Figure 3 Re-processing of single-use respiratory equipment. Shown from left to right: a single-use nozzle for CPAP with mucus residue still remaining after cleaning; oxygen tubing rinsed in tap water and air drying; and an Ambubag that was unclear if it was single-use or not as the manual was in Portuguese.

Whole genome sequencing analysis

Whole genome analysis of 14 isolates from 11 patients was conducted by the Microbiological Diagnostic Laboratory Public Health Laboratory in Melbourne, Australia. The whole genome sequencing was carried out following their standard protocols on an Illumina NextSeq 500, with subsequent bioinformatic analysis using the in-house Nullarbor pipeline (<https://github.com/tseemann/nullarbor>). In the bioinformatic analysis Australian isolates of the same sequence type were included for contextual purposes. The analysis revealed the AB investigation strain to be an *Acinetobacter baumannii* sequence type 2 (ST2), harbouring a *bla*_{OXA-23} carbapenemase gene and a 16S rRNA methyltransferase *armA* gene conferring high-level aminoglycoside resistance. The phylogenetic analysis showed the isolates to be highly clonal, with evidence of micro evolution over the outbreak period (**Figure 4**).

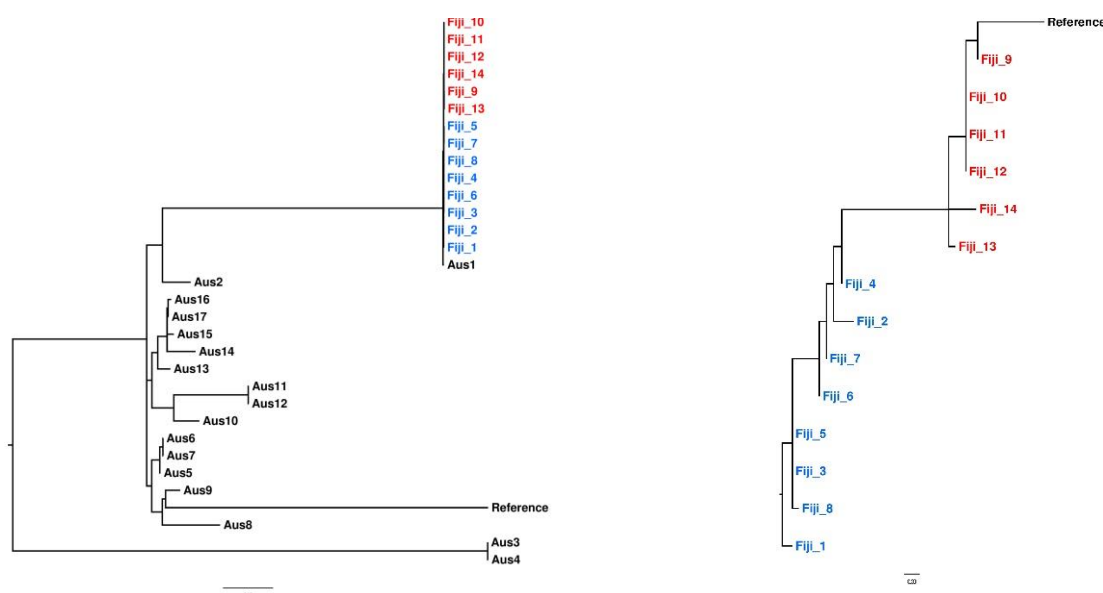


Figure 4 Phylogenetic analysis of *Acinetobacter baumannii* ST2 outbreak isolates in blue (collected in December to Feb) and red (collected May to June), in context with published ST2 isolates from Australia. The second tree shows the evolution of the outbreak isolates, from early to late in the outbreak, in blue and red, respectively.

Evaluation of infection control practices

The evaluation of infection control practices at CWMH that I assisted with involved visits to and interviews with staff in each ward and area in the hospital. This was thorough and provided a useful and interesting analysis of the hospital operational system as a whole. In all the wards the aforementioned supply issues were evident, with the associated infection control deficits of poor hand hygiene compliance, multi-assess of sterile fluids, inconsistent use of personal protective equipment and reprocessing of single-use respiratory equipment (**Figure 5**). Only one out of four autoclaves in the hospital was operational, and the operational autoclave did not

have any functioning recording device to ensure that it reached adequate temperature and pressure during the sterilisation cycle. In addition to this sub-optimal operation, this situation also meant that should there be a failure with the remaining autoclave, the hospital would be paralyzed as no equipment or waste could be sterilized until a replacement machine could be sourced and delivered. This would have far reaching adverse impacts as the CWMH is a referral hospital for all of Fiji and some neighbouring countries.

Health care workers form part of the transmission chain and arguments can be made to screening for MROs among the work force. However, in the current situation such concerns are overshadowed by the more immediate IPC issues identified.

A concerning fact was the discovery of reports from 11 previous outbreak investigations from 2006 to 2016 that had identified the same infection control problems and supply issues and made very similar recommendations to those that our outbreak response team presented. However, the response from the MOHMS this time seemed very encouraging, and at the time of writing there have been no further outbreaks of *Acinetobacter baumannii* in the NICU.



Figure 5 Infection control issues. Clockwise from top left: autoclaved gauze packed in butcher's paper that does not maintain sterility; saline solution diluted with tap water for wound irrigation and wetting of wound pads in surgical ward; overfilled sharps containers due to very low numbers of containers; multi-access of single use ampoules, multi-access of 1L sterile saline for multiple patients.

My role

I was deployed as a short-term WHO contractor with field epidemiology and laboratory skills. The laboratory skills complemented Dr Lyman's medical skills from her background as a physician, allowing us to tackle problems from multiple angles. This was particularly useful when it came to conducting interviews with various staff members at the hospital.

My role in the outbreak response involved a range of tasks, including:

- Assemble historical data from 2015 onwards on *Acinetobacter baumannii* in the NICU and PICU at the CWMH to establish baseline data to contextualise the outbreak.
- Establish a case definition, create a line list of infected patients in the NICU and extract demographic and clinical data from medical charts.
- Conduct descriptive analysis of the extracted data and produce visual representations.
- Review of the literature on *Acinetobacter baumannii* and other multi-resistant organisms (MRO) in the Pacific.
- Conduct interviews with nursing staff and doctors in the NICU, with laboratory staff in the microbiology unit, medical supply personnel at the CWMH and representatives at the FPBS.
- Interpret whole genome sequencing and phylogenetic data.
- Prepare and give regular briefings to the WHO Representative at the Fiji WHO office and the Permanent Secretary of MOHMS.
- Prepare and deliver a presentation for the MOHMS and CWMH hospital staff at the mid-point of the mission, and a final presentation to the MOHMS, FPBS and Executives from the three major hospitals at the conclusion of the mission.
- Provide a technical debriefing teleconference with the WHO Western Pacific Office.
- Write a final technical report for the WHO to the MOHMS (drafted the outbreak response section and reviewed the complete report).

While I was mainly focussed on the outbreak response, Dr Lyman and I also helped Dr Zimmerman with the evaluation of infection control practices at the CWMH, as this was the largest hospital and there was a very limited time to conduct the evaluation. Dr Lyman and I also assisted in training of the IPC nursing team at the CWMH in basic surveillance of MROs. I set up and trained the IPC nursing team in the use of an Excel spreadsheet for ongoing monitoring of MROs. I assisted Dr Lyman in training of NICU staff in infection control procedures such as contact precautions and movement patterns of equipment to reduce risk of transmission.

Following my return to Australia I have given presentations on the GOARN deployment to fellow MAEs and staff at the National Centre for Epidemiology and Population Health. I have also had

the opportunity to present to the staff at the infectious diseases and infection prevention and control units at the Canberra Hospital, as well as at a Canberra Hospital Grand Rounds seminar, together with Dr Nicholas Coatsworth and Wendy Beckingham.

Lessons learned

At the time of deployment, I had been in the MAE program less than 5 months and had a case of impostor syndrome as I was sitting on the flight to Fiji. I had been well briefed on how to prepare and what to expect on a deployment by my academic supervisor, Dr Katrina Roper, who had extensive experience of international deployments. But still, flying into an unknown situation with only very brief Terms of Reference indicating the situation and no previous experience with outbreak responses, made me admittedly nervous. This dissipated within the first few hours of commencing the work. The first briefings with the local WHO office and at the CWMH painted a dire situation with significant knowledge gaps. Dr Lyman and I established a plan and got working. This is how the MAE training functions: learning by doing.

It was a fantastic learning opportunity. The situation forced me to be fully engaged and take on what needed to be done, regardless if I felt comfortable or competent for the task. I learnt from Dr Lyman and Dr Zimmerman how important it was to triangulate the information that you received, especially with regards to areas where there may be political or personal interests involved. This also became apparent in terms of people's expectations and what they thought the mission should include. This was both from local staff at the CWMH and the MOHMS, but also from the Western Pacific Region WHO (WPRO) office that had a wide range of suggestions of additional work. Staying on target with the Terms of Reference and the time frame became very important, and also to acknowledge that a lot of these suggestions fell outside the expertise of the outbreak response team.

Nothing motivates like seeing suffering patients and their families, and hospital staff working hard under challenging circumstances to save lives. You simply want to do everything that you can to help. This motivation was critical, as I also learned that there is very little down-time during a mission, even if you are on a paradise island. A normal day would often be work at the hospital gathering information during the day, go back to the hotels at 5pm to do analysis of the data, followed by seeking input or advice from home offices (the CDC in Dr Lyman case and Dr Roper in my case), with days often ending at midnight. Every day. 7 days a week. The support from home became invaluable, both in terms of work input but most importantly debriefing.

While the study identified plausible causes and routes of transmission, should time have afforded an analytical study would have allowed more statistically reliable causal attribution to be explored. An appropriate study design would have been a case-control study (as per Chapter

3) or a cohort study. Suitable reference groups for such analytical studies were available in the form of infants with overlapping admissions to those in the current study, but without *A. baumannii* infection or colonisation. As both groups would be composed of patients admitted to the NICU, one could argue that this would technically be a case-case study, but the analysis procedure is the same as for a case-control study.

Having commenced a project on vancomycin resistant enterococci in the NICU at the Canberra Hospital, the challenges of the IPC unit at the CWMH became very apparent. At the Canberra Hospital the IPC unit have a well-recognised and respected role in the hospital system, providing them with authority to implement effective action in emergency situations. The IPC unit at the CWMH on the other hand were composed of relatively junior staff, who held little authority in the rigid hierarchical hospital system, making their work very difficult. The vulnerabilities of paper-based systems also became evident, where in contrast to the computer-based system of medical charts at Canberra Hospital, there often were missing or incomplete medical charts for patients in CWMH, which had an effect on the analysis. With all this said, I do recognise that Fiji probably have one of the more developed health care systems in the region, Australia and New Zealand aside. Finally, what was similar between the NICUs in the two countries was the impressive commitment and hard work of the nurses and doctors.

Public health implications

The most significant public health implication of the GOARN mission was that we managed to stop the outbreak. The immediate cessation in transmission was likely due to changes in infection control practices in the NICU, most significantly stopping the re-use of single use respiratory equipment but also reduced sharing of other equipment, cohorting of infected patients, and changed movement patterns of equipment and staff in the NICU. The MOHMS action of releasing emergency funds to procure consumable equipment for the NICU, including single-use respiratory equipment and disinfection agents, also assisted in ceasing transmission. The influx of equipment was also intended to estimate the usage and requirements of the NICU, which had operated at a starved level for such a long time that the staff were unable to tell the outbreak response team what the minimum levels of consumable equipment required for normal operation were. This information was to be used to inform future budget estimates.

The evaluation of the infection control practices highlighted a large number of deficits, which resulted in a list of short-, medium- and long-term recommendations. These ranged from relatively small consumable items, such as hand sanitizer of adequate strength and small volume containers of sterile saline solution, to large items such as new autoclaves. The evaluation also

identified gaps in human resources and lack of articulated public health strategies. The MOHMS was going to seek international assistance to establish such guidelines.

In August 2018, Dr Zimmerman was invited back to follow up on the recommendations and to conduct another evaluation. She reported in conversations that there had not been no further outbreaks with *Acinetobacter baumannii* in the NICU.

Ethics

Ethics approval for the inclusion of this piece of work and the report in the bound volume was obtained from the Australian National University Human Research Ethics Committee (Protocol number 2018/537).

Acknowledgements

I would like to thank Dr Meghan Lyman and Dr Peta-Anne Zimmerman for being excellent team members to deploy with, and for teaching me the inner workings of an outbreak response and how to work effectively in the WHO bureaucracy. Thanks also to Dr Zimmerman for ongoing contact and stimulating discussions about public health. Huge thanks to my academic supervisor, Dr Katrina Roper for preparing and supporting me during the deployment. It made the whole experience seem possible and provided an invaluable stability during the time in country. Thank you to Professor Martyn Kirk and the ARM network members for putting my name forward to the WHO, and to Dr Anthony Stewart at the WHO for selecting me to be part of the team.

I would like to acknowledge the Fijian WHO Office for their warm welcome and their assistance in the mission. In particular, the direct operating contact at the WHO office, Asaeli Raikabakaba, provided valuable guidance and mediated contacts essential to the successful work. The staff at CWMH, particularly Sister Susanna and Dr Ravi Naidu, for their daily assistance in navigating the hospital and arranging interviews with people and providing helpful clarifications of hospital processes. Finally, I would like to acknowledge the support of the Permanent Secretary Philip Davies at the MOHMS and his commitment to the investigation and translation of the findings and recommendations.



Figure 6 Sister Susana, head nurse of IPC team together with Dr Lyman. Our colleague from the Fiji WHO office, Asaeli Raikabakaba, together with Dr Lyman and myself.

MAE core activity requirements

The MAE core activity requirements fulfilled in this project was: Conduct an outbreak investigation

APPENDIX 2A – Technical report: *Acinetobacter baumannii* outbreak in the NICU at the Colonial War Memorial Hospital, Suva, Fiji, December 2016 – July 2017

The report was written on behalf of WHO by the outbreak response team at the conclusion of the GOARN mission.



ACINETOBACTER BAUMANNII OUTBREAK IN NICU AT THE COLONIAL WAR MEMORIAL HOSPITAL SUVA, FIJI, DECEMBER 2016 – JULY 2017

Technical report

11 July 2017 – 9 August 2017

Authors:
Dr Peta-Anne Zimmerman
Dr Meghan Lyman
Dr Patiyan Andersson

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LIST OF ABBREVIATIONS

AMS	Antimicrobial stewardship
CHW	Children's ward
CSF	Cerebrospinal fluid
CSSD	Central sterilizing supply department
CSU	Catheter specimen of urine
CVC	Central venous catheter
CWMH	Colonial War Memorial Hospital
DoA	Date of admission
DoB	Date of birth
DoFPS	Date of first positive specimen
ETT	Endotracheal tube
FPBS	Fiji Pharmaceutical and Biomedical Services
GOARN	Global Outbreak Alert and Response Network
HAI	Healthcare associated infection
ICC	Infection Control Committee
IPC	Infection prevention and control
IPCP	Infection prevention and control program
MOHMS	Ministry of Health and Medical Services
MDRAB	Multi drug resistant <i>Acinetobacter baumannii</i>
MDRO	Multi drug resistant organism
MDU-PHL	Microbiological Diagnostic Unit Public Health Laboratory
NICU	Neonatal intensive care unit
OGT	Orogastric tube
OT	Operating Theatre
PICU	Paediatric intensive care unit
SCM	Supply chain management
SXT	Trimethoprim- sulfamethoxazole
UVC	Umbilical venous catheter
WPRO	Western Pacific Regional Office of WHO
WHO	World Health Organization

MISSION BACKGROUND

The Fiji Ministry of Health and Medical Services (MOHMS) requested the support of WHO to investigate 12 neonatal intensive care unit (NICU) patients at the Colonial War Memorial Hospital (CWMH) in Suva with *Acinetobacter baumannii* resistant to all tested antibiotics (referred to as AB investigation strain in this report). The 12 cases were reported by the MOHMS as having occurred in two clusters from 13 December 2016 – 26 February 2017 and 27 May – 23 June 2017. The AB investigation strain was isolated in the blood or cerebrospinal fluid (CSF) samples from these patients, all of whom died.

The purpose of the Global Outbreak Alert and Response Network (GOARN) mission was to assist with the epidemiological investigation of the outbreak of multi-drug resistant *A. baumannii* (MDRAB) in the NICU at the CWMH. A review of the infection prevention and control (IPC) practices at the CWMH and hospitals in Lautoka and Labasa was to be conducted at the same time as requested by the MOHMS.

TERMS OF REFERENCE

These are the specific terms of reference for the mission:

Outbreak investigation

1. Literature review of published and/or unpublished data and studies that will assist with collection of information relevant to the current review of MDRAB cases in CWMH.
2. Review the case records and line listing of the cases from the two recent NICU clusters, and collect any additional data needed for the epidemiological investigation
3. Conduct a retrospective audit of sterile site infections among admissions to NICU at CWMH since Jan 2015
4. Review the surveillance system for health care associated infections at CWMH and specifically in NICU and Paediatric Intensive Care Unit (PICU)
5. If required, extend these investigations to adult Intensive Care Unit (ICU).

Review of Infection Prevention and Control (IPC) practices and antimicrobial stewardship

1. Review current IPC policy and audit IPC practices at CWMH, with a focus on NICU and other high dependency wards
2. Conduct a retrospective review of restricted antibiotics usage and prescribing practices
3. Identify any risks for the spread of MDRAB posed by engineering controls¹, IPC policies and procedures, staff movements, work practices in NICU and other high dependency wards
4. In collaboration with the hospital pharmacy, review supply chain management of essential drugs, materials and supplies for antimicrobial stewardship and good IPC practice
5. Review the current Terms of Reference, membership and procedures of the IPC Committee
6. Conduct ward visits and interview CWMH staff and other key informants

¹ Engineering controls of the physical environment aim to reduce the concentration of infectious agents in the environment and the likelihood of their spread. They include, but are not limited to, the physical layout of the facility, adequate environmental ventilation, the spatial separation between patients, and facilities for hand washing and hand hygiene.

7. Conduct training and presentations to key health workers including the CWMH IPC Committee members
8. Interview World Health Organization (WHO) technical staff, including verification/validation of collated information
9. Synthesise and summarise information gathered in a detailed report, including key conclusions and recommendations
10. Provide a debriefing to the CWMH IPC Committee and senior management, Ministry of Health and Medical Services senior executives, and WHO

Amendments to Terms of Reference (TORs):

On 13 July 2017, the TORs were amended following a discussion between WHO and the consultants with the aim of clarifying the intent and feasibility of activities described in the original TORs. For example, the original TOR #3 was changed from "Conduct a retrospective audit of sterile site infections in patients admitted to NICU at CWMH since Jan 2015" to that defined in TOR #3 below. What was in and out of scope of TOR #4 was also better defined. These changes did not affect either the overall intent or focus of the GOARN mission.

Outbreak investigation:

TOR #3. Conduct a count of the number of *Acinetobacter baumannii* and *Klebsiella pneumoniae* infections in blood stream infections (and possibly other sterile sites if such data is readily available) in NICU since Jan 2015, to establish a baseline for the current NICU outbreak.

TOR #5. As required, extend the investigations to count *Acinetobacter baumannii* and *Klebsiella pneumoniae* infections in the PICU and ICU.

Review of IPC practices and antimicrobial stewardship

TOR #4. The team will not be able to do a detailed review of supply chain management (SCM) of essential drugs and antimicrobial stewardship (AMS) but will conduct interviews with pharmacists and Fiji Pharmaceutical and Biomedical Services Centre (FPBS) staff in order to understand the current procurement and supply system in place. There are currently two Australian pharmacists working on AMS with FPBS and CWMH over a 12 month period, and as such are better placed to address these issues than the GOARN team during the short mission.

GOARN TEAM

Name	Dr Peta-Anne Zimmerman
Institution	Griffith University/Gold Coast Hospital and Health Service/Menzies Health Institute, Queensland/Australasian College for Infection Prevention and Control
Role in team	Infection Prevention and Control Consultant Conduct review of IPC practices at CWMH, Lautoka and Labasa hospitals Training of IPC team
Location	Suva, Lautoka, Labasa
Time in country	12 July - 24 July 2017

Name	Dr Meghan Lyman
Institution	US Centers for Disease Control and Prevention

Role in team	Epidemiologist Conduct epidemiological investigation of NICU outbreak at CWMH Assist in review of IPC practices at CWMH Training of IPC team and NICU staff
Location	Suva
Time in country	11 July - 3 Aug 2017

Name	Dr Patiyan Andersson
Institution	National Centre for Epidemiology and Population Health, Australian National University
Role in team	Epidemiologist Conduct epidemiological investigation of NICU outbreak at CWMH Assist in review of IPC practices at CWMH Assist in training of IPC team and NICU staff
Location	Suva
Time in country	12 July - 9 Aug 2017

OBJECTIVES

Overall objectives of the mission:

- Outbreak investigation
- Review of IPC practices and antimicrobial stewardship

Outputs:

- MDRAB situation analysis and audit report
- Key health workers and IPC Committee members trained on IPC practices and outbreak interventions
- Final technical report with key findings and recommendations

GOARN TEAM ACTIVITIES

Summary of GOARN team activities (**Annexes 1 and 2** provide the details)

- Epidemiological investigation of outbreak in NICU at CWMH (M. Lyman and P. Andersson)
- Review of Infection Prevention and Control capacity in Fiji in collaboration with relevant IPC teams (Lead by P-A. Zimmerman, assisted at CWMH by M. Lyman and P. Andersson)
- Provision of guidance at divisional hospital and national levels (P-A. Zimmerman, M. Lyman and P. Andersson)
- Ensuring key stakeholder agreement to IPC implementation work plan (P-A. Zimmerman, M. Lyman and P. Andersson)
- Workshops with IPC team at CWMH (Lead by P-A. Zimmerman, assisted by M. Lyman and P. Andersson)
- Collaboration with key stakeholders and Infection Control Committees at each facility
- Provision of locally relevant feedback at each facility (P-A. Zimmerman)
- Review, evaluation, and reporting of IPC at Lautoka Hospital (P-A. Zimmerman)
- Review, evaluation, and reporting of IPC at Labasa Hospital (P-A. Zimmerman)
- Review, evaluation, and reporting of IPC at CWMH (P-A. Zimmerman, M. Lyman and P. Andersson)
- Workshops conducted at CWMH with IPC team (P-A. Zimmerman, M. Lyman and P. Andersson)
- Development of workplan for IPC implementation with CWMH IPC team (P-A. Zimmerman)
- On-site guidance on improving IPC practices at CWMH NICU (M. Lyman)

- Development of workplan for improving IPC practices in NICU at CWMH (M. Lyman)
- Development of electronic databases and analysis components for ongoing MDRO surveillance with IPC team (P. Andersson)
- Briefing of Permanent Secretary of Health and Ministry of Health and Medical Services (MOHMS) partners (P-A. Zimmerman, M. Lyman and P. Andersson)
- Development of reports documenting investigation (P-A. Zimmerman, M. Lyman and P. Andersson)

ACKNOWLEDGEMENTS

Many thanks to all who organised this mission in the WHO HQ GOARN Operations Support Team, WHO South Pacific Office | Division of Pacific Technical Support, WHO Western Pacific Regional Office (WPRO) and the Ministry of Health and Medical Services of Fiji. Special thanks to the in-country counterparts who we respect and acknowledge for their expertise and assistance.

We would also like to acknowledge the support from our home institutions, Griffith University, US Centers for Disease Control and Prevention and the Australian National University for their invaluable input during the course of the investigation, and the Microbiological Diagnostic Unit Public Health Laboratory, Peter Doherty Institute for Infection and Immunity, University of Melbourne which conducted the full genome sequencing of the clinical specimens.

1. EXECUTIVE SUMMARY

From December 2016 to June 2017, the Colonial War Memorial Hospital (CWMH) in Suva, Fiji, identified 12 neonatal intensive care unit (NICU) patients with *Acinetobacter baumannii* resistant to all tested antibiotics isolated from blood or cerebrospinal fluid (CSF) samples (referred to as the AB investigation strain throughout this report). All 12 patients died. These 12 case-patients were reported by CWMH as having occurred in two clusters from 13 December 2016 – 26 February 2017 and 27 May – 23 June 2017. The purpose of the GOARN mission from 11 July – 9 August 2017 was to assist with the epidemiological investigation of the outbreak and to conduct a review of the infection prevention and control (IPC) practices at the CWMH and hospitals in Lautoka and Labasa as requested by the Fiji Ministry of Health and Medical Services (MOHMS).

The epidemiological and laboratory investigations revealed an *A. baumannii* strain resistant to all tested antibiotics including meropenem, which was more common in the NICU than other paediatric wards. Along with a rise in the number of patients testing positive for this strain, there had been an increase in invasive infections and deaths among these patients.

A review of admissions to the NICU and paediatric ICU (PICU) from 1 December 2016 – 31 July 2017 identified two additional patients with the AB investigation strain considered part of the second cluster, bringing the total to 14 patients with this strain of *A. baumannii* in blood or CSF specimens (sterile site infections). Nine blood culture isolates and 5 cerebrospinal fluid isolates from 11 of these patients were sent to the Microbiological Diagnostic Unit Public Health Laboratory, University of Melbourne in Australia for whole genome sequencing, with 3 patients having samples from both sites sent for testing. Multilocus sequence typing (MLST) of the isolates showed 14 belonging to sequence type 2 (ST2) genotype but two different sub-groups clustering by sample collection date based on whole genome sequencing, with one group evolving from the other.

In addition, 20 patients tested positive for the AB investigation strain on specimens collected from sites other than blood and CSF. While these case-patients were very ill on admission to the ICU, many did not have cultures positive for this strain on admission. While respiratory conditions and ventilator support were observed for nearly all for case-patients, many of the other characteristics and exposures of these case-patients varied.

In collaboration with the Infection Control Committees and staff of the Colonial War Memorial, Lautoka, Labasa Hospitals, an evaluation of IPC policies, practices and infrastructure was conducted at each facility using a standardised assessment tool. Findings indicated systemic infrastructure issues not conducive to support effective and consistent IPC practices due to the unreliable supply of: single patient use respiratory equipment leading to inappropriate and unsafe reprocessing of patient care items; personal protective equipment; intravenous fluids, medication and associated equipment; and hand hygiene equipment and supplies. Associated with, but not limited to these findings is: the need for greater leadership support; inconsistent cleaning methodologies; and non-specific healthcare associated infection and hand hygiene surveillance. The findings of the current investigation are consistent with reports from similar outbreaks spanning 10 years.

The varied exposures of these case-patients and the multiple infection control gaps identified suggest that cross-contamination likely resulted in multiple sources of transmission within the ICUs, rather than one point-source of transmission of the *A. baumannii* investigation strain. Improving implementation of IPC practices, especially hand hygiene, contact precautions, environmental cleaning, and equipment decontamination, will prevent ongoing transmission of *A. baumannii* and other organisms in the paediatric

ICUs and hospital-wide. An appropriate and uninterrupted supply of personal protective equipment, other IPC equipment and supplies, and the equipment and consumables needed for individual patient care, is essential for good IPC practice.

It is recommended that there be a consistent commitment, not only at a NICU or facility level but at a whole of health service level, to support and strengthen IPC practice in the delivery of safe care through appropriate supply management and strong and consistent leadership in IPC. A work plan to this end was developed in collaboration with the MOHMS, Infection Control Committees, and staff identifying clear and achievable short, medium, and long-term goals for remediation across the whole health sector. In order to effect long term and sustainable improvements IPC practices, linkage with other health systems strengthening approaches is needed.

2. INTRODUCTION

Healthcare-associated infections (HAI) due to *A. baumannii*, a highly resilient bacterium capable of surviving for extended time on surfaces, are often associated with invasive devices or contaminated environment. Outbreaks of multi-drug resistant organisms (MDROs) in NICUs occur in a patient population that does not have many of the risk factors often associated with MDROs, including prior antibiotic use, hospital admission, or other exposure to healthcare.

There are few publications describing the antimicrobial resistance in Fiji hospitals, but data published thus far have described a high prevalence of *A. baumannii*. Naidu *et al* investigated nosocomial infections in the ICU at CWMH during 2011-12, and described the most common species in respiratory and blood specimens which were *Klebsiella pneumoniae* and *A. baumannii*.¹ Mortality was noted to be very high among these patients, and 55% of those who died had a blood stream infection. Kumar *et al* studied bacterial isolates from neonates with suspected sepsis at the CWMH in 2012, and found that *E. coli*, *K. pneumoniae* and *A. baumannii* were the most common bacteria isolated.² Mortality was highest in patients with bacteria isolated from blood or from an endotracheal tube.

CWMH is the largest hospital in Fiji, with 514 beds and often operating at full occupancy. CWMH provides the only NICU in the central division of Fiji (population of 342,000 in 2007) with 30 beds and approximately 500 admissions per year and also serves as the referral centre for Fiji. CWMH has 550-850 childbirths per month, but has noticed a recent increase in the number of deliveries.

The NICU consists of 4 wards: one designated for the most severely ill patients; one designated as a step-down unit for slightly less severely ill patients; one to receive neonates from outside hospitals awaiting screening culture results prior to NICU admission; and one for preterm or underweight (but otherwise well) neonates and their mothers. There is a total 9-10 nurses staffing these 4 NICU rooms per shift. While equipment is designated for NICU use, there is some equipment that may be occasionally shared with other paediatric units (i.e. ventilators and infusion pumps can be shared with PICU).

After identifying a potential outbreak of 12 patients with *A. baumannii* in blood or CSF in the CWMH NICU from December 2016 to June 2017, the MOHMS requested assistance from WHO to conduct an epidemiological investigation. The CWMH Infection Control Committee identified the infections as having occurred in two distinct clusters from clusters from 13 December 2016 – 26 February 2017 (7 cases) and 27 May – 23 June 2017 (5 cases). The objectives of the investigation were to identify potential risk factors or exposures associated with these infections and simultaneously conduct an infection control assessment of the three referral hospitals (CWMH, Lautoka and Labasa Hospitals) to identify any gaps in IPC.

Subsequent to a request for assistance to WHO-DPS, a GOARN team was assembled and deployed to perform these two objectives in parallel. In addition, WHO coordinated with the Microbiological Diagnostic Unit Public Health Laboratory, Peter Doherty Institute for Infection and Immunity, University of Melbourne, to conduct whole genome sequencing of *A. baumannii* isolates and carry out a phylogenetic analysis.

3. METHODS AND DATA SOURCES

3.1 EPIDEMIOLOGICAL INVESTIGATION

3.1.1 Case finding

Following the identification of the first cases of multi-drug resistant *A. baumannii* cases in December 2016, screening specimens from blood, urine, and rectal swabs have been collected from all patients on admission to NICU. Additional specimens are collected as clinically indicated for suspected infection during the admission.

The CWMH microbiology laboratory performs culturing, isolation, and antimicrobial susceptibility testing of *A. baumannii*. The panel of antibiotics routinely tested for *A. baumannii* includes Ampicillin, Doxycycline, Chloramphenicol, Trimethoprim-sulfamethoxazole (SXT), Gentamycin, Cephalothin, Ceftriaxone, Ciprofloxacin, Amikacin and Meropenem, but Colistin can be tested upon clinician request. If the microbiology lab detects any isolate resistant to 4 of 5 first-line antibiotics (Ampicillin, Chloramphenicol, SXT, Gentamycin or Cephalothin), it characterizes it as a multidrug-resistant organism (MDRO) and alerts the IPC team who documents these results in a MDRO log.

To conduct case-finding and establish a baseline of the occurrence of multidrug-resistant *A. baumannii* in the CWMH NICU, the GOARN team reviewed the IPC team MDRO log for paediatric patients to identify all specimens positive for *A. baumannii* collected from 1 January 2015 to 31 July 2017. This information was used to determine whether there was an increase in patients with positive specimens and develop a case definition used to gather more detailed patient information.

3.1.2 Case definitions

For this investigation, the GOARN team developed the following case definitions:

- An invasive case was defined as a blood or CSF specimen positive for the AB investigation strain (resistant to all tested antibiotics) collected from a patient in a paediatric ICU (NICU or PICU) from 1 December 2016 to 31 July 2017.
- A less-invasive case was defined as a specimen other than blood or CSF which was positive for the AB investigation strain based on an identical antibiotic sensitivity profile collected from a patient in a paediatric ICU (NICU or PICU) from 1 December 2016 –31 July 2017. This case definition does not include clinical signs or symptoms and includes both patients that qualify as being infected and colonized.²

3.1.3 Epidemiological analysis

Epidemiological data were collected from invasive and less-invasive case-patients' medical charts. Data were collected on patient demographics, illness information (e.g. symptoms, date of illness or sepsis onset, use of inotropes, procedures, use of total parenteral nutrition (TPN), blood transfusions), invasive devices, (central catheters, urinary catheters, mechanical ventilation), clinical outcomes, antibiotic treatment and laboratory specimen results. For neonates, data were also collected on perinatal and delivery history (e.g. type of delivery, delivery complications, evidence of prolonged rupture of the membranes, requirement of positive pressure ventilation or resuscitation at delivery), neonate information (e.g. gestational age,

² Colonization is the culture of the AB investigation strain from a body surface specimen, e.g. skin, mouth, rectum or airway, without causing clinical evidence of disease in the patient.

birthweight, diagnoses or comorbidities, feeding), and maternal information (e.g. antenatal care, comorbidities, prior admissions or antibiotics). Most of the maternal charts were unavailable so epidemiological data on the case-patients' mothers or prenatal/perinatal exposures were limited.

3.1.4 Environmental sampling

Environmental sampling was conducted in June by CWMH during the second cluster of cases, including samples from a sink, ventilator, TPN, and distilled water, but details about how these samples were collected were not available. Environmental testing of TPN and distilled water were subsequently repeated. All environmental samples were processed by the microbiology laboratory, but methods specific for environmental sampling were not used (i.e. methods to compensate for low bacterial load or 'destructive sampling' recommended to test biofilms as sources of transmission).

3.1.5 Whole genome sequencing

Fifteen blood or CSF samples from the 12 patients initially identified as part of the outbreak were sent to the Microbiological Diagnostic Unit Public Health Laboratory (MDU-PHL) at the University of Melbourne, Australia, for whole genome sequencing to assess relatedness of these strains. Three patients had both blood and CSF collected.

3.2 INFECTION PREVENTION AND CONTROL EVALUATION

Description of assessment tool (Annex 3)

The purpose of the evaluation at the CWMH, Lautoka and Labasa Hospitals using the Infection Prevention and Control Programme Evaluation tool (Annex 3) was to provide an assessment of the status of the infection prevention and control program (IPCP) and healthcare IPC activities in a given healthcare facility. The assessment tool used does not consider the risk of individual patients or specific cases nor other aspects related to care outside of surveillance, prevention, and control of health care associated infections (HAI). It should not be considered an accreditation system; however, the tool may be used internally as a continuous quality improvement activity or as an external review tool by appropriately qualified IPC technical consultants.

This evaluation tool is an adaptation of the “Nosocomial Infection Program Rapid Evaluation Guide” created by the Pan American Health Organization and the “Audit Tools for Monitoring Infection Control Standards” from the Infection Control Nurses Association. To comprehensively evaluate an IPCP it is essential to examine both theoretical and practical aspects. This tool combines those most essential standards of an IPCP including how policy and guidelines translate into the healthcare environment and patient care.

The evaluation provides information on a number of aspects that should be included in an IPCP. These aspects have been organized in eight areas that include similar topics. In each area, some components considered being essential in a good program have been selected. In each component, standards have been established to best describe an acceptable component. Then, indicators have been established so that the presence of the standards could be considered objectively. A single standard may have several indicators and a single component may have several standards. Space has been provided for each indicator to enter what source was used to verify its presence.

A list of suggested verifiers is provided. These simply offer orientation or sources of information for the evaluator/s that can be used to determine whether a certain indicator is present. The evaluator/s can use other methods to establish the presence of indicators. A glossary is also provided to assist with clarification

of terms used. According to this tool, evaluation of the IPCP is based solely on the presence of indicators. Some of these indicators can only be assessed by observation of the clinical situation. Full methodology on how the evaluation tool is applied can be found in **Annex 3**.

Infection prevention and control program evaluations were conducted at Lautoka, Labasa and CWMH. Feedback from these evaluations was provided to each facility verbally to the senior staff and Medical Superintendents, with a completed copy of the evaluation (**Annexes 4-6**). Workshops were conducted at the CWMH with the Infection Prevention and Control team on:

1. Healthcare associated surveillance strategies, with a targeted surveillance plan produced (see recommendations in Section 7)
2. Infection control liaison/link nurse program implementation plan
3. Development of short, medium, and long-term goals for the IPC programs throughout Fiji (see Section 7). This was presented to the Permanent Secretary of Health and to MOH key stake holders (presentation slides included as **Annex 9**).

4. RESULTS

4.1 EPIDEMIOLOGICAL INVESTIGATION

4.1.1 Case finding

There was a total of 173 MDRAB isolates collected from 127 patients from 1 January 2015 to 31 July 2017. The frequency of MDRAB isolates per month demonstrates an increase starting in December 2016 for both the NICU and PICU (**Figure 1**). Several different AST patterns were identified, including ones that were sensitive to meropenem (n=54), ones that were resistant to meropenem but sensitive to other antibiotics (n=15), and ones that were resistant to all antibiotics tested (AB investigation strain, n=102). For two isolates the sensitivity to meropenem was not available.

Figure 1 demonstrates differences in the distribution of the different strains between the paediatric ICUs (NICU and PICU). *A. baumannii* isolates sensitive to meropenem were more common in the PICU, while the highly resistant AB investigation strain was more common in the NICU. Sporadic specimens collected from NICU patients with the AB investigation strain indicate that it occurred as early as January 2015. The number of all specimens, and specifically blood and CSF specimens, positive for the AB investigation strain, increased from December 2016; increased testing until July 2017 in response to the outbreak may account for some of the increase observed. It should be noted that the PICU specimens positive for the AB investigation strain were collected during the same time as the NICU outbreak. The children's ward had very few *A. baumannii* isolates (n=11), all but one of which were sensitive to meropenem. In December 2015, one sample showed multidrug resistance.

A total of 40 patients were identified by review of the MDRO log book using the investigation case definitions; 33 patients from NICU and 7 patients from PICU. Among the 40 case-patients, the GOARN team was unable to locate the patient charts for 2 NICU and 4 PICU patients, resulting in a total of 34 patients (31 NICU and 3 PICU) included in the epidemiological analysis. **Table 1** presents the line listing of the 34 case-patients for whom clinical data were available, of whom 14 were classified as invasive cases and 20 as less-invasive cases. One case-patient included in the analysis was still in the NICU at the time of writing the report.

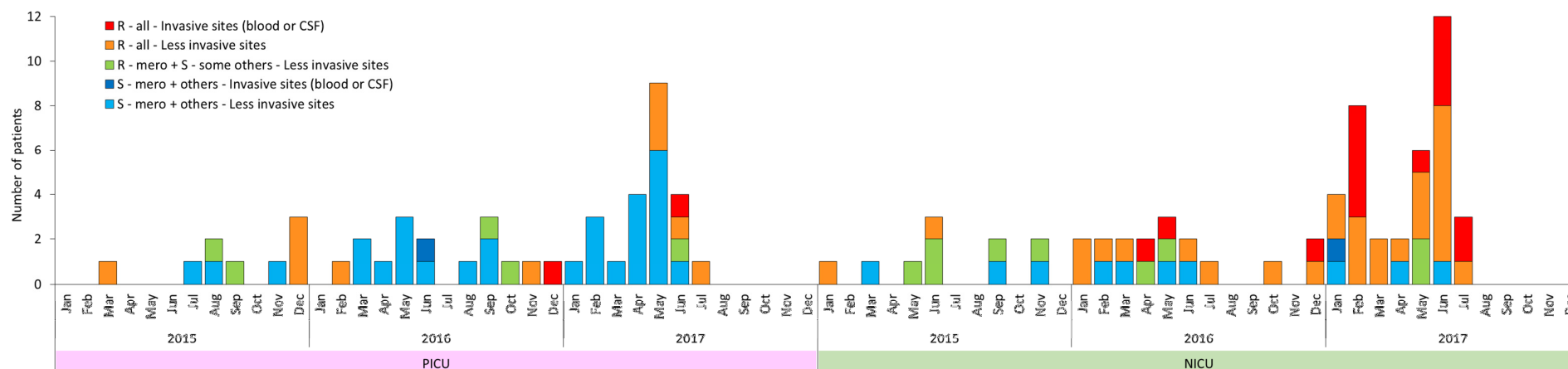
When the case definition was applied to the patients originally identified as part of the outbreak, one of these patients did not qualify as an invasive case because s/he had an *A. baumannii* strain sensitive to

several antibiotics including meropenem isolated from the blood; however, the AB investigation strain isolated from a longline tip.

From 1 December 2016 to 31 July 2017, there were 293 admissions to NICU and 164 admissions to PICU, meaning that the proportion of patients with the AB investigation strain was 10.6% for NICU and 1.8% for PICU. The invasive cases were observed to form two clusters from over the outbreak period from 13 December 2016 to 23 June 2017. However, as shown in **Table 2**, there were patients with the AB investigation strain present in the NICU throughout the outbreak period.

4.1.2 Microbiological description of the cases

Among the 34 case-patients, a total of 74 specimens were positive for the AB investigation strain. The specimen types for individual patients can be found in **Table 1**. The most common specimen type positive for AB investigation strain was endotracheal tubes tips or aspirates (29/78, 37%) followed by blood samples (12/78, 15%).

Figure 1 - Patients with specimen positive for *Acinetobacter baumannii* in paediatric wards at the CWMH, from 1 January 2015 – 31 July 2017

Only the most invasive positive specimen is shown for each patient, unless two specimens have isolates with different antimicrobial resistance profiles, in which case both are included. Patients with the AB investigation strain are shown in red (invasive sites) and orange (less-invasive sites); patients with an *A. baumannii* resistant to meropenem, but sensitive to some other antibiotics tested are labelled in green; and patients with an *A. baumannii* sensitive to most antibiotics, is shown in dark blue (invasive sites) and light blue (less invasive sites). The NICU ward is dominated by the AB investigation strain, while the PICU and CHW (data not shown) are dominated by sensitive *A. baumannii* strain(s).

Table 1 – Specimens positive for *A. baumannii* investigation strain by case patient

Date of birth (DoB), date of admission (DoA), date of first positive specimen (DoFPS), ward, and type and number of specimen collected from the 34 case-patients, December 2016-July 2017. The type of the first positive specimen is marked in yellow, and in the case of multiple positive specimen on the first day, all are indicated for that patient. Samples subjected to whole genome sequencing (WGS) are marked in bold red text (patient NV had a blood samples sent for WGS, but this strain was a sensitive strain and therefore not included in the table).

Case ID	Ward	Date of birth	Date of admission	Date of first positive specimen	MLST Type	Group	Blood culture	Chest drain	CSF	Urine	Central venous catheter tip	Endotracheal tube tip/ aspirate	Long line tip	Oro-gastric tube	Peritoneal drain	Pus swab	Rectal swab	Umbilical catheter tip	Total
1	NICU	03-Dec-16	03-Dec-16	13-Dec-16	2	1	1					3							4
2	NICU	16-Dec-16	16-Dec-16	26-Dec-16	NT					1		1							2
3	NICU	29-Dec-16	30-Dec-16	09-Jan-17	NT			1		1		1							3
4	NICU	04-Jan-17	04-Jan-17	13-Feb-17	2	1			1										1
5	NICU	03-Jan-17	04-Jan-17	10-Jan-17	NT								1						1
6	NICU	07-Feb-17	07-Feb-17	15-Feb-17	NT							1							1
7	NICU	12-Feb-17	12-Feb-17	15-Feb-17	2	1	1		1			1	1						4
8	NICU	18-Feb-17	18-Feb-17	23-Feb-17	2	1			1			1						1	3
9	NICU	20-Feb-17	20-Feb-17	23-Feb-17	2	1	1		1			1	1						4
10	NICU	21-Feb-17	22-Feb-17	24-Feb-17	NT							1						1	2
11	NICU	25-Feb-17	25-Feb-17	26-Feb-17	2	1	1										1		2
12	NICU	07-Mar-17	11-Mar-17	15-Mar-17	NT					1		3		1			1		6
13	NICU	15-Mar-17	15-Mar-17	16-Mar-17	NT							1							1
14	NICU	27-Mar-17	28-Mar-17	02-Apr-17	NT							1							1
15	NICU	16-May-17	16-May-17	24-May-17	NT					1		1							2
16	NICU	25-May-17	25-May-17	27-May-17	2	2	1		1			2						1	5
17	NICU	26-May-17	26-May-17	30-May-17	NT							1						1	2
18	NICU	28-May-17	28-May-17	01-Jun-17	NT							1							1
19	NICU	29-May-17	29-May-17	02-Jun-17	2	2	1					1							2

Case ID	Ward	Date of birth	Date of admission	Date of first positive specimen	MLST Type	Group	Blood culture	Chest drain	CSF	Urine	Central venous catheter tip	Endotracheal tube tip/ aspirate	Long line tip	Oro-gastric tube	Peritoneal drain	Pus swab	Rectal swab	Umbilical catheter tip	Total
20	NICU	04-Jun-17	04-Jun-17	20-Jun-17	NT								1						1
21	NICU	07-Jun-17	07-Jun-17	12-Jun-17	2	2	1					2							3
22	NICU	08-Jun-17	08-Jun-17	09-Jun-17	2	2	1	1											2
23	NICU	08-Jun-17	08-Jun-17	08-Jun-17	NT							1							1
24	NICU	09-Jun-17	09-Jun-17	25-Jun-17	NT							1							1
25	NICU	13-Jun-17	13-Jun-17	21-Jun-17	NT					1		1	1						3
26	NICU	14-Jun-17	14-Jun-17	20-Jun-17	NT					1		1						1	3
27	NICU	16-Jun-17	17-Jun-17	21-Jun-17	NT							1							1
28	NICU	22-Jun-17	22-Jun-17	23-Jun-17	2	2	1					1							2
29	NICU	23-Jun-17	24-Jun-17	01-Jul-17	NT							1							1
30*	NICU	17-Jul-17	17-Jul-17	21-Jul-17	NT		1												1
31	NICU	18-Jul-17	18-Jul-17	20-Jul-17	NT		1		2										3
32	PICU	18-Dec-15	19-Nov-16	08-Dec-16	NT										1				1
33	PICU	23-Jul-06	03-May-17	06-May-17	NT							1							1
34*	PICU	01-May-15	14-May-17	20-Jun-17	NT		1				1					1			3
Total							12	2	7	6	1	29	5	1	1	1	2	5	74

MLST: Multilocus sequence typing

NT: Not tested

CSF: Cerebrospinal fluid

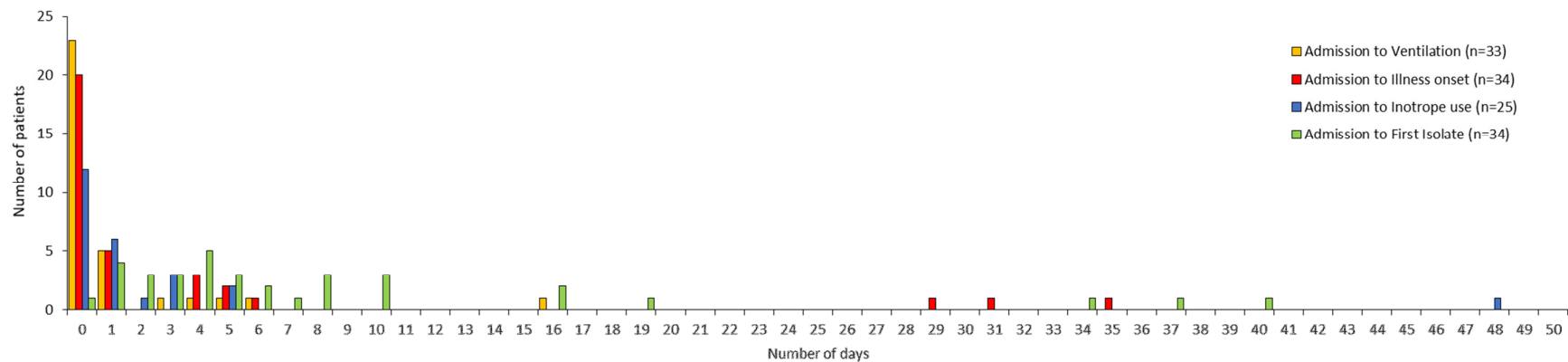
*Two patients (Cases 30 and 34) were still admitted at the conclusion of the investigation.

Table 2 - Admission timeline of patients by week, 3 December 2016 – 31 July 2017

Invasive cases are shown in red; less-invasive cases are shown in orange. "X" indicates the first AB investigation strain positive specimen.

Case ID	Ward	Week in 2016										Week in 2017																												
		46	47	48	49	50	51	52	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	
1	NICU			X																																				
2	NICU						X																																	
3	NICU									X																														
4	NICU									X																														
5	NICU														X																									
6	NICU													X																										
7	NICU														X																									
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31	NICU																																				X		>>>	
32	PICU					X																																		

Figure 2 - Length of stay from admission to ventilation, illness onset, inotrope use and first AB investigation strain positive specimen for case-patients



4.1.3 Epidemiological description of the cases

The frequency of specific epidemiological characteristics for invasive and less-invasive cases can be found in **Table 3**. Only one of the invasive case-patients and two of the less-invasive case-patients were older than 2 months of age and were admitted to the PICU; all others were admitted to the NICU.

Ten (71%) of invasive cases and 19 (95%) less-invasive cases were iTaukei. Most of the invasive (8, 57%) and non-invasive (14, 70%) cases had a respiratory diagnosis as the reason for admission to the ICU. All 14 of the invasive cases (100%) and all but one of the non-invasive cases (19, 95%) had mechanical ventilation prior to the positive specimen being collected. These frequencies were reported to be much higher than estimates by paediatricians, stating that 60% of NICU and 40% of PICU require mechanical ventilation. Positive-pressure ventilation within 24 hours of admission was very common for invasive (13, 93%) and non-invasive cases (16, 80%).

Central lines were also common, especially among the invasive cases. While blood transfusions can also be common among PICU/NICU patients, all 14 invasive cases had a blood transfusion prior to the first positive specimen, as did many of the less-invasive cases (14, 70%).

Case-patients with recent births (<2 months old), were delivered by both caesarean section and vaginal delivery. Only one invasive case and one less-invasive case were delivered outside of CWMH, both of whom had a specimen negative for AB investigation strain on admission.

The gestational age of the neonatal case-patients at delivery varied, but only 2 (15%) invasive cases and 3 (17%) less-invasive cases were considered very preterm. Similarly, while the birthweights of the neonates at delivery varied, 13 (72%) of less-invasive cases were normal birthweight, while 3 (23%) invasive cases were normal birthweight.

While it was uncommon for cases to be very preterm or very low birth weight, case patients often had other medical problems resulting in their admission to the NICU. Most cases did not have other known risk factors for infection such as premature rupture of membranes (PROM) or meconium aspiration.

As shown in Table 3, endotracheal tube tips were the most common specimen type positive for the AB investigation strain in both invasive (8, 57%) and less-invasive cases (17, 85%). Twelve (86%) invasive cases had multiple positive samples, but this was uncommon for less-invasive cases (7, 35%). It was infrequent for invasive case-patients (3, 21%) and less-invasive case-patients (3, 15%) to have their first specimens positive for the AB investigation strain collected within a day of ICU admission, and even fewer patients had a positive specimen from the date of admission.

Table 3 - Demographic and clinical characteristics of the 34 case-patients, 1 December 2016 - 31 July 2017

Characteristics	All case-patients	Invasive case-patients ¹	Less-invasive case-patients ²
General characteristics	n=34	n=14	n=20
Ethnicity			
iTaukei	29 (85%)	10 (71%)	19 (95%)
Fijians of Indian descent	5 (15%)	4 (29%)	1 (5%)
Age			
< 2 months	31 (91%)	13 (93%)	18 (90%)
2 months to <6 months	0 (0%)	0 (0%)	0 (0%)
6 months to <1 year	1 (3%)	0 (0%)	1 (5%)
>1 year	2 (6%)	1 (7%)	1 (5%)
Ward			
NICU	31 (91%)	13 (93%)	18 (90%)
PICU	3 (9%)	1 (7%)	2 (10%)
Microbiology Results			
Specimen type			
Blood	12 (35%)	12 (88%)	N/A ²
CSF	6 (18%)	6 (43%)	N/A ²
ETT	25 (74%)	8 (57%)	17 (85%)
First cultures collected positive for AB investigation strain	3 (9%)	0 (0%)	3 (15%)
First AB positive specimen collected on day of ICU admission	2 (6%)	0 (0%)	2 (10%)
First AB positive specimen collected within one day of ICU admission	6 (18%)	3 (21%)	3 (15%)
Multiple specimen positive for AB investigation strain	19 (56%)	12 (86%)	7 (35%)
Admission diagnoses			
Respiratory	22 (65%)	8 (57%)	14 (70%)
Birth defect	4 (12%)	1 (7%)	3 (15%)
Risk factors/Exposures			
Ventilation before positive culture	33 (97%)	14 (100%)	19 (95%)
PPV/ventilation within 24 hours of admission	29 (85%)	13 (93%)	16 (80%)
Central line before culture positive	27 (79%)	13 (93%)	14 (70%)
IV phlebitis before culture positive	4 (12%)	1 (7%)	3 (15%)
Inotropes	22 (65%)	9 (64%)	13 (65%)
TPN before culture positive	8 (24%)	4 (29%)	4 (20%)
Blood transfusion before culture positive	28 (82%)	14 (100%)	14 (70%)
Treatment			
Treated with meropenem	23 (68%)	11 (79%)	12 (60%)
Initiation of meropenem during last day of life	5 (15%)	4 (29%)	1 (5%)
Treated with colistin	12 (35%)	7 (50%)	5 (25%)
Initiation of colistin during last day of life	3 (9%)	2 (14%)	1 (5%)
Outcomes			
Death	23 (68%)	12 (86%)	11 (55%)

Characteristics	All case-patients	Invasive case-patients ¹	Less-invasive case-patients ²
Perinatal characteristics	n=31	n=13	n=18
Delivery type			
Caesarian section	12 (39%)	4 (31%)	8 (44%)
Vaginal delivery	19 (61%)	9 (69%)	10 (56%)
Delivery location			
CWM	29 (94%)	12 (92%)	17 (94%)
Outside hospital	1 (3%)	1 (8%)	0 (0%)
Home	1 (3%)	0 (0%)	1 (6%)
Gestational age			
Term	15 (48%)	4 (31%)	11 (61%)
Mod-late preterm	11 (35%)	7 (54%)	4 (22%)
Very preterm	5 (16%)	2 (15%)	3 (17%)
Birthweight			
Normal	16 (52%)	3 (23%)	13 (72%)
LBW	7 (23%)	5 (38%)	2 (11%)
VLBW	8 (26%)	5 (38%)	3 (17%)
Meconium in amniotic fluid on delivery	11 (35%)	4 (31%)	7 (39%)
Concern for meconium aspiration	7 (23%)	3 (23%)	4 (22%)
Premature ruptures of membranes (PROM)	7 (23%)	4 (31%)	3 (17%)

¹ Blood or CSF specimen; ² Specimen(s) other than blood or CSF only

The median time from admission to onset of illness was 0 days (range 0-35 days), with 59% of patients having onset of illness on the day of admission, as shown in Figure 2. However, the illness onset is not necessarily attributable to an *A. baumannii* infection and may reflect illness due to the patients' other medical conditions. Of the 25 patients requiring inotropes, the median length of time from admission to initiation of inotrope was 1 day (range 0-48 days). Inotropes were initiated on the day of NICU admission for 48% of these patients.

The median time between admission and the first positive *A. baumannii* specimen was 5 days (range 0-40 days), with 65% of patients having a positive isolate within the first week. All but one of the case-patients required ventilation during their admission, with a median of 0 days (range 0-16 days), and 70% of patients ventilated on the day of admission.

As seen in Table 3, eleven (79%) invasive cases and 12 (6%) less-invasive cases were treated with Meropenem, but treatment with Colistin was less common (7 [50%] invasive cases; 5 [25%] less-invasive cases). However, this does not reflect the appropriateness of antibiotic treatment or that several patients had the first positive samples collected by clinicians after death.

The case fatality rate among invasive cases was 86% (12 of 14 invasive case-patients) at the conclusion of the investigation, while death was less common among non-invasive cases (11 of 20 non-invasive case-patients, 55%). This is illustrated in **Figure 3**, which also includes patients admitted to the NICU before the outbreak. From this figure, it appears that there has been a sharp increase in both number of patients, and deaths of patients, with the AB investigation strain.

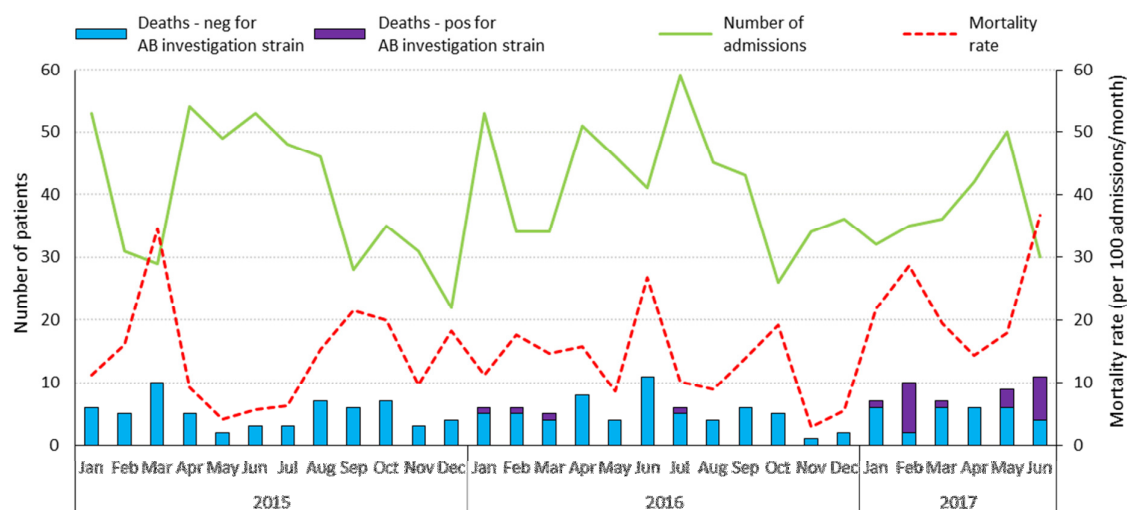
Figure 3 - Outcomes for NICU patients with the AB investigation strain isolated from invasive and less invasive sites, 1 January 2015 – 31 July 2017)



Patients who died are marked in solid bars, and patients who survived are marked with hashed bars. Only one positive specimen (the most invasive) is shown for each patient; red: invasive site; yellow: less-invasive site. Along with an increase in AB investigation strain positive specimens from invasive sites, there has been an increase in the number of deaths with positive specimens.

Although **Figure 4** shows that overall number of neonatal deaths in the NICU varied over time, the data suggests an increase in the proportion of patients positive for the *A. baumannii* investigation strain among those who died in 2017. The overall mortality rate increased from 1 December 2016 to 30 June 2017, with peaks occurring at the same time as the two clusters of invasive cases. The June 2017 mortality rate is at the highest level over the 30 month period since 1 January 2015.

Figure 4 – NICU admissions, number of deaths with and without the AB investigation strain and mortality rate per 100 NICU admissions, 1 January 2015 – 30 June 2017



While this investigation focused on the NICU because of high numbers of cases from the NICU, there were three PICU cases (two invasive cases and one less-invasive case) included in the analysis because they occurred during the same time as the NICU cases and may be epidemiologically related as some exposures (such as equipment) can be shared between these units. These PICU patients had unique hospital courses and exposures, often different than those of the neonates in the NICU. Two PICU cases had severe chronic medical problems and had a specimen positive for the AB investigation strain after long hospital stays (2-4 weeks). The other PICU case was transferred in a critical condition from an outside hospital and had a specimen positive for the AB investigation strain and a sensitive strain several days after admission. Of note, there is also an anecdotal report that one of these patients was mechanically ventilated on a ventilator borrowed from the NICU.

4.1.4 Environmental sampling

Environmental samples tested by CWMH were negative for *A. baumannii*; specific results can be found below.

Table 4 - Results of environmental sampling

Environmental sample location	Culture result
Hand hygiene sink	Negative
Ventilator	Negative
TPN	Corynebacterium (repeat culture was negative)
Distilled water from dental clinic	Pseudomonas aeruginosa (repeat culture was negative)

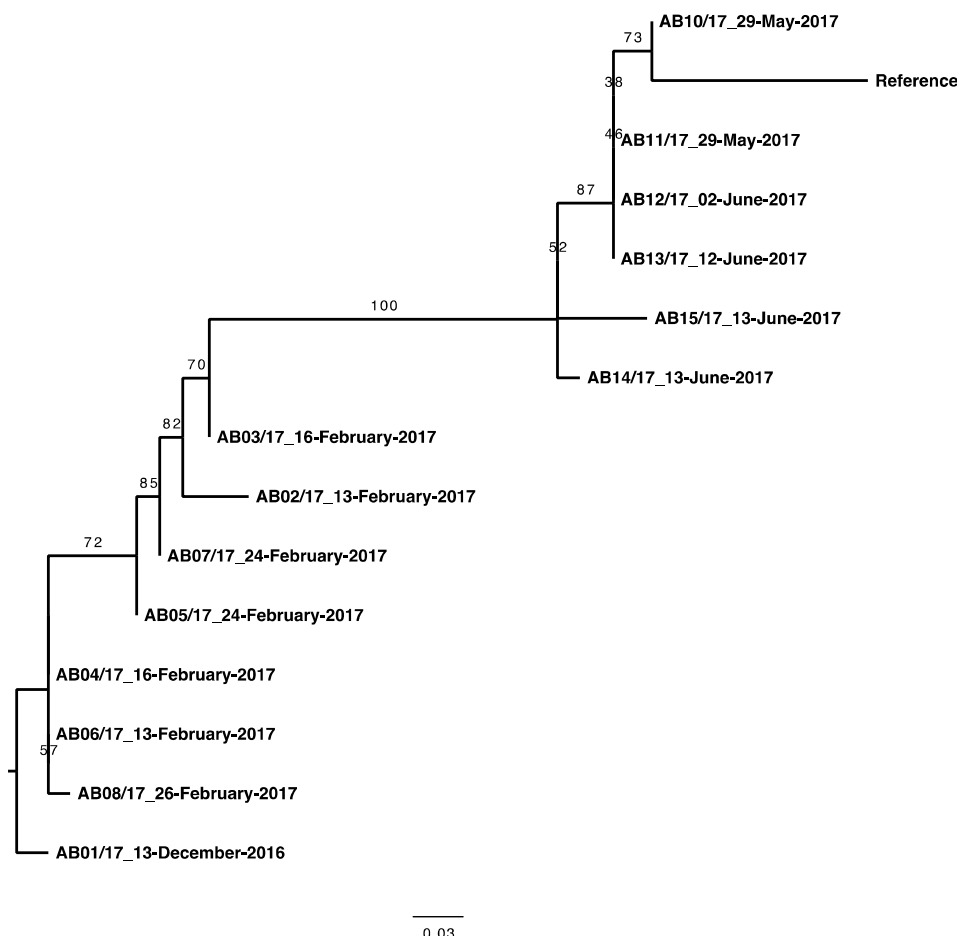
4.1.5 Whole genome sequencing

Nine (9) blood culture isolates and 5 cerebrospinal fluid isolates were sent to the Microbiological Diagnostic Unit Public Health Laboratory, University of Melbourne (MDU-PHL), for whole genome sequencing, with 3 patients having samples from both sites sent for testing. *In silico* multilocus sequence typing of the isolates showed 14 belonging to sequence type 2 (ST2) and one isolate belonging to ST107.

Upon review of the original microbiology results, it was discovered that the blood culture sample for the patient with ST107 grew a non-investigation strain of AB which was sensitive to Meropenem, while another longline tip sample from this patient grew the AB investigation strain.

All other samples sent for analysis grew the AB investigation strain. All the ST2 isolates contained the plasmid-mediated carbapenemase gene *bla*_{OXA-23}, and all but one contained the 16S rRNA methyltransferase gene *armA* (conferring high-level aminoglycoside resistance). This is a commonly observed clone internationally.⁴⁻¹⁰

For the ST2 isolates the MDU-PHL used genome wide single nucleotide variants, with recombinant sites removed, to reconstruct the phylogenetic relationship between all the samples. The resulting phylogenetic tree is presented in **Figure 5**. The analysis shows that the ST2 isolates form two groups of isolates. Group 1 is composed of isolates from the first cluster and group 2 is composed of isolates from the second cluster, and the results suggest that group 2 evolved from group 1. The nucleotide variations accumulated over the three months between the two clusters suggest that the strain is capable of evolving reasonably rapidly.

Figure 5 - Maximum-likelihood tree inferred from recombination-free alignment

Bootstrap support values are shown on each branch. Tips are labelled with the reference number and date of isolate. The tree was rooted using the oldest isolate in the collection.

4.2 INFECTION PREVENTION AND CONTROL EVALUATION

Utilising the tool described in the methods section, facility wide IPC evaluations were conducted in collaboration with the ICC and other IPC staff of each facility, with evaluation scores shown in **Table 5**. The results indicate an inability to provide evidence based IPC practice for the delivery of safe and effective care, putting staff in a position of “making do” or “improvising” in the absence of adequate supplies. For example, the lack of disposable, single-patient-use equipment, leads to reprocessing of equipment that cannot be effectively decontaminated, such as nasal prongs and other respiratory equipment which is implicated in similar outbreaks.

Table 5 - Results of Infection Prevention and Control Evaluations, July 2017 (each completed tool attached, Annexes 4-6)

Attribute assessed	Lautoka %	Labasa %	CWMH %
Organisation	71.4	100	57.1
Epidemiological surveillance of infections	41.2	41.2	35.3
Microbiology	83.3	58.3	75
Intervention strategies	56.4	81.6	44.3
Sterilisation and high-level disinfection	63.6	45.5	45.5
Personnel health	42.9	57.1	42.9
Hospital environment and sanitation	76.8	73.6	60.6
Total	62.2	65.3	51.5

Compliant: 85% or above

Partial compliance: 76-84%

Minimal compliance: 75% or below

Specific IPC issues for ALL facilities:

- Inconsistent use of contact precautions and decontamination protocols in the NICU (and all high-risk units)
- Poor hand hygiene compliance
- Inadequate isolation facilities
- Inconsistent use of personal protective equipment
- Inconsistent identification and use of transmission based precautions
- Reprocessing single use items respiratory equipment
- Inadequate cleaning of equipment between patients
- Decanting of solutions into inappropriate vessels (without appropriate decontamination)
- Multi-access of sterile solutions (IV medications and IV solutions)
- Poor IV therapy administration and practices
- Inappropriate antiseptic and disinfectant agents
- Unsafe disposal of sharps
- Inability to verify sterility of equipment and consumables processed by hospital sterile services
- Lack of planned maintenance for all equipment
- Overcrowding

Completed IPCP evaluation audit findings are presented in **Annexes 3-5**, for each hospital respectively. Each facility received feedback at the end of each evaluation, and reviews were conducted with the relevant IPC teams, with peer-to-peer teaching performed throughout.

4.3 PREVIOUS MDRO OUTBREAK INVESTIGATIONS

It is important to note that CWMH has had at least 10 MDRO outbreaks documented since 2006 caused by various organisms including *A. baumannii*, *K. pneumoniae*, *Enterobacter aerogenes*, *Serratia marcescens*. Investigations of these outbreaks (including those by previous WHO consultants) resulted in very similar findings and recommendations as this investigation, including poor IPC practices, many of which result from inadequate and inconsistent supply of consumables and equipment. This has led to the perpetuation of poor IPC practices (including hand hygiene,

standard and transmission based precautions, safe injecting practices, and aseptic technique) based on a concern for the availability of supplies. This ultimately impacts upon patient safety and enables the transmission of healthcare associated infections.

5. DISCUSSION

There have been clinical specimen positive for the AB investigation strain from CWMH NICU patients as early as January 2015, with several sporadic cases detected from January to November 2016. However, since December 2016 there has been an increase in both invasive and less-invasive cases and an increase in mortality among these patients.

While many patients in the current outbreak had illness onset on the day of admission or the day after admission to a paediatric ICU at CWMH, the first specimen taken following ICU admission was negative for *A. baumannii* for most cases, suggesting that these patients were likely not colonized or infected on admission. Even though it is possible that transmission could occur at delivery prior to NICU admission, the lack of early positive specimens and the variety of delivery locations (labour ward for vaginal deliveries and the operating theatre for caesarean sections) suggests that transmission was occurring within the NICU due to persistent contamination of the NICU environment.

Because clinical management is often similar for all NICU patients, it can be difficult to identify a common exposure unique to the cases that are part of a cluster. Invasive devices such as mechanical ventilation and central lines are common practice for all neonates requiring admission to the NICU, but information about specific exposures of each case-patient (such as the exact ventilator device) used was not documented to compare exposures of individual case-patients in more detail.

It is possible that the source of *A. baumannii* within the NICU is multifocal (i.e. multiple contaminated surfaces or equipment). Considering that this bacterium can survive on surfaces for extended periods of time and in biofilms, the infection control assessment identified multiple issues in IPC that could have resulted in cross-contamination, including lack of appropriate cleaning of the patient environment and equipment as well as lack of appropriate transmission-based precautions. Previous outbreak experience with this organism has demonstrated that frequently multiple sources are contaminated in the hospital environment¹¹⁻²⁶, with eradication typically needing a thorough, comprehensive approach to cleaning and disinfection of patient care equipment as well as ensuring appropriate compliance with hand hygiene and contact precautions.

While multiple sources of transmission are likely, the high frequency of positive pressure ventilation within 24 hours of birth, the high frequency of mechanical ventilation prior to a positive specimen, and the high frequency of positive specimens from ETT tubes may suggest a respiratory source of transmission such as shared ventilators or respiratory equipment inadequately cleaned between patients. This concern is further highlighted by the lack of single-use disposable respiratory equipment and inadequate cleaning of shared respiratory equipment found during the infection control assessment. While the PICU case-patients may have not shared the same environment, they may have been exposed to the same contaminated equipment as NICU cases, including a NICU ventilator for one of the PICU case-patients. This theory is supported by genomic testing results demonstrating that all invasive cases had a single strain and it is highly likely that the same strain would also be found in specimens from less-invasive sites if they had been tested.

While the high mortality of cases is alarming, it is difficult to determine the contribution of the *A. baumannii* in the deaths of these patients, especially because not all deaths were attributed to the *A. baumannii* infection in the medical chart. Nevertheless, the bacteria likely put an added burden on an already fragile and sensitive patient population and are dangerous in an intensive care environment. Once the IPC, infrastructure, and medical supply chain issues are resolved, it is expected that HAI transmission will be markedly reduced.

Many of the infection control gaps identified were associated with a lack of consistent equipment and consumables present in all three health facilities evaluated, preventing the appropriate implementation of IPC practices. Based on the evidence provided by each of the IPC teams and committees, supply staff, and clinicians, these deficiencies appear systemic.

While it is impossible to identify a specific point source for this outbreak, the wide variety of poor IPC practices suggest that all IPC issues should be addressed to improve patient safety. The greatest concerns for this specific outbreak are:

1. The reuse and reprocessing of single patient use respiratory equipment
2. The lack of consistent availability of hand hygiene equipment and IPC consumables
3. The use of IV solutions and medications for longer than 24 hours after first access, and multi-access for multiple patients
4. The lack of effective cleaning of patient care equipment between patients
5. Inadequate application of standard and transmission based precautions, particularly contact precautions

6. LIMITATIONS OF THE STUDY

Due to the manual nature of medical charts, logs, and other surveillance systems, the documentation needed for a more comprehensive investigation was not consistently available for all patients. The GOARN team encountered several occasions where important data, such as microbiology laboratory results or the medication administration record, were missing from the patient charts.

Occasionally, there were inconsistencies in the data from different data sources, including microbiology results from one data source which may have been different or not present in another data source. For example, while the neonatal deaths registry did not consistently include microbiology results it did include three patients in 2016 with *A. baumannii* from an invasive body site; these cases were not documented in the MRO log and did not have AST data included. These patients were discovered late in the investigation, and there was insufficient time to locate and examine the patient charts.

Only limited information on the mothers of the case-patients was available as the medical charts for most of the mothers were not located; it is therefore not possible to assess exposures related to the mother's experience during pregnancy or at delivery.

Because clinical management is very similar for all NICU patients, without a case-control study it can be difficult to identify exposures unique to the cases, or a common exposure to all patients, which may be important in transmission of the AB investigation strain.

There was also insufficient time to conduct an observational study of practices and procedures within the NICU, following patients from the time of admission to final outcome (discharge or death), which could provide a more detailed understanding of specific risk factors associated with policies and practices in the unit and individual critical control points for intervention.

Since all the sequence type 2 isolates had the same AST profile (resistant to all antibiotics used at CWMH), this finding was extrapolated to suggest that all isolates with this AST profile belonged to the ST2 lineage. This is highly probable, but cannot be proven without performing whole genome sequencing. Whole genome sequencing of a wider selection of samples, including some from less invasive sites, would be needed to confirm whether one or more clones of MDRA were present in the NICU from December 2016 to July 2017. However, any additional sequencing results would not alter the recommendations for outbreak control and IPC strengthening.

7. ACTIONS AND RECOMMENDATIONS

7.1 IMMEDIATE ACTIONS TAKEN

Based on concerns about ongoing transmission, some targeted measures were taken immediately to prevent further transmission.

- On-site training and assistance was provided on implementing effective contact precautions in the NICU for neonates with a specimen positive for an MDRO (especially resistant *Acinetobacter baumannii*), including dedicating equipment to these patients to reduce shared equipment, improving appropriate hand hygiene and glove use for contact with these patients and their environment, maximizing space between patients, and daily education for NICU staff.
- On-site training and assistance was also provided on effective cleaning of the environment and patient equipment, including guidance for cleaning with the cleaning agents currently available as well as supporting the MOHMS in the emergency procurement of certain essential single-use, disposable equipment.
- Investigation findings were shared with administrators, clinicians, and staff from the MOHMS and CWMH to inform the immediate changes above.

Processes to improve IPC implementation in the NICU were established for CWMH staff to continue (see **Annex 7**, CWMH Workplan), including:

- Development of an ongoing IPC education or training program for all staff including non-clinical cleaning staff and visitors, focusing first on staff working in the NICU and then expanding to other wards. This includes a plan for orienting visitors about important IPC practices (especially hand hygiene and contact precautions) where compliance is low and may include visual aids and a monitoring system for tracking staff and visitor training. This may also include a simulation component for staff to demonstrate competency in these IPC practices (i.e. having staff demonstrate how they would care for a neonate on contact precautions or how they would clean equipment).
- Development of a system to monitor compliance with IPC practices. While hand hygiene audits are conducted by the infection control team, this information may not be effectively communicated back to the frontline staff and used to inform improvement initiatives. In addition to hand hygiene, it may also be beneficial to conduct audits or monitor indicators of other infection control practices, such as contact precautions or cleaning/disinfection.

Monitoring compliance of these activities may be complicated, but can be accomplished by choosing specific, measurable actions to audit (such as use of gloves when contacting a neonate and their environment or disinfection of equipment for patients on contact precautions (including stethoscope) and by developing tools (such as an audit tool for contact precautions or daily cleaning checklist to ensure regular cleaning of each patient environment).

- Education on IPC for patients and families who come into contact with the health facility should be available and accessible;
- Development of patient feedback system for patients to express their concerns related to IPC.

7.2 RECOMMENDATIONS

Given the recent cases and the concern of ongoing transmission for many months, CWMH will need to devote significant resources for tracking and stopping this outbreak. First, it is recommended that CWMH continue ongoing surveillance for resistant *Acinetobacter baumannii*, focusing on high risk areas such as ICUs. If future cases (invasive and/or less-invasive) occur, documentation of patient location within a unit and documentation of specific equipment used for these patients (e.g. which ventilator) will be helpful to identify possible common sources of transmission.

Continued screening for *A. baumannii* may not be beneficial for outbreak control for a few reasons. First, it is likely that the source of *A. baumannii* is within the NICU; screening for MDROs is typically employed to prevent these organisms from gaining entry to a vulnerable patient population. Second, there is no consensus method for screening patients for carriage of *A. baumannii* and the sensitivity of surveillance cultures is low even when multiple body sites are sampled. Therefore, regular screening cultures to identify carriage or colonization may not be cost-effective, and resources are likely better spent on infection control prevention activities.

Additional support for “destructive sampling” has been offered via Dr Karen Vickery of Macquarie University in NSW, Australia. Destructive sampling involves items being destroyed to detect pathogens in biofilms, so any items considered for this form of testing would have to be replaced. Given the plethora of IPC practice issues that require rectification at this time, and these recommendations have been made since 2007 via various outbreak investigation reports, such sampling does not appear to be of priority at this time.

Based on the epidemiological investigation and infection control assessments, recommendations and a related action plan were drafted (included below) and shared with MOHMS and hospital leadership to identify and ensure implementation of important short, medium, and long-term actions aimed at:

- Improving IPC practices, including appropriate hand hygiene, transmission-based precautions (especially contact precautions), use of sterile medications/solutions for injections
- Improving cleaning of patient care environment and equipment, including avoiding reuse of single-use, disposable equipment and ensuring effective sterilization of items
- Effectively implementing the Infection Control Committee, including improving technical capacity of IPC team, implementing targeted healthcare-associated infection surveillance, conducting staff training on IPC, developing a IPC nurse liaison program. All activities to be overseen by the IPC Committee, in which leadership is included according to the Terms of Reference) and the hospital’s risk management/clinical governance structure and used to make management and policy decisions

- Developing standardized regional, national, and facility guidance, policies, or standard operating procedures (SOPs) on IPC.

Many of the short-term activities will focus on the high-risk areas such as ICUs initially but will then be applied to other patient care areas. There are multiple challenges in effectively implementing these activities which will require actions from multiple responsible parties during a timeframe outlined in the action plan, including knowledge and training, supplies and resources, effective oversight and monitoring systems. The MOHMS and hospital leadership voiced commitment to following this action plan and meeting regularly to assess progress and obstacles to implementation.

Finally, in order to effect sustainable improvements in IPC practices, there is a need for a longer term health systems approach to the problems identified in order to reduce likelihood and impact of MDRO outbreaks.

7.2.1 Proposed action plan for hospital infection prevention and control

All IPC principles, practices, and guidelines should be in line with recognised standards, evidence-based principles and accepted best practices, but this is not achievable due to the nature of the current context and resource limitations. However, there are key recommendations to be implemented **FOR ALL FIJI HEALTH FACILITIES** (unless otherwise noted) on a short, medium and long-term basis which have been discussed and agreed upon by stakeholders. This action plan includes specific activities, the target group for implementation, responsible persons, and the timeframe for completion. WPRO has suggested organizing these recommendations into health system areas, rather than in order of priority (included in appendix). These recommendations include aspects OTHER than IPC needs (Annexe 8).

Short term plan (14 days) as of 26 July 2017				
Area of action	Target group	Individual components	Responsible persons	Timeframe
Cease reprocessing of all respiratory equipment in all high-risk units. Respiratory equipment should be single patient use and disposed of after patient discharge	All ICUs Burns Unit Operating Theatre (OT)	Ensure implementation and adherence	Medical Superintendent	Effective immediately and continuous
		Decision to be made whether to purchase single-use disposable equipment, or reusable equipment that can effectively be cleaned	Medical Superintendent	Completed within 1 month
		Ensure reliable supply of respiratory equipment (whichever option is chosen above)	FPBS Hospital supply staff	Continuous
		Ambu bags and masks MUST be either discarded or thoroughly cleaned and disinfected between patients with NEW oxygen tubing – follow SOP from IPC team on cleaning of the NICU environment for all high-risk areas	Staff of all ICUs and OT	Effective immediately and continuous
Hand hygiene compliance must be improved, with initial focus on high risk units and then to other departments.	All ICUs Burns Unit	Ensure implementation and adherence, through reports from IPC Committee	Medical Superintendent	Effective immediately and continuous
	All wards (longer term)	Adequate and consistent provision of hand hygiene supplies (70% alcohol hand rub at each ICU bed, liquid soap and paper towel at each hand basin)	FPBS Hospital supply staff	Continuous
		Hand hygiene training, focusing on the 5 moments	ICC	Effective immediately

Short term plan (14 days) as of 26 July 2017				
Area of action	Target group	Individual components	Responsible persons	Timeframe
		of hand hygiene to be conducted		and continuous
		30 moments a week auditing for a month (use HHA tool) and then collect 30 moments per month. Set a hand hygiene compliance goal of 80% facility wide. Feedback at time of audit and weekly/monthly feedback to relevant department staff	IPC team	Effective immediately and continuous
All contact with patients in ICUs requires use of gloves and plastic disposable apron, to be changed and discarded between patients. Eye protection required at every ICU bed.	All ICUs Burns	Ensure implementation and adherence	Medical Superintendent	Effective immediately and continuous
		Plastic disposable aprons, N95 masks, disposable gowns, eye protection are required to be added to the stock list	FPBS	Continuous
		All staff in ICUs should use gloves and plastic disposable aprons	IPC team	Effective immediately and continuous
For IV fluids, IV medications and dressing use, only use sterile solutions.	All ICUs Burns OT	Ensure implementation and adherence	Medical Superintendent	Effective immediately and continuous
		Small volume normal saline required: 10mls, 100mls, 500mls	FPBS	Effective immediately and continuous
	All wards (longer term)	Ensure adequate supply of IV medicines such that they do not have to be shared.	FPBS	Effective immediately and continuous
		Cease use of multi-access solutions for multiple patients. If necessary, solutions are dedicated to single patient use only and kept for a maximum of 24hrs – only if re-sealable	IPC team Staff of all ICUs	Effective immediately and continuous
IV giving sets must be replaced in 72hrs; IV fluids should be changed	All units	Ensure implementation and adherence	Medical Superintendent	Effective immediately and continuous

Short term plan (14 days) as of 26 July 2017				
Area of action	Target group	Individual components	Responsible persons	Timeframe
every 24hrs		A consistent and adequate supply of IV consumables must be maintained	FPBS	Continuous
		If IV lines must be disconnected from patient, ensure sterility of line by adding a sterile bung or other IV component to the end of the line until next use	IPC team Staff of all units	Effective immediately and continuous
Improve cleaning of patient care environment and patient care equipment.	All units	Ensure implementation and adherence	Medical Superintendent	Effective immediately and continuous
		All equipment must be cleaned with a neutral detergent between patients. In the current situation, use of 1% sodium hypochlorite after cleaning is advisable (ICUs). This is using disposable cloths, which ARE disposed of after each use	IPC team Staff in all units	Effective immediately and continuous
		All sticky residues to be removed from equipment.	Cleaning staff Staff in all units	Effective immediately and continuous
		Ensure curtain cleaning schedules (monthly) are performed	Cleaning staff	Effective immediately and continuous
Produce and use signage to indicate the need for transmission based precautions	All units	Ensure implementation and adherence	Medical Superintendent	Effective immediately and continuous
		Produce and use signage to indicate the need for transmission based precautions	IPC team	Effective immediately and continuous
		Appropriate use of signage to be verified by IPC staff daily.	IPC team	Effective immediately and continuous
All high-risk units to receive training	All ICUs	Ensure implementation	Medical Superintendent	Effective immediately

Short term plan (14 days) as of 26 July 2017				
Area of action	Target group	Individual components	Responsible persons	Timeframe
from IPC team on new initiatives (see all above recommendations) for implementation and adoption in their units. This can then be rolled out to all other units.	Burns OT			and continuous
	All wards (longer term)	Conduct the training	IPC team	Effective immediately and continuous
Specific to CWMH				
There is currently no capacity to ensure sterility of equipment being processed through the ONE operational autoclave at CWMH. Three autoclaves are currently inoperable	All units	A contingency plan for autoclave failure must be created.	Permanent Secretary Medical Superintendent	Effective immediately
		A plan for sourcing appropriate replacement autoclaves for the CSSD	Permanent Secretary Medical Superintendent	Effective immediately
Change sterilization practices of small items (swabs, gauze, etc.) to sterilization pouches which are heat sealed and autoclaved, instead of wrapping in butchers' paper which cannot maintain sterility	CSSD	Ensure implementation and adherence	Medical Superintendent	Effective immediately and continuous
		Ensure reliable supply of sterilization pouches	FPBS Hospital supply	Continuous
		Purchase heat sealers for the CSSD	Supply	Effective immediately
		Acquire chemical indicators to be placed inside wrapped packs for sterilization	FPBS CSSD	Completed within 1 month
Log book kept of autoclave loads	CSSD	Log book kept of autoclave loads (as per protocol at Lautoka)	CSSD Nursing Manager	Effective immediately and continuous

Medium term plans (1-3 months)				
Area of action	Target group	Individual components	Responsible persons	Timeframe
Consistent provision of equipment/consumables to support IPC practices by clinicians	All clinical areas	Ensure implementation	Medical Superintendent	Completed within 1 month
		Hand hygiene equipment/consumables throughout health facilities	FPBS Hospital supply	Continuous
		PPE – consistent supply	FPBS Hospital supply	Continuous
Monthly Infection Control Committee meetings (with minutes)	Infection Control Committee	Monthly Infection Control Committee meetings (with minutes). Activities and outcomes, monitoring and evaluation of all IPC activities	Infection Control Committee	Commenced within 1 month
Review of Terms of Reference and activities of ICC	Infection Control Committee	Updated TORs and activities, goal setting with roles and responsibilities identified	Infection Control Committee	Completed within 1 month
Purchase clippers for surgical site preparation.	Surgical units OT	Ensure implementation	Medical Superintendent	Completed within 1 month
		Purchase of clippers	Hospital supply	Completed within 1 month
		Ensure consistent and adequate supply of clippers	Hospital supply	Continuous
Targeted healthcare associated infection surveillance, to establish baseline data and allow trend analysis to detect deviations from the norm (e.g. outbreaks)	All units	Establish: - Standard operating procedures for the collection, analysis and reporting of data - Minimum data set - Focus on clinical, not environmental surveillance - Cease M/C/S of tips (IDC, NGT, ETT, OGT, CVC) – unless clinically indicated	Medical Superintendent IPC Committee	Completed within 3 months

Medium term plans (1-3 months)				
Area of action	Target group	Individual components	Responsible persons	Timeframe
		- Elective surgery only – LSCS and hernia repair (divided between superficial and deep incisional) - Central line associated blood stream infections (CLABSI) ICU - Catheter associated urinary tract infection (CAUTI) ICU MROs of significance: - Extended spectrum beta-lactamase (ESBL) producing organisms - Multi-resistant <i>Staphylococcus aureus</i> (MRSA) - Multi-resistant <i>Acinetobacter baumannii</i> (MDRAB)		
Implement Infection Control Link/Liaison Nurse Program. This will raise the profile of IPC in all units, allow for succession planning for IPC team, and build capacity and leadership of IPC team	All units	Ensure implementation	Medical Superintendent	Completed within 3 months
		Expressions of interest from ward staff (opinion leaders, leadership qualities)	IPC team	Completed within 1 month
		Training to include: - Shadow of IPC team members - Hand hygiene Australia modules – auditing process (freely available at http://www.hha.org.au/) - Australian Commission for Quality and Safety in Healthcare modules (freely available at http://infectionprevention.e3learning.com.au/) - Environmental auditing process	IPC team	Completed within 3 months

Medium term plans (1-3 months)				
Area of action	Target group	Individual components	Responsible persons	Timeframe
		Activities to include: • Hand hygiene audits • Environmental audits – cleaning, waste, sharps • Monthly education sessions with IPC team • Audit reports to IPC teams monthly		
Improve general cleaning capacity of the facilities, including training of cleaning staff in-line with the needs of the facility and for cleaners' safety	Cleaning staff		Medical Superintendent IPC team Cleaning staff	Completed within 1 month

Long term plan (>3 months)				
Area of action	Target group	Individual components	Responsible persons	Timeframe
Review and update of IPC Guidelines to include targeted surveillance activities	All HCWs	IPC Guidelines for the region and Fiji	MOHMS to liaise with WHO and SPC	Completed within 4 months
Review and update of IPC Policy for Fiji to include targeted surveillance activities and methodologies, IPC practices identified in short term and medium term goals	Fiji Health Services	New and updated policy to support IPC practice for Fiji.	Fiji MoH Policy Department All IPC Committees All IPC teams MOHMS	Completed within 4 months
Capacity and leadership building of IPC team through formal training of IPC staff	IPC staff	Develop a training plan	Permanent Secretary Medical Superintendents Donor agencies	Completed within 6 months
Review of and development of plan for improved sterilization practices for all health services	All health facilities	Quality assurance of sterility of equipment in Fiji	Permanent Secretary Medical Superintendents Donor agencies	Completed within 4 months
MoH IPC Clinical Services Network establishment	All IPC teams	Capacity and leadership building of IPC team	MOHMS All IPC Committees	Completed within 6 months
Seek external support to assist with IPC and CSSD capacity and development in Fiji, for 12 months (previous AusAID volunteer advertisement attempted unsuccessfully)	All health services	Capacity and leadership building of IPC team	Permanent Secretary Nursing Manager	

8. ANNEXES

1. Daily Mission Travel Schedule and Key Persons Met (P-A Zimmerman)
2. Daily Mission Travel Schedule and Key Persons Met (M. Lyman and P. Andersson)
3. Infection Prevention and Control Programme Evaluation tool
4. IPCP Evaluation Lautoka
5. IPCP Evaluation Labasa
6. IPCP Evaluation CWMH
7. CWMH Workplan
8. WPRO Additional recommendations as of the 1 August 2017
9. Presentation to the Permanent Secretary of Health 26 July 2017

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APPENDIX 2B – Presentation of the final mission findings for the Permanent Secretary of the MOHMS, and Executives and senior medical staff from the CWMH, Lautoka and Labasa hospitals.

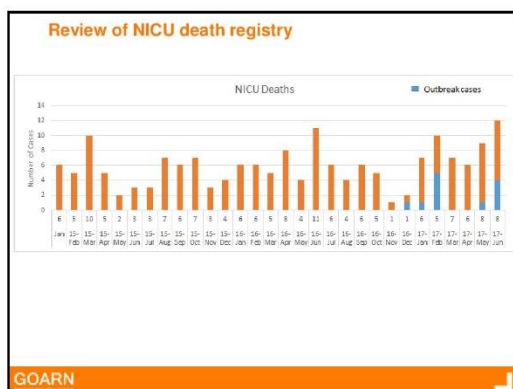
Multi Resistant *A. baumannii* support, Fiji

Prelim. debrief – 26th July, 2017

GOARN Team:
 Dr Meghan Lyman (Epidemiology, Infection Prevention and Control)
 Dr Patiyan Andersson (Epidemiology)
 Dr Peta-Anne Zimmerman (Infection Prevention and Control)

Activities

- Review of Pediatric MDR Culture Registry
- Review of Pediatric Death Registry
- Chart review of NICU case-patients
- Infection Prevention and Control Assessment
 - Infection prevention and control program evaluations
 - Lautoka District Hospital 13-14th July
 - Labasa District Hospital 17-18th July
 - CWMH 19-20th July
 - Review of IPC policies and documents
 - Review of surveillance
 - Clinical Observations
 - Surveillance workshop for CWMH IPC team 20th July
 - On-site assistance for IPC implementation in CWMH NICU



Epidemiologic characteristics

	Patients with MDR AB in blood/CSF n=11	All patients with MDR AB specimen n=27
Microbiology Results		
Specimen type		
Blood	9 (82%)	10 (37%)
CSF	5 (45%)	5 (19%)
ETT	8 (73%)	21 (78%)
Culture on admission positive for MDR AB	1 (9%)	4 (15%)
Outcomes		
Death	11 (100%)	19 (70%)
Treated with Meropenem	8 (73%)	16 (59%)
Treated with Colistin	5 (45%)	9 (33%)

Epidemiologic characteristics

	Patients with MDR AB in blood/CSF n=11	All patients with MDR AB specimen n=27
Risk factors/Exposures		
Mechanical ventilation	11 (100%)	25 (96%)
PPV/ventilation within 24h of admission	11 (100%)	23 (85%)
Diagnosed with respiratory illness	10 (91%)	25 (93%)
Central line	10 (91%)	22 (85%)
IV phlebitis	2 (18%)	8 (30%)
Intubates	10 (91%)	20 (74%)
TPN	3 (27%)	7 (26%)
Blood transfusion	11 (100%)	24 (89%)

Epidemiologic characteristics – Neonatal variables

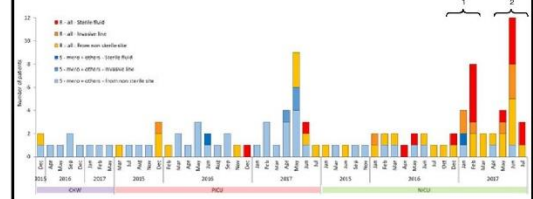
	Neonates with MDR AB in blood/CSF n=11	All neonates with MDR AB specimen n=24
Delivery type		
Cesarian section	3 (27%)	8 (33%)
Vaginal delivery	8 (73%)	16 (67%)
Delivery location		
CWM	10 (91%)	22 (92%)
Outside hospital	1 (9%)	1 (4%)
Home	0 (0%)	1 (4%)
Gestational age		
Term	4 (36%)	12 (50%)
Mod-late preterm	5 (45%)	7 (29%)
Very preterm	2 (18%)	5 (21%)
Birthweight		
Normal	3 (27%)	12 (50%)
LBW	5 (45%)	6 (25%)
VLBW	3 (27%)	6 (25%)

Epidemiologic characteristics – Neonatal variables

	Neonates with MDR-AB in blood/CSF n=11	All neonates with MDR-AB specimen n=24
Neonatal sepsis		
EOS	6 (55%)	12 (50%)
LOS	5 (45%)	9 (38%)
Sepsis unlikely (other diagnosis)	0 (0%)	3 (12%)
Respiratory problem at delivery	5 (45%)	11 (46%)
Delivery Risk factor/Exposures		
Meconium in amniotic fluid on delivery	4 (36%)	8 (33%)
Concern for meconium aspiration	3 (27%)	6 (25%)
PPV at delivery	6 (55%)	11 (46%)
PROM	4 (36%)	4 (17%)

GOARN

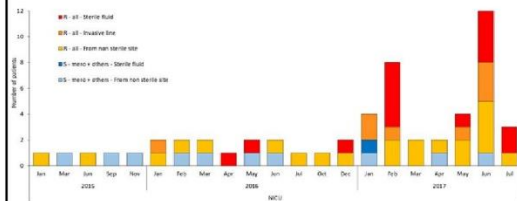
A. baumannii in NICU, PICU, CHW 2015-2017



- Distinct antibiotic resistance patterns between wards
- NICU – Resistant to all tested antibiotics (incl meropenem)
- PICU & CHW – Sensitive to meropenem and others

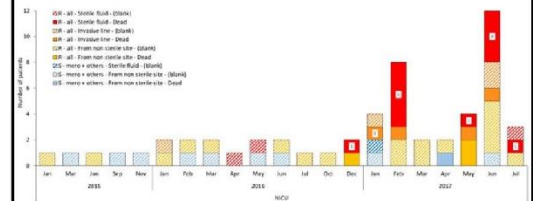
GOARN

Additional case finding



GOARN

Additional case finding



- 6 possible additional cases
- 3 invasive lines
- 3 non-sterile sites

GOARN

Genetic relationship of isolates

Sample #	Date collected	Initials	Site	MLST	Cluster
AB01/17	13-Dec-2016	SL	Blood	2	1
AB02/17	13-Feb-2017	LM	Blood	2	1
AB03/17	16-Feb-2017	NR	Blood	2	1
AB04/17	16-Feb-2017	NR	CSF	2	1
AB05/17	24-Feb-2017	MC	Blood	2	1
AB06/17	13-Feb-2017	MC	CSF	2	1
AB07/17	24-Feb-2017	AM	CSF	2	1
AB08/17	26-Feb-2017	AR	Blood	2	1
AB09/17	12-Feb-2017	NV	Blood	307	
AB10/17	29-May-2017	AD	Blood	2	2
AB11/17	29-May-2017	AD	CSF	2	2
AB12/17	2-Jun-2017	AV	Blood	2	2
AB13/17	12-Jun-2017	VY	Blood	2	2
AB14/17	13-Jun-2017	SN	Blood	2	2
AB15/17	13-Jun-2017	ST	Blood	2	2

GOARN

INFECTION PREVENTION AND CONTROL

GOARN

Chapter 2 – GOARN outbreak response in Fiji

Infection Prevention and Control Program Evaluations

	Lautoka %	Labasa %	CWMH %
Organization	71.4	100	57.1
Epidemiological Surveillance of Infections	41.2	41.2	35.3
Microbiology	83.3	58.3	75
Intervention Strategies	56.4	81.6	44.3
Sterilization and High-level Disinfection	63.6	45.5	45.5
Personnel Health	42.9	57.1	42.9
Hospital Environment and Sanitation	76.8	73.6	60.6
TOTAL	62.2	65.3	51.5

- Compliant 85% or above
- Partial compliance 76-84%
- Minimal compliance 75% or below

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General clinical IPC practice

- Poor hand hygiene compliance
- Inadequate isolation facilities
- Inconsistent use of personal protective equipment
- Inconsistent identification and use of transmission based precautions
- Reprocessing single use items
- Inadequate cleaning of equipment between patients



GOARN

General clinical IPC practice

- Multi-access of sterile solutions
 - IV medications
 - IV solutions
- Poor IV therapy administration and practices
- Inappropriate antiseptic and disinfectant agents
- Unsafe disposal of sharps
- Inability to verify sterility of equipment and consumables processed by hospital sterile services
- Lack of planned maintenance for all equipment
- Overcrowding



GOARN

Previous outbreak reports from CWMH

Year	Month(s)	Organism
2006	Jan-Nov	<i>K. pneumoniae</i> (MR)
2007	Jun-Jul	<i>E. aerogenes</i>
2007	Nov-Dec	<i>S. marcescens</i>
2007		<i>A. baumannii</i>
2011	Jul-Aug	ESBL
2011-12	Nov-Jan	<i>K. pneumoniae</i> (ESBL)
2012	Mar-Jul	<i>A. baumannii</i>
2012	Aug-Oct	<i>A. baumannii</i>
2013		
2015		<i>K. pneumoniae</i> (ESBL)
2016	Jun	<i>A. baumannii</i>

Previous report findings:

- Insufficient supplies and consumables to meet IPC requirements
- Reprocessing and inadequate cleaning of respiratory equipment
- Multi-access of 1L saline bottles and other sterile IV solutions
- Poor hand hygiene practices due to lack of soap and ABHR

GOARN

Interim Recommendations – short term (within 14 days)

- Cease reprocessing of all respiratory equipment in all high risk units. Respiratory equipment should be single patient use and disposed of after patient discharge
- Hand hygiene compliance must be improved, with initial focus on high risk units and then to other departments.
- All contact with patients in ICUs require use of gloves and plastic disposable apron, to be changed and discarded between patients.
- For IV fluids, IV medications and dressing use, only use sterile solutions. Cease use of multi-access solutions for multiple patients.
- Improve cleaning of patient care environment and patient care equipment.
- Produce and use signage to indicate the need for transmission based precautions

GOARN

Interim Recommendations – short term (within 14 days)

- A contingency plan for autoclave failure must be created PLUS a plan for sourcing appropriate replacement autoclaves for the CSSD
- Change sterilization practices of small items (swabs, gauze, etc) to sterilization pouches which are heat sealed and autoclaved, instead of wrapping in butchers paper which cannot maintain sterility.
- Acquire chemical indicators to be placed inside wrapped packs for sterilisation
- Log book kept of autoclave loads (as per protocol at Lautoka)

GOARN

Interim Recommendations – mid term (within 1-3 months)

- Consistent provision of equipment/consumables to support IPC practices by clinicians
- Monthly Infection Control Committee meetings (with minutes)
- Review of Terms of Reference and activities of ICC
- Purchase clippers for surgical site preparation.
- Targeted healthcare associated infection surveillance, to establish baseline data and allow trend analysis
- Implement Infection Control Link/Liaison Nurse Program.
- Improve general cleaning capacity of the facilities, including training of cleaning staff in-line with the needs of the facility and for cleaners' safety

GOARN

Interim Recommendations – long term (>3 months)

- Review and update of IPC Guidelines to include targeted surveillance activities
- Review and update of IPC Policy for Fiji to include targeted surveillance activities and methodologies, IPC practices identified in short term and medium term goals
- Capacity and leadership building of IPC team through formal training of IPC staff
- Review of and development of plan for improved sterilisation practices for all health services
- MoH IPC Clinical Services Network establishment
- Seek external support to assist with IPC and CSSD capacity and development in Fiji, for 12 months

GOARN

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APPENDIX 2C – Presentation for MAE scholars and staff at the National Centre for Epidemiology and Population Health

A similar presentation was given to the Infectious Diseases and Infection Control units at the Canberra Hospital, and at a Canberra Hospital Grand Rounds seminar.

Chapter 2 – GOARN outbreak response in Fiji

Investigating a nosocomial outbreak of *Acinetobacter baumannii* in Fiji
 – GOARN deployment –

Dr Patiyon Andersson, M.Phil. Applied Epidemiology scholar

Meghan Lyman, Peta-Anne Zimmerman, Corinne Capuano, Kunhee Park, Asaeli Raikabakaba, Viema Blaukula, Angela Merianos, Rose Aynsley, Philip Davies, James Forng, Ravi Naidu, Susana Veikoso, Susan Ballard, Mark Schultz, Katrina Roper, Martyn Kirk

Australian National University GOARN World Health Organization Ministry of Health Fiji CDC Griffith University

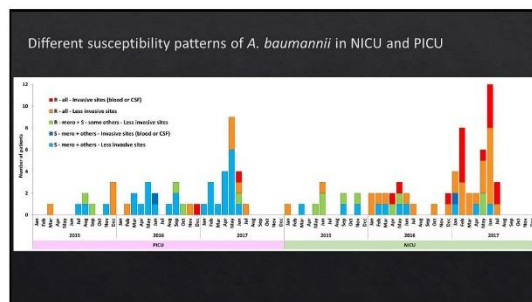
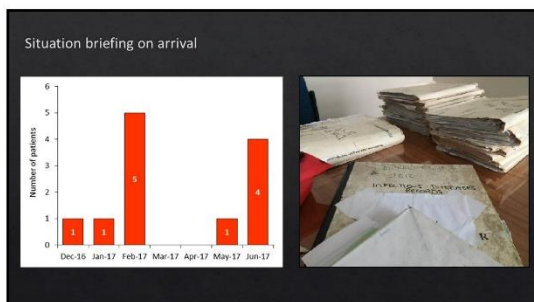
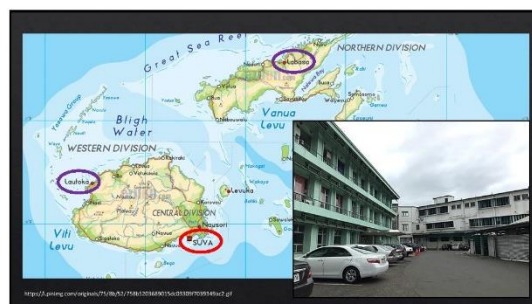


◆ **Mission brief**

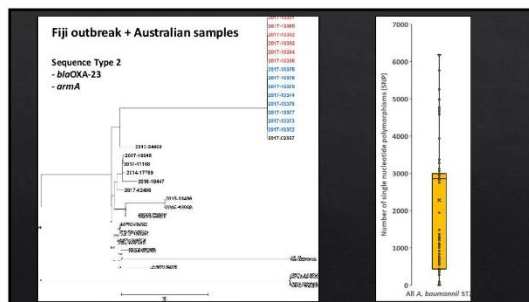
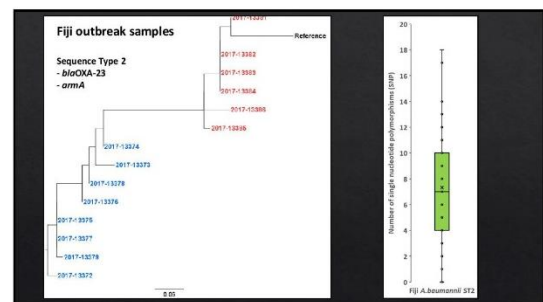
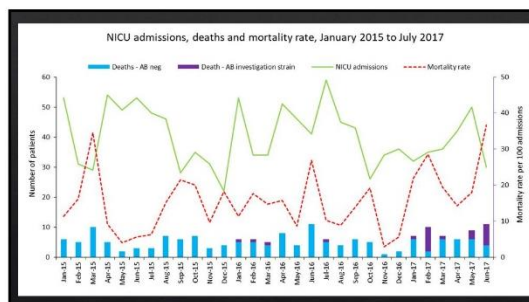
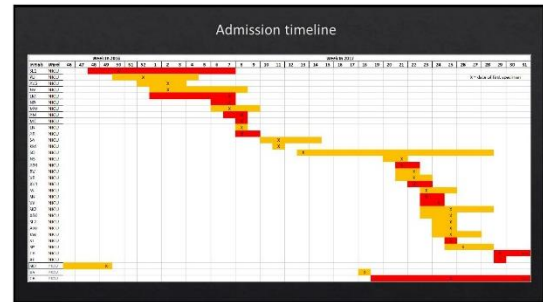
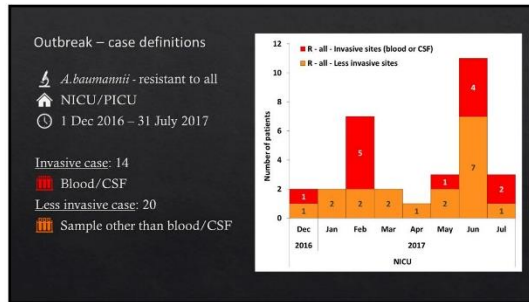
- Investigation 2 outbreaks - Colonial War Memorial Hospital
 - Dec 2016 – Feb 2017 | May – June 2017
 - 7 + 5 patients in the neonatal intensive care unit (NICU)
 - A. baumannii* resistant to all antibiotics – blood/CSF
- Evaluation of Infection Prevention and Control (IPC) practices

◆ **Team**

- Dr Meghan Lyman – Epidemiologist (US CDC)
- Dr Peta-Anne Zimmerman – IPC expert (Griffith Uni)

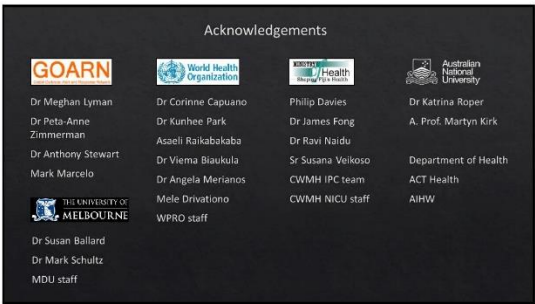
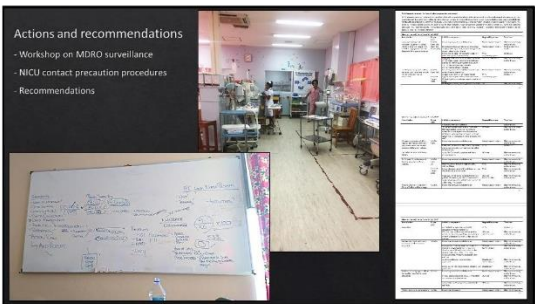



Chapter 2 – GOARN outbreak response in Fiji



Chapter 2 – GOARN outbreak response in Fiji

General Characteristics	All cases n=34	Invasive cases n=14	Less-invasive cases n=20
Ward			
NICU	31 (91%)	13 (93%)	18 (90%)
PICU	3 (9%)	1 (7%)	2 (10%)
Specimen type			
Blood	12 (35%)	12 (88%)	N/A
CSF	6 (18%)	6 (43%)	N/A
ETT	25 (74%)	8 (57%)	17 (85%)
Risk factors/Exposures			
Ventilation before positive culture	33 (97%)	14 (100%)	19 (95%)
PPV/ventilation within 24 hours of admission	29 (85%)	13 (93%)	16 (80%)
Central line before culture positive	27 (79%)	13 (93%)	14 (70%)
Blood transfusion before culture positive	28 (82%)	14 (100%)	14 (70%)
Outcomes			
Death	23 (68%)	12 (86%)	11 (55%)



CHAPTER 3

Vancomycin resistant enterococci outbreak in the Neonatal Intensive Care Unit at the Canberra Hospital

**The Canberra Hospital
ACT Health**

“As our world continues to generate unimaginable amounts of data, more data lead to more correlations, and more correlations can lead to more discoveries.”

Hans Rosling

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ABBREVIATIONS

ACT	Australian Capital Territory
aOR	adjusted odds ratio
ASC	active screening culture
CH	Canberra Hospital
CPAP	continuous positive airway pressure
DNA	deoxyribonucleic acid
ELBW	extremely low birth weight (<1000 grams)
ICU	intensive care unit
ID	infectious diseases (unit)
IPC	infection prevention and control (unit)
LBW	low birth weight (≥ 1500 grams to <2500 grams)
MIC	minimum inhibitory concentration
MRO	multi-resistant organism
NICU	neonatal intensive care unit
OR	odds ratio
RNA	ribonucleic acid
SCN	special care nursery
SNP	single nucleotide polymorphism
ST	sequence type
TPN	total parenteral nutrition
VIF	variance inflation factor
VLBW	very low birth weight (≥ 1000 grams to <1500 grams)
VRE	vancomycin resistant enterococci
WGS	whole genome sequencing

PROLOGUE

Study rationale

This was the first known outbreak of vancomycin resistant enterococci (VRE) in the neonatal intensive care unit (NICU) and Special Care Nursery (SCN) at the Canberra Hospital (CH). The outbreak began in January 2017 and was successfully controlled in late May 2017. Although the outbreak had been successfully terminated, there remained questions as to how the VRE had contaminated the unit, the risk factors for transmission and whether the VRE had originated from other wards in the hospital or from a source in the community. To answer these questions, I was tasked with conducting an epidemiological study which also included molecular genetic characterisation of the isolated VRE strains for comparison with other VRE from the ACT.

A concise version of this chapter was prepared as a manuscript and submitted for publication to the journal *Infection Control and Hospital Epidemiology*.

My role

This project provided a great opportunity for “field work” for a MAE placed in the Australian Government Department of Health, and also allowed me to put my previous experience in molecular genetics to good use. I was the only person working directly on the project and was responsible for the project design, with input from the infectious diseases (ID) and the infection prevention and control (IPC) units.

The work involved the design and coordination of the study, a review of the existing literature and obtaining ethics approvals from the ACT Health and ANU Human Research Ethics Committees. I extracted demographical and clinical data from medical records and created a line list of all patients and performed statistical analysis of the extracted variables. I liaised with the Microbiological Diagnostic Unit Public Health Laboratory (MDU-PHL) in Melbourne on whole genome sequencing and bioinformatic analysis, which included a face-to-face meeting. I was responsible for drafting and coordinating a manuscript submitted to the peer-reviewed scientific journal *Infection Control and Hospital Epidemiology*.

I have had opportunity to showcase this work several times: as a long oral presentation at the Australian Public Health Conference 2018, in Cairns (**Appendix 3A**); as a long oral presentation at the 9th Southeast Asia and Western Pacific Bi-regional TEPHINET Scientific Conference, in Vientiane, Lao People’s Democratic Republic (**Appendix 3A**); as a poster presentation at the ACT Health CHARM conference in Canberra (**Appendix 3B**); and as an oral presentation for the staff at the infectious diseases and infection prevention and control units at the Canberra Hospital (**Appendix 3A**).

Lessons learned

The biggest lesson that I learned from this project was planning and foresight, particularly with regard to having a good idea of what analysis will be conducted and which variables will be required for the analysis. Even with an electronic system for the medical records, it is very time consuming to go back through the records of all patients to find additional data. We had to do this repeatedly during the outbreak response in Fiji (Chapter 2), and despite being two people and having only 34 patients, it was time consuming. In the VRE study where I had 109 patients to analyse on my own, I had to make the data extraction streamlined. The Fiji work provided a good understanding of the important clinical variables in infants, and together with a thorough literature review and consultation process with the ID and IPC units, I managed to arrive at an analysis plan for the VRE outbreak that did not require many changes over the course of the project. However, despite these precautions, there were some additional details that required going through the records repeatedly. With the benefit of hindsight, some of this could have been avoided by conducting further consultation at the start of the project, for instance with the nursing and cleaning staff in the NICU.

In this project I learned to use STATA for my analysis. I came to appreciate how useful it is to have a reproducible analysis pathway, especially when you are working on several different projects and there may be days in between looking at the analysis. As a scientist the added transparency, and reproducibility for other researcher is also a very attractive feature, and one that I will incorporate in my work henceforth.

As mentioned in the previous chapter, it was highly interesting to have the opportunity to work with outbreaks in NICUs in two different countries with contrasting resource availability.

Public health implications

The molecular genetic findings of the study showed that the VRE in the NICU was highly similar to a VRE strain endemic to CH, and most likely introduced from another unit in the hospital, possibly through staff working in other units in addition to the NICU and SCN. The strain is part of a growing number of clones with a particular genetic characteristic, and that are becoming increasingly dominant in Australia. The study adds to a growing number of publications of these novel highly successful clones of VRE establishing themselves in hospitals around the country. The study generated 45 genomes that now are publicly available and can be used for future comparative genomic projects.

The outbreak has led to the implementation of 6-monthly screening of the NICU. This will minimise the time that VRE colonisation would go undetected among patients, especially those with long admissions, and allow for earlier interventions.

Acknowledgements

Big thanks to Nicholas Coatsworth for taking me in and supervising me during the project. And to Wendy Beckingham and the IPC team for their help in obtaining patient data and their endless patience in answering questions. I'd like to acknowledge Karina Kennedy, Kathryn Daveson and Ming Chen for their intellectual input and fruitful discussions. Thanks to Claire Gorrie and Susan Ballard for the whole genome sequencing and bioinformatic work, and for good discussions and insightful comments to the manuscript.

I would also like to acknowledge the effective response of the staff in the Neonatal Intensive Care Unit, the Special Care Nursery and the Infection Prevention and Control Unit at the Canberra Hospital in containing this outbreak and for their assistance in this investigation, and to ACT Pathology for their assistance in providing isolates for sequencing.

MAE core activity requirements

The MAE core activity requirements fulfilled in this project was: Conduct an epidemiological study, presentation at a conference, and preparation of a manuscript for publication in a peer reviewed journal.

Travel grant awarded

I was awarded a Vice Chancellors HDR Travel Grant from the Australian National University to support my attendance and oral presentation at the 9th Southeast Asia and Western Pacific Bi-regional TEPHINET Scientific Conference in Vientiane, Lao People's Democratic Republic.

ABSTRACT

Background: Nosocomial infections with vancomycin resistant enterococci (VRE) are cause of significant morbidity and mortality worldwide. Colonisation usually precedes infections and therefore it is crucial to minimise the burden of colonisation in highly vulnerable patient populations. This study investigates the first occurrence of VRE colonisation in the neonatal intensive care unit (NICU), a restricted clinical environment, at the Canberra Hospital. The aim was to determine risk factors for colonisation and whether the VRE originated from within the hospital.

Methods: Demographic and clinical variables for a cohort of 14 colonised infants and 77 non-colonised infants, representing all admitted patients at the NICU and SCN over the outbreak period January to May 2017, were analysed using multivariate logistic regression to assess possible transmission pathways for VRE colonisation. Whole genome sequencing of the VRE isolates was used to determine the origin of the outbreak strain.

Results: Transmission was ceased following implementation of enhanced infection control measures. Absence of routine VRE screening in the NICU caused a delay in the detection of cases. Multivariate regression analysis revealed a strong association between low gestational age and colonisation, with 6.47-fold and 8.63-fold increased risk for very preterm and extremely preterm infants, respectively. Whole genome sequencing showed the isolates to be highly clonal *Enterococcus faecium* ST1421 harbouring a *vanA* gene and closely related to other ST1421 previously sequenced from the Canberra Hospital. No environmental samples were positive for VRE. Due to staffing shortages there was a high proportion of non-regular staff in the NICU during the period preceding the outbreak.

Conclusion: The colonisation of NICU patients was with a highly successful clone endemic to the Canberra Hospital likely introduced into the NICU environment from other wards, possibly through staff working across multiple wards. Subsequent cross contamination spread it among susceptible premature neonates. Implementation of ongoing routine surveillance screening in the NICU could lead to earlier identification of colonisation and faster implementation of interventions.

1 BACKGROUND

Enterococci are gram-positive bacteria that form part of the normal bacterial flora of the gastrointestinal system in many people. These bacteria may also be pathogenic and cause infections. Two species of the enterococcal family are responsible for the majority of human infections: *Enterococcus faecalis* and *Enterococcus faecium*. Traditionally the former has been the dominant pathogen for the two in most countries, however, the trend is changing and an increase in *E. faecium* is now observed in many areas.(1) A trait that makes enterococci highly successful and persistent is their ability to become resistant to antimicrobials. Enterococci are intrinsically resistant to a range of antibiotics and also are highly efficient in acquiring resistance genes through the exchange of mobile genetic elements carrying antimicrobial resistance elements.(2-4) Resistance to vancomycin, a glycopeptide class antibiotic, is one of the most significant resistance markers in enterococci and is conferred by acquisition of the *van* operon.(2) The operon consists of several genes, with the level of vancomycin resistance mostly determined by the ligase gene, of which *vanA* and *vanB* are the most common in *E. faecalis* and *E. faecium*. Vancomycin resistance is defined as having a minimum inhibitory concentration (MIC) of $\geq 32 \mu\text{g/ml}$, but the *vanA* and *vanB* operons confer high level resistance with MIC $> 256 \mu\text{g/ml}$.

Vancomycin resistant enterococci (VRE) pose a significant problem in health care settings across the world.(5) Following the emergence of VRE 30 years ago, it is now a major cause of health care associated infections, often in patients with significant co-morbidities. There are limited options of antibiotic therapy available for treatment of these infections. The first VRE in Australia, a *vanA E. faecium*, was reported in 1995.(6) Although the VRE landscape in Australia was initially dominated by *E. faecium* harbouring the *vanB* operon, since 2012 there has been a shift towards strains with the *vanA* operon.(7, 8) This emergence of *vanA* harbouring strains was shown to be polyclonal and thought to have arisen within successful hospital-adapted clones.(8)

Infections are often preceded by colonisation, where bacteria are carried in the gastrointestinal system asymptotically. (9-11) The ratio of asymptomatic colonisation to clinically detected infection is thought to be 10:1.(3) Studies have shown that a significant proportion of patients in the health care system are colonised and have an elevated risk of infection and subsequent morbidity and mortality.(9-14) While VRE may be less virulent compared with some other multi-resistant organisms, the limited treatment options are a cause for concern, in particular for highly vulnerable patient populations such as preterm neonates where infections remain a significant cause of mortality.(15) Many guidelines and efforts are therefore aimed at not only preventing infections but also reducing colonisation and spread of colonisation. In a hospital setting it is assumed that VRE is transmitted between patients via the hands of health care staff

or through the hospital environment.(10) Risk factors for VRE colonisation and infection include: admission to intensive care unit (ICU), prolonged hospital stay, residence in long-term care facilities, exposure to colonised/infected patients, exposure to contaminated surfaces, colonisation pressure of the unit, presence of invasive devices, prior antibiotic use and severity of illness.(3) Neonates requiring intensive care have many factors predisposing them for colonisation and VRE may quickly spread within this patient group.(16, 17)

Between January and May in 2017, the Canberra Hospital (CH) experienced its first outbreak of VRE colonisation in the neonatal intensive care unit (NICU) and the special care nursery (SCN). The situation was swiftly brought under control by the rapid implementation of infection control measures that led to the termination of transmission. However, identification of the origin and transmission pathway remained to be elucidated and is the subject of this study.

2 METHODS

2.1 Description of the outbreak and response measures

The outbreak was identified following the detection of VRE in four neonates transferred from CH to a secondary care facility in Canberra between 27 January 2017 and 9 March 2017. The interventions described in this section were conducted during the outbreak and preceded my involvement in this project. As such, it is important to note that I am not taking any credit for this work but have included it as an introduction to the methods section to provide context for the work that I undertook.

Active screening culture (ASC) protocols were implemented at CH on the 15 March 2017, which encompassed screening of neonates at first bowel movement after admission, followed by weekly screening. Faecal samples were collected on swabs and cultured directly onto chromogenic chromID™ VRE agar plates (BioMerieux) and incubated for at least 48 hours. Enterococcus species were identified by MALDI-TOF (Bruker Daltonics) and vancomycin resistance confirmed by Vitek 2 (BioMerieux). Van genotype was determined by Xpert *vanA/vanB* (Cepheid) PCR. Screening immediately identified eight patients in the NICU and SCN colonised with VRE. During the following ASC period another two patients were found to be colonised with VRE. The outbreak was declared contained on the 26 May, following three weeks (24 days) without positive screening cultures.

In addition to the ASC protocols, contact precautions for all VRE colonised patients was implemented as was cohorting of VRE colonised patients into specific areas of the two wards. A VRE working group was established and review of infection control policies, operational protocols and cleaning practice in the two units was also performed. Microbial testing of high-touch environmental surfaces and equipment commonly used between infants was conducted, including weigh machines, length measurer, IV trolleys, ultrasound equipment, cord of the blinds, exit door plate to NICU and SCN, bottle warmers and door handles to isolation rooms. Moistened BD CultureSwab™ (Becton, Dickinson and Company) were used for environmental sampling and sent in Stuart's transport media for microbiological analysis. None of the environmental samples tested positive during the ASC screening period.

2.2 Setting and population

The Canberra Hospital is an adult and paediatric tertiary care centre with 672 beds serving a population of approximately 550,000. The neonatal care service is composed of two sections: the NICU with 21 beds, in two bed bays with one isolation room; and the SCN with 15 beds, in two bed bays with one isolation room. The NICU provides intensive care for seriously ill or premature infants or infants requiring a high level of observation. The SCN provides step-down

care for infants from the NICU or those infants directly admitted requiring care outside of the NICU.

2.3 Study design

A retrospective cohort study was conducted, capturing all patients admitted in the NICU and SCN during the period of 18 December 2016 to 6 May 2017. The timeframe covers the outbreak period and was defined by the earliest admission date of a VRE positive patient and the latest discharge date of a VRE positive patient.

The cohort study design is considered to be superior in the hierarchy of evidence compared with a case-control study, mainly due to the fact that the whole population is used for analysis. Cohort studies uses relative risk or risk ratio (RR) as risk measures, which is more intuitive compared with the odds ratio (OR) used in case-control studies. In some scenarios the $OR \approx RR$, but when the incidence of the outcome exceeds 10% of the population the OR is recognised to be inflated.

However, there are three potential limitations that should also be taken into consideration with regard to the use of a cohort study in this instance. Firstly, the cases and non-cases were selected based on the outcome variable (colonised vs not colonised) and not based on whether they were exposed or not as would be the selection criteria for a cohort study. Secondly, the statistical analysis model for binary outcome variables in a cohort study is log-binomial regression, which is highly vulnerable to collinearity among exposure variables, causing failures in convergence of the model. Thirdly, as a result of the previous point the use of logistic regression is very common for similar studies in the literature and using a risk measure expressed as odds ratio, while less intuitive may allow for easier comparisons with previous studies.

2.4 Variables and definitions

Colonisation was used as the outcome variable and was defined as patients admitted to the NICU and SCN during the period 18 December 2016 to 6 May 2017 and had one or more cultured specimen positive for a VRE. Non-colonised patients were defined as any patient that was admitted to the NICU or SCN during the same period and had no positive cultured specimens and at least one negative cultured specimen for a VRE.

Plausible exposure variables were identified from published literature and from discussions with infectious disease and infection prevention and control specialists. Patient variables collected are listed in **Table 1** and **Table 2**.

Data analysis was carried out in STATA v.15 (StataCorp LLC, Texas, USA) and the scripts used are provided in **Appendix 3C**. To determine significant risk factors for colonisation univariate regression was conducted on all variables. A log binomial regression model was first explored

but found to fail for some exposure variables with continuous values. Zou proposed a solution to the problem by using a modified Poisson regression with robust error variances (18). This model was used for the calculation of RR and 95% confidence intervals for all exposure variables in the univariate analysis.

However, even this modified model failed to converge when attempting a multivariate analysis. A common cause for this is collinearity between exposure variables. The relationship between variables was therefore assessed using Pearson's correlation coefficients and multi-collinearity analysis using the *Collin* custom STATA script. The former shows the pairwise relationship between variables and expressed as R^2 . The multi-collinearity analysis highlights variables that are collinear with one of more of the other variables in the test but does not provide information on which variables interact. The measure of collinearity is the variance inflation factor (VIF) and is $1/(1-R^2)$. A VIF of >5 is considered an indication for caution (this corresponds to a $R^2=0.8$).

In the end a logistic regression model had to be used. Variables with a $p < 0.1$ in the univariate analysis were selected for inclusion in a backward-stepwise multivariate logistic regression model with the p -value threshold for elimination set at 0.05.

2.5 Whole genome sequencing

Eleven VRE isolates obtained from patients in the outbreak were referred to the Microbiological Diagnostic Laboratory Public Health Laboratory for whole genome sequencing (WGS). Isolates were not available from the first three patients in the outbreak. Genomic DNA was extracted using the JANUS automated workstation with the Chemagic Viral DNA/RNA kit (PerkinElmer). Unique dual indexed libraries were prepared using the Nextera XT DNA sample preparation kit (Illumina). Libraries were sequenced on the Illumina NextSeq 500 with 150-cycle paired end chemistry as described by the manufacturer's protocols. The Nullarbor pipeline (version 2.0, <https://github.com/tseemann/nullarbor>) was used for all bioinformatics analysis with an in-house ST1421 reference genome.(19) Gubbins was used to detect regions of recombination, which were removed, and IQtree was used to infer the maximum likelihood phylogeny from the resulting core SNP alignment. (20-23)

2.6 Ethics

Ethics approval for the study was obtained from the ACT Health Human Research Ethics Committee (Protocol number ETHLR.17.155) and from the Australian National University Human Research Ethics Committee (Protocol number 2017/536).

3 RESULTS

3.1 Outbreak cohort

During the study period of 18 December 2016 to 6 May 2017 a total of 91 patients were admitted to the NICU and SCN at TCH. Of these, 14 were found to be colonised with VRE during their admission. The remaining 77 were negative for VRE throughout their admission, resulting in a VRE prevalence of 15.4%. Latest discharge date of a non-colonised patient was 26 June 2017. The admission timelines for all patients is shown in **Figure 1**. Most patients had relatively long hospital admissions and frequently moved bed space.

3.2 Risk factors for VRE colonisation

3.2.1 Univariate analysis

Univariate modified Poisson regression was performed to assess the predictive value of individual variables on the colonisation outcome. Increased risk of colonisation were observed for early gestational age, low birth weight, length of stay, requirement for respiratory support with ventilation or CPAP or high-flow oxygen, use of incubator with humidity, infection with other organisms, total parenteral nutrition (TPN), presence of central lines, bed moves, select antibiotics and antenatal steroids (**Table 1**). Significant differences in frequency or duration of use were seen for bed moves, ventilation, CPAP, incubator use, TPN, radiology and phototherapy (**Table 2**). Interestingly, the mean durations of antibiotics use were not significantly different between colonised and non-colonised patients.

Table 1 Univariate analysis for risk of VRE colonisation with categorical exposure variables. Variables are given as number of patients, with per centage in brackets. For categorical analysis of gestational age, due to presence of zero values the “Normal” and “Moderate to late preterm” were combined and used as reference group.

Variable	Case (%) n=14	Control (%) n=77	RR	95% CI	p-value
Male sex	9 (64.3)	41 (53.3)	1.48	0.53-4.08	0.453
Gestational age categories			2.84	1.78-4.53	<0.001
Normal	0	30 (39.0)	} 1		
Moderate to late preterm	4 (28.6)	35 (45.5)			
Very preterm	3 (21.4)	5 (6.5)	6.47	1.75-23.87	0.005
Extremely preterm	7 (50)	7 (9.1)	8.63	2.91-25.55	<0.001
Gestational weight categories			2.13	1.41-3.20	<0.001
Normal (≥2500g)	2 (14.3)	33 (42.9)	1		
LBW (≥1500g <2500g)	3 (21.4)	32 (41.6)	1.55	0.24-9.88	0.645
VLBW (≥1000g <1500g)	3 (21.4)	5 (6.5)	9.9	1.31-74.73	0.026
ELBW (<1000g)	6 (42.9)	7 (9.1)	14.14	2.35-85.23	0.004
Born at TCH	12 (85.7)	69 (89.6)	0.74	0.19-2.86	0.664
Delivery, caesarean section	6 (42.9)	35 (45.5)	0.91	0.34-2.44	0.858

Variable	Colonised n=14 (%)	Not colonised n=77 (%)	RR	95% CI	p-value
Resuscitation at delivery	10 (71.4)	45 (58.4)	1.64	0.55-4.85	0.374
PPV	4 (30.8)	36 (46.8)	0.90	0.24-3.36	0.875
Intubation	6 (46.2)	9 (11.7)	3.60	1.18-11.02	0.025
Respiratory support					
Ventilation	5 (35.7)	7 (9.1)	3.66	1.46-9.12	0.005
CPAP, days	9 (64.3)	23 (29.9)	3.32	1.21-9.12	0.020
High-flow oxygen	3 (21.4)	2 (2.6)	4.69	1.89-11.64	0.001
Incubator	11 (78.6)	44 (57.1)	2.40	0.71-8.07	0.157
with humidity	8 (57.1)	8 (10.4)	6.25	2.50-15.61	<0.001
Feeding tube	14 (100)	76 (98.7)	1.55	0.94-2.56	0.088
Total parenteral nutrition	10 (71.4)	24 (31.2)	4.19	1.42-12.40	0.010
Radiology	12 (85.7)	46 (59.7)	3.41	0.81-14.45	0.095
Phototherapy	13 (92.9)	53 (68.8)	4.92	0.67-36.10	0.117
Central line	9 (64.3)	15 (19.5)	5.03	1.86-13.58	0.001
Peripheral line	9 (64.3)	60 (77.9)	0.57	0.21-1.54	0.271
Comorbidities					
Infection with other organisms	7 (50)	13 (16.9)	3.55	1.40-8.98	0.007
Thrombocytopenia	2 (14.3)	5 (6.5)	2.00	0.55-7.27	0.292
Hyponatraemia	3 (21.4)	10 (13.0)	1.64	0.52-5.12	0.397
Hypoglycaemia	5 (35.7)	36 (46.8)	0.68	0.24-1.87	0.453
Antibiotic therapy					
Benzylpenicillin	10 (71.4)	35 (45.5)	2.67	0.90-7.94	0.077
Gentamicin	11 (78.6)	36 (46.8)	3.43	1.02-11.57	0.047
Ampicillin	3 (21.4)	3 (3.9)	3.86	1.45-10.26	0.03
Azithromycin	0	1 (1.3)	-	-	-
Cephazolin	0	1 (1.3)	-	-	-
Cotrimoxazole	0	1 (1.3)	-	-	-
Erythromycin	1 (7.1)	0	-	-	-
Flucloxacillin	6 (42.9)	8 (10.4)	4.13	1.68-10.12	0.002
Linezolid	0	1 (1.3)	-	-	-
Meropenem	1 (7.1)	1 (1.30)	3.42	0.78-15.07	0.104
Vancomycin	2 (14.3)	2 (2.6)	3.63	1.19-11.09	0.024
Metronidazole	2 (14.3)	2 (2.6)	3.63	1.19-11.09	0.024
Nystatin drops	9 (64.3)	11 (14.3)	6.39	2.40-17.02	<0.001
Nystatin cream	9 (64.3)	11 (14.3)	6.39	2.40-17.02	<0.001
Maternal issues (for three patients the maternal information was not available)					
Diabetic mother	1 (7.1)	21 (28.4)	0.23	0.03-1.68	0.148
Twin pregnancy	4 (28.8)	11 (14.9)	1.95	0.70-5.42	0.202
Chorioamnionitis	0	10 (13.5)	1	-	-
PROM	5 (35.7)	13 (17.1)	2.22	0.84-5.86	0.106
Antenatal medication					
Antibiotics	3 (25.0)	14 (19.4)	1.31	0.40-4.36	0.656
Steroids	6 (50.0)	9 (12.5)	4.6	1.71-12.38	0.003
Multivitamin	2 (16.7)	22 (30.6)	0.50	0.12-2.13	0.349
Vitamin D	4 (33.3)	13 (18.1)	1.97	0.67-5.82	0.219

Table 2 Univariate analysis for risk of VRE colonisation with continuous exposure variables. Duration in days, unless stated by variable title. For continuous variables the mean $\pm$ standard deviation (SD) is given. The mean does not include patients for which the variable was not used.

Variable	Colonised n=14	Not colonised n=77	RR	95% CI	p-value
Gestational age, weeks	29.3 $\pm$ 4.1	34.9 $\pm$ 4.2	0.81	0.74-0.89	<0.001
Range, weeks	24-35.6	24.6-41.5			
Gestational weight, grams	1324.6 $\pm$ 701.5	2369.1 $\pm$ 901.0	0.999	0.998-0.999	<0.001
Range, grams	492-2747	540-4230			
Length of stay	55.2 $\pm$ 35.6	20.7 $\pm$ 23.6	1.04	1.02-1.06	<0.001
Bed moves	3.57 $\pm$ 2.44	2.69 $\pm$ 1.57	1.21	1.01-1.46	0.044
Ward switches	1.14 $\pm$ 1.17	0.90 $\pm$ 0.74	1.33	0.75-2.36	0.328
Respiratory support					
Ventilation	15.3 $\pm$ 31.1	3.7 $\pm$ 5.8	1.01	1.00-1.02	0.006
CPAP	32.6 $\pm$ 18.7	7.2 $\pm$ 15.8	1.04	1.02-1.06	<0.001
High-flow oxygen	2.4 $\pm$ 2.0	5 $\pm$ 0	0.78	0.56-1.10	0.161
Incubator	31.4 $\pm$ 21.9	7.6 $\pm$ 8.0	1.04	1.03-1.06	<0.001
with humidity	14.5 $\pm$ 1.9	13 $\pm$ 4.9	1.08	0.92-1.27	0.328
Central line					
Umbilical Vein Catheter (UVC)	3.9 $\pm$ 4.4	0.7 $\pm$ 2.1	1.06	0.93-1.20	0.417
Umbilical Artery Catheter (UAC)	1.8 $\pm$ 2.5	0.6 $\pm$ 1.8	0.92	0.68-1.23	0.558
Peripherally Inserted Central Catheter (PICC)	7.9 $\pm$ 11.3	1.5 $\pm$ 4.6	1.05	0.99-1.11	0.094
TPN	17.3 $\pm$ 12.5	7.6 $\pm$ 4.3	1.06	1.03-1.09	<0.001
Radiology	8.5 $\pm$ 6.2	4.3 $\pm$ 4.5	1.09	1.03-1.15	0.002
Phototherapy	5.5 $\pm$ 3.8	3.9 $\pm$ 2.6	1.14	1.01-1.29	0.039
Antibiotic therapy					
Benzylpenicillin	3.1 $\pm$ 1.8	2.7 $\pm$ 1.0	1.17	0.85-1.62	0.339
Gentamicin	4.5 $\pm$ 3.1	3.6 $\pm$ 2.2	1.10	0.94-1.30	0.244
Ampicillin	5.3 $\pm$ 3.8	3.0 $\pm$ 0	1.20	0.80-1.79	0.377
Azithromycin	0	3 $\pm$ 0	-	-	-
Cephazolin	0	1 $\pm$ 0	-	-	-
Cotrimoxazole	0	41 $\pm$ 0	-	-	-
Erythromycin	3 $\pm$ 0	0	-	-	-
Flucloxacillin	3.5 $\pm$ 2.1	4.1 $\pm$ 3.2	0.94	0.74-1.20	0.636
Linezolid	0	2 $\pm$ 0	-	-	-
Meropenem	6 $\pm$ 0	2 $\pm$ 0	-	-	-
Vancomycin	3 $\pm$ 0	5.5 $\pm$ 4.9	0.77	0.49-1.22	0.273
Metronidazole	3 $\pm$ 1.4	3.5 $\pm$ 0.7	0.71	0.22-2.32	0.568
Nystatin drops	13.3 $\pm$ 4.9	10.5 $\pm$ 5.5	1.07	0.94-1.21	0.300
Nystatin cream	13.3 $\pm$ 4.9	12.1 $\pm$ 5.8	1.03	0.92-1.14	0.621

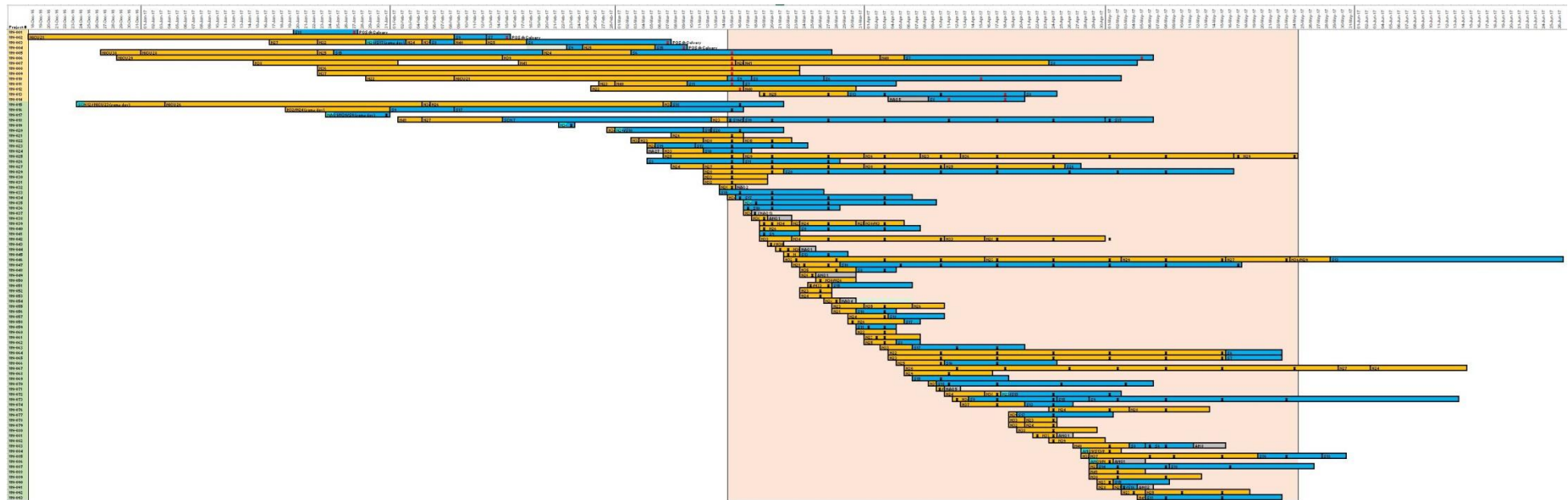


Figure 1 Admission timeline of all 91 patients admitted in the NICU or SCN wards during the outbreak period. Time in days is shown at the top of the figure, and on the left is a list of all the patients, colonised in yellow (n=14) and non-colonised in green (n=77). Admission is shown as coloured bars, where yellow=NICU and blue=SCN. The period during which the active screening culture protocol was active is indicated in light brown. Days on which patients were screened for VRE is indicated by an “X”, red=positive VRE culture, black=negative VRE culture.

Chapter 3 – Epidemiological study of VRE in NICU

	gestational age	preterm categories	birthweight	birthweight categories	length of stay (days)	resuscitation (y/n)	ventilation (y/n)	CPAP (y/n)	CPAP_days	high-flow oxygen (y/n)	TPN (y/n)	TPN (days)	infection (y/n)	incubator with humidity (y/n)	incubator (days)	central line (y/n)	UVC (days)	UAC (days)	PICC (days)	radiology (days)	benzylpenicillin (y/n)	gentamicin (y/n)	ampicillin (y/n)	flucloxacillin (y/n)	nystatin drops (y/n)	nystatin cream (y/n)
gestational age	1																									
preterm categories	-0.849	1																								
birthweight	0.8924	-0.7233	1																							
birthweight categories	-0.8836	0.8203	-0.9015	1																						
length of stay (days)	-0.7049	0.7856	-0.6348	0.7268	1																					
resuscitation (y/n)	-0.3716	0.4024	-0.331	0.3432	0.2789	1																				
ventilation (y/n)	-0.4402	0.5821	-0.3649	0.481	0.5087	0.1825	1																			
CPAP (y/n)	-0.5067	0.6331	-0.4642	0.5936	0.5932	0.3134	0.3932	1																		
CPAP_days	-0.6888	0.8228	-0.588	0.7073	0.7561	0.337	0.5051	0.601	1																	
high-flow oxygen (y/n)	-0.1129	0.0819	-0.093	0.0935	0.1489	0.0498	0.0482	0.2941	0.154	1																
TPN (y/n)	-0.5774	0.6005	-0.5708	0.6086	0.5341	0.1603	0.5046	0.3827	0.4898	0.0563	0.1467	0.6958	1													
TPN (days)	-0.6047	0.6597	-0.5443	0.6204	0.5681	0.2094	0.6203	0.423	0.5664	0.1467	0.6958	1														
infection (y/n)	-0.3042	0.3261	-0.36	0.3953	0.563	0.1038	0.2637	0.3872	0.247	0.1508	0.3581	0.3089	1													
incubator with humidity (y/n)	-0.7488	0.885	-0.6582	0.7961	0.8237	0.3737	0.5025	0.6272	0.8047	0.1692	0.4787	0.4854	0.3823	1												
incubator (days)	-0.6901	0.7209	-0.63	0.697	0.7425	0.2666	0.4907	0.499	0.7273	0.2354	0.5254	0.607	0.2488	0.7448	1											
central line (y/n)	-0.4793	0.6241	-0.4258	0.5434	0.5987	0.2292	0.5775	0.3949	0.5685	0.1189	0.5687	0.5176	0.405	0.7062	0.5533	1										
UVC (days)	-0.3262	0.4469	-0.3176	0.4086	0.4805	0.1841	0.3991	0.403	0.4237	0.2116	0.4023	0.3367	0.3284	0.5831	0.42	0.7288	1									
UAC (days)	-0.5286	0.673	-0.4791	0.5673	0.5986	0.2955	0.6663	0.3898	0.6598	0.049	0.447	0.3071	0.3096	0.6772	0.5052	0.6811	0.4053	1								
PICC (days)	-0.6089	0.7242	-0.5131	0.6188	0.6779	0.2416	0.6688	0.4382	0.5848	0.1169	0.4646	0.5911	0.375	0.7254	0.7086	0.6359	0.2679	0.6817	1							
radiology (days)	-0.5892	0.7213	-0.529	0.6597	0.8479	0.305	0.6027	0.5916	0.6585	0.1961	0.5334	0.5309	0.6351	0.7587	0.6345	0.6744	0.5319	0.7139	0.762	1						
benzylpenicillin (y/n)	-0.2762	0.4042	-0.2327	0.2902	0.4043	0.1982	0.2728	0.3006	0.2685	0.1204	0.4346	0.2986	0.283	0.3618	0.3576	0.4689	0.3643	0.3207	0.3558	0.3827	1					
gentamicin (y/n)	-0.3202	0.4582	-0.3076	0.377	0.5093	0.2066	0.3121	0.2981	0.3612	0.1053	0.52	0.3357	0.4604	0.4469	0.3853	0.5292	0.4063	0.3944	0.3683	0.5124	0.8922	1				
ampicillin (y/n)	-0.1168	0.0974	-0.1847	0.1762	0.1581	-0.0567	0.1582	-0.0102	0.0528	0.0188	0.344	0.3742	0.3937	0.1099	0.1819	0.3434	0.1533	0.0267	0.3459	0.3086	0.0974	0.2571	1			
flucloxacillin (y/n)	-0.3727	0.4309	-0.4073	0.4816	0.5912	0.0958	0.3739	0.3876	0.3258	0.0538	0.3632	0.3524	0.8034	0.5231	0.3358	0.5051	0.4566	0.4298	0.4858	0.7212	0.2579	0.4126	0.3776	1		
nystatin drops (y/n)	-0.6496	0.685	-0.5877	0.6551	0.7432	0.2666	0.3422	0.4428	0.6767	0.1312	0.4129	0.4657	0.4232	0.8005	0.671	0.5857	0.4802	0.4579	0.5316	0.5627	0.3361	0.4073	0.0729	0.4356	1	
nystatin cream (y/n)	-0.6496	0.685	-0.5877	0.6551	0.7432	0.2666	0.3422	0.4428	0.6767	0.1312	0.4129	0.4657	0.4232	0.8005	0.671	0.5857	0.4802	0.4579	0.5316	0.5627	0.3361	0.4073	0.0729	0.4356	1	1

Figure 2 Correlation coefficients between risk variables. Coefficients >0.67 to 0.80 or <-0.67 to -0.80 are marked pink, and coefficients >0.8 or <-0.8 are marked red.

The relationships between variables with a significant association in the univariate analysis are shown in **Figure 2**. There was strong correlation between the gestational age variable and birthweight, CPAP days and incubator with humidity. The first is a function of the gestational age, and the latter two are standard treatments for the infants with underdeveloped lungs and skin respectively. These factors are also in turn correlated with a longer hospital admission. Flucloxacillin was frequently prescribed for infections other than VRE in the infant population, explaining this link. The two nystatin treatments are standard anti-fungal prophylaxis used for infants when in humidity chambers. Use of central lines is also correlated with early gestational age. The multi-collinearity analysis shows high values for the same variables (**Table 3**), with a particularly high caution for the “incubator with humidity” variable, which is covariant with several other variables as described above.

Table 3 Multi-collinearity analysis of variables associated with colonisation in the univariate analysis. A VIF of ≥ 5 is considered cautionary. VIF=variance inflation factor, R^2 =correlation coefficient.

Variable	VIF	R^2
preterm categories	11.7	0.9146
birthweight categories	4.69	0.7869
length of stay (days)	8.78	0.8861
resuscitation (y/n)	1.35	0.2619
ventilation (y/n)	3.8	0.7371
CPAP (y/n)	2.81	0.6447
CPAP (days)	6.32	0.8418
high-flow oxygen (y/n)	1.45	0.3094
TPN (y/n)	3.14	0.6815
TPN (days)	7.38	0.8646
infection (y/n)	4.97	0.7989
incubator with humidity (y/n)	22.54	0.9556
incubator (days)	4.56	0.7805
central line (y/n)	6.46	0.8453
UVC (days)	4.76	0.7899
UAC (days)	7.84	0.8725
PICC (days)	11.36	0.912
radiology (days)	11.16	0.9104
benzylpenicillin (y/n)	9.33	0.8928
gentamicin (y/n)	10.64	0.906
ampicillin (y/n)	2.67	0.6255
flucloxacillin (y/n)	4.76	0.7898
nystatin drops (y/n)	4.51	0.7785
Mean VIF	6.83	

3.2.2 Multivariate analysis

Variables with a $p < 0.1$ in the univariate analysis were selected for inclusion in a backward stepwise multivariate logistic regression model. Collinearity was observed with the

benzylpenicillin and gentamicin variables, and with nystatin cream and nystatin drops, where inclusion of both in the multivariate model resulted in a failure to converge. When only gentamicin and one of the nystatin treatments were included the model successfully completed. The final reduced multivariate model showed significant association with only gestational age (WHO preterm categories), with an odds ratio (OR) of 4.08, (95%CI 2.01-8.27). A likelihood ratio test of the full model and the reduced model showed no significant contributions from the removed exposure variables ($p=0.709$). The OR of the gestational age variable resulting from the logistic regression is higher than the previously calculated RR of this variable in the univariate analysis using the modified Poisson regression. Given the incidence of colonisation was relatively high, the logistic regression is likely overestimating the risk association, and the univariate RR of 2.84 provides a more reliable measure. The stratified RR for gestational age shows that infants that were very preterm or extremely preterm had a 6.47-fold or 8.63-fold risk, respectively, of being colonised compared with infants that were moderate to late preterm or full term.

3.3 Whole genome sequencing

Vancomycin resistant *E. faecium* isolates from eleven of the infants in the outbreak were whole genome sequenced. *In silico* multi locus sequence typing (MLST) showed that all the isolates were sequence type 1421 (ST1421), with the allelic profile *atpA*(1), *ddl*(1), *gdh*(1), *purK*(1), *gyd*(1), *pstS*(0), *adk*(1). These *pstS* null strains were previously classified as non-typeable but have now been assigned sequence types in the MLST scheme, following the definition of *pstS* null alleles as 0. ST1421 is a single locus variant of ST17, a common hospital associated clone. The genomic analysis confirmed the initial PCR based results showing the presence of the *vanA* gene.

Phylogenetic reconstruction of the 11 isolates are shown in context with 7 *E. faecium* ST1421 *vanA* isolates collected over a 9-day period in late 2016 from the orthopaedic ward of CH, and 27 consecutive *E. faecium* ST1421 *vanA* isolated during a one-month period in late 2015 at ACT Pathology (including CH and other ACT hospitals) (**Figure 3**). The violin plot shows that all 11 isolates were highly clonal with single nucleotide polymorphism (SNP) distances ranging from 0 to 5 core genome substitutions (**Figure 4**), a considerably smaller range compared with that of the sample set as a whole (0-59 SNPs). The orthopaedic isolates which were collected over a short time period show a much greater pairwise SNP range (2-44 SNPs), and with three separate clusters in the phylogenetic tree.

Raw sequence reads have been uploaded to the Sequence Read Archive at the National Center for Biotechnology Information under BioProject PRJNA495857. The sample names are listed in **Appendix 3D**.

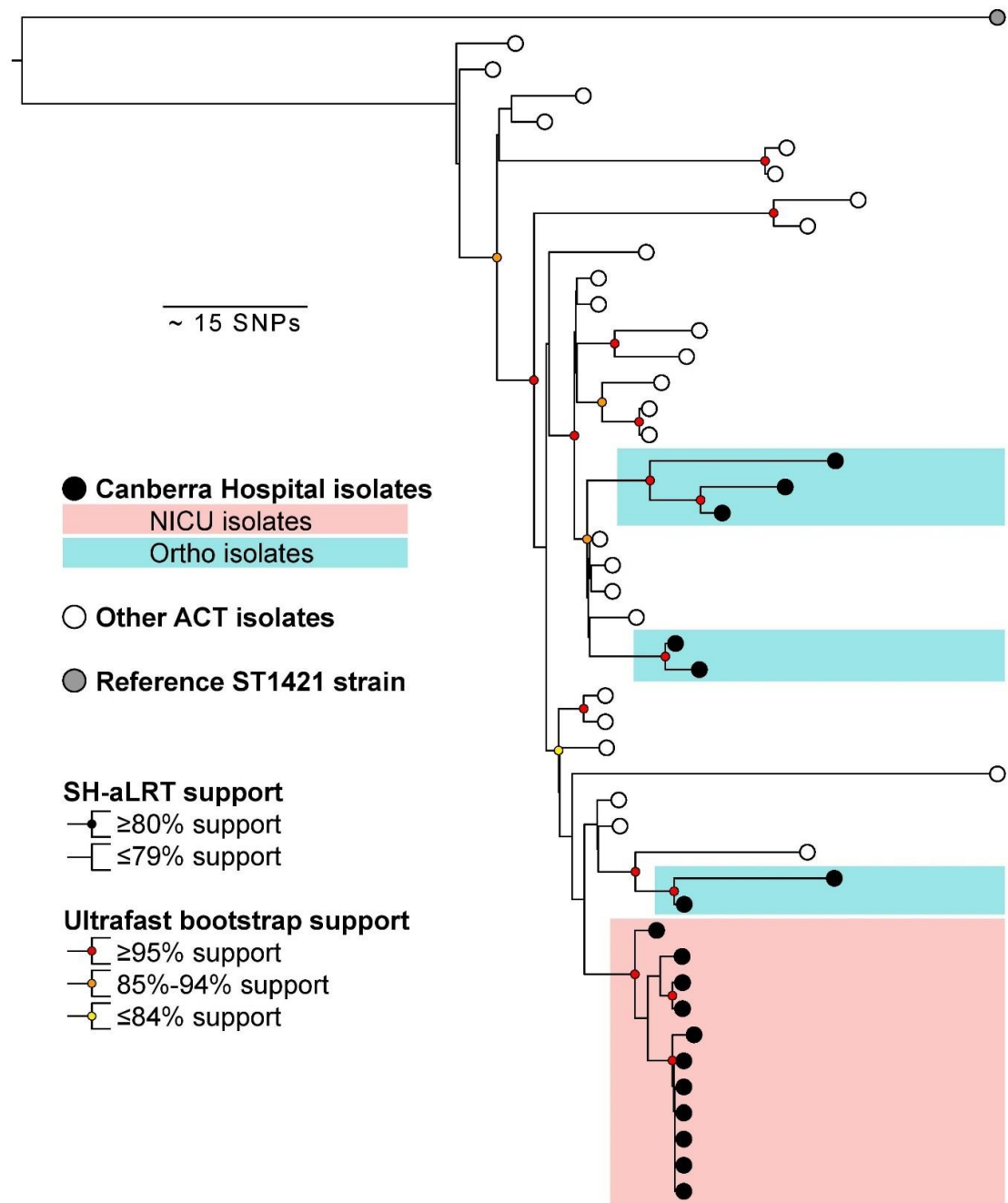


Figure 3 Maximum likelihood phylogenetic reconstruction based on core genome SNPs. Whole genome sequencing data for isolates from 11 of the infants in the outbreak (isolates not available from 3 infants), seven ST1421 isolates from the orthopaedic unit at CH and 27 ST1421 submitted from ACT Pathology during late 2015. NICU outbreak cluster is highlighted in pink and orthopaedic clusters are highlighted in teal.

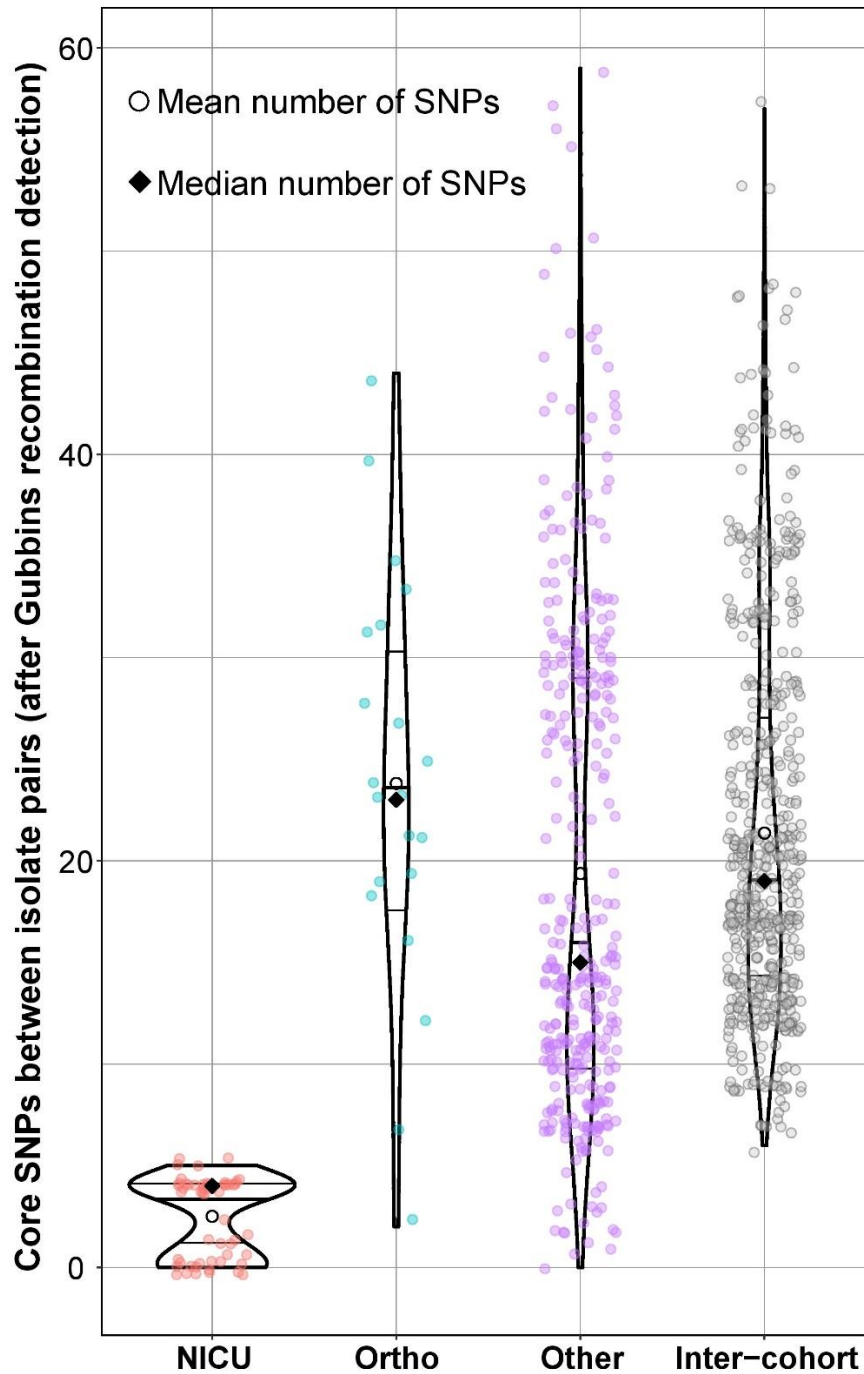


Figure 4 Violin plots showing the range of pairwise SNP distances between isolates within each of the cohorts: isolates from 11 of the infants in the NICU outbreak (pink), seven ST1421 isolates from the orthopaedic unit at CH (teal) and 27 ST1421 submitted from ACT Pathology during late 2015 (purple), and the inter-cohort (grey). Shown is the mean, median, and interquartile ranges of pairwise SNP distances.

3.4 Patient ward and bed movements

There were many bed movements among the NICU and SCN patients, both within and between the NICU and SCN wards, as can be seen from the pattern in **Figure 1**. Colonised patients had an average of 3.6 bed movements during their admission, and non-colonised patients had an average of 2.7 bed movements. The difference was not statistically significant. Movement between the NICU and SCN wards was less pronounced with averages of 1.14 and 0.90 for colonised and non-colonised patients, respectively. The heat map of bed occupancy for infants colonised with VRE during the outbreak period shows that some bed spaces were more frequently used (**Figure 5**). Bed space 40 in the NICU was used for cohorting of colonised infants during the ASC.

There were some instances where patients were moved into bed spots immediately following the previous patient, some with time-gaps as short as 29 min and 60 min.

3.5 Staffing aspects

During interviews with the head nurse of the NICU it was revealed that the unit had experienced staffing shortages in the time leading up to and during the outbreak period. The shortages led to the frequent use of non-regular staff to fill shifts, including staff that also worked in other units in the hospital. Anecdotally some staff would move from a half-day shift in one unit straight into a half-day shift in the NICU. This is obviously a concern for possible transmission of VRE from other units into the NICU. The shortages also resulted in the frequent movement and clustering of infants such that a smaller number of staff would be able to provide appropriate monitoring and care of multiple patients.

Despite repeated efforts we have not been able to obtain staffing data from the Canberra Hospital and therefore were unable to explore these potential transmission pathways further.

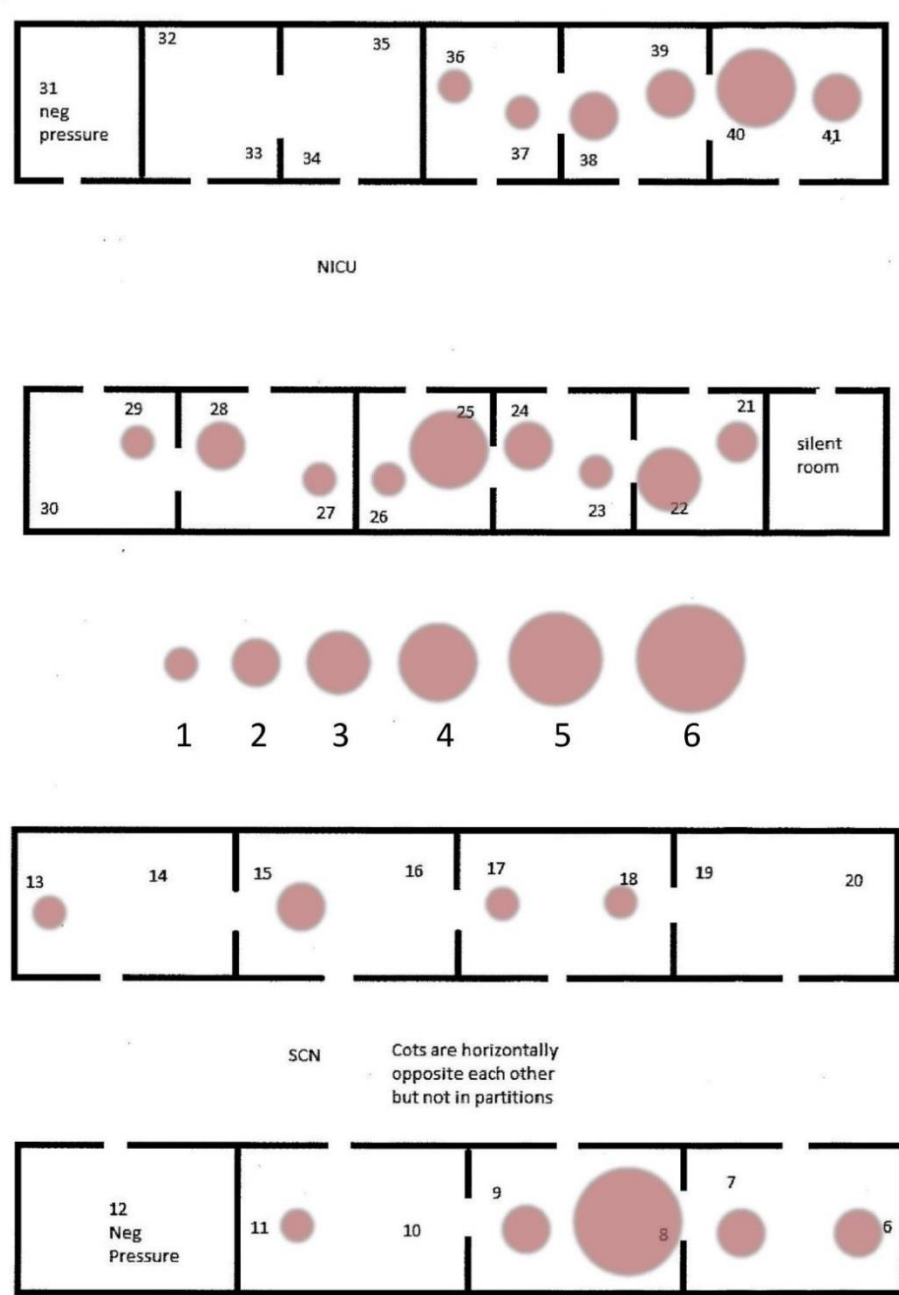


Figure 5 Heat map of colonised patient locations during admission. The size of the dot indicates how many different patients occupied the bed space during the outbreak period. Some patients moved during their admission and may have occupied multiple beds.

4 DISCUSSION

The outbreak subject to this investigation represents the first known occurrence of VRE colonisation in the NICU and SCN wards at CH. Neonates in these units have no contact with other patients and interactions only with a limited number of health care workers, immediate carers, and the hospital environment. VRE colonisation in this patient group must therefore be a direct result of a breakdown in infection control procedures within these units. Colonisation and infection with VRE have been identified among patients in other wards of CH, suggesting that a cross contamination event could have led to the introduction of VRE into the NICU/SCN environment, similar to that described in a previous study.(24) Once the environment had been contaminated it is possible that procedures within the units led to dissemination of VRE to several patients.

The range of variables found to be associated with colonisation at a univariate level in our study is consistent with those observed in the literature. Variables associated with VRE colonisation previously observed in NICU outbreaks include: prematurity (17, 25-27); low birth weight (1, 17, 25-27); prepartal antibiotics (25); longer duration of antibiotic therapy (1, 17, 26, 28); administration of second line antibiotics (16), long hospitalisation (17, 26-29); mechanical ventilation (26, 27); presence of a central line (17, 26, 27); presence of peripheral lines (17); parenteral nutrition (17, 26, 27); major surgery (26); episodes of clinical features compatible with infection (26); nasogastric feeding (17, 27); ultrasonography (27); administration of CPAP (17); use of oxyhood (17); procedures by non-NICU staff (17); and consultations by non-NICU staff (17).

Many of the above risk factors are covariant with each other, and cause problems with interactions in the analysis process. The level of covariation is obvious for some variables. For instance, several of the antibiotics used for infants are co-administered, such as benzylpenicillin and gentamicin, and the nystatin cream and nystatin oral drops. Other interactions are less obvious. The aforementioned benzylpenicillin and gentamicin combination is used as an empirical treatment for presumed infection in premature infants. As such, these two antibiotics will have a strong correlation with a low gestational age. Similarly, premature infants have an underdeveloped skin barrier and are treated in an incubator with humidity. This environment is very conducive to fungal infections and nystatin cream and nystatin oral drops are used as antifungal prophylaxis. Therefore, both the nystatin treatments and the treatment in an incubator with humidity will be associated with a low gestational age. These interactions make it difficult to identify unique risk factors associated with VRE colonisation. Multiple regression analysis was used to try to detangle these interactions.

In this study we found that after adjusting for all other variables only gestational age remained significantly associated with colonisation. Our results agree with published data. In previous studies that have conducted a multivariate analysis, most observed a similar drastic reduction in the number of associated variables: gestational age only (25); gestational age, longer duration in hospital, use of antibiotics and presence of central lines (26); birth weight and days of antimicrobial therapy (17); administration of second line antibiotic and hospital admission during specific period (16); gestational age, anti-MRSA therapy, and ultrasonography (27). There may be several mechanisms by which gestational age contribute to colonisation. Premature infants have been shown to become colonised with a lower species complexity, composed of few *Bifidobacteria* spp. and higher rate of potentially pathogenic bacteria.(30-34) The establishment of a gut microbiome is further disrupted by empiric use of antibiotics.(31, 33, 35) Furthermore, birth at an early gestational age usually results in a longer hospital stay, thereby increasing the exposure time to potentially contaminated health care settings.

As there was no routine testing for VRE conducted for admitted patients prior to the outbreak response it is difficult to establish with certainty when the introduction of VRE into the units occurred. The frequent transfers to the secondary care hospital, which routinely test transferred infants for MROs, suggests it is likely that this was a relatively recent introduction as there had not been any previous alerts. As most of the patients were admitted prior to the ASC screening, they may have been colonised at any previous time point. There were two infants who may have had exposures outside CH, with one admitted on day 41 of life. The other was born at CH but transferred to another hospital for a procedure, after which the patient was readmitted to the NICU at CH. Two patients were admitted after the commencement of the ASC screening. Their admission histories show only exposure to the SCN ward while some other patients only had exposure to the NICU ward, thus indicating that both wards were likely to be contaminated and had transmission events.

Following the alert of VRE positive infants transferred to the secondary level hospital a suite of measures was implemented to control the outbreak. Several of these measures have previously been proven to be successful in the eradication of large scale VRE outbreaks, such as formation of a VRE executive working group, mass screening, cohorting of carriers, environmental screening and review of cleaning procedures and operational protocols.(36) It is well recognised that the hospital environment can be a reservoir for VRE.(10, 37-39) In our study there were no positive swabs indicating environmental contamination, although this could also be due failure to identify the contaminated sites to sample or methodological failures, such as inhibition due to residual cleaning agents on the sampled surfaces. The frequent bed movement of patients is a potential concern, especially if there is insufficient cleaning of the evacuated bed spot in

between patients. There were two observed instances in the colonised patient cohort where the turn-around times (29 and 60 minutes) were unlikely to have been sufficient to conduct a thorough clean and decontamination of the patient environment.

A genomic analysis of the rise of Australian *E. faecium* *vanA* in recent years showed that the expansion was polyclonal and not the result of expansion of a single successful clone.(8) The 2014 Australian Enterococcal Sepsis Outcome Program (AESOP) showed that *E. faecium* had five dominating sequence types: ST17, ST117, ST203, ST555, and ST796.(40) An interesting feature in Australia is the recent emergence of health care associated *E. faecium* strains where the *pstS* allele has been deleted from the genome, initially described by Carter and colleagues.(41) These strains were shown to be present in multiple Australian jurisdictions and nearly universally displayed a vancomycin resistant phenotype. There was significant diversity in the core genome among the 66 studied isolates, with a maximum pairwise SNP distance of 4543. The phylogenetic reconstruction showed clustering of isolates by hospitals. In a recent study of 240 *E. faecium* *vanA* isolates from 12 ICUs in New South Wales, Australia, 60.0% were ST1421 and 24.2% ST1424 (allelic profile *atpA*(9), *ddl*(1), *gdh*(1), *purK*(1), *gyd*(12), *pstS*(0), *adk*(1)) .

The range of pairwise SNP distances within the 45 samples analysed in the present study is considerably smaller than that described for the national sample set presented by Carter *et al.*, supporting the observation of clustering of clones by hospitals described in Carter *et al* and van Hal *et al*. The ST1421 samples from the NICU outbreak form a tight cluster clearly derived from a ST1421 clonal lineage endemic in the CH environment. The samples were highly clonal, with short internal branch lengths suggestive of a recent point source introduction and subsequent transmission within the unit. In contrast, the dispersed nature of the samples from the orthopaedic unit distributed between multiple clusters in the phylogenetic tree is indicative of multiple exposures and introductions, which is interesting considering the relatively short time period over which these samples were collected. The orthopaedic ward has a patient population with a much more diverse exposure history, compared with the naïve patient population of the NICU. The data supports the hypothesis that VRE causing colonisation in the NICU/SCN was likely acquired from cross-contamination in the hospital, rather than being imported from the community.

There are two main limitations to this study. Firstly, the lack of routine VRE screening makes it difficult to determine the exact time point of VRE acquisition in patients and the introduction of the organism into the units. Secondly, the dearth of data on ST1421 and VRE in general in the wider community outside the health care system limits our ability to exclude the possibility that the VRE observed in the NICU and SCN was introduced from a community source, rather than

from an intra-hospital transmission event. One additional limitation is the potential misclassification bias of colonisation status. As the patients were not screened on discharge, there may have been patients assigned as controls that became colonised between the last screening point and their discharge. With the weekly screening frequency this would be highly unlikely, but not impossible.

The presence of a disseminated VRE clone within the hospital increases the probability of future outbreaks. Implementation of routine surveillance screening for MROs regularly during the NICU admission, would lead to earlier detection of colonisation in the future.(42) The already high and increasing rates of VRE seen in Australia, means constant vigilance is advisable to prevent large-scale outbreaks in the future.

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APPENDIX 3A – Presentation at the 9th Southeast Asia and Western Pacific Bi-regional TEPHINET Scientific Conference, Vientiane, People's Democratic Republic of Lao, 5-9 November 2018 and at the PHAA Australian Public Health Conference, Cairns 26-28 September 2018

Format: Long oral (10min + 5 min questions)

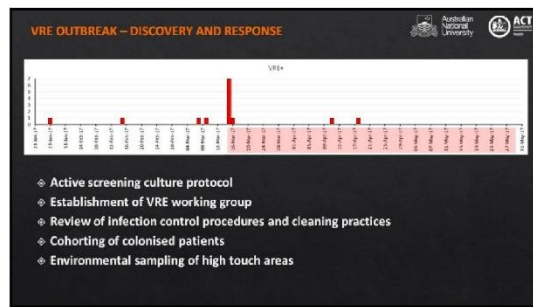
A similar presentation was also given to staff in the Infectious Diseases and the Infection Control units at the Canberra Hospital, in April 2018

Chapter 3 – Epidemiological study of VRE in NICU

Vancomycin resistant enterococci in the neonatal intensive care unit at Canberra Hospital – an unfortunate premiere –

Dr Patlyan Andersson
M.Phil. Applied Epidemiology scholar

Australian National University ACT Health

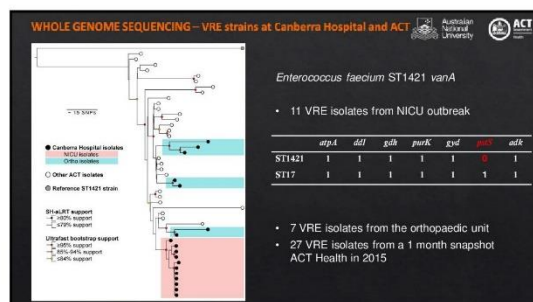


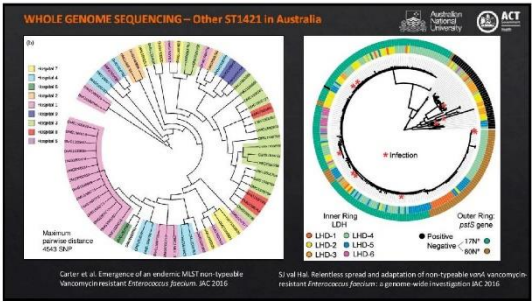
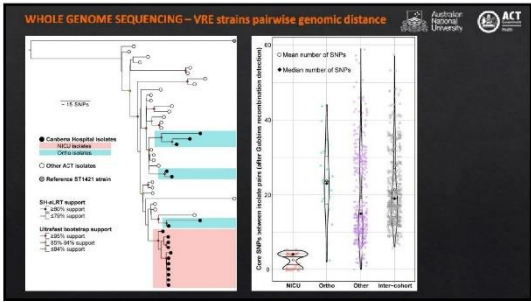
RISK FACTORS FOR VRE COLONISATION – Univariate analysis

Risk Factor	Colonised (n=14)	Non-colonised (n=77)
Low gestational age		
Low birth weight		
Resuscitation		
Increased length of stay		
Respiratory support		
Infection with other organisms		
Total parenteral nutrition		
Central/peripheral lines		
Phototherapy		
Radiology		
Antibiotic administration		
- gentamicin		
- ampicillin		
- flucloxacillin		
- nystatin cream/drops		
Antenatal steroids		

RISK FACTORS FOR VRE COLONISATION – Multivariate analysis

Variable	aOR	95% CI	p-value
Low gestational age	3.68	1.94-7.00	<0.001





CONCLUSION

- Outbreak of a highly clonal *Enterococcus faecium* ST1421 vanA
- Likely introduced to the NICU environment from other wards in the Canberra Hospital

TAKE HOME MESSAGE

- *PatS*(null) sequence types harbouring *vanA* are becoming increasingly common
- Consistent and frequent routine screening is required for early detection of colonisation in highly vulnerable patient groups

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APPENDIX 3B – Poster presentation at the ACT Health CHARM conference, Canberra, 31 July – 2 August 2018.



Outbreak of Vancomycin Resistant Enterococci in the Neonatal Intensive Care Unit at Canberra Hospital



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BACKGROUND

Nosocomial infections with vancomycin resistant *Enterococci* (VRE) are a cause of significant morbidity and mortality worldwide. Colonisation usually precedes infections and therefore it is crucial to minimise the burden of colonisation in highly vulnerable patient populations.

This study investigates the first outbreak of VRE colonisation in the neonatal intensive care unit (NICU) and special care nursery (SCN) at the Canberra Hospital. The outbreak was identified following the detection of VRE in four neonates transferred from the Canberra Hospital to the Calvary Hospital. A suite of measures was implemented to control the outbreak: formation of a VRE executive working group, active screening cultures, cohorting of carriers, environmental screening and review of cleaning procedures and operational protocols. The rapid implementation of infection control measures led to the successful termination of transmission.

This study investigates the transmission pathways and origins of the outbreak.

AIMS

To investigate:

1. clinical factors associated with VRE colonisation in NICU patients
2. if the VRE was introduced from within the Canberra Hospital

METHODS

Investigation of transmission pathways

A retrospective case-control study was conducted, capturing all patients admitted in the NICU and SCN during the time period of 18 December 2016 to 6 May 2017. Colonisation was used as the outcome variable. Data on demographic and clinical exposure variables were extracted from patient medical records. Logistic regression was used to assess the degree of association with colonisation.

Investigation of the origin of the VRE strain

Culture isolates from 11 of the VRE positive patients were sent for whole genome sequencing and bioinformatic analysis at the Microbial Diagnostic Unit Public Health Laboratory (MDU-PHL). Outbreak isolates were analysed in relation to VRE isolates from the ACT previously sequenced by the MDU-PHL.

RESULTS – Case-control study

During the study period a total of 91 patients were admitted in the NICU and SCN at the Canberra Hospital. Of these, 14 were found to be colonised with VRE during their admission. The remaining 77 were negative for VRE throughout their admission, resulting in a VRE prevalence of 15.4%.

Increased odds of colonisation were observed for: gestational age, birth weight, length of stay, resuscitation at delivery, requirement for respiratory support with ventilation, CPAP or high-flow oxygen, use of incubator with humidity, infection with other organisms, total parenteral nutrition (TPN), radiology, phototherapy, presence of central lines, some antibiotics and antenatal steroids. Significant differences in duration of use were seen for CPAP, incubator use, central lines, TPN and radiology. The mean duration of antibiotic use were not significantly different between colonised and non-colonised patients.

The final reduced multivariate model showed significant association only with gestational age (WHO categories), aOR 3.97, 95%CI 1.94-7.00.

CONCLUSIONS

- Extremely premature and very premature neonatal patients had an increased susceptibility to be colonised compared with moderate to term patients.
- The colonisation of NICU patients was with a highly successful clone endemic to the Canberra Hospital likely introduced into the NICU environment from other wards.

RESULTS – Genomic epidemiology

All 11 isolates from the outbreak were *Enterococcus faecium* harbouring a *vanA* gene conferring vancomycin resistance. *In silico* multi locus sequence typing (MLST) showed that all the isolates were sequence type 1421 (ST1421), with the MLST profile *atpA(1)*, *ddl(1)*, *gdh(1)*, *purK(1)*, *gyd(1)*, *pstS(0)*, *adk(1)*. The *pstS* null strains were previously classified as non-typeable VRE, and first described by Carter *et al.*¹ A snapshot of 2015 VRE isolates from the ACT, showed that 69% of these were *pstS* null ST1421 and ST1424. Recent studies have shown that specific ST1421 and ST1424 clones are endemic in Australian hospitals.^{1,2}

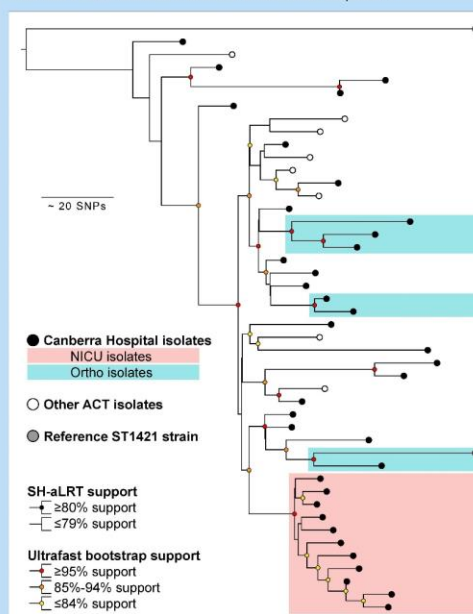


Figure 1. A phylogenetic reconstruction with recombination removed, shows that the NICU isolates form a tight cluster and are most closely related to ST1421 isolates previously sequenced from the Canberra Hospital, supporting the hypothesis of an introduction to the NICU from another ward in the hospital.

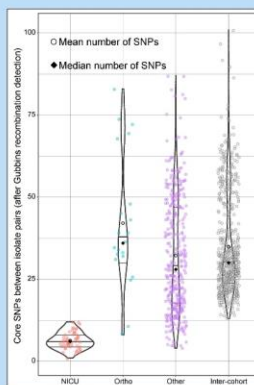


Figure 2. Violin plots showing the range of pairwise single nucleotide polymorphism (SNP) distances within each of the datasets: NICU, orthopaedics and other ACT isolates. The tight clustering of the NICU isolates, compared with all the isolates, is indicative of a recent point source introduction. In contrast the orthopaedic isolates collected over an 8 day period show a greater diversity suggestive of multiple exposures and introductions. This is also evident in Fig 1 where the isolates form three separate clusters.



References

1. Carter G.P. *et al.* (2016) Emergence of endemic MLST non-typeable vancomycin-resistant *Enterococcus faecium*. *J Antimicrob Chemother.*
2. van Hal S.J. *et al.* (2017) Polyclonal emergence of *vanA* vancomycin-resistant *Enterococcus faecium* in Australia. *J Antimicrob Chemother.*

Study was approved by the Human Research Ethics Committees at ACT Health (ETHR.17.155) and Australian National University (2017/536)

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APPENDIX 3C – STATA script used for data analysis

Chapter 3 – Epidemiological study of VRE in NICU

```
*****
*       VRE outbreak in NICU and SCN at the Canberra Hospital 2017
*****

/*
This is the analysis file for the above outbreak
Modified on 18 Mar 2019
Patiyan Andersson

Background:
The outbreak of colonisation with VRE occurred during the first
5 months of 2017 and involved 14 patients. The first 4 patents were
detected at
Calvary Hospital following transfer from the Canberra Hospital (TCH)
and the
remaining 10 were detected when active surveillance cultures were
implemented at
TCH.
Initailly I was provided with a list of 109 patients (14 colonised and
95 non-
colonised). However, 16 of the non-colonised patients had admissions
that did not
overlap with the cases, and therefore were excluded. A further 2
patients did not
have any test data and were excluded.
Final number of patients = 91
Cases = 14
Controls = 77
*/

*****
clear
cd "D:\STATA\VRE_NICU\"
capture log close
log using "D:\STATA\VRE_NICU\VRE NICU log 190318.log", replace

import excel "D:\STATA\VRE_NICU\VRE NICU data 180501.xlsx",
sheet("Line list raw data") firstrow
save "D:\STATA\VRE_NICU\VRE NICU data 190318.dta", replace

* later on when the data file already exisits, you can start here
* use "D:\STATA\VRE_NICU\VRE NICU data 180501.dta"

set more off

*****
* Remove observations to be excluded
*****
describe
* 77 variables and 109 observations

* Use the Projectstatus variable to identify observations to drop
codebook Project_status
/*
Projectstatus
Project status
      type:  string (str8)
```

```

unique values: 3                                missing "": 0/109

      tabulation:  Freq.  Value
                   14    1
                   77    2
                   18    0

```

There are no missing values, so proceed to drop the ones marked 0 as this are the excluded ones
*/

```

drop if Project_status==0
* (18 observations deleted)

```

```

*****
* Drop messy free text variables which are split up in other columns
*****
* can be done in one line, but split up for clarity

```

```

drop initials dob colonised admission_date discharge_date
drop exclusion_reason
drop WGS
drop resuscitation
drop baby_issues
drop ward_movements
drop delivery_location
drop respiratory_requirements
drop radiology
drop antibiotic_treatment
drop central_line_type
drop issues
drop birthhospital
drop APGAR
drop mother_admission_date
drop antenatal_meds
drop date_first_VRE
drop specimen_first_VRE
drop los_first_isolate
drop other_pos_VRE_cultures
drop species_first_VRE
drop susceptibility_profile_first_VRE
drop neg_cultures
drop urinary_catheter
drop Isoletteuse Isolettewithhumidity

```

```

*****
* Convert string variables
*****
describe

```

```

destring TPN_days, replace
destring phototherapy_days, replace
destring Isolettewithhumiditydays, replace

```

Chapter 3 – Epidemiological study of VRE in NICU

```
*****
* Label yes/no variables
*****

label define listname 0"no" 1"yes" 9"unknown"
label values infection listname
label values thrombocytopaenia listname
label values hyponatraemia listname
label values hypoglycaemia listname
label values respiratory_distress listname
label values peripheral_line listname
label values diabetic_mother listname
label values twin_pregnancy listname
label values chorioamnionitis listname
label values prom listname
label values substance_use listname
label values antibiotics listname
label values steroids listname
label values multivitamin listname
label values vitD listname

*****
* Label other variables
*****

* The project status needs to be recoded such that controls=0 and
cases=1
recode Project_status 2=0
/* Label the variable for Project status:
- Case
- Control
*/
label define listname_status 1"Case" 0"Control"
label values Project_status listname_status

/* Label the variable for sex:
- Female
- Male
*/
label define listname_sex 1"Female" 2"Male"
label values sex listname_sex

/* Label the variable for delivery type:
- vaginal delivery (VD)
- caesarian section (CS)
*/
label define listname_deliv 1"VD" 2"CS" 9"unknown"
label values delivery_type listname_deliv

/* Label the variable for resusitation groupings:
- Positive pressure ventialtion (PPV)
- Intubation and mechanical ventilation (Ventilation)
- None
- Unknown (not in clinical notes)
```

```

*/
label define listname_resus 0"None" 1"PPV" 2"Ventilation" 9"Unknown"
label values resuscitation_groupings listname_resus

/* Label the variable for inborn or transfer:
- Born at TCH (TCH)
- Transfer
*/
label define listname_born 0"Transfer" 1"TCH"
label values inbornortransfer listname_born

/* Label the variable for oral tube:
- Nasogastric tube (NGT)
- Orogastric tube (OGT)
- Both NGT and OGT
- None
*/
label define listname_oral 0"None" 1"NGT" 2"OGT" 3"NGT and OGT"
label values oral_tube listname_oral

*****
* Recode all unknown values to missing
*****
* This has to be done to avoid them affecting the calculations.
recode respiratory_distress 9=.
recode delivery_type 9=.
recode resuscitation_groupings 9=.
recode diabetic_mother 9=.
recode twin_pregnancy 9=.
recode chorioamnionitis 9=.
recode prom 9=.
recode substance_use 9=.
recode antibiotics 9=.
recode steroids 9=.
recode multivitamin 9=.
recode vitD 9=.

*****
* Do summary stats on categorical variables for cases and controls
*****
* Run chi2 analysis on each of the variables against Project_status
foreach var of varlist delivery_type-respiratory_distress oral_tube
peripheral_line diabetic_mother-vitD {
tab Project_status `var', row chi2 exact
}

*****
* Generate yes/no variable for antibiotic variables
*****
gen Benzylpenicillin_yn=1 if Benzylpenicillin>=1
replace Benzylpenicillin_yn=0 if Benzylpenicillin<1
label values Benzylpenicillin_yn listname

gen Gentamicin_yn=1 if Gentamicin>=1

```

Chapter 3 – Epidemiological study of VRE in NICU

```
replace Gentamicin_yn=0 if Gentamicin<1
label values Gentamicin_yn listname

gen Ampicillin_yn=1 if Ampicillin>=1
replace Ampicillin_yn=0 if Ampicillin<1
label values Ampicillin_yn listname

gen Azithromycin_yn=1 if Azithromycin>=1
replace Azithromycin_yn=0 if Azithromycin<1
label values Azithromycin_yn listname

gen Cephazolin_yn=1 if Cephazolin>=1
replace Cephazolin_yn=0 if Cephazolin<1

gen Cotrimoxazole_yn=1 if Cotrimoxazole>=1
replace Cotrimoxazole_yn=0 if Cotrimoxazole<1

gen Erythromycin_yn=1 if Erythromycin>=1
replace Erythromycin_yn=0 if Erythromycin<1

gen Flucloxacillin_yn=1 if Flucloxacillin>=1
replace Flucloxacillin_yn=0 if Flucloxacillin<1

gen Linezolid_yn=1 if Linezolid>=1
replace Linezolid_yn=0 if Linezolid<1
label values Linezolid_yn listname

gen Meropenem_yn=1 if Meropenem>=1
replace Meropenem_yn=0 if Meropenem<1

gen Vancomycin_yn=1 if Vancomycin>=1
replace Vancomycin_yn=0 if Vancomycin<1

gen Metronidazole_Flagyl_yn=1 if Metronidazole_Flagyl>=1
replace Metronidazole_Flagyl_yn=0 if Metronidazole_Flagyl<1

gen Nystatin_drops_Nilstat_yn=1 if Nystatin_drops_Nilstat>=1
replace Nystatin_drops_Nilstat_yn=0 if Nystatin_drops_Nilstat<1

gen Nystatin_cream_Mycostatin_yn=1 if Nystatin_cream_Mycostatin>=1
replace Nystatin_cream_Mycostatin_yn=0 if Nystatin_cream_Mycostatin<1

label values Metronidazole_Flagyl_yn Vancomycin_yn Meropenem_yn
Flucloxacillin_yn Erythromycin_yn Cotrimoxazole_yn Cephazolin_yn
Nystatin_drops_Nilstat_yn Nystatin_cream_Mycostatin_yn listname

*****
* Generate yes/no variable for other variables
*****
gen UVC_yn=1 if UVC>=1
replace UVC_yn=0 if UVC<1
label values UVC_yn listname

gen UAC_yn=1 if UAC>=1
replace UAC_yn=0 if UAC<1
label values UAC_yn listname
```



```

gen PICC_yn=1 if PICC>=1
replace PICC_yn=0 if PICC<1
label values PICC_yn listname

gen Isolette_yn=1 if Isolettedays>=1
replace Isolette_yn=0 if Isolettedays<1
label values Isolette_yn listname

gen Isolettewithhumidity_yn=1 if Isolettewithhumiditydays>=1
replace Isolettewithhumidity_yn=0 if Isolettewithhumiditydays<1
label values Isolettewithhumidity_yn listname

gen ventilation_yn=1 if ventilation_days>=1
replace ventilation_yn=0 if ventilation_days<1
label values ventilation_yn listname

gen CPAP_yn=1 if CPAP_days>=1
replace CPAP_yn=0 if CPAP_days<1
label values CPAP_yn listname

gen highflow_oxygen_yn=1 if highflow_oxygen_days>=1
replace highflow_oxygen_yn=0 if highflow_oxygen_days<1
label values highflow_oxygen_yn listname

gen radiology_yn=1 if radiology_days>=1
replace radiology_yn=0 if radiology_days<1
label values radiology_yn listname

gen TPN_yn=1 if TPN_days>=1
replace TPN_yn=0 if TPN_days<1
label values TPN_yn listname

gen phototherapy_yn=1 if phototherapy_days>=1
replace phototherapy_yn=0 if phototherapy_days<1
label values phototherapy_yn listname

* collapse UVC, UAC and PICC into a new yes/no variable
'central_line_yn'
gen central_line_yn=1 if UVC_yn==1 | UAC_yn==1 | PICC_yn==1
replace central_line_yn=0 if central_line_yn==.
label values central_line_yn listname

* collapse resuscitation groups into a new yes/no variable
'resuscitation_yn'
gen resuscitation_yn=1 if resuscitation_groupings==1 |
resuscitation_groupings==2
replace resuscitation_yn=0 if resuscitation_groupings==0 |
resuscitation_groupings==.
label values resuscitation_yn listname

*****
* Gestational age
*****

gen preterm_cat=1 if gestational_age>=37
replace preterm_cat=2 if gestational_age>=32 & gestational_age<37
replace preterm_cat=3 if gestational_age>=28 & gestational_age<32

```

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```
replace preterm_cat=4 if gestational_age<28
label define preterm 1"Normal" 2"Moderate to late" 3"Very" 4"Extreme"
label values preterm_cat preterm
label variable preterm_cat "WHO gestational age categories"

/* log binomial (model the determinants and predict the likelihood of
the outcome)
There will be a problem with the 0 value in the above table. Recode
data to collapse the two first categories.
*/
gen preterm_cat2=1 if gestational_age>=32
replace preterm_cat2=2 if gestational_age>=28 & gestational_age<32
replace preterm_cat2=3 if gestational_age<28
label define preterm2 1"Moderate to normal" 2"Very" 3"Extreme"
label variable preterm_cat2 "WHO gestational age categories"

*****
* Birthweight
*****
/* Divide the data into the WHO standard categories for birthweights.
Normal >= 2500g
Low birthweight (LBW) = >=1500g & <2500g
Very low birthweight (VLBW) = >=1500g & <1500g
Extremely low birthweight (ELBW) = <1000g
*/

gen birthweight_cat=1 if birthweight>=2500
replace birthweight_cat=2 if birthweight>=1500 & birthweight<2500
replace birthweight_cat=3 if birthweight>=1000 & birthweight<1500
replace birthweight_cat=4 if birthweight<1000
label define BW_categories 1 "Normal" 2"LBW" 3 "VLBW" 4 "ELBW"
label values birthweight_cat BW_categories
label variable birthweight_cat "WHO birthweight categories"

*****
* Bed and ward movements
*****
*Get summary stats on the continuous variables
bysort Project_status: summarize bed_moves, detail
bysort Project_status: summarize ward_switch, detail

*****
* Categories with data counted in days
*****
/* Currently these variables are coded in number of days, with 0 days
if the patient did not receive the treatment. These patients will skew
the average days of treatment, especially if there are a larger
proportion of patients that did not receive the treatment in one group.
*/

*Reformat all 0s to .
foreach var of varlist ventilation_days-radiology_days TPN_days-
Isolettewithhumiditydays UVC-PICC {
    replace `var'=. if `var'==0
```

```

    }

*Get summary stats on the continuous variables
foreach var of varlist ventilation_days-radiology_days TPN_days-
Isolettewithhumiditydays {
    bysort Project_status: summarize `var', detail
}

*****
* Antibiotics - in number of days
*****
/* Currently this is coded in number of days, with 0 days if the
patient did not receive the antibiotic. These patients will skew the
average days of treatment, especially if there are a larger proportion
of patients that did not receive the antibiotic in one group.
*/

*Recode all 0 to missing.
foreach var of varlist Benzylpenicillin-Nystatin_cream_Mycostatin {
    replace `var'=. if `var'==0
}

*Get summary stats on the continuous variables
foreach var of varlist Benzylpenicillin-Nystatin_cream_Mycostatin {
    bysort Project_status: summarize `var', detail
}

*****
* Log binomial regression (model the determinants and predict the
likelihood of the outcome)
* - univariate analysis
*****

* exposure variables with categorical values
foreach var of varlist sex delivery_type-inbornortransfer infection-
respiratory_distress oral_tube peripheral_line diabetic_mother-vitD
Benzylpenicillin_yn-Ampicillin_yn Flucloxacillin_yn Meropenem_yn-
LOS_cat {
    glm Project_status `var', fam(poisson) link(log) nolog
    vce(robust) eform
}

* exposure variables with continuous values
foreach var of varlist birthweight gestational_age bed_moves
ward_switch ventilation_days-radiology_days TPN_days-
Isolettewithhumiditydays Benzylpenicillin-Ampicillin Flucloxacillin
Meropenem-PICC los_in_hospital {
    glm Project_status `var', fam(poisson) link(log) nolog
    vce(robust) eform
}

```

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```
* exposure variables with categorical values split up
glm Project_status i.resuscitation_groupings, fam(poisson) link(log)
nolog vce(robust) eform

glm Project_status i.oral_tube, fam(bin) link(log) nolog eform

glm Project_status i.preterm_cat, fam(bin) link(log) nolog eform

glm Project_status i.preterm_cat2, fam(bin) link(log) nolog eform

glm Project_status i.birthweight_cat, fam(bin) link(log) nolog eform

*****
* Logistic regression - multivariate analysis
*****
/* When building the multivariate model, there are many variables that
are likely to be related, that we have have to take into
consideration. For instance, LOS will likely be related to gestational
age and birthweight (and the latter two are certainly linked).
*/

* Check correlation between independent variables that had a
univariate p<0.1
correlate gestational_age preterm_cat2 birthweight birthweight_cat
los_in_hospital resuscitation_yn ventilation_yn CPAP_yn CPAP_days
highflow_oxygen_days TPN_yn TPN_days infection Isolettewithhumidity_yn
Isolettedays central_line_yn UVC UAC PICC radiology_days
Benzylpenicillin_yn Gentamicin_yn Ampicillin_yn Flucloxacillin_yn
Nystatin_drops_Nilstat_yn Nystatin_cream_Mycostatin_yn

/* Check for collinearity.
This can be done using a VIF command following a regress command. The
linear regression can be run, followed by the VIF command. Make sure
only to pay attention to the VIF numbers, ignore the regression
coefficient as this would be inaccurate for the categorical data you
have. There is a user-written command that can be downloaded "collin"
which tests variables for collinearity, without the need to run the
preceeding regression. Individual VIF values above 10 and average of 6
are cause for concern. Other papers state any VIF above 4.
*/
findit collin
collin preterm_cat2 birthweight_cat los_in_hospital resuscitation_yn
ventilation_yn CPAP_yn CPAP_days highflow_oxygen_days TPN_yn TPN_days
infection Isolettewithhumidity_yn Isolettedays central_line_yn UVC UAC
PICC radiology_days Benzylpenicillin_yn Gentamicin_yn Ampicillin_yn
Flucloxacillin_yn Nystatin_drops_Nilstat_yn

/*
This does not indicate any variables that are critically collinear,
but there are
certainly some to look out for: PICC, gestational age, LOS and
radiology.

Best approach would be to test each one of these in a regression and
stepwise put in the other variables and see what happens to the OR.
*/
```

```

*****
* Backwards stepwise multivariate logistic regression
*****
/*Start the model with all relevant variables. These are removed one
by one, with the model rerun after each removal. A p value for
variable removal is defined. */

/* All variables that had a p<0.1 were included at the start of the
full model Benzylpenicillin_yn was an exeption, due to strong
collinearity with Gentamicin_yn making the model fail to converge.
*/

stepwise, pr(0.05): logistic Project_status preterm_cat2
birthweight_cat los_in_hospital ventilation_yn CPAP_yn
highflow_oxygen_yn infection Isolettewithhumidity_yn TPN_yn
radiology_yn central_line_yn Benzylpenicillin_yn Gentamicin_yn
Ampicillin_yn Flucloxacillin_yn Vancomycin_yn Metronidazole_Flagyl_yn
Nystatin_cream_Mycostatin_yn bed_moves

* test the reduced model in a lrtest to see if it holds up
logistic Project_status preterm_cat2 birthweight_cat los_in_hospital
ventilation_yn CPAP_yn highflow_oxygen_yn infection
Isolettewithhumidity_yn TPN_yn radiology_yn central_line_yn
Benzylpenicillin_yn Gentamicin_yn Ampicillin_yn Flucloxacillin_yn
Vancomycin_yn Metronidazole_Flagyl_yn Nystatin_cream_Mycostatin_yn
bed_moves
estimates store A

logistic Project_status preterm_cat2
estimates store B

lrtest A B, stats

* test the reduced model using the Lroc to see if it holds up

logistic Project_status preterm_cat2 birthweight_cat los_in_hospital
ventilation_yn CPAP_yn highflow_oxygen_yn infection
Isolettewithhumidity_yn TPN_yn radiology_yn central_line_yn
Benzylpenicillin_yn Gentamicin_yn Ampicillin_yn Flucloxacillin_yn
Vancomycin_yn Metronidazole_Flagyl_yn Nystatin_cream_Mycostatin_yn
bed_moves
estat gof, table group(10)

logistic Project_status preterm_cat
estat gof, table group(10)

* To get a summary graph with both ROC curves on it
logistic Project_status preterm_cat2 birthweight_cat los_in_hospital
ventilation_yn CPAP_yn highflow_oxygen_yn infection
Isolettewithhumidity_yn TPN_yn radiology_yn central_line_yn
Benzylpenicillin_yn Gentamicin_yn Ampicillin_yn Flucloxacillin_yn

```

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```
Vancomycin_yn Metronidazole_Flagyl_yn Nystatin_cream_Mycostatin_yn  
bed_moves  
lroc  
predict xb1, xb  
  
logistic Project_status preterm_cat  
lroc  
predict xb2, xb  
  
roccomp Project_status xb1 xb2, graph summary
```

APPENDIX 3D – BioSample numbers for sequence reads submitted to the Sequence Read Archive at the National Center for Biotechnology Information under BioProject PRJNA465857.

SampleID	DataSet	ST	BioProject	BioSampleAccession	Specimen source type
AUSMDU0004167	ST1421 Reference Strain	1421	PRJNA433676	SAMN08628413	Trachea aspirate
AUSMDU0004324	Other	1421	PRJNA495857	SAMN10232983	Anal swab
AUSMDU0004325	Other	1421	PRJNA495857	SAMN10232984	Rectal swab
AUSMDU0004326	Other	1421	PRJNA495857	SAMN10232985	Rectal swab
AUSMDU0004328	Other	1421	PRJNA495857	SAMN10232986	Anal swab
AUSMDU0004331	Other	1421	PRJNA495857	SAMN10232987	Perianal swab
AUSMDU0004334	Other	1421	PRJNA495857	SAMN10232988	Leg swab
AUSMDU0004335	Other	1421	PRJNA495857	SAMN10232989	Urine
AUSMDU0004336	Other	1421	PRJNA495857	SAMN10232990	Anal swab
AUSMDU0004337	Other	1421	PRJNA495857	SAMN10232991	Perianal swab
AUSMDU0004338	Other	1421	PRJNA495857	SAMN10232992	Other
AUSMDU0004341	Other	1421	PRJNA495857	SAMN10232993	Perianal swab
AUSMDU0004342	Other	1421	PRJNA495857	SAMN10232994	Perianal swab
AUSMDU0004343	Other	1421	PRJNA495857	SAMN10232995	Swab
AUSMDU0004345	Other	1421	PRJNA495857	SAMN10232996	Swab
AUSMDU0004346	Other	1421	PRJNA495857	SAMN10232997	Abdominal cavity aspirate
AUSMDU0004347	Other	1421	PRJNA495857	SAMN10232998	Perianal swab
AUSMDU0004350	Other	1421	PRJNA495857	SAMN10232999	Swab
AUSMDU0004351	Other	1421	PRJNA495857	SAMN10233000	Perianal swab
AUSMDU0004352	Other	1421	PRJNA495857	SAMN10233001	Swab
AUSMDU0004353	Other	1421	PRJNA495857	SAMN10233002	Perianal swab
AUSMDU0004354	Other	1421	PRJNA495857	SAMN10233003	Anal swab
AUSMDU0004355	Other	1421	PRJNA495857	SAMN10233004	Urine
AUSMDU0004356	Other	1421	PRJNA495857	SAMN10233005	Perianal swab
AUSMDU0004358	Other	1421	PRJNA495857	SAMN10233006	Perianal swab

SampleID	DataSet	ST	BioProject	BioSampleAccession	Specimen source type
AUSMDU0004359	Other	1421	PRJNA495857	SAMN10233007	Groin swab
AUSMDU0004362	Other	1421	PRJNA495857	SAMN10233008	Swab
AUSMDU0004363	Other	1421	PRJNA495857	SAMN10233009	Rectal swab
AUSMDU0016978	Ortho	1421	PRJNA495857	SAMN10232976	Unknown
AUSMDU0016979	Ortho	1421	PRJNA495857	SAMN10232977	Unknown
AUSMDU0016980	Ortho	1421	PRJNA495857	SAMN10232978	Unknown
AUSMDU0016981	Ortho	1421	PRJNA495857	SAMN10232979	Unknown
AUSMDU0016982	Ortho	1421	PRJNA495857	SAMN10232980	Unknown
AUSMDU0016983	Ortho	1421	PRJNA495857	SAMN10232981	Unknown
AUSMDU0016984	Ortho	1421	PRJNA495857	SAMN10232982	Unknown
AUSMDU0008939	NICU	1421	PRJNA495857	SAMN10232965	Faecal swab sample
AUSMDU0008940	NICU	1421	PRJNA495857	SAMN10232966	Faecal swab sample
AUSMDU0008941	NICU	1421	PRJNA495857	SAMN10232967	Faecal swab sample
AUSMDU0008942	NICU	1421	PRJNA495857	SAMN10232968	Faecal swab sample
AUSMDU0008943	NICU	1421	PRJNA495857	SAMN10232969	Faecal swab sample
AUSMDU0008944	NICU	1421	PRJNA495857	SAMN10232970	Faecal swab sample
AUSMDU0008945	NICU	1421	PRJNA495857	SAMN10232971	Faecal swab sample
AUSMDU0008946	NICU	1421	PRJNA495857	SAMN10232972	Faecal swab sample
AUSMDU0008947	NICU	1421	PRJNA495857	SAMN10232973	Faecal swab sample
AUSMDU0008948	NICU	1421	PRJNA495857	SAMN10232974	Faecal swab sample
AUSMDU0008949	NICU	1421	PRJNA495857	SAMN10232975	Faecal swab sample

CHAPTER 4

Modelling the burden of invasive pneumococcal disease in Australia

Australian Institute of Health and Welfare

“It is the mark of an educated mind to rest satisfied with the degree of precision which the nature of the subject admits and not to seek exactness where only an approximation is possible.”

Aristotle

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ABBREVIATIONS

ABS	Australian Bureau of Statistics
ACT	Australian Capital Territory
ADHD	attention deficit hyperactivity disorder
AIHW	Australian Institute of Health and Welfare
BCoDE	Burden of Communicable Diseases in Europe
BoVPD	Burden of Vaccine Preventable Diseases
CDNA	Communicable Diseases Network Australia
CFR	case fatality ratio
DALY	disability adjusted life years
DW	disability weights
EAC	expert advisory committee
ECDC	European Centre for Disease Prevention and Control
ERP	estimated resident population
EU/EEA	European Union/European Economic Area
GBDS	Global burden of disease study
Hib	Haemophilus influenzae B
ICD	International Statistical Classification of Diseases
IPD	invasive pneumococcal disease
MeSH	Medical Subject Headings
NHMD	national hospital morbidity database
NMD	national mortality database
NNDSS	national notifiable diseases surveillance system
NSW	New South Wales
NT	Northern Territory
PCV	pneumococcal conjugate vaccine

Chapter 4 – Modelling the burden of IPD

PERT	Project Evaluation and Review Techniques (distribution)
PPV	pneumococcal polysaccharide vaccine
RSV	respiratory syncytial virus
SA	South Australia
SAS	Statistical Analysis Software®
Vic	Victoria
VP shunt	ventriculoperitoneal shunt
VPD	vaccine preventable disease
WA	Western Australia
WHO	World Health Organization
YLD	years lost to disability
YLL	years of life lost

PROLOGUE

Study rationale

This piece of work was contracted to the Australian Institute of Health and Welfare (AIHW) from the Commonwealth Department of Health. The project relates to the vaccine preventable diseases (VPD) currently part of the National Immunisation Program and had two main components: production of a series of fact sheets as communication tools showing the secular trends of VPDs and associated vaccine interventions through the history (**Appendix 4A**); and modelling of the burden of VPDs to be used to inform and prioritise future proposed vaccine interventions. Prevalence-based burden of disease studies already produced by AIHW estimates the current burden but are unable to make projections of future burden. The incidence-based models developed in this project will fulfil this purpose and complement the current efforts.

My role

I was very fortunate to be offered to go to AIHW at the commencement of the burden of vaccine preventable diseases (BoVPD) project. The exposure to the data resources and high level of data analysis that is conducted there provided a fantastic learning opportunity. I was required to undertake several courses both at AIHW and the Australian Bureau of Statistics (ABS) which provided a foundation to understand and work with, what arguably can be a mindboggling amount of data. The work at AIHW also introduced me to a new statistical analysis software and language, SAS.

Of the 17 VPDs in the project I selected invasive pneumococcal disease (IPD) to be the disease to focus on – both for the factsheet and development of burden of disease model. The decision was based on that it was one of the diseases that would need to most work in terms of literature review, model adjustment and data considerations. I also participated in overall discussions on the design of the fact sheets, and the direction and choice of burden of disease models. In the early stage of the project I assisted by liaising between AIHW and the Department of Health to establish what exactly the expected outputs were. I ran the early tests of the European Centre for Disease Control application BCoDE that was going to be adapted for use in the project, to understand the function of each of the components in the model and the effects on the burden estimate produced.

I drafted the IPD public factsheet, which included drafting the text, data extraction and graphical representation. I also assisted the team with design, development and review of the factsheets for other VPDs.

For the development of the incidence-based burden of disease model for IPD I conducted a structured literature review on long-term sequelae of IPD to inform adjustment to model variables and adapt the existing BCoDE application to the Australian context. I extracted data on incident cases of IPD from the National Notifiable Diseases Surveillance System (NNDSS); data on IPD related deaths from NNDSS and the National Mortality Database (NMD); data on clinical categories from the National Hospital Morbidity Database (NHMD), the NNDSS IPD public dataset and published IPD annual reports. SAS scripts were written for the extraction and manipulation of NNDSS, NMD and NHMD data.

I presented the draft model for IPD and discussed queries at the Expert Advisory committee meetings.

Lessons learned

I learned that model building is incredibly time consuming, even when starting with an existing model. There are many variables, and it takes a lot of testing to figure out what each does and its effect in the model. And while most of the components can be well informed, for some there is not sufficient available literature and one has to rely on input from experts in the field, or even what just seems to be the best reflection of reality. The models can perpetually be improved and should not be viewed as final static products, even though the file name may say “Final_final_model.xlsx”.

I had the opportunity to learn SAS, a statistical language new to me at the time. It of course was somewhat confusing to learn this statistical package at the same time as STATA, and to distinguish the syntax. However, in the public health world developing the ability to learn new software and languages is an asset and having a basic grasp of the syntax in several languages will help. Having these SAS scripts was essential to the work, both to allow reproducibility but also to be able to quickly update data when the input needed adjustment in response to new information or decisions in the development process. The scripts also allowed anyone in the team to pick up the work in people’s absence.

Over the course of the project I developed an understanding of the difficulties and considerations when working with historical data. Coding standards will change over time, such as the International Statistical Classification of Diseases (ICD) which are used for morbidity and mortality coding, and that these changes may have a drastic impact on your data. Additionally, data variables may not have been consistently collected over the history of the data available.

An important lesson therefore was to cross reference data, visualise and examine it carefully, and always be critical of the extracted data.

The time at AIHW has also taught me the care required to avoid re-identification through small numbers in publications. There are a range of rules, which may differ between dataset, institutes and/or jurisdiction, as to how small numbers of people may be identified in different situations. This is a very important consideration, and one that I will take with me into my future work.

Public health implications

The incidence-based burden of disease models allows for the comparison of the burden of VPDs and can through the calculation of disease burden averted be used to inform and prioritise proposed future vaccine interventions. The models will be used by the Department of Health to allow in-house calculations of burden estimates to compare with those presented by industry, for instance pharmaceutical companies, and to assess the validity of estimates presented. The estimates for the comparison year show the effects of vaccination programs and can be used for public health communications.

The fact sheet will be presented on the AIHW website and is a resource for the public. It will provide easily accessible and interpretable information for the public on the benefits and effects of vaccination programs and provides “good news” stories on vaccination for the Department of Health.

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MAE core activity requirements

Within this project the following MAE core activities were completed: analysis of a public dataset; conducting a critical literature review; and communication for a lay-audience.

ABSTRACT

Background: Disability adjusted life years (DALY) is an estimate that expresses and allows comparison of the burden of diseases in a population. It is composed of two measures, years of life lost to disability (YLD) and years of life lost due to premature death (YLL). There are multiple ways in which the DALY estimate can be calculated. In this study an incidence-based model is used, which calculates the occurrence of the disease in the period of interest and the predicted future stream of ill health connected to these disease occurrences. This piece of work focusses on invasive pneumococcal disease (IPD) and is part of a large project to produce burden of disease estimates for vaccine preventable diseases in Australia. Pneumococcal disease is caused by *Streptococcus pneumoniae* and is defined as invasive when the bacterium is isolated from a normally sterile site. There are three main clinical manifestations of IPD: pneumonia, septicaemia and meningitis. Long-term complications can occur following the meningitis events and include impairments to hearing, vision, motor function, cognitive ability and seizure disorders and behavioural problems.

Methods: An incidence-based model recently published by the European Centres for Disease Control and Prevention was adapted to the Australian setting. Adjustments to the model variables was informed by a systematic literature review. Disability weights were updated to those published in the 2016 Global Burden of Disease Study. Incidence data was extracted from the Australian from the National Notifiable Diseases Surveillance System (NNDSS). Mortality data was extracted from both the NNDSS and the National Mortality Database (NMD). Data on the proportions of each clinical manifestation was obtained from the National Hospital Morbidity Database (NHMD). The reference year for the study was 2015, with annual incidence data averaged from a three-year period, 2014 to 2016. Case fatality ratio (CFR) were calculated from a 10-year period 2007 to 2016. 2005 was used as a historic comparison year for all diseases in the study. In addition, for IPD 2003 was used as a pre national vaccination introduction comparison year.

Results: The DALY estimates for IPD in 2015 using NNDSS CFRs was 3,794.70 years, with YLDs and YLLs contributing 680.39 years and 3,114.31 years, respectively. There was a considerable difference in CFRs calculated using mortality data from the NNDSS compared with NMD, with the latter producing a DALY estimate of 2015.94 years. There had been a reduction in IPD burden in 2015 compared with the pre national vaccination program comparison year 2003, when the DALY estimate was 4,515.78 years. The main effect was seen in the under 5 years age-group, the target of the national vaccination program introduced in 2005, with a reduction in DALYs from

1,622.01 years to 755.74 years. For adults aged 40 and above, the DALY estimate increased from 2,295.24 years to 2,510.95 years, along with a change in distribution between YLDs and YLLs.

Conclusions: IPD contributes the second highest overall burden of the vaccine preventable diseases in the larger study, with only influenza recording a higher overall burden. IPD displays a high burden of disease, at both on the population level and for the individual. There has been an observable positive effect of the introduction of a national infant vaccination program for IPD. The model developed will allow the Department of Health to make projections of the estimated burden in response to different intervention scenarios.

1 BACKGROUND

1.1 Invasive pneumococcal disease

1.1.1 Disease

Pneumococcal disease is caused by the bacterium *Streptococcus pneumoniae*. It is a Gram-positive bacterium and is carried in the nasopharynx of many people without causing any symptoms. (1, 2) When it is symptomatic, the disease can generally be divided in two major groups, non-invasive and invasive disease. Non-invasive disease is localised to mucosal membranes and includes otitis media, sinusitis, bronchitis and pneumonia. Invasive pneumococcal disease (IPD) occurs when the bacterium is found in a normally sterile site (e.g. blood stream or cerebrospinal fluid), with the common clinical manifestations being: bacteraemic pneumonia (pneumonia with the bacterium also found in the blood stream), occult bacteraemia (bacterium spread directly from nasopharynx to blood stream) and meningitis (inflammation of the membranes around the brain). (2, 3) Of these the bacterial pneumonia is by far the most common manifestation in adults, while occult bacteraemia is most common among children. In rare cases the bacteria can also infiltrate soft tissue, joints or bones. Death may occur in these acute disease episodes, with the elderly most at risk.

Long term complications following the initial acute disease episodes cause additional burden. The most significant arise following the meningitis events and include: hearing impairment, cognitive impairment, motor impairment, visual impairment, seizure disorders, behavioural disturbances and clinical impairments such as hydrocephalus.(4) The severity of the sequelae may vary, but most mean a lifelong disability.

Streptococcus pneumoniae is a major cause of morbidity and mortality throughout the world, with most of the disease occurs among individuals as the extreme of ages, the infants and the elderly. WHO estimates 1.6 million deaths every year attributed to the disease, and a significant proportion of those are deaths among children under 5 years of age, mainly in developing countries. (5). In the most recent annual report for IPD in Australia for 2012, the national rate was 8.0 per 100,000 population, with rates in children under 1 years of age 18.1 per 100,000 and adults aged 85 years and above of 38.7 per 100,000. (6) The rates are significantly higher among indigenous people at a national rate of 42.0 per 100,000, and with rates as high as 64.8 per 100,000 for children under 1 year. In Australia the case fatality ratio (CFR) in 2012 varied from 0.5% to 14.2% for age-groups <5 years and 65+ years, respectively. For more recent, but yet to be published data please see the IPD factsheet in **Appendix 4A**.

Streptococcus pneumoniae is spread through direct contact with secretions from a carrier or infected individual. (2) The bacterium may then be carried by the person for several months before disease occurs. It is unknown how effective such transmission events are in eliciting a natural immune response and future immunity. Most of the colonisation occurs during early childhood and is gradually cleared as the individual grows older. The rates of adult colonisation vary greatly and depends on the continued exposure to other carriers, for instance children or close quarter living arrangements. (3)

The major virulence factor in *S. pneumoniae* is its polysaccharide capsule. (3) The capsular proteins also form the basis for the serotyping classification system of pneumococci, with more than 90 different capsular serotypes identified. (3) While there is a large range of serotypes, most of the disease is caused by a limited number of serotypes. In 2012, 54% of all IPD cases in Australia were accounted for by 6 major serotypes. (6)

1.1.2 Diagnosis

In Australia, only cases of IPD are notifiable and these notifications form the basis for and are the subject of this piece of work.

Pneumococcal disease is not always confirmed with bacterial diagnosis due to the invasive nature of many of the confirmatory techniques, which is not always justifiable in milder cases of the disease. Invasive pneumococcal disease on the other hand is much more likely to be confirmed with laboratory diagnosis due to the severity of the disease. (7) Enhanced IPD surveillance data is collected for all cases aged under 5 years and over 50 years in all jurisdictions. (6) Cases aged 5-49 years are subjected to enhanced follow-up in all jurisdictions except New South Wales and two public health units in Queensland (Metro South and Gold Coast Public Health Units). It is therefore thought that the National Notifiable Diseases Surveillance System data is representative of the IPD cases in Australia.

The case definition for invasive pneumococcal disease is:

Isolation of Streptococcus pneumoniae from a normally sterile site; OR
Positive nucleic acid test for S. pneumoniae

Definitive diagnosis of *S. pneumoniae* infection involves isolation through culturing and biochemical characterisation of the bacteria from a clinical specimen. Caution is taken if there is significant presence of normal flora, as this would indicate sampling from a non-sterile site or a contaminated specimen. (7) The isolation of the bacterium relies of the specimen being obtained prior to commencement of antibiotic treatment, as this has a significant impact on the sensitivity

of the technique. Pneumococcal antigen tests are complementary to culture and may assist in confirming suggestive culture results as these generally stay positive for longer following the commencement of antibiotic treatment.

There are several nucleic acid tests using polymerase chain reaction to detect specific pneumococcal target sequences in specimen. The tests usually include multiple pneumococcal targets as well as targets in other common causes of infection, in particular bacterial meningitis. (7) These techniques have high sensitivity and are more rapid than culturing. However, the lack of standardisation between laboratories can make comparisons challenging.

1.1.3 Treatment

Treatment of IPD with antibiotic therapy is currently effective. However, there is a growing concern internationally of increasing resistance to commonly use antibiotic classes such as penicillins, cephalosporins, trimethoprim-sulfamethoxazole, macrolides and fluoroquinolones, which reduces the pool of available treatment options. (5) In Australia the situation is relatively good, with only a moderate proportion of isolates displaying resistance. In 2012, 10% of isolates were found to have reduced susceptibility to penicillin and 2% showing reduced susceptibility to ceftriaxone/cefotaxime. (6)

1.1.4 Prevention

Vaccination is the most effective way to prevent pneumococcal disease. Most vaccines will provide protection against multiple serotypes of *S. pneumoniae* (so called multivalent vaccines). There have been several changes and expansions to the specific serotypes included throughout the history of pneumococcal vaccines in Australia. This has been in response to a change in epidemiology driven by the emergence of new serotypes that take the place previously occupied by the serotypes whose incidence has been reduced following the use of vaccines.

There are two main types of pneumococcal vaccines – pneumococcal conjugate vaccine (PCV) and pneumococcal polysaccharide vaccine (PPV). (8) Conjugate vaccines are immunogenic in young infants and elicit an immune memory. Polysaccharide vaccines contain a broader spectrum of serotypes but only elicit a poor immune response in children under 2 years of age.

As of the 9 April 2018 the recommendations for immunisation under the National Immunisation Program are (8):

- All children (except those specified below) – 3 doses of 13vPCV at 2, 4 and 12 months of age

- Aboriginal and Torres Strait Islander children living in Queensland, Northern Territory, South Australia or Western Australia – 4 doses of 13vPCV at 2, 4, 6 and 12-18 months of age
- All children with underlying medical conditions associated with increased risk of IPD – 4 doses of 13vPCV at 2, 4, 6 and 12 months and one dose of 23vPPV at 4 years
- Non-indigenous adults – 1 dose of 23vPPV at 65+ years
- Indigenous adults – 2 doses of 23vPPV at 50+ years (second dose 5 years after first)
- Indigenous adults (15 years or older) with underlying medical conditions associated with increased risk of IPD – may have extra doses of 23vPPV

In Australia a universal pneumococcal vaccination scheme using a 7vPCV for infants and young children was introduced in 2005, with the introduction having occurred two years prior for at-risk infants. This resulted in a significant drop in pneumococcal incidence, with the greatest effect seen in the under 5-year age group (for data see the Factsheet for IPD in **Appendix 4A**). The data presented in the Factsheet also show an associated reduction among individuals not part of the vaccination target group, with an encouraging reduction observed in the other risk groups such as adults 65 years or older. This concurrent reduction was attributed to herd immunity. However, due to serotype replacement, when serotypes not included in the vaccines fill the niche left by the reduction in vaccine serotypes, changes had to be made to the vaccine composition. In Australia this effect was predominantly seen by the emergence of serotype 19A, which also was observed elsewhere in the world. The introduction of the 10vPCV and the subsequent 13vPCV has resulted in the reduction of these emerging serotypes (6), but it is an ever-changing landscape and future adaptation and serotype replacement is inevitable.

1.2 Burden of disease models

1.2.1 Disability Adjusted Life Year measure

Burden of disease studies aim to estimate a common measure that allows comparison of the effect of different diseases on a population at or over a particular timeframe and can be used to describe the relative impact of diseases and to inform future public health interventions. One such measure is the Disability Adjusted Life Years (DALY), which captures the combined quantification of burden of disease in terms of morbidity and mortality. The morbidity is quantified as Years of Life lived with Disability due to the disease (YLD) and mortality is quantified as Years of Life Lost due to premature death (YLL). The YLL is measured as the gap

between the age at death and an aspirational life expectancy of the individual. The measure of disability relies on disability weights (DW), a weighting system representing the health loss associated with different health states, following large scale studies of epidemiological data and social preferences. (9-11) The disability weight has a value between 0 (full health) and 1 (death). The choice of disability weighting system will have a significant impact on the estimates produced, as will the choice of methodology for the model and the associated assumptions.

There are three conceptual models that can be used for calculating DALY estimates in burden of disease studies: pure prevalence-based burden of disease models (rarely used), incidence-based burden of disease models and hybrid burden of disease models. (12) The difference between models is mainly in the disease measure used as input for the model and how the effects of the disease are treated over time. It should be noted that these differences between models mean that the DALY estimates calculated does not measure the same burden and are not interchangeable nor directly comparable. The choice therefore comes down to the data available and the intended use of the DALY measure.

1.2.2 Pure prevalence-based burden of disease model

A pure prevalence-based burden of disease model calculates the gap between the health experienced and the aspirational full health at a point in time. (12) It uses the prevalence of the disease experienced during the time of interest (e.g. in the year 2015) to calculate the YLD. The YLL is calculated by measuring the number of deaths due to the disease that occurred during the time of interest (e.g. in the year 2015), but also considers the number of people that would still have been alive during the time of interest if it wasn't for their pre-mature death due to the disease. For instance, if a person died at age 45 in 2010 and had an aspirational life expectancy of 80 years (YLL in 2010 of $80-45=35$), in 2015 they would still count for 30 years of YLL. This aspect of the model is not intuitive as one does not really experience being dead and therefore one would not expect the current population to be at poorer health because individuals have died pre-maturely in the past.

In a prevalence-based model there is no attribution of particular health states - for example hearing loss as a sequelae of IPD or hearing loss as a result of prolonged exposure to loud music at rock concerts, are not distinguished. Instead each health state is measured on its own, that is, prevalence of IPD and, separately, prevalence of hearing loss. In this case the prevalence will include any hearing loss, regardless of the causative pathway (e.g. resulting from IPD or invasive meningococcal disease or a rock concert).

This model is often called a pure prevalence-based model and, due to the somewhat counter intuitive nature of the YLL measurement, it is rarely used. It could theoretically be used to estimate for instance the impact of a disease on the available work force of a population in a particular year but other models are preferred. Instead, when people talk about prevalence-based models, they are most often referring to hybrid models, which are described below.

1.2.3 Incidence-based burden of disease model

An incidence-based burden of disease model calculates the occurrence of the disease in the period of interest and the predicted future stream of ill health connected to these disease occurrences. (12) The YLD is calculated from the incidence of acute disease and the predicted long-term sequelae associated with the acute disease episodes. The YLL is calculated from deaths occurring in the period of interest, as the difference between the aspirational life expectancy and the age at death of the individual.

In these models it is critical to be well informed regarding the causal attribution of downstream health states to the initial acute disease episode. The only observed data in the model is the incidence of the initial acute disease episodes, and the future long-term effects are modelled based on predictions from previously published data. Therefore, it is important that this data is tailored to the population being investigated.

The incidence-based models are commonly used, and particularly suited to measure burden of communicable diseases, with short acute disease episodes but potential long-term consequences. It can for instance be used model the effects of various proposed vaccination campaigns for vaccine preventable diseases.

1.2.4 Hybrid burden of disease model (“prevalence-based” model)

A hybrid burden of disease model is as the name suggest a combination of the two models above and is often what people refer to when talking about a prevalence-based burden of disease model. The hybrid model calculates the experience of the disease in the time period of interest and the effects of deaths going forward. (12) The YLD is calculated using the prevalence of the disease, just as in the pure-prevalence-based model. The YLL on the other hand is calculated as in the incidence-based model, from deaths occurring in the period of interest, as the difference between the aspirational life expectancy and age at death of the individual. This solves the counter-intuitive way of handling deaths seen in the pure-prevalence-based model, but arguably generates a different problem; that the YLD and YLL measures are calculated based on two

different time frames. These models have been critiqued for not having a consistently describable quantity of measurement.

Despite this drawback the hybrid model has many benefits, the main being its simplicity with regards to the input data required as all the necessary data can be measured in the period of interest. This avoids the technical complications of making accurate predictions of future long-term sequelae (as in the incidence-based model) or having accurate records of previous premature deaths that should still be accounted for (as in the pure-prevalence based model).

1.2.5 Existing burden of disease studies

Burden of disease studies are an important tool for informing health policy and are performed on national, regional and global scales. The first Global Burden of Disease Studies (GBDS) was commissioned by the World Bank and started with the reference year 1990 (incidence-based model). (13) The next study was conducted for the reference year 2001 (incidence based model) (14), and saw a number of subsequent smaller updates. A major update was made for reference year 2010, which also saw the transition to a hybrid model. (15) The most recent updates have been for reference years 2013, 2015 and 2016, with all providing re-calculated data back to 1990 in response to advancements in burden of disease methodology. (16-19)

In Australia the first burden of disease study was conducted for reference year 1996 (incidence-based model). (20) Separate national and Aboriginal- and Torres Strait Islander Peoples-specific studies were produced for reference year 2003 (both incidence-based models). For reference year 2011 the method was changed to a hybrid model, which also meant that the study conducted a re-calculation of the 2003 estimates using the new methodology. (21, 22) At the time of writing, a 2015 estimate is being prepared by AIHW, still using the hybrid model.

The European Centres for Disease Prevention and Control (ECDC) recently undertook a burden of disease study in EU/EEA countries with a focus on communicable diseases for the period 2009-2013. (23) In this study an incidence-based model was chosen, such that future long-term sequelae could be included. This allowed the team to estimate the potential future burden avoided following various public health interventions, such as vaccination programs. The intent of our study is for the end product to be used for similar purposes, and therefore the methodology in the ECDC burden of disease study will be used as a base and adapted to suit the Australian setting.

2 METHODS

2.1 BCoDE model and app

An open-access application - the BCoDE tool kit - was developed as part of the European Centres for Disease Control's burden of communicable disease in Europe (BCoDE) study. (23, 24) The BCoDE tool kit allows the user to explore the DALY burden of 32 selected communicable diseases in various European countries or regions by entering age- and sex-specific incidence for the disease of interest. A custom population can also be used, allowing the application to be adapted to non-European settings as well.

In the BCoDE study, a disease progression model was constructed for each disease based on literature reviews. The models take as input the sex- and age-specific disease incidence, population and life expectancy. The remaining components in the conceptual model of the disease are functions of the base incidence. Each of the calculation steps permit a measure of uncertainty through the specification of ranges and distributions within these. Together with the iterative Monte Carlo simulation, the model provides 95% confidence intervals for the resulting burden of disease measures.

2.2 Disease tree

The disease model tree for IPD in the BCoDE tool kit was adapted for this project with minimal structural changes (**Figure 1**). As with the default model all clinical categories of pneumonia, meningitis and septicaemia were input together, as one single incidence number.

The only major change for this study compared with the standard model was that the "*Multiple impairment*" long-term sequelae category was not included in our model. This was justified by fact that each of the long-term sequelae in a patient would be accounted for in the individual long-term sequelae categories, and therefore to include those in the "Multiple impairment" category would essentially result in a double count.

In our model the incidence of the long-term sequelae are calculated from the total incidence of IPD. As these sequelae are consequences of the meningitis events, appropriate adjustments for the proportion of IPD cases with meningitis were included in the calculations to account for this.

As with the default BCoDE model time-discounting and age-weighting were not used in the model. Time-discounting is when future disability is given less weight compared with current disability and is commonly used in economical modelling. It is expressed as a depreciation rate, for instance of 3% per year, where the DALY estimate is reduced by 3% for each year. This means

that health states with a long duration, will gradually contribute less to the DALY estimate as time goes by. For this model, there is no justification to think that the disability experienced will be any less just on the account of time passing. Age-weighting assigns different significance to deaths at different ages, with death at younger ages given more significance. Again, in this model it was not justifiable to believe that any death should be valued higher just because of the age of the individual at the time of death.

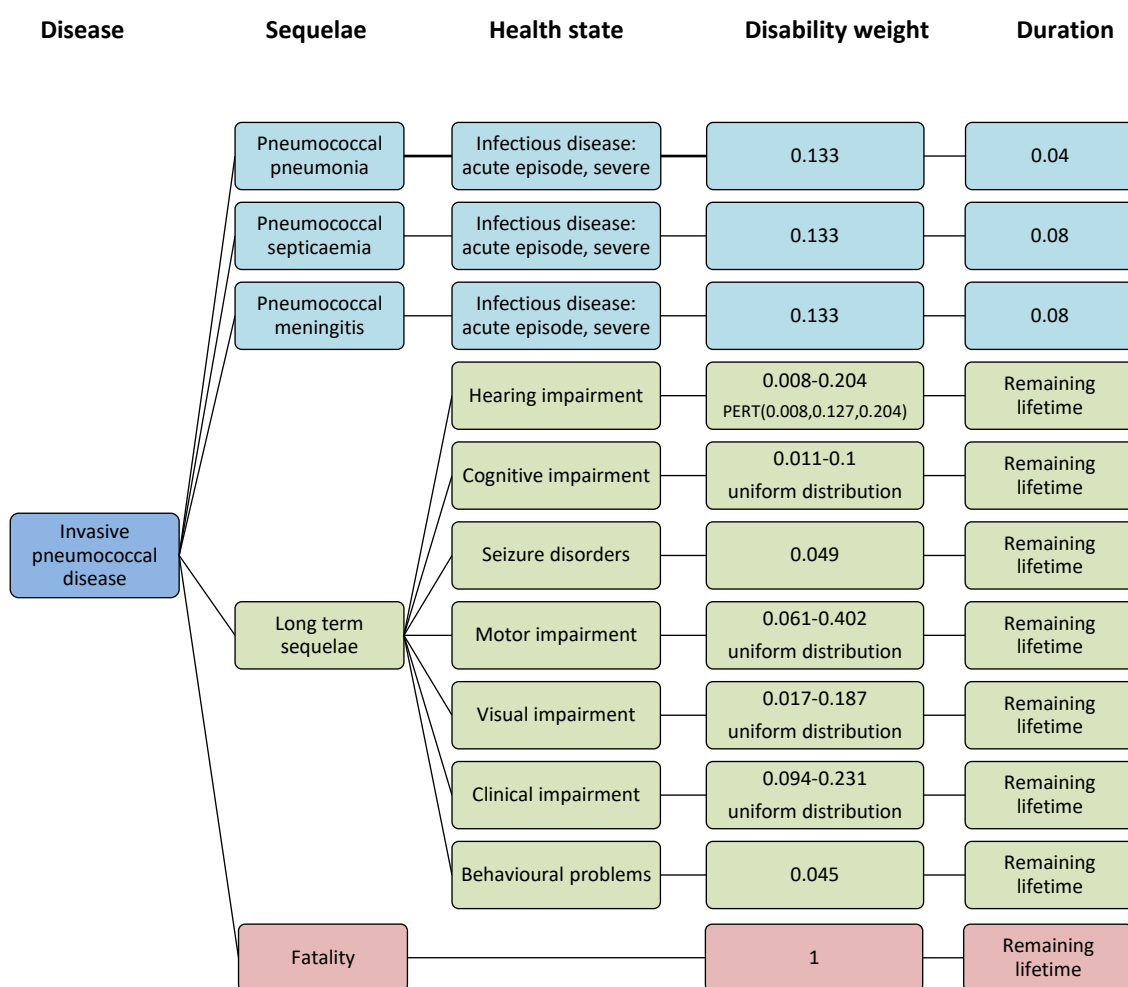


Figure 1 Modified disease model for estimating burden of disease associated with invasive pneumococcal disease.

2.3 Model inputs

2.3.1 Population estimates and life expectancy

The Australian estimated resident population from the 2016 Census was used as the population input for the model (**Table 1**).

A very important component for a burden of disease model is the potential life span of individuals in the population. This is used to calculate both the YLD and YLL and represents the health gap. Most commonly used is a reference life table that shows the maximum aspirational life span regardless of sex at each age. Using the same reference life tables across different populations allows for comparison of the burden. This may seem counterintuitive as the difference in life expectancy between males and females is well established, as is the difference in life expectancy between different countries and populations. The emphasis here is the word “aspirational”; burden of disease studies uses life expectancy under ideal circumstances and is therefore considered to be the same regardless of sex or population. For this study a reference life table developed at AIHW specifically for this study was used (**Table 1**).

2.3.2 Incidence of IPD

National incidence was used as input for the model and calculated from a three-year average centred on 2015 of the number of IPD cases reported to the National Notifiable Diseases Surveillance System (NNDSS). The NNDSS was established in 1990 with the support of the Communicable Disease Network Australia, and coordinates the national surveillance of more than 50 communicable diseases or disease groups.(25) The case definition for IPD states that only confirmed cases are notified; confirmed cases require laboratory definitive evidence only.(7) Initial notifications are made to State and Territory health authorities, who provide de-identified unit records to the Australian Government Department of Health for collation, analysis and publication on the internet.

As IPD is clinically well-defined and cases are followed up it is assumed that there is no under-notification of cases. Incidence was extracted from NNDSS line listed data.

Table 1 Estimated resident populations for 2015, 2005 and 2003 and life expectancy table

Age	Estimated resident population 2015		Estimated resident population 2005		Estimated resident population 2003		Life expectancy table	
	Female	Male	Female	Male	Female	Male	Female	Male
0	149,960	158,134	124,742	132,477	127,686	121,273	84.8	84.8
1–4	606,774	640,233	673,833	710,978	522,930	497,247	84.1	84.1
5–9	747,561	788,504	673,600	705,932	682,601	647,081	80.1	80.1
10–14	686,241	724,997	496,754	523,566	703,262	667,589	75.2	75.2
15–19	718,137	754,616	694,794	719,854	693,648	666,720	70.2	70.2
20–24	822,319	859,773	671,866	680,687	686,750	663,262	65.3	65.3
25–29	895,280	898,069	755,485	745,033	676,288	673,022	60.3	60.3
30–34	879,065	875,193	738,508	729,890	747,724	761,226	55.4	55.4
35–39	789,525	785,555	769,398	758,248	720,877	730,935	50.5	50.5
40–44	837,491	819,072	731,606	719,486	755,254	765,722	45.7	45.7
45–49	796,162	768,727	666,528	658,928	692,759	702,917	40.9	40.9
50–54	791,206	769,904	610,845	615,600	647,251	650,127	36.1	36.1
55–59	736,692	710,741	643,600	677,441	578,102	566,080	31.5	31.5
60–64	654,825	629,304	465,778	469,508	433,865	427,212	27.0	27.0
65–69	583,757	573,559	381,924	372,941	350,695	360,951	22.5	22.5
70–74	434,260	416,395	322,067	297,039	299,204	325,975	18.3	18.3
75–79	332,461	298,201	296,617	247,212	237,596	294,773	14.3	14.3
80–84	251,121	198,492	233,586	158,302	143,958	218,712	10.7	10.7
85+	297,120	171,358	205,680	96,511	87,147	192,316	7.7	7.7
All ages	12,009,957	11,840,827	10,157,211	10,019,633	9,787,597	9,933,140		

2.3.3 Fatality estimates

Death data used for determining the case fatality proportion for the IPD model is available in two data sources, the NNDSS and the National Mortality Database (NMD). The NMD holds records for deaths in Australia from 1964, and is administered by the Australian Institute of Health and Welfare (AIHW).(26) It contains the causes of death (both underlying and associated) and demographic details of the person. For all of the diseases in the burden of vaccine preventable diseases project data from the two sources were compared to ensure reliability.

Death data in the NNDSS include deaths within the first 1 to 2 weeks of diagnosis.(6) Enhanced IPD surveillance data collection is performed for all ages in ACT, NT, Tasmania, SA, WA and Queensland (except Metro South and Gold Coast Public Health Units).(27) In NSW and Victoria enhanced follow-up is only conducted for patients aged under 5 years and 50 years or over. Prior to 2012, Victoria collected enhanced follow-up data for all ages. As a consequence of the variation in follow-up, it is assumed that the number of deaths is underestimated in the 5-49 year age-group. The NNDSS data request submitted by AIHW for this project did not include IPD clinical categories and therefore the deaths could not be stratified by both age and clinical category for comparison with the NMD death data. The additional data was requested and kindly provided by the Department of Health. As this was outside the original NNDSS request and to avoid any issues with identification due to small numbers, only aggregate data in larger age-groups (<5 years, 5-64 years and 65+ years) were provided.

The National Mortality Database contains death data from the cause of death unit record files which is compiled and coded to International Classification of Disease (ICD-10) by the Australian Bureau of Statistics using data from the Registrars of Births, Deaths, and Marriages (all deaths are registered here) and the National Coronial Information System (contains additional information from coroner-certified deaths). The NMD includes data on causes of deaths (underlying and associated) and personal demographics. The underlying cause of death is the disease or condition which initiated the sequence of events resulting in death, and the associated cause of death is any other disease or conditions that contributed to the death but were not the underlying cause. The Australian mortality data is thought to be complete. Notably for this study, if the death occurred and certificate issued while the laboratory results were still pending, the death may not be attributed to the infectious cause subsequently identified in the laboratory data. Data was extracted from the NMD if the underlying or associated cause of death were coded to ICD-10 codes J13 (pneumococcal pneumonia), A40.3 (pneumococcal septicaemia) or G00.1 (pneumococcal meningitis).

As the model only uses incident cases as input, the case fatality proportion by age-group and sex was calculated from the fatality data and used in the model. To ensure consistency for vaccine preventable diseases with low number of fatalities, a 10-year average (for the period 2007 to 2016) was used as basis for the case fatality proportion calculations.

2.3.4 Literature review to inform adjustment of BCoDE model

The ECDC IPD model is based on a review of the literature and the long-term sequelae included are the most common presentations following these events. For our study, I conducted a targeted review to inform suitable adjustments to the default disease model to adapt it to an Australian context. Using Medical Subject Headings (MeSH) terms the following searches were made:

- "Pneumococcal Infections/complications"[Mesh] AND "Australia"[Mesh] AND ("humans"[MeSH Terms] AND English[lang])
- "Pneumococcal Infections/complications"[Mesh] AND (Review[ptyp] AND "humans"[MeSH Terms] AND English[lang])
- "Meningitis, Bacterial/complications"[Mesh] AND (Review[ptyp] AND "humans"[MeSH Terms] AND English[lang])

Decisions to adjust the variables in the BCoDE model were made if studies of Australian populations or recent meta-analyses showed markedly differing values to those of the default BCoDE model. Information from Australian studies were prioritised above international meta-analyses (these studies often contained data from Australian populations, but the numbers would be diluted by the inclusion of other studies).

2.3.5 Long term sequelae – transition probabilities and disability weights

There is a range of long-term sequelae that may follow from the meningitis events, each with a range of severities. This section aims to summarise the clinical features included in each sequelae category and the range of severity. In our model, the duration of these sequelae is assumed to be for the remainder of the life of the patient. The health states and associated disability weights used in each sequelae category are presented in detail in **Appendix 4B**.

Hearing impairment - includes disability ranging from unilateral mild hearing impairment to bilateral hearing loss. It is clinically well defined following audiometric testing, with distinct thresholds for severity. (28)

Cognitive impairment - is defined by reduction in IQ with different thresholds or speech/language impairment, and is detected and characterised using neuropsychological testing. (28)

Seizure disorder - as a sequelae should be distinguished from the seizure events associated with the acute phase of the bacterial meningitis. Usually clinically well defined, the seizure episodes are assumed to be controlled with long-term antiepileptic treatment. (28)

Motor impairment - includes a wide range of disability from isolated hypotonia, motor delay, ataxia, gait or coordination difficulties to more severe impairment, spasticity or paresis of one or more limbs. (28)

Clinical impairment - includes mild cerebral dilation, but most commonly refers to pathologies such as hydrocephalus and the invasive shunt devices used to treat non-communicative hydrocephalus. (28)

Visual impairment - includes disability ranging from unilateral visual disturbance, diplopia or nystagmus to reduced bilateral visual acuity. (28)

Behavioural problems - is a somewhat ill-defined complication and is sometimes included in the cognitive impairment category of sequelae. For the purpose of this work, it is defined as attention deficit hyperactivity disorder (ADHD). (28)

The disability weights used for the acute disease episodes and the long-term sequelae were those used in the Global Burden of Diseases 2016 study. (29) Health states relevant to this study and the associated disability weights are presented in Appendix A.

2.3.6 Sensitivity analysis

To assess the impact of decisions made in adjustments of the original BCoDE model for IPD a sensitivity analysis was conducted. The variables analysed were: CFR calculated from NNDSS versus NMD data; original disability weights versus updated disability weights; and original transition probabilities for long-term sequelae versus adjusted transition probabilities.

2.3.7 Comparisons with historic time points

To assess the impact of vaccine interventions and changes in epidemiology over time data from 2005, 10 years prior to the target year, was analysed for all VPD in the larger BoVPD study. As the first IPD vaccines were introduced nationally in 2005, a pre-vaccination period centred on 2003 was also included as a reference year for this disease.

2.3.8 Data analysis software used

The whole data ecosystem at AIHW uses the SAS software suite developed by SAS Institute (North Carolina, United States of America). Data manipulation and analysis was performed in SAS Enterprise Guide 7.1™. Scripts used in the project are presented in **Appendix 4C**.

Simple data manipulation and graphics were done in Microsoft Excel 2010™.

The BCoDE toolkit was used to run the burden of disease models. It is an open access software available for download at: <https://ecdc.europa.eu/en/publications-data/toolkit-application-calculate-dalys>.(24)

2.3.9 Data requests and ethics approvals

The NNDSS data used for this study was part of a large data request from AIHW to the Department of Health for the entire Burden of Vaccine Preventable Diseases project.

The study was approved by Human Research Ethics Committees at ACT Health (protocol number ETHLR.17.172) and Australian National University (protocol number 2017/376)

3 RESULTS

3.1 Model inputs

3.1.1 Incidence of IPD

National incidence was used as input for the model and calculated from a three-year average centred on 2015 of the number of IPD cases reported to the NNDSS. Over the period 2014 and 2016 there were 4,727 cases of IPD reported, an average of 1576 cases per year. The three-year averages number of cases by age-group was also calculated for 2005 and 2003, and are presented in **Table 2**.

Table 2 Three-year averages of IPD notifications for the reference year 2015 and comparison years 2005 and 2003. Data used in final model is highlighted.

Age	Average 2014-2016		Average 2004-2006		Average 2002-2004	
	Female	Male	Female	Male	Female	Male
0	24	33	46	70	123	84
1–4	64	95	119	162	303	206
5–9	21	26	23	34	45	32
10–14	8	15	7	16	18	8
15–19	9	13	12	20	27	16
20–24	11	13	16	23	30	18
25–29	15	18	23	25	34	26
30–34	21	29	36	48	61	42
35–39	29	36	34	53	65	51
40–44	37	44	45	62	57	40
45–49	34	50	27	51	53	32
50–54	53	55	43	52	48	41
55–59	60	63	49	57	67	50
60–64	71	69	55	67	69	50
65–69	60	74	45	62	61	49
70–74	48	62	45	61	72	51
75–79	45	52	48	64	71	51
80–84	35	44	48	53	64	60
85+	78	62	69	56	61	93
All ages	725	851	788	1036	1328	1000

The choice of using three-year averaged incidence data was consistent across all vaccine preventable diseases in the larger BoVPD project. To ensure that this average was representative, 5-year and 10-year averages were also calculated to assess any periodic

variation. The 5-year and 10-year averages for 2015 were 1,620 and 1,628 respectively. For IPD there were no concerns in using the 3-year average of incidence data.

3.1.2 Fatality related to IPD

In the National Mortality Database (NMD) IPD related deaths have an underlying or associated cause of death coded to ICD-10 G00.1 (pneumococcal meningitis), A40.3 (pneumococcal septicaemia) or J13 (pneumococcal pneumonia). There was a large difference in number of deaths recorded in the NNDSS compared with NMD. For the time period of 2007-2016 there were 1232 deaths recorded in the NNDSS. For the same period there were 260 deaths recorded in the NMD with IPD as underlying cause of death, and 496 deaths recorded with IPD as underlying or associated cause of death. The breakdown by 5-year age groups is shown in **Figure 2**.

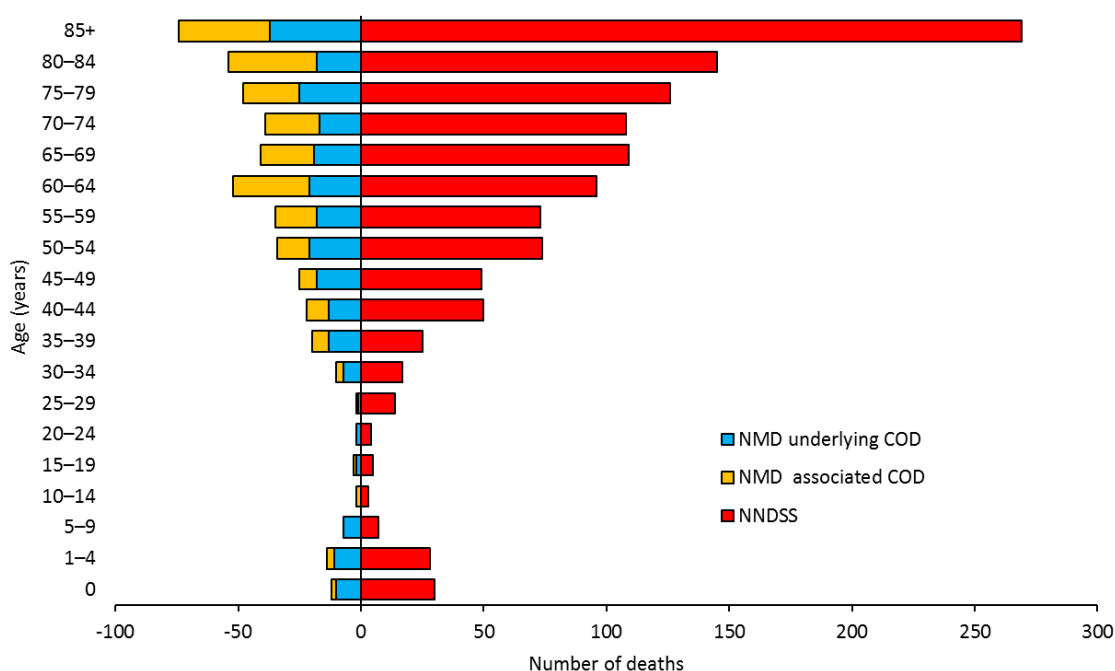


Figure 2 Deaths recorded in NMD and NNDSS from 2007 to 2016, by age-group.

To assess if there was a difference with regards to deaths in patients presenting with different clinical categories, these data were extracted from the two sources. It should be noted that this makes the assumption that all IPD cases in the NMD is a subset of the IPD cases in the NNDSS. While this is highly likely, to verify this would require a data linkage study, which was beyond the scope of this MAE project.

Table 3 shows that the biggest discrepancy is seen for the pneumonia category among elderly patients, where only 14% of the cases notified in NNDSS are observed in NMD. It should be noted that this makes the assumption that all IPD cases in the NMD is a subset of the IPD cases in the NNDSS. While this is highly likely, to verify this would require a data linkage study, which was beyond the scope of this MAE project.

Table 3 Mortality data from the NMD and the NNDSS over the period 2007-2016, by clinical category and age-groups.

NNDSS	Pneumonia	Bacteraemia	Meningitis	Total
<5 years	4	14	22	40
5 to <65 years	232	98	65	395
65+ years	540	152	35	727
Total	776	264	122	1162

NMD [§]	Pneumonia (J13)	Septicaemia (A40.3)	Meningitis (G00.1)	Total
<5 years	3 / 4	8 / 10	10 / 12	21 / 26
5 to <65 years	68 / 121	33 / 65	22 / 28	123 / 214
65+ years	77 / 151	29 / 86	10 / 19	116 / 256
Total	148 / 276	70 / 161	42 / 59	260 / 496

NMD/NNDSS ratio	Pneumonia [§]	Bacteraemia/ Septicaemia [§]	Meningitis [§]	Total [§]
<5 years	75.0% / 100%	57.1% / 71.4%	45.5% / 54.5%	52.5% / 65.0%
5 to <65 years	29.3% / 52.2%	33.7% / 66.3%	33.8% / 43.1%	31.1% / 54.2%
65+ years	14.3% / 28.0%	19.1% / 56.6%	28.6% / 54.3%	16.0% / 35.2%

[§] Underlying cause of death and underlying+associated cause of death (separated by a slash).

Age-group specific case fatality ratio were calculated using NNDSS IPD incidence data from 2007-2016 as the denominator and NMD 2007-2016 data (only underlying COD) or NNDSS 2007-2016 mortality data as numerator (**Table 4**). As IPD only became notifiable in 2001 this limited the time range available for calculation of CFRs for the comparator years 2005 and 2003. Both NNDSS data and NMD data were tested in the models.

Table 4 Case fatality ratio for 2007-2016, 2001-2006 and 2001-2004 from NNDSS and for 2007-2016 from NMD. Data used in final model is highlighted.

Age	NNDSS 2007-2016		NNDSS 2001-2006		NNDSS 2001-2004		NMD 2007-2016	
	Female	Male	Female	Male	Female	Male	Female	Male
0	0.062	0.039	0.018	0.039	0.015	0.034	0.029	0.013
1–4	0.019	0.015	0.012	0.025	0.009	0.023	0.012	0.008
5–9	0.006	0.015	0.012	0.025	0.009	0.023	0.012	0.008
10–14	0.006	0.015	0.012	0.025	0.009	0.023	0.012	0.008
15–19	0.029	0.006	0.012	0.025	0.009	0.023	0.012	0.008
20–24	0.029	0.006	0.012	0.025	0.009	0.023	0.012	0.008
25–29	0.029	0.030	0.012	0.025	0.009	0.023	0.012	0.008
30–34	0.029	0.030	0.012	0.025	0.009	0.023	0.012	0.008
35–39	0.029	0.030	0.012	0.025	0.009	0.023	0.012	0.035
40–44	0.052	0.057	0.012	0.025	0.009	0.023	0.012	0.035
45–49	0.052	0.057	0.062	0.095	0.065	0.096	0.031	0.035
50–54	0.064	0.082	0.062	0.095	0.065	0.096	0.031	0.035
55–59	0.064	0.082	0.062	0.095	0.065	0.096	0.031	0.035
60–64	0.064	0.082	0.062	0.095	0.065	0.096	0.031	0.035
65–69	0.103	0.110	0.062	0.095	0.065	0.096	0.031	0.035
70–74	0.103	0.110	0.083	0.183	0.076	0.169	0.031	0.035
75–79	0.158	0.110	0.083	0.183	0.076	0.169	0.049	0.054
80–84	0.150	0.159	0.083	0.183	0.076	0.169	0.049	0.054
85+	0.191	0.220	0.251	0.193	0.207	0.193	0.049	0.054

3.1.3 Literature review to inform adjustment of BCoDE model

To inform suitable adjustments to the default BCoDE disease model to adapt it to an Australian context a literature review was conducted using Medical Subject Headings (MeSH) terms outlined in **Table 5**. All searches were limited to publications from 1990 onwards. Publications were used if they included quantifiable data on the incidence of sequelae following IPD episodes. A large number of publications were excluded as they only described sequelae as a possible consequence of IPD in the introductions but contained no data from cases.

Table 5 Literature review search terms and selection process.

Search terms	Total hits (1990 onwards)	Selected from title	Selected from abstract	Used in study
"Pneumococcal Infections/complications"[Mesh] AND "Australia"[Mesh] AND ("humans"[MeSH Terms] AND English[lang])	8	6	4	2
"Pneumococcal Infections/complications"[Mesh] AND (Review[ptyp] AND "humans"[MeSH Terms] AND English[lang])	151	9	3	2 [§]
"Meningitis, Bacterial/complications"[Mesh] AND (Review[ptyp] AND "humans"[MeSH Terms] AND English[lang])	207	15	6	3 [§]
Additional publications included from references				1

[§] Studies not mutually exclusive

3.1.4 Long term sequelae - transition probabilities and disability weights

The BCoDE model uses point estimates for the transition probabilities based on the meta-analysis publication by Edmond *et al.*(28). The disability weights used for the sequelae are expressed as ranges with a uniform distribution, derived from the Haagsma *et al* publication.(9) Following section outlines the review of the literature and the justification for the changes made to the default setting in the BCoDE model for IPD (**Error! Reference source not found.****Table 6, Table 7, Table 8**). As previously explained, the “Multiple impairment” category was omitted to avoid double counting, and therefore the transition probability for this was set to 0% (zero).

Table 6 Disability weights for post-pneumococcal meningitis sequelae used in three previous studies.

Sequelae	BCoDE (24)	Global BoD (30) (IPD specific)	Aus BoD (31) (not specific for IPD)
Hearing impairment	0.008-0.103	0.010-0.215	0.010-0.204
Cognitive impairment	0.044-0.188	0.011-0.043	0.043-0.200
Seizure disorders	0.057-0.088	0.049-0.552	0.049-0.552
Motor impairment	0.011-0.421	0.010-0.402	0.010-0.402
Visual impairment	0.004-0.171	0.017-0.187	0.003-0.187
Clinical impairments	0.004-0.421	-	0.094-0.231
Behavioural problems	0.070-0.108	0.045 (ADHD)	0.045 (ADHD)

3.1.4.1 Hearing impairment

Both Australian pneumococcal meningitis specific studies have data divided into minor hearing impairment and major hearing impairment (**Table 7, Table 8**). (32, 33) The ratio between minor and major hearing impairment was approximately 40:60 for both studies. The combined prevalence of major and minor sequelae was 21.2% and 18.0%. The midpoint of the combined prevalence estimates at 19.6% was supported by the global meta-analyses by Jit (34) and Lucas *et al* (4) (estimate for children, and one of the adult studies), but was significantly higher than the estimate in Edmond *et al* (28). The second adult study in Lucas *et al* (4) screened all adult patients regardless of clinical indication, which may explain the high prevalence. If only patients with clinical indications of hearing loss were included, the prevalence dropped to 31%.

Major hearing impairment included severe (DW=0.158) to profound (DW=0.215) bilateral hearing loss, and minor hearing impairment included mild (DW=0.01) to moderate (DW=0.027) bilateral or any severity of unilateral (DW=0.008) hearing loss (**Table 6**). (30)

For the model a transition probability of 19.6% of pneumococcal meningitis cases was used, with a disability weight range of 0.008-0.215 with a 40:60 PERT distribution. The skew was calculated as $(0.008+0.215)*0.6=0.1338$, resulting in the following syntax: PERT(0.008,0.1338,0.215).

3.1.4.2 Cognitive impairment

There was a large difference between the two Australian studies, with both using the terms *developmental delay* and *learning problems*, but neither of them provided a break down by severity (**Table 7**). (32, 33) The global meta-analyses did not provide much direction, with Lucas *et al* 2016 supporting the higher Australian estimate, and Edmond *et al* 2010 supporting the lower (**Table 8**). If the behavioural problems are considered part of the spectrum, the Edmond *et al* 2010 estimate would be higher at 8.8%. This sequelae category can be heavily affected by

the study design, exemplified by the Grimwood study which included active school-based follow-up of cognitive impairment and behavioural problems providing a more accurate measure, and resulting in high prevalence of these sequelae while the other sequelae had relatively low prevalence. Nevertheless, the King&Richmond 2004 and the Lucas *et al* 2016 are the most recent papers, therefore we will use the higher of the Australian estimates in this study. The adult study in Lucas *et al* 2016, was also a long-term follow-up with dedicated testing of cognitive functions.

For cognitive impairments the disability weights range from 0.011 for *borderline intellectual functioning* to 0.200 for *profound intellectual disability* (**Table 6**).⁽³⁰⁾ However, the severe and profound categories describe the individual to have very low intelligence and almost no language. In the light that most of the data on cognitive impairment following pneumococcal meningitis is from school-based assessments, we believe that the individuals in these two most severe categories are unlikely to be included.

For the model a transition probability of 15.7% of pneumococcal meningitis cases was used, with a disability weight range of 0.011 to 0.1 (*moderate intellectual disability*) with a uniform distribution.

3.1.4.3 Seizure disorder

There was a large difference between the two Australian studies, with neither specifying the severity (**Table 7**).^(32, 33) Again, the global meta-analyses did not provide much help, with Lucas *et al* 2016 supporting the higher Australian estimate, Edmond *et al* 2010 supporting the lower, and the Jit (34) falling in between (**Table 8**). The adult estimate in Lucas *et al* 2016 was for pre- and in-hospital seizures, which would be related to the acute infectious episode and not a long-term sequelae. The average of the two Australian studies 8.7% was used.

The full range of disability weights for seizure disorders range from 0.049 to 0.552 (**Table 6**).⁽³⁰⁾ However, most burden of disease studies consider long-term seizures disorders to be a medically controlled, with the disability weight 0.049.

For the model a transition probability of 8.7% of pneumococcal meningitis cases was used, with a disability weight 0.049 (*generic uncomplicated disease, worry and daily medication*).

3.1.4.4 Motor impairment

The prevalence of motor deficit in the two Australian studies was similar (**Table 7**).^(32, 33) Surprisingly these were higher than the prevalence reported in any of the global meta-analyses. The highest of the adult studies included in Lucas *et al* 2016, assessed pre- and in-hospital cerebral infarcts which may not all necessarily result in long-term sequelae (**Table 8**). The

sequelae category is clinically well defined, and the Australian estimates were thought to be accurate.

The disability weights for motor impairment range from 0.010 (mild) to 0.402 (severe) (**Table 6**).⁽³⁰⁾ The Australian studies described these sequelae as hemiparesis, quadriplegia, hemiplegia, cranial nerve palsy or spastic cerebral palsy, suggesting motor deficits in the moderate to severe range.

For the model a transition probability of 17.7% of pneumococcal meningitis cases was used, with a disability weight range of 0.061 (*moderate*) to 0.402 (*severe*) with a uniform distribution.

3.1.4.5 Clinical impairment

The only Australian study that included data on clinical impairment was Grimwood *et al*, and this study did not have the bacterial meningitis episodes broken down by causative pathogen (**Table 7**).⁽³⁵⁾ This means that a greater reliance had to be put on the global meta-analyses. Both the Jit (34) and Lucas *et al* (4) publications reported a higher proportion of patients with clinical impairments (hydrocephalus and hydrocephalus with a ventriculoperitoneal shunt) compared with the Edmond *et al* (28) publication (**Table 8**). The Jit (34) data was based on 18 publications, while the Lucas *et al* and Edmond *et al* were based on 2 and 1 publications respectively, making the Jit 2010 data most reliable.

There are no specific health states for hydrocephalus or hydrocephalus with a ventriculoperitoneal shunt, and therefore no easily applicable disability weights. The health states of “traumatic brain injury: long-term consequences, minor, with and without treatment” (0.094), “traumatic brain injury: long-term consequences, moderate, with and without treatment” (0.231) and “indwelling device/drain” (0.131) are the most appropriate close matches (**Table 6**).⁽³⁰⁾ In a review of hydrocephalus in children, it stated that 34% will develop epilepsy and up to 20% will have headaches.⁽³⁶⁾ Further, the review reported that in adulthood over 40% of patients reported severe headaches, 45% required treatment for depression and 43% were dependent on care. Following this data an even distribution between the minor and moderate health state was appropriate.

For the model a transition probability of 6.7% of pneumococcal meningitis cases was used, with a disability weight range of 0.094 (minor) to 0.231 (moderate) with a uniform distribution.

3.1.4.6 Visual impairment

Only one Australian study had data on visual impairment (**Table 7**).⁽³³⁾ The reported prevalence was higher than those presented in Edmond *et al* and Jit (**Table 8**).^(28, 34) The Jit measure was

based on two studies, one of which has no patients with visual impairment.(34) Given the dearth of global data, we used the Australian estimate for our study.

The disability weights for visual impairment range from “monocular distance vision loss due to pneumococcal meningitis” (0.017) to “blindness due to pneumococcal meningitis” (0.187) (**Table 6**).⁽³⁰⁾ There is no data provided on the severity in the Australian study, so the full range was used.

For the model a transition probability of 4.5% of pneumococcal meningitis cases was used, with a disability weight range of 0.017 to 0.187 with a uniform distribution.

3.1.4.7 Behavioural problems

The only Australian study that included data on behavioural was Grimwood *et al*, and this study did not have the bacterial meningitis episodes broken down by causative pathogen (**Table 7**).⁽³⁵⁾ Additionally this study was a long-term follow-up and designed to capture learning difficulties and behavioural problems, likely explaining the high prevalence reported. Edmond *et al* analysis specifies behavioural problems as a separate category.⁽²⁸⁾ Lucas *et al* had this incorporated in the cognitive impairment category, which may explain the high prevalence reported in this category (**Table 8**).⁽⁴⁾ This may also have been inflated due to the inclusion of the Grimwood *et al* study.⁽³⁵⁾ In the absence of other data, the Edmond *et al* estimate was used.⁽²⁸⁾

The BCoDE model used the somewhat peculiar health state of “subacute sclerosing panencephalitis” (0.070-0.108) for this category (**Table 6**). We believed that the health state of attention deficit hyperactive disorder” (0.045) was more appropriate.⁽³⁰⁾

For the model a transition probability of 4.6% of pneumococcal meningitis cases was used, with a disability weight 0.045.

Table 7 Summary of pneumococcal meningitis cases with a long-term disability in Australian studies.

	Davis & McIntyre (32)	King & Richmond (33)		Hannah & Wild (37)	Grimwood <i>et al.</i> (35)
	Pneumococcal, NSW	Pneumococcal, WA		Bacterial meningitis, WA	Bacterial meningitis, Vic
Long-term sequelae	n=104 [§]	n=89 [§]	Average [#]	n=270 (n=36) [†]	n=109 [‡]
Major impairment					
Hearing impairment (bilateral severe, profound)	13.5% (14/104)	11.2% (10/89)	12.4%	2.8% (2.8%) [†]	2.8%
Cognitive impairment (IQ <70)	5.8% (6/104)	15.7% (14/89)	10.3%	1.6%	3.7%
Seizure disorder	3.8% (4/104)	13.5% (12/89)	8.7%	2.4%	3.7%
Motor impairment (paresis, spasticity, palsy)	17.3% (18/104)	18.0% (16/89)	17.7%	2.8% (2.8%) [†]	1.8%
Clinical impairment (hydrocephalus, VP shunt)	-	-	-	-	1.8%
Visual impairment	-	4.5% (4/89)	4.5%	-	0.9%
Minor impairment					
Hearing impairment (mild, moderate, unilateral)	7.7% (8/104)	6.7% (6/89)	7.2%	-	6.4%
Cognitive impairment (IQ 70-80, educational deficit)	-	-	-	-	14.7%
Motor impairment	-	-	-	-	-
Behavioural problems	-	-	-	-	22.9%

[§] Pneumococcal meningitis cases[#] Average proportion based on data from King & Richmond and Davis & McIntyre. For hearing impairment, the major and minor impairments in King & Richmond were combined.[†] Publication is based on cases of bacterial meningitis. The 36 cases attributed to *Streptococcus pneumoniae* are stated in brackets, of which 1 case had hearing impairment and 1 case had cerebral palsy (motor impairment), with the associated proportions stated in brackets. Due to low numbers this is not included in calculation of average.[‡] Publication is based on cases of bacterial meningitis. There is no break down by causative agent, and the cases are from 1983-1986 when Hib still was a dominant pathogen. Therefore, this data is not used in calculation of average.

Table 8 Summary of pneumococcal meningitis cases with a long-term disability in global meta-analyses.

Long-term sequelae	Edmond <i>et al</i> 2010 (28)	Edmond <i>et al</i> 2010 (28)	Jit 2010 (34)	Lucas <i>et al.</i> 2016 (4)	
	Pneumococcal	Pneumococcal	Pneumococcal	Pneumococcal (children)	Pneumococcal (adults)
Major impairment					
Hearing impairment (bilateral severe, profound)	6.7%	7.5% [§]	20.9% (17.1-24.7%)	23% (14, 32%)	45.5% (22, 69%)
Cognitive impairment	3.1%	4.2% [§]	-	16% (10, 22%)	37%
Seizure disorder	2.5%	2.5% [§]	6.5% (3.3-9.7%)	14.3% (13.5, 15%)	31%
Motor impairment (paresis, spasticity, palsy)	3.3%	5.8% [§]	10.5% (5.9-15.1%)	8.5% (3, 14%)	23.5% (11, 22, 36%)
Clinical impairment (hydrocephalus, VP shunt)	3.4%	3.3% [§]	6.7% (2.2-11.1%)	12.5% (4, 21%)	4%
Visual impairment	1.1%	1.1% [§]	2.4% (0-5.7%)	-	-
Minor impairment					
Hearing impairment (mild, moderate, unilateral)	4.6%		-	-	-
Cognitive impairment (IQ 70-80, educational deficit)	3.0%		-	-	-
Motor impairment	2.7%		-	-	-
Behavioural problems	4.0%	4.6% [§]	-	-	-

[§] Combined major and minor sequelae data in this publication, which was used in the ECDC BCoDE model.

3.1.4.8 Transition probabilities used in model

The input into the model was incident cases of IPD of all clinical categories, and all subsequent calculations are based on from these numbers. Therefore, as the long-term sequelae arise from the pneumococcal meningitis events the transition probabilities had to be adjusted for this. According to the NNDSS data for the years 2014-2016, 2004-2006 and 2002-2004, pneumococcal meningitis respectively accounted for 9.5%, 7% and 6.3% of all IPD cases where a clinical category had been assigned. **Table 9** shows the final adjusted transition probabilities used in the model.

Table 9 Summary of final transition probabilities used to estimate incidence of long-term sequelae from all incident IPD cases with a clinical category assigned.

Sequelae	Meningitis cases only	2015 (9.5% of all cases)	2005 (7.0% of all cases)	2003 (6.3% of all cases)
Hearing impairment	19.6%	1.9%	1.4%	1.2%
Cognitive impairment	15.7%	1.5%	1.1%	1.0%
Seizure disorders	8.7%	0.8%	0.6%	0.5%
Motor impairment	17.7%	1.7%	1.2%	1.1%
Visual impairment	4.5%	0.4%	0.3%	0.3%
Clinical impairments	6.7%	0.6%	0.5%	0.4%
Behavioural problems	4.6%	0.4%	0.3%	0.3%

3.1.5 Age-group redistribution for meningitis sequelae

The age-group distribution among patients with pneumococcal meningitis may be different from the overall age-group distribution of invasive pneumococcal disease. The model adjusted for this potential discrepancy by applying a redistribution factor to the calculated incidences of each of the long-term meningitis associated sequelae. To calculate the re-distribution factors data on IPD meningitis events (ICD-10 G00.1) were extracted from the National Hospital Morbidity Database (NHMD), for the years 2014-2016, 2004-2006 and 2002-2004. **Table 10** shows the number of meningitis cases observed during these periods, and the resulting distribution of cases between the different age-groups.

Theoretically the data available in the IPD Public Dataset could also have been used, but the age-group categorisations in the available data were not compatible with the age-group categories

used in my model (<1 year and 1-4 years). The overall numbers of meningitis events in the NHMD and the IPD Public Dataset were comparable.

Table 10 Age-group specific redistribution proportions of meningitis sequelae cases, for years 2015, 2005 and 2003.

Age	2015		2005		2003	
	Re-distribution (cases)		Re-distribution (cases)		Re-distribution (cases)	
	Female	Male	Female	Male	Female	Male
0	0.110 (16)	0.159 (29)	0.214 (21)	0.221 (27)	0.285 (45)	0.242 (31)
1–4	0.062 (9)	0.088 (16)	0.214 (21)	0.164 (20)	0.253 (40)	0.234 (30)
5–9	0.014 (2)	0.027 (5)	0.061 (6)	0.025 (3)	0.051 (8)	0.039 (5)
10–14	0.048 (7)	0.060 (11)	0.010 (1)	0.041 (5)	0.013 (2)	0.031 (4)
15–19	0.028 (4)	0.027 (5)	0.010 (1)	0.025 (3)	0.019 (3)	0.016 (2)
20–24	0.014 (2)	0.049 (9)	0.010 (1)	0.008 (1)	0.013 (2)	0.016 (2)
25–29	0.007 (1)	0.011 (2)	0.010 (1)	0.025 (3)	0.025 (4)	0.008 (1)
30–34	0.041 (6)	0.011 (2)	0.041 (4)	0.057 (7)	0.044 (7)	0.039 (5)
35–39	0.028 (4)	0.044 (8)	0.020 (2)	0.041 (5)	0.019 (3)	0.023 (3)
40–44	0.034 (5)	0.044 (8)	0.051 (5)	0.049 (6)	0.038 (6)	0.031 (4)
45–49	0.028 (4)	0.022 (4)	0.010 (1)	0.074 (9)	0.025 (4)	0.008 (1)
50–54	0.083 (12)	0.060 (11)	0.061 (6)	0.041 (5)	0.025 (4)	0.070 (9)
55–59	0.076 (11)	0.115 (21)	0.092 (9)	0.049 (6)	0.019 (3)	0.047 (6)
60–64	0.145 (21)	0.060 (11)	0.071 (7)	0.090 (11)	0.076 (12)	0.023 (3)
65–69	0.103 (15)	0.066 (12)	0.051 (5)	0.033 (4)	0.038 (6)	0.070 (9)
70–74	0.062 (9)	0.088 (16)	0.020 (2)	0.025 (3)	0.019 (3)	0.063 (8)
75–79	0.069 (10)	0.038 (7)	0.000 (0)	0.016 (2)	0.013 (2)	0.016 (2)
80–84	0.028 (4)	0.022 (4)	0.031 (3)	0.008 (1)	0.019 (3)	0.008 (1)
85+	0.021 (3)	0.005 (1)	0.020 (2)	0.008 (1)	0.006 (1)	0.016 (2)
All ages	1 (145)	1 (182)	1 (98)	1 (122)	1 (158)	1 (128)

3.1.6 Summary of numbers used for model input

Table 11 shows a summary of the models run in this project, including those use for the sensitivity analysis and for the comparison years.

Table 11 Overview of models and main variables. Variables in red indicate a change from the final 2015 model. NNDSS data only available from earliest 2001.

Model	Population	Incident cases	Deaths	Transition probabilities	Disability weights
Final 2015 model	2015 ERP	2014-2016	2007-2016 NNDSS	Adjusted	Adjusted
2015 recent deaths	2015 ERP	2014-2016	2014-2016 NNDSS	Adjusted	Adjusted
2003 comparison	2003 ERP	2002-2004	2001-2004 NNDSS	Adjusted	Adjusted
2005 comparison	2005 ERP	2004-2006	2001-2006 NNDSS	Adjusted	Adjusted
NMD deaths model	2015 ERP	2014-2016	2007-2016 NMD	Adjusted	Adjusted
BCoDE default	2015 ERP	2014-2016	2007-2016 NNDSS	BCoDE default	BCoDE default
BCoDE adjusted	2015 ERP	2014-2016	2007-2016 NNDSS	BCoDE default	Adjusted

ERP = Estimated resident population

3.2 DALY estimates for IPD

3.2.1 DALY estimate for IPD in Australia 2015

There are many variables in the model that will have an effect on the DALY estimate produced, and for IPD the factor that had the biggest influence was the data source used for establishing the case fatality ratios. Following the literature review and input from the Expert Advisory Committee it was decided that the NNDSS provided the most realistic and accurate measure of deaths.

The final modelled DALY, YLD and YLL estimates for reference year 2015 are presented in **Table 12**. The model showed that of the 3,787 DALYs, the majority, 82%, is composed of years of life lost to premature deaths. The estimated number of deaths was 127, and close to the average (n=123) observed nationally for the period 2007 to 2016 used to calculate the CFR, but higher

than the observed number of deaths ($n=105$) in 2015. Of the years of life lost to disability only a small proportion, 1.8% was attributed to acute disease episodes of IPD, with the majority being accounted for by long-term sequelae following the meningitis events. Among these long-term sequelae, motor impairment and hearing loss accounted for 43.7% and 25.3%, respectively, of the years lost to disability.

To allow comparison with other populations and/or time points, the estimates were normalised to the population. The estimates per 100,000 population were 6.61 for incidence, 0.53 for deaths, 2.85 for YLD, 13.03 for YLL, and 15.88 for DALY. Each case of IPD contributed to nearly two and a half years of disability (2.40).

3.2.2 Sensitivity analysis

A sensitivity analysis was conducted to assess the impact of decisions made in the adjustments of the original BCoDE model for IPD (**Table 13**). When comparing the results above with a model using a smaller time frame of deaths (2014-2016) for calculation of CFR, the YLL is reduced by 334.39 years. This is a consequence of fewer deaths ($n=110$) which is consistent with the average number of observed deaths over that period ($n=111$). Using a CFR based on NMD data resulted in a reduction of the YLL estimate by 1,750.11 years, and nearly halving the DALY estimate.

Using Australian incidence, population and CFR data with the BCoDE default settings for the IPD model showed an increase in YLDs assigned to acute disease episodes and a reduction in YLD assigned to long-term sequelae. The former is the result of the very high disability weight associated with the “intensive care unit admission” health state used (0.655). Even though the duration was shorter at 7 days ($0.655 \times 0.02 = 0.0131$), compared with the 2 to 4 weeks and a disability weight of 0.133 used in the adjusted model ($0.133 \times 0.04 = 0.0053$ and $0.133 \times 0.08 = 0.0106$), the resulting burden was higher. The lower transition probabilities in the default model explains the reduction in YLD estimate for the long-term sequelae. Finally, when the disability weights were adjusted in the above model, it was observed that these had marginal effects on the YLDs from the long-term sequelae and the overall DALY estimate, although there was a proportionally large reduction in YLDs generated by acute disease episodes.

3.2.3 DALY estimates for comparison years 2005 and 2003

In the larger BoVPD project, 2005 was chosen as the comparison year. However, 2003 was a more suitable comparison year for IPD as this was before both the introduction of vaccinations for at-risk infants (2003) as well as the universal national infant vaccination program (2005). The DALY estimates for both 2003 and 2005 are presented in **Table 14**. Compared with 2005, there

was a 9% (370.50 years) reduction in DALYs, a 9% (324.27 years) reduction in YLLs and a 6% (46.24 years) reduction in YLDs in the estimates for 2015. In contrast, a comparison of the pre-vaccination 2003 comparison year and the 2015 estimate, showed a 16% (729.37 years) reduction in the DALYs, with a 14% (519.0 years) and 24% (210.35 years) reduction in YLL and YLD, respectively. This suggests that there was an immediate effect of the at-risk infant vaccination program. The largest proportional reduction was seen for the YLD estimates of acute disease episodes, at 32% (6.02 years). While proportionally the largest changes were seen in YLDs, the YLLs remain the major driver for the DALYs. From here on, only the 2003 comparison year will be considered.

In a comparison of the 2003 and 2015 estimates by age-group, the largest improvements were seen in the age-groups targeted with the vaccination programs, with reductions in both the YLD and YLL estimates (**Figure 3**), translating to 44%, 66% and 54% reductions in DALYs for the under 1 year old, 1 to 4 year olds and 5-9 year olds, respectively. For individuals 10 years and older, the reductions were much less prominent, and for some age-groups there were increases in DALY estimates, most prominently in the 40 to 44 years age-group with a 160% increase. In **Figure 3** there are visibly three larger age groupings with distinct differences in burden: <5 year olds, 5-39 year olds and 40+ years. In 2003, the distribution of DALYs was 36%, 13% and 51%, for respective age-group. In 2015 the distribution had changed to 19%, 14% and 67%, for respective age-group. Despite an overall reduction in DALYs from 2003 to 2015, the 40+ year age-group actually has seen an increase in 2015 to 2528.36 DALYs compared with the 2003 estimate of 2295.24 DALYs.

The pattern of YLD and YLL distribution appears to have changed between 2003 and 2015 in these age-groups, with a larger proportion of the DALY estimate composed of YLDs (**Figure 3**). In the age-groups 10-24 years, an increase of 25-31% in YLD proportion was seen, while the remaining age-groups have more modest increases in the proportion (1-9%). For a small number of age-groups there was a reduction in the proportion of YLD in the DALY estimate. As the YLD estimate is largely driven by the sequelae resulting from the meningitis events, this will be affected by the changes in the distribution of meningitis cases among age-groups between different years. As shown in **Table 10**, there was a decrease in the proportion of meningitis cases in the two youngest age groups and an increase in the 10-24 years and older age-groups.

As the Australian population was smaller in 2003 compared with 2015, this affected the population specific estimates. The estimates per 100,000 population for 2003 were 1.8 times

the 2015 estimate for incidence, 1.3 times for deaths, 1.6 times for YLD, 1.4 times for YLL, and 1.4 times for DALY. The DALY per case was lower, 0.8 times the 2015 estimate.

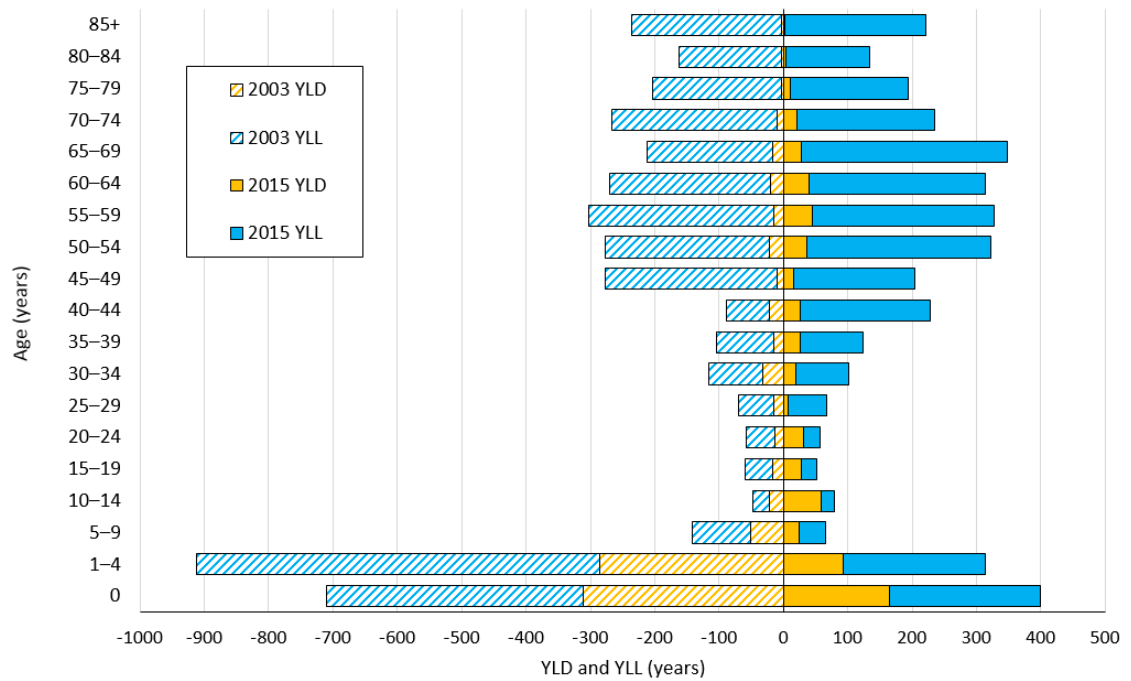


Figure 3 Comparison of YLD and YLL estimates for years 2003 and 2015, by age-group.

Table 12 DALY estimates for IPD model for 2015 using a 10-year NNDSS case fatality ratio.

	Cases	YLD	YLL	DALY
Overall burden		680.09 (618.60 – 742.86)	3,106.67 (3,105.96 – 3,107.39)	3,786.76 (3,724.64 – 3,850.02)
Acute infection				
Cases	1,576	12.58 (11.70 – 13.48)	0	12.58 (11.70 – 13.48)
Deaths	127.17	0	3,106.67 (3,105.96 – 3,107.39)	3,106.67 (3,105.96 – 3,107.39)
Sequelae				
Motor impairment	26.75	292.45 (235.73 – 349.63)	0	292.45 (235.73 – 349.63)
Hearing impairment	29.89	168.24 (143.50 – 192.38)	0	168.24 (143.50 – 192.38)
Cognitive impairment	23.60	61.97 (49.14 – 75.69)	0	61.97 (49.14 – 75.69)
Clinical impairments	9.44	72.15 (63.46 – 80.24)	0	72.15 (63.46 – 80.24)
Visual impairment	6.29	30.30 (23.36 – 36.73)	0	30.30 (23.36 – 36.73)
Seizure disorders	12.59	29.04 (29.04 – 29.05)	0	29.04 (29.04 – 29.05)
Behavioural problems	6.29	13.34 (13.33 – 13.34)	0	13.34 (13.33 – 13.34)

Table 13 Sensitivity analysis of the DALY estimates for 2015 from five models: NNDSS 10-year case fatality ratio (CFR), NNDSS 3-year CFR, NMD 10-year CFR, BCoDE default model (with Australian population, incidence and CFR data), BCoDE model with adjusted disability weights (with Australian population, incidence and CFR data). Data in red indicate a change compared with the 2015 estimate.

	Raw numbers		
	YLD	YLL	DALY
Final 2015 model (NNDSS CFR 2007-2016)	680.09	3,106.67	3,786.76
Acute infection	12.58	3,106.67	3,119.26
Sequelae	667.50	0	667.50
Recent deaths model (NNDSS CFR 2014-2016)	680.15	2,772.28	3,452.43
Acute infection	12.60	2,772.28 ↓	2,784.88
Sequelae	667.55	0	667.55
NMD deaths model (NMD CFR 2007-2016)	679.17	1,356.56	2,035.73
Acute infection	12.57	1,356.56 ↓	1,369.13
Sequelae	666.59	0	666.59
BCoDE default model (Australian data)	279.42	3,110.16	3,389.58
Acute infection	33.56 ↑	3,110.16	3,143.71
Sequelae	245.87 ↓	0	245.87
BCoDE adjusted model (Australian data + adjusted DW)	268.22	3,106.69	3,374.91
Acute infection	12.56	3,106.69	3,119.25
Sequelae	255.66 ↓	0	255.66

Table 14 Comparison of the DALY estimates from three models, all using NNDSS case fatality ratio but from different years: 2015, 2005 (BoVPD comparison year) and 2003 (pre national infant vaccination program). Transition probabilities were adjusted to account for the meningitis proportion of all incident cases in 2005 and 2003. Population adjusted estimates used the ERP for the respective year.

	Raw numbers			Per 100,000 population					DALY per case
	YLD	YLL	DALY	Incidence	Deaths	YLD	YLL	DALY	
NNDSS case fatality ratio 2015	680.09	3,106.67	3,786.76	6.61	0.53	2.85	13.03	15.88	2.40
Acute infection	12.59	3,106.67	3,119.26						
Sequelae	667.50	0	667.50						
NNDSS case fatality ratio 2005	725.99	3,430.93	4,156.91	9.05	0.65	3.60	17.00	20.60	2.28
Acute infection	14.58	3,430.93	3,445.51						
Sequelae	711.41	0	711.41						
NNDSS case fatality ratio 2003	890.10	3,625.69	4,515.78	11.81	0.68	4.51	18.39	22.90	1.94
Acute infection	18.60	3,625.69	3,644.29						
Sequelae	871.50	0	871.50						

4 DISCUSSION

The benefit of DALY estimates is that it allows comparison of the burden of health conditions or diseases (if the same model principle has been used). In **Figure 4** the DALY rate of each VPDs in the larger BoVPD study is visualised by the size of the bubble, with the x and y positions determined by the death- and incidence-rates, respectively. It shows that in the context of VPDs IPD accounts for a large burden each year. Only influenza has a higher overall burden, as a result of a very large number of incident cases and number of deaths. However, if the rate of burden is considered, IPD has a high burden both on the population level and for the individual, as illustrated by its position in the top right corner of **Figure 5**. Diseases in the upper right corner of this figure have a significant impact on the health of people and are associated with significant health care costs. In **Figure 5** there are also examples of diseases with a high individual but low population burden, such as tetanus and diphtheria, and diseases with a low individual burden but high population burden, such as influenza.

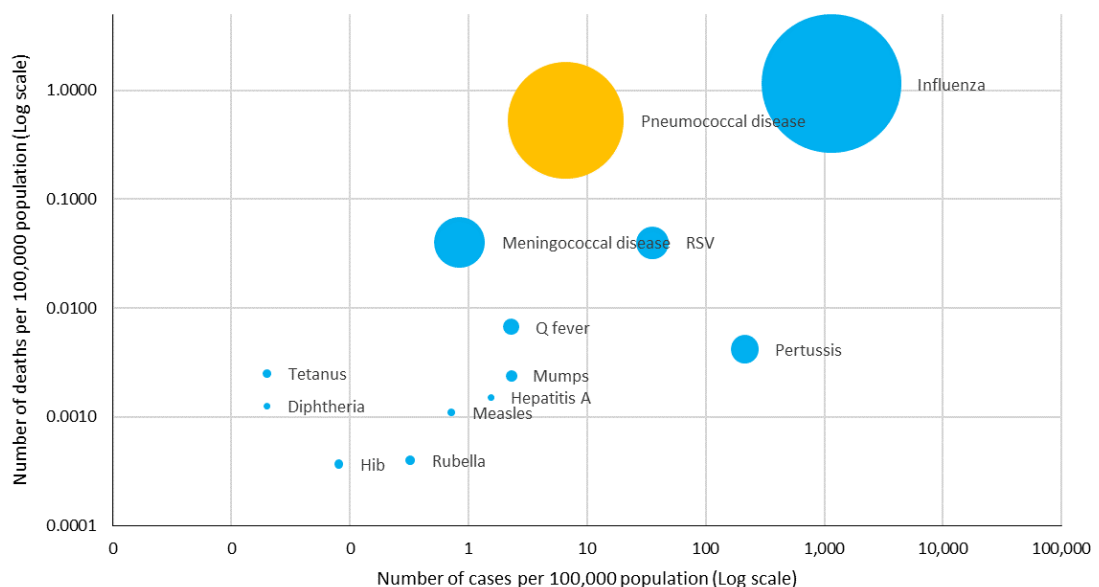


Figure 4 Bubble chart of DALY estimates, death- and incidence rates for VPDs in the BoVPD study. Size of the bubble indicates the number of DALYs per 100,000 population. Hib=*Haemophilus influenza* B, RSV=Respiratory syncytial virus.

Compared to the estimates presented for Europe (23) using the same burden of disease model the IPD DALY estimates for Australia 2015 are lower. It should be noted that the European estimate comprises a large number of countries, with a range of health care systems. The European study reported 30.1 DALYs per 100,000 population for IPD, which is twice the estimate

presented in this study (15.91 years). The reason for this could be the higher incidence rate (11.0 compared with 6.61 per 100,000 population) and the higher death rate (1.18 compared with 0.53 per 100,000 population). However, the YLD rate estimates are similar (2.49 compared with 2.85 per 100,000 population) indicating that the higher incidence seen in Europe is cancelled out by the increased transition probabilities for long-term sequelae used in our modified model. In our model there are more individuals with long term sequelae. The difference in DALY estimate, is almost exclusively due to a higher death rate. The lower DALY estimate observed in our study does not change the categorisation of IPD as disease with a high population burden (DALYs per 100,000 population) and a high individual burden (DALY per case).

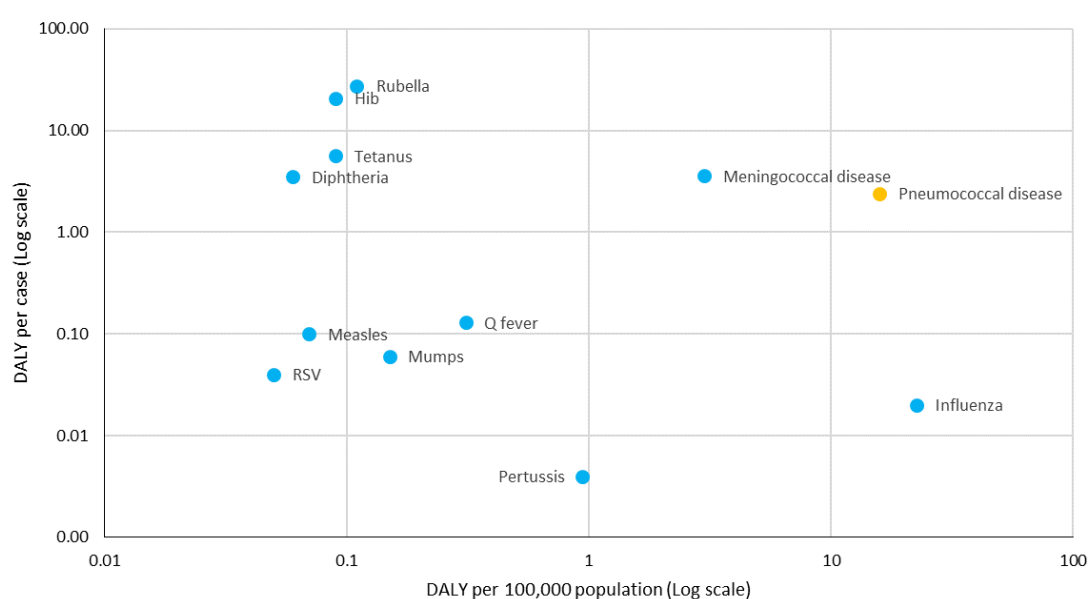


Figure 5 Scatter plot of the DALY per case and DALY per 100,000 population for VPDs in the BoVPD study. Hib=*Haemophilus influenza B*, RSV=Respiratory syncytial virus

Despite the encouraging reduction in burden of IPD among children under the age of 5 years, 50% of the burden is still borne by adults ages 40 years and above. In fact, the estimates in this study show that there was both an increase in raw DALYs and proportion of total DALYs in the 40+ year age-group from 2003 to 2015. The reduction observed in deaths in this age-group between the time points is counteracted by an increase in meningitis cases (see **Table 10**) and by extension sequelae resulting from these events, as well as an increase in hospitalisations which likely maintain the burden (for data see the Factsheet for IPD in **Appendix 4A**). The stratum specific DALY rate for this age-group did not change markedly between the two time points, indicating that an increasing aging population may contribute to the increase.

An interesting observation from the current study is that in contrast to the reduction in incidence of IPD, there was an increase in the individual burden seen for years 2003, 2005 and 2015, with the DALY per case 1.94, 2.28 and 2.40, respectively. While there had been a 32% reduction in incidence between 2003 and 2015, there was only a 16% reduction in DALYs. From a YLD point of view this is likely a result of the increased proportion of meningitis cases, which was 6.3%, 7% and 9.5% in 2003, 2005 and 2015, respectively. In particular the aforementioned increase in the 25-44 age group would lead to a greater number of YLD per case. In terms of the YLL per case the increase is likely driven by an increased CFR in the infant age group, and to some extent in the 40+ years age-groups. Deaths at a young age will contribute a large number of YLLs to the DALY estimate. It should be emphasised that there had not been an increase in deaths in these age-groups but an increase in the proportion of fatal cases. One could make the case that there may have been changes in the knowledge of sequelae related to IPD or changes to the sensitivity of diagnosis, leading to a greater number of sequelae detected and attributed for each case. However, as the same transition probabilities and disability weights are used for all three models, such differences would not come into play in the model. Similarly, one may expect that an increasing life expectancy might have an influence as it would mean more years lost or lived with disability. However, to allow for robust comparisons, the same life expectancy table is used in all models, regardless of time period.

A second interesting observation from this study was the large discrepancy between the numbers of IPD related deaths registered in the NNDSS in comparison with the NMD. The difference varied by age-group and clinical category, and whether underlying cause of death and associated cause of death in NMD were considered. It ranged from 100% of deaths in the NNDSS were also recorded in the NMD (pneumonia in <5 year old, using both underlying and associated cause of death) to only 14% of deaths in the NNDSS also recorded in the NMD (pneumonia in 65+ year old, using only underlying cause of death) (**Table 3**). For most age-groups and clinical categories, there are far fewer deaths recorded in the NMD. The reasons for this may be many.

The NMD cause of death is derived from the individual's death certificate, and data from the Registrars of Births, Deaths and Marriages and in some cases the National Coronial Information System.(26) If an individual was admitted to hospital with invasive pneumococcal pneumonia, but died from a cardiovascular event prior to the laboratory identification of causative agent of the pneumonia, the cardiovascular event may be stated as the underlying cause of death and unspecified pneumonia may be stated as an associated cause of death (but not invasive pneumococcal pneumonia). While deaths of young people are likely investigated by the coroner,

if the individual was elderly and the death not unexpected, there may not be any further follow up, and the death not attributed to IPD. The NNDSS on the other hand will retrospectively follow up on IPD notifications (all ages in most jurisdictions, with the exception of 5-49 year olds in NSW, 2 PHUs in Queensland and Victoria since 2012) and record deaths as associated with the notified disease if the death occurred within 1-2 weeks of the diagnosis. (6) Because the case definition for notification of IPD requires laboratory confirmation, it is certain that these individuals died with IPD, but not necessarily from IPD. It should be noted that due to the lack of follow-up in some states the NNDSS still considers that the number of deaths recorded may be an underestimate.

The difference between the two data sources is of such a magnitude that the choice becomes critical as it will have significant impact on the estimates produced by the model. Following input from the expert advisory committee it was deemed that the NNDSS provided the most representative mortality data for this project. However, it is an area that warrants future investigation.

One limitation of the developed model is that it only considers invasive pneumococcal disease. A pneumococcal vaccine will offer protection against all of infections of the serotypes included in the vaccine composition, not just invasive disease. In fact, most of the incidence of pneumococcal disease is non-invasive disease, in particular there is a large proportion of pneumonia that is non-invasive (i.e. without associated bacteraemia). Otitis media and sinusitis are also common non-invasive manifestations of pneumococcal disease. While these disease manifestations will often not be as severe, with a shorter duration and incur a lower disability weight, and therefore a lower individual DALY estimate; the high incidence means that the contribution of such non-invasive pneumococcal disease manifestations is likely to be notable. The difficulty in incorporating these into the model is the frequent presence of other bacteria, including other pathogens, such as *Moraxella catarrhalis*, *Haemophilus influenzae*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* or respiratory viruses.(38) Only infections where the causative agent is *Streptococcus pneumoniae* should be included in the model, and therefore attribution becomes critical. It is a very interesting potential expansion of the current model and has been suggested as a continuation of the BoVPD project in the future.

Another limitation of the model developed for IPD is the scarce amount of literature available on sequelae following IPD episodes for Australian populations. Only two publications provided significant data, and two additional ones providing partial data to inform the transition probabilities. The relatively limited sample size used in these studies further compound the

problem, where it is difficult to inform appropriate distribution of health states observed and assign distribution curves for the range of disability weights. Furthermore, none of the publication were recent, and contained data from the 80s and 90s. In light of this, one would expect to exclusively use contemporary data from large meta-analyses of global data, but the substantial increased incidence of sequelae reported in the old Australian studies could not be ignored. As more data becomes available the model assumptions can be refined. Although aspects are noted here as a limitation, the careful consideration of all available data in a systematic review of the literature becomes one of the strengths of the study.

5 CONCLUSIONS

This study produced a well-informed incidence-based burden of disease model for invasive pneumococcal disease in Australia. The modelled DALY estimates show that IPD is a vaccine preventable disease with a high burden on both the population level and for the individual. The model complements existing prevalence-based burden of disease models for Australia by using a forward projection of burden generated by incident IPD cases and allowing prediction of disease burden averted in response to proposed interventions.

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APPENDIX 4A – Factsheet for invasive pneumococcal disease



Australian Government
Australian Institute of
Health and Welfare



Pneumococcal disease in Australia

Quick facts

- Invasive pneumococcal disease (IPD) rates have dropped across all age groups—due to the ‘herd immunity’ effect—since vaccination was introduced for infants in the early to mid-2000s
- The very young, the very old, and people with other medical conditions are at most risk from severe outcomes from pneumococcal disease
- IPD rates are still relatively high among Aboriginal and Torres Strait Islander people, who are exposed to a wider range of the bacteria that cause IPD.

What is pneumococcal disease?

Pneumococcal disease is caused by *Streptococcus pneumoniae* bacteria (also known as pneumococcus). These bacteria are commonly found in the nose and throat of some people, most of whom remain healthy. They can be spread between people by droplets made by coughing and sneezing.

Pneumococcus bacteria can cause infections of the inner ear, sinus, lungs (pneumonia) and elsewhere. The most severe infections occur in places usually free of bacteria (for example the blood stream or membranes around the brain), and are known as invasive pneumococcal disease (IPD).

Young children, older adults, Indigenous Australians, and people with underlying illnesses are at a higher risk of IPD than others. Adults with IPD are most likely to have pneumonia with a blood stream infection while in children, a blood stream infection is most common. Around 3 in 10 children with IPD in the membranes around the brain (called ‘meningitis’) die.

Vaccination against invasive pneumococcal disease

There are a large number of different types of pneumococcus bacteria, which cause invasive pneumococcal disease (IPD). Vaccines are designed to protect against the most common types of bacteria known to cause serious disease.

Pneumococcal vaccination protecting against IPD is available in the National Immunisation Program for children at 2, 4 and 6 months, with a possible booster dose at 12–18 months. Vaccination is also recommended for adults at 65 years of age, and for Aboriginal and Torres Strait Islander adults at 50 years of age.

Having a large percentage of vaccinated children in the community also leads to less IPD cases in people of other ages. This is due to the protective effect known as ‘herd immunity’, where diseases have less opportunity to spread, and those who are susceptible to infection may be indirectly protected as they are less likely to be exposed.

In 2017, 94% of Australian 1 year olds were fully vaccinated against pneumococcal disease, however there is local variation in vaccination coverage.

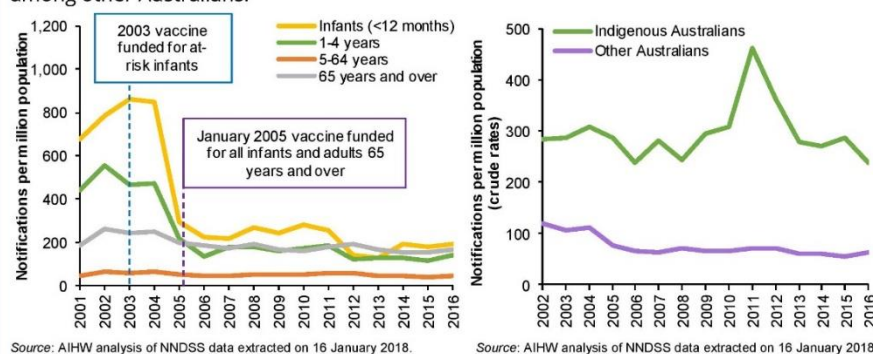
www.aihw.gov.au



Invasive pneumococcal disease cases

Since 2001, invasive pneumococcal disease (IPD) has been a notifiable disease in Australia, which means that diagnosed cases of IPD are reported to state or territory health departments. This way, a public health response can be undertaken to try and prevent further cases.

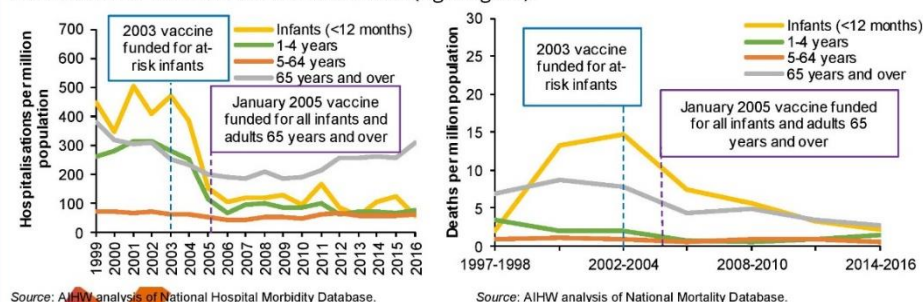
The number of IPD notifications fell drastically after vaccines were introduced for infants, however, IPD rates remain higher in the youngest and oldest Australians. In 2016, there were 1,666 IPD notifications, 234 (14%) of which were for children under 5 and 613 (37%) for people 65 years or older. The notification rate has remained consistently greater among Indigenous Australians than among other Australians.



Hospital visits and deaths due to pneumococcal disease

In 2016, there were 2,434 hospital admissions for pneumonia, meningitis or blood stream infections caused by pneumococcus bacteria. Almost 5% (113) of these were for children aged under 5. Hospitalisation rates for children under 5 have fallen since funding of the pneumococcal vaccine for all infants (left figure).

Between 1997 and 2016, pneumonia, meningitis or blood stream infection caused by pneumococcus bacteria caused 622 deaths. The death rate has decreased since vaccination was introduced for all infants in the mid-2000s (right figure).



AIHW

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APPENDIX 4B – Health states and disability weights

Table 15 Sequelae, health states, lay description and disability weights relevant to IPD from GBD 2016.

Reference: *Global Burden of Disease Collaborative Network. Global Burden of Disease Study 2016 (GBD 2016) Disability Weights. Seattle, United States: Institute for Health Metrics and Evaluation (IHME), 2017*

Sequelae	Health state	Description	Disability Weight
Acute infections			
	Infectious disease, acute episode, severe	has a high fever and pain, and feels very weak, which causes great difficulty with daily activities.	0.133
Permanent disability following meningitis			
Hearing loss			0.010–0.215
	Hearing loss, mild	has great difficulty hearing and understanding another person talking in a noisy place (for example, on an urban street).	0.010
	Hearing loss, moderate	is unable to hear and understand another person talking in a noisy place (for example, on an urban street), and has difficulty hearing another person talking even in a quiet place or on the phone.	0.027
	Hearing loss, severe	is unable to hear and understand another person talking, even in a quiet place, is unable to take part in a phone conversation. Difficulties with communicating and relating to others cause emotional impact at times (for example worry or depression)	0.158
	Hearing loss, profound	is unable to hear and understand another person talking, even in a quiet place, is unable to take part in a phone conversation, and has great difficulty hearing anything in any other situation. Difficulties with communicating and relating to others often cause worry, depression, and loneliness.	0.204
	Hearing loss, complete	cannot hear at all in any situation, including even the loudest sounds, and cannot communicate verbally or use a phone. Difficulties with communicating and relating to others often cause worry, depression or loneliness.	0.215

Sequelae	Health state	Description	Disability Weight
Cognitive difficulties			0.011–0.200
	Borderline intellectual functioning	is slow in learning at school. As an adult, the person has some difficulty doing complex or unfamiliar tasks but otherwise functions independently.	0.011
	Intellectual disability / mental retardation, mild	has low intelligence and is slow in learning at school. As an adult, the person can live independently, but often needs help to raise children and can only work at simple supervised jobs.	0.043
	Intellectual disability / mental retardation, moderate	has low intelligence, and is slow in learning to speak and to do even simple tasks. As an adult, the person requires a lot of support to live independently and raise children. The person can only work at the simplest supervised jobs.	0.100
	Intellectual disability / mental retardation, severe	has very low intelligence and cannot speak more than a few words, needs constant supervision and help with most daily activities, and can do only the simplest tasks.	0.160
	Intellectual disability / mental retardation, profound	has very low intelligence, has almost no language, and does not understand even the most basic requests or instructions. The person requires constant supervision and help for all activities.	0.200
Seizure disorder	Generic uncomplicated disease: worry and daily medication	has a chronic disease that requires medication every day and causes some worry but minimal interference with daily activities.	0.049
	Epilepsy, seizures 1-11 per year	has sudden seizures two to five times a year, with violent muscle contractions and stiffness, loss of consciousness, and loss of urine or bowel control.	0.263
	Epilepsy, seizures $\geq$ once a month	has sudden seizures one or more times each month, with violent muscle contractions and stiffness, loss of consciousness, and loss of urine or bowel control. Between seizures the person has memory loss and difficulty concentrating.	0.552
Motor deficit			0.010–0.402

Sequelae	Health state	Description	Disability Weight
Visual disturbance	Motor impairment, mild	has some difficulty in moving around but is able to walk without help.	0.010
	Motor impairment, moderate	has some difficulty in moving around, and difficulty in lifting and holding objects, dressing and sitting upright, but is able to walk without help.	0.061
	Motor impairment, severe	is unable to move around without help, and is not able to lift or hold objects, get dressed or sit upright.	0.402
			0.031–0.187
	Distance vision, mild impairment	has some difficulty with distance vision, for example reading signs, but no other problems with eyesight.	0.003
	Distance vision, moderate impairment	has vision problems that make it difficult to recognize faces or objects across a room.	0.031
	Distance vision, severe impairment	has severe vision loss, which causes difficulty in daily activities, some emotional impact (for example worry), and some difficulty going outside the home without assistance.	0.184
	Distance vision blindness	is completely blind, which causes great difficulty in some daily activities, worry and anxiety, and great difficulty going outside the home without assistance.	0.187
	Behavioural problems	Attention deficit hyperactivity disorder	0.045
Clinical impairment			0.089-0.214
	Traumatic brain injury, long-term consequences, minor		0.089
	Traumatic brain injury, long-term consequences, moderate		0.214
	Invasive device / drain		0.131

APPENDIX 4C – SAS scripts

```

/*****
/*      This program was written by Patiyan Andersson      */
/*      Created 9 August 2018                               */
/*      Last updated 9 August 2018                         */
*****/

/*
Purpose: To extract data on the estimated resident population
for specific years used in the models (here 2003)
*/

libname Pat "\\vault2\vault\imru\Pat";
libname vpd "\\vault2\vault\imru\vpd";

proc format;                                * Formatting to make it easier to read;
    value sexf
        1 = "Males"
        2 = "Females";

    value ageGf
        0='<1'
        1='1 to 4'
        2='5 to 9'
        3='10 to 14'
        4='15 to 19'
        5='20 to 24'
        6='25 to 29'
        7='30 to 34'
        8='35 to 39'
        9='40 to 44'
        10='45 to 49'
        11='50 to 54'
        12='55 to 59'
        13='60 to 64'
        14='65 to 69'
        15='70 to 74'
        16='75 to 79'
        17='80 to 84'
        18='85+';

run;

data work.ERP_2003 (keep=sex agegroup population);
set work.australianerp2003;                * Reading in line
                                           * listed data population
                                           * extracted data for
                                           * 2003;

    format sex sexf. AgeGroup ageGf.;      * Use the formats
                                           * defined above;

run;

* Table of population numbers by sex and age-groups;

proc tabulate data=work.erp_2003;
    class agegroup sex;
    freq Population;
    table agegroup, sex;
run;

```



```

/*****
/* This program was written by Patiyan Andersson      */
/* Created on 19 July 2018                          */
/* 1st updated on 9 August 2018                     */
*****/

/*
Purpose: To extract incidence data on IPD for various years
*/

libname Pat "\\vault2\vault\imru\Pat";
libname vpd "\\vault2\vault\imru\vpd";

proc format;                                * Formatting to make it easier to read;
  value sexf
    1 = "Males"
    2 = "Females";

  value ageGf
    0 = '<1'
    1 = '1 to 4'
    2 = '5 to 9'
    3 = '10-14'
    4 = '15-19'
    5 = '20-24'
    6 = '25-29'
    7 = '30-34'
    8 = '35-39'
    9 = '40-44'
    10 = '45-49'
    11 = '50-54'
    12 = '55-59'
    13 = '60-64'
    14 = '65-69'
    15 = '70-74'
    16 = '75-79'
    17 = '80-84'
    18 = '85+';

run;

/*****
/* Extraction of NNDSS data for comparison year 2015 */
*****/

data Pat.nndss_line (keep=disease year sex agegroup LargeAgeG IPD);
set vpd.nndss_line;                        * Reading in line listed data from
                                           the NNDSS: nndss_line.sas7bdat;

  where 2014 <= year <= 2016;
  if disease = "Pneumococcal Disease (Invasive)" then IPD = 1;
  if IPD=1;

  /* To pull out the incidence data for collapsed age-groups,
  include the three lines below
  if agegroup in (0,1) then LargeAgeG = 1;
  if agegroup in (2,3,4,5,6,7,8,9,10,11,12,13) then LargeAgeG = 2;
  if agegroup in (14,15,16,17,18) then LargeAgeG = 3;
  */

  format sex sexf. AgeGroup ageGf.;      * Use the formats defined
above;

```

Chapter 4 – Modelling the burden of IPD

```
run;

* Table of deaths, by underlying and associated COD, sex and age-
groups;

proc tabulate data=Pat.nddss_line;
    class agegroup sex;
    var IPD;
    table agegroup, sex;
run;

/*****
/* Extraction of NNDSS data for comparison year 2005 */
*****/

data Pat.nddss_line (keep=disease year sex agegroup LargeAgeG IPD);
set vpd.nddss_line;
    where 2004 <= year <= 2006;
    if disease = "Pneumococcal Disease (Invasive)" then IPD = 1;
    if IPD=1;
    format sex sexf. AgeGroup ageGf.;
run;

* Table of deaths, by underlying and associated COD, sex and age-
groups;

proc tabulate data=Pat.nddss_line;
    class agegroup sex;
    var IPD;
    table agegroup, sex;
run;

/*****
/* Extraction of NNDSS data for comparison year 2003 */
*****/

data Pat.nddss_line (keep=disease year sex agegroup LargeAgeG IPD);
set vpd.nddss_line;
    where 2001 <= year <= 2006;
    if disease = "Pneumococcal Disease (Invasive)" then IPD = 1;
    if IPD=1;
    format sex sexf. AgeGroup ageGf.;
run;

* Table of deaths, by underlying and associated COD, sex and age-
groups;

proc tabulate data=Pat.nddss_line;
    class agegroup sex;
    var IPD;
    table agegroup, sex;
run;

/*****
/* This program was written by Patiyan Andersson */
/* Created on: 19 July 2018 */
*****/
```

```

/*      Last updated: 31 July 2018                                */
/*****/

/*
Purpose: To extract data on IPD deaths from the NMD.
*/

libname Pat "\\vault2\vault\imru\Pat";
libname vpd "\\vault2\vault\imru\vpd";

proc format;                                * Formatting to make it easier to read;
    value sexf
        1 = "Males"
        2 = "Females";

    value ageGf
        0='<1'
        1='1 to 4'
        2='5 to 9'
        3='10 to 14'
        4='15 to 19'
        5='20 to 24'
        6='25 to 29'
        7='30 to 34'
        8='35 to 39'
        9='40 to 44'
        10='45 to 49'
        11='50 to 54'
        12='55 to 59'
        13='60 to 64'
        14='65 to 69'
        15='70 to 74'
        16='75 to 79'
        17='80 to 84'
        18='85+';

    value codf
        1="Underlying COD"
        2-100="Associated COD"; * Collapse remaining cause of
death groups into associated;

run;

/*****/
/* DEATH DATA FROM NATIONAL MORTALITY DATABASE (NMD) 2007-2016 */
/*****/

* Join the individual year datasets into one file, and in the process
only keep necessary fields;

data Pat.NMD_2007_2016_joined (keep=mort_id year sex age_at_death
age_group cause_of_death_ICD10 cod_number cod3 cod4 IPD death
AgeGroup);
set    work.r_mrtydofd_causeofdeath07
       work.r_mrtydofd_causeofdeath08
       work.r_mrtydofd_causeofdeath09
       work.r_mrtydofd_causeofdeath10
       work.r_mrtydofd_causeofdeath11
       work.r_mrtydofd_causeofdeath12
       work.r_mrtydofd_causeofdeath13

```

Chapter 4 – Modelling the burden of IPD

```
work.r_mrtydifd_causeofdeath14
work.r_mrtydifd_causeofdeath15
work.r_mrtydifd_causeofdeath16
;

* Have to divide up infants (<1 year old) from the 1-4 year olds;
if 121 <= age_at_death <= 700 then AgeGroup = 0;          * infants;
  else if age_at_death in (1,2,3,4) then AgeGroup = 1;      * 1-4
years;
  else AgeGroup = age_group;                                * the
remaining age-groups are kept as before;

* Reduce the complexity of the ICD10 coding, to make it easier to
identify IPD specific codes;
cod3= substr(cause_of_death_ICD10,1,3);
cod4= substr(cause_of_death_ICD10,1,4);

if cod4 in ('G001','A403') or cod3 = 'J13' then IPD= 1;

death = 1;

if IPD=1;                                                    * To ensure that it only
                                                            keeps lines with COD
                                                            associated with IPD;
format sex sexf. AgeGroup ageGf.;                          * Use the formats defined
above;
run;

/*
Some records are being double counted - if the underlying COD is IPD
and an associated COD is IPD. To solve this we have to collapse the
mort_id (underlying=1, associated=2+). This means that for individuals
with one IPD COD they will have 1 in the collapsed column and
individuals with an underlying and an associated COD, will have 2 in
the collapsed column.
*/
proc summary data=Pat.NMD_2007_2016_joined nway;
  class mort_id year sex agegroup; * Collapse on mort_id (each unique
person);
  var death;                                                    * Count deaths for each
mort_id, if they both have an uCOD and aCOD, this will be 2;
  output out=work.joined_summ (drop=_type_ _freq_) sum=;
run;

/* Count the number of individuals, rather than the value of
mort_id */
data work.joined_summ_deaths;
  set work.joined_summ;
  no_double_count_deaths = 1;          * Only count the deaths one, a line
count essentially;
  drop death;
run;

* Visualise in a table of unique deaths by sex and 19 category age
groups;
proc tabulate
data=work.joined_summ_deaths;
  class AgeGroup sex;
  freq no_double_count_deaths;
  table AgeGroup, sex;
```

```

run;

/*****
/*      This program was written by Patiyan Andersson      */
/*      Created 19 July 2018                                */
/*      Last updated 9 August 2018                          */
*****/

/*
Purpose: To extract data on meningitis cases by age group and sex,
to calculate appropriate re-distribution of incidence of the long-term
sequelae following meningitis events
*/

libname Pat "\\vault2\vault\imru\Pat";
libname vpd "\\vault2\vault\imru\vpd";

/* Format variables to make it easier to read */

proc format;
    value sexf
        1 = "Males"
        2 = "Females";

    value ageGf
        1='<1'
        2='1 to 4'
        3='5 to 9'
        4='10 to 14'
        5='15 to 19'
        6='20 to 24'
        7='25 to 29'
        8='30 to 34'
        9='35 to 39'
        10='40 to 44'
        11='45 to 49'
        12='50 to 54'
        13='55 to 59'
        14='60 to 64'
        15='65 to 69'
        16='70 to 74'
        17='75 to 79'
        18='80 to 84'
        19='85+';

run;

/*****
/* Data extraction for pre-vaccine comparator year 2015 for IPD */
*****/

data work.VPD_IPD;                                *Create temporary working
space;                                              space;
    set VPD.VPDHOSP_DATE;                          *Use existing dataset
                                                    available in the VPD folder;
    if calyear in (2014,2015,2016);                *Extract only relevant
                                                    years, change for 2005
                                                    and 2003;
    if vpd in (8);                                  *VPD code 8 = IPD;

```

Chapter 4 – Modelling the burden of IPD

```

    *if Principal_diagnosis ='G001';          *if only interested in
                                              G001 = meningitis ICD-
                                              10 code;
    format sex sexf. AGE_GROUP ageGf.; *Use formats defined above;
run;

proc tabulate
data=work.vpd_ipd;
    var seps;
    class principal_diagnosis age_group sex;
    table age_group, principal_diagnosis*sex;
run;

/*****
/* Data extraction for standard comparator year 2005 for BoVPD */
*****/

data work.VPD_IPD;
    set VPD.VPDHOSP_DATE;
    if calyear in (2004,2005,2006);
    if vpd in (8);
    format sex sexf. AGE_GROUP ageGf.;
run;

proc tabulate
data=work.vpd_ipd;
    var seps;
    class principal_diagnosis age_group sex;
    table age_group, principal_diagnosis*sex;
run;

/*****
/* Data extraction for pre-vaccine comparator year 2003 for IPD */
*****/

data work.VPD_IPD;
    set VPD.VPDHOSP_DATE;
    if calyear in (2002,2003,2004);
    if vpd in (8);
    format sex sexf. AGE_GROUP ageGf.;
run;

proc tabulate
data=work.vpd_ipd;
    var seps;
    class principal_diagnosis age_group sex;
    table age_group, principal_diagnosis*sex;
run;
```

CHAPTER 5

Evaluation of the surveillance system for yellow fever at the Australian border

**Australian Government Department of Health
Office of Health Protection**

*“The work of epidemiology is related to unanswered questions, but
also to unquestioned answers.”*

Patricia Buffler

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ABBREVIATIONS

ABF	Australian Border Force
AIR	Australian Immunisation Register
DAWR	Australian Government Department of Agriculture and Water Resources
CDC	Centers for Disease Control and Prevention
CHBO	Chief Human Biosecurity Officer
DIBP	Australian Government Department of Immigration and Border Protection
DoH	Australian Government Department of Health
eIPC	electronic incoming passenger card
FP	false positive
FN	false negative
IHR	International Health Regulations (2005)
IPC	incoming passenger card
NSW	New South Wales
PPV	positive predictive value
The Act	Biosecurity Act 2015
TP	true positive
TN	true negative
VIC	Victoria
WHO	World Health Organization
YFAC	Yellow Fever Action Card

PROLOGUE

Study rationale

Australia is considered free of the mosquito-borne viral disease yellow fever but does have a competent vector for the disease in parts of the country. It is therefore critical from a public health perspective to prevent the possible introduction of the yellow fever virus into the domestic mosquito population. One such safety measure is a surveillance system at the Australian border that screens for unprotected travellers that may be carrying the virus.

The project came about from two drivers. The first driver was queries raised at a meeting of the Chief Human Biosecurity Officers (CHBO) from each jurisdiction regarding the number of travellers that pose a potential risk of introducing yellow fever to Australia and the reasons for their decision not to vaccinate. Both the CHBOs and the Principal Medical Advisors at the Commonwealth Department of Health (DoH) frequently receive questions regarding these areas. The second driver was the proposed development and transition to an electronic Incoming Passenger Card for Australia, and whether the yellow fever surveillance questions or processes required updating prior to incorporation. As no summary data are collected or available for the surveillance system, it was not known how well it was working in its current state.

My role

My role was to distil the queries from CHBOs into knowledge gaps and design a project to answer these. As the information collected in surveillance system is used for immediate action and no data is stored, the traditional process of surveillance evaluation with stakeholder interviews was not appropriate. Instead I decided to obtain answers to the CHBO questions by using a survey targeting travellers identified as potential risks.

I developed and tested the survey, and sought agreement from Department of Agriculture and Water Resources through the Department of Health to use Biosecurity Officers at the border to conduct the survey of target passengers for a limited period. Following the return of completed surveys I entered the data into Excel and performed descriptive and statistical analysis of the data. I evaluated the performance of the surveillance system using the CDC guidelines, with an emphasis on the data quality, acceptability, sensitivity and positive predictive value. The results were presented in a report to the Commonwealth Department of Health and the CHBOs. The report formed the basis for this chapter, and therefore has not been included as an attachment.

The results were also presented in a minute to the Deputy Secretary of the Department of Health.

I was fortunate to be invited to present the findings from the evaluation to a wider audience at the 2018 Northern Territory Centre for Disease Control Conference in Darwin (**Appendix 5A**).

Lessons learned

This surveillance project along with the traveller with illness checklist evaluation came about in the same CHBO meeting and showed me how the MAEs are seen as a resource to find answers to questions in public health. I heard the phrase “This could be a good MAE project” twice that day and would hear it plenty more times during the coming two years.

The main lesson that I learned for this project was around conducting and analysing surveys. I found that you should only conduct paper-based surveys if there is absolutely no other option, as it is a lot of data entry work... especially when you have 1100 surveys. I also learned that you should test the survey on people outside the group you are working with, to ensure that none of the questions can be misinterpreted, and that you must explicitly state when you only want one answer in multiple choice questions. In retrospect it would have been good to have a question regarding the reason for travel (e.g. tourism, business, visiting friends and relatives), which would have allowed stratify the population and provide suggestions for more targeted interventions or information.

The project provided a good insight into the legislation that governs the border measures and our public health systems, and how different government departments interact with each other. It also produced interesting discussions regarding whether recommendations should only be feasible and economically viable to implement, or if there is a merit in having aspirational recommendations as well to spark future conversations.

Public health implications

The evaluation identified opportunities for improvement in the surveillance system, with a large number of false positives resulting in unnecessary use of resources and inconvenience for travellers. Recommendations of changes were made to minimise these effects in the new electronic incoming passenger card system. It was also suggested that the new electronic system be used to collect data for ongoing monitoring of the system and changes in epidemiological trends.

The project also highlighted a lack of unified documentation of the objectives, case definitions and operation of the surveillance system. In the development of such documentation it was suggested that recommendations regarding travel to areas in Australia with competent vectors should be included and provided to travellers identified to have been potentially exposed to yellow fever overseas.

Acknowledgements

I would like to thank Rhonda Owen, Joel Willis and Susan Gavin for their support and supervision in this project. Big thanks to Callum Mack for interesting discussions about all aspects of the project, and for patiently answering all my questions regarding legislation. Thanks also to the Border Health team for providing a welcoming and fun environment to work in, and for having highly entertaining telephone conversations.

MAE core activity requirements

The MAE core activity requirements fulfilled in this project was: Evaluation of a surveillance system, Oral conference presentation.

ABSTRACT

Background: The purpose of the surveillance system is to mitigate the risk of travellers introducing yellow fever into the Australia. Yellow fever virus is the causative agent of yellow fever, a mosquito-borne viral acute haemorrhagic disease endemic to parts of Africa and South/Central America and the Caribbean. The primary vector for yellow fever, *Aedes aegypti*, is widely distributed in North Queensland and parts of Central and South Queensland, and introduction of yellow fever has the potential to cause outbreaks. The surveillance system is composed of three steps: question 11 on the incoming passenger card (IPC), regarding whether the traveller has visited Africa or South/Central America or the Caribbean in the past 6 days; assessment by an Australian Border Force officer whether the traveller has been to a yellow fever risk country and if they have a valid certificate; and verbal information on yellow fever and provision of a Yellow Fever Action Card by a Biosecurity Officer to any traveller that has visited a yellow fever risk country and is unable to provide valid proof of vaccination. The system had not previously been assessed, and there were queries from key stakeholders regarding the number of travellers posing a risk of introducing yellow fever, and the reasons for choosing not to vaccinate. Additionally, the evaluation would serve to inform the transition of the IPC to an electronic format.

Methods: A paper-based survey assessing the potential exposure to yellow fever, the knowledge of yellow fever and reasons for not having a certificate and/or vaccination was developed. The survey was offered to all travellers referred to a Biosecurity Officer at the Sydney Kingsford Smith and Melbourne Tullamarine airports during the period 1 August to 31 October. The survey was voluntary and provided prior to the Biosecurity Officer administering the Yellow Fever Action Card to the traveller.

Results: Over the three-month period 1310 travellers were offered to participate in the voluntary survey. This represented all travellers referred to a Biosecurity Officer at both airports. A total of 1103 travellers participated, 59 individuals declined, and 148 individuals were unable to participate due to language barriers.

Analysis showed that 193 (17.5%) of the participating travellers had not visited a yellow fever risk country and should not have been referred to a Biosecurity Officer. Thirty-nine (3.5%) travellers did not disclose countries visited. Of the remaining 871 travellers; 456 stated they were vaccinated but had lost/forgotten the certificate or were unaware that the certificate had to be shown; 24 stated they were vaccinated but had not received a certificate; and 8 travellers did not respond to the question. Finally, the survey found that 407 travellers were unvaccinated

and had visited a yellow fever risk country, therefore posing a risk of introducing yellow fever to Australia. This equates to approximately 135 travellers per month and estimated as 1% of all travellers arriving from Africa or South/Central America or the Caribbean to the two airports.

Conclusions: The evaluation found the surveillance system for yellow fever at the Australian border to be inefficient due to a large proportion of false positives. There were two main mechanisms for these: travellers who had not visited a yellow fever risk country; and travellers who were vaccinated but unable to show a valid certificate.

Recommendations: In the electronic incoming passenger card system it is recommended to incorporate the following: easy adaptation of changes to the list of yellow fever risk countries; a series of selections allowing the traveller to specify their previous locations; automatic filtering of potentially exposed unimmunised travellers; retention of certificate in traveller's electronic border security profile and provision of regular reports to Health. Recommendations were also made to publish a unified document from the Departments' of Health, Agriculture and Home Affairs describing the surveillance system. Further, it was recommended to evaluate the cost benefit of raising the public awareness of issues related to yellow fever. Finally, aspirational recommendations were made to explore the possibilities of using information in the Australian Immunisation Record (AIR) to generate new certificates to replace lost ones, and to link the AIR to the immigration profile of Australian citizens.

1 INTRODUCTION

1.1 Yellow fever

Yellow fever is a mosquito-borne viral acute haemorrhagic disease endemic to parts of Africa and South/Central America and the Caribbean. The yellow fever virus belongs to the genus *Flavivirus*, family *Flaviviridae*, and is related to Dengue virus, Zika virus and Japanese encephalitis.(1) The incubation period is 3-6 days, with a proportion of infections being asymptomatic. This is more common in endemic areas, with the ratio in Africa of asymptomatic to symptomatic disease estimated at 7-12:1.

The disease is mainly spread by mosquitoes belonging to the *Aedes* and *Haemagogus* species. There are two forms of the disease, depending on the reservoir – sylvatic and urban.(1) In the sylvatic, or jungle form, monkeys act as the reservoir and the virus is passed on to mosquitoes through a blood meal from an infected monkey. If the mosquitoes in turn bite a human, the virus may be transmitted and cause disease. In densely populated urban areas, the virus can be transmitted from human to human via a mosquito vector, most commonly the urban adapted *Aedes aegypti*.

There are 47 countries worldwide that are endemic or have regions that are endemic for yellow fever.(2) Thirty four of these are in Africa (**Figure 1**) and 13 are in South or Central America (**Figure 2**). It is estimated that 90% of cases occur in Africa, which has a higher force of infection as a consequence of frequent mixed transmission cycles, involving both sylvatic and urban vector species.(1) A modelling study in 2013 predicted 180,000 cases (95% CI 51,000 – 380,000) and 78,000 deaths (95% CI 19,000-180,000) each year.(3)

In contrast to endemic areas, outbreaks of yellow fever usually occur when infected people enter an area that is previously unaffected but where a competent vector resides (4). Mosquitoes become infected when feeding on the infected people and establish a new transmission chain in the area. This can occur in urban areas where the *Aedes aegypti* mosquito resides and with sufficiently high population numbers to sustain transmission within the urban cycle. Outbreaks may also occur through the sylvatic cycle, when expansion of human habitation lead to increasing contact with non-human primate reservoirs of yellow fever, where humans may be infected by bites from infected mosquitoes that have fed on infected non-human primates, but no human-to-human transmission occurs. However, the concern in the latter situation is that if there is *A. aegypti* present in the area, a high infection pressure may lead to the establishment of an urban transmission cycle as well.

Due to the presence of a competent vector in North Queensland and parts of Central and South Queensland (5), part of the mandatory entry process at the Australian border requires arriving travellers to declare on the Incoming Passenger Card (IPC) if they have stayed overnight or longer in Africa or South/Central America or the Caribbean in the preceding 6 days. Should this be indicated Australian Border Force will assess if the traveller has been to a yellow fever endemic country/area, and if this is the case the traveller must produce a valid certificate of yellow fever vaccination or prophylaxis (hereafter referred to as the Certificate). While travellers without a valid Certificate will not be refused entry to Australia, they will be provided with information on yellow fever and instructed to seek medical attention should symptoms develop, and possibly also be provided advice regarding travel to areas in Queensland where the vector is present. Most travellers will likely not be aware of the reason for the question when completing the IPC.

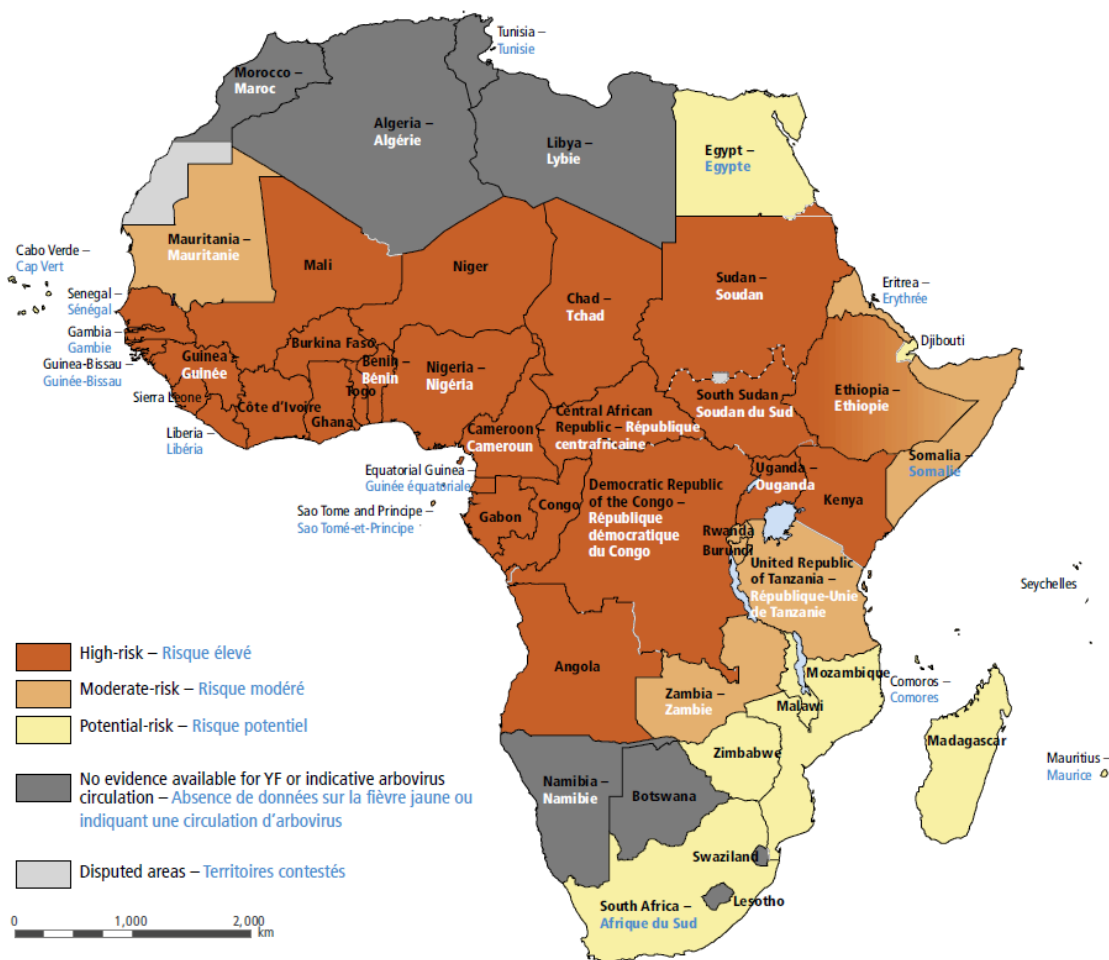


Figure 1. Areas with risk of yellow fever transmission in Africa.(2)

1.2 Yellow fever clinical progression

When symptomatic, the illness has two stages with the first characterised by fever, muscle pain, nausea, vomiting, headache and weakness.(6) The second more serious stage occurs in 15-25% of patients who enter a toxic phase within 48 hours of recovering from the initial symptoms. The symptoms of the toxic phase involve visible bleeding, jaundice, and kidney and liver failure. The case-fatality rate varies widely, but can be 20-60%. The observation that the case fatality in South America is higher (40-60%) compared with Africa (20%), is poorly understood.(1) Related to this is the observation of lethality of yellow fever among some South American non-human primate hosts, while most non-primate hosts in Africa seem to have asymptomatic infections, which may indicate ancestry and co-evolution between virus and hosts in the African setting.



Figure 2 Areas with risk of yellow fever transmission in South and Central America.(2)

1.3 Yellow fever diagnostics, treatment and preventability

In Australia the laboratory diagnosis of yellow fever involves: demonstration of anti-yellow fever virus IgM antibodies in the blood by ELISA or in liver samples by labelled antibodies; detection of viral genome in blood or liver tissue by PCR or hybridisation probes; and/or serological diagnosis with significant rise of IgG levels to yellow fever.(1, 6)

Even with the current advances in modern medicine there is no specific therapy available for yellow fever, with only supportive therapy available for symptomatic cases. This is particularly concerning in developing countries with low resources and a more basic health system. Prevention therefore remains the main focus of public health measures.

Vaccination is recognised as the most effective way to prevent yellow fever.(7) The vaccine contains the attenuated live virus strain 17D, is considered safe and effective, and can be administered from 9 months of age. Younger infants are susceptible to neuroinvasion due to an immature blood-brain barrier therefore contraindicating the use of the vaccine.(1) Serological studies show that by the 10th day post-vaccination 90% of subjects had measurable antibodies, and nearly all subjects by day 30.

A single dose is now considered to provide life-long immunity. Previously it was recommended to have a booster dose every 10 years, and therefore the certificate of vaccination or prophylaxis (Certificate) expired after 10 years. On the 11 July 2016, WHO amended the *WHO International Health Regulations 2005* (IHR) such that a Certificate is now recognised to be valid for the life of the vaccinated person.(8, 9) Vaccination campaigns are often used in conjunction with other public health interventions such as education and vector control.

Control of mosquitoes is also an effective intervention.(2) The aim is to eliminate or reduce the number of vectors in a particular hot spot area, thereby reducing transmission and ultimately breaking the cycle. This is achieved by elimination of adult and larval populations through use of insecticide sprays, as well as reduction of mosquito breeding grounds by removal of standing water or reduction in access to water sources.

In addition to vaccination and active vector control, normal precautions to prevent/reduce mosquito bites are recommended, such as long-sleeved shirts and long pants, use of mosquito repellent, and mosquito nets for sleeping.

1.4 Public health importance of yellow fever

Despite the existence of an effective vaccine that provides long duration immunity, yellow fever remains endemic in regions of the world that are unable to establish or sustain effective public health programs. Adding to this is the lack of financial means and infrastructure for mosquito control programs in these regions. This results in an additional burden on already vulnerable populations.

While yellow fever is not endemic in Australia, the competent vector *Aedes aegypti* is present in North Queensland and parts of Central and South Queensland.(5, 10) It is therefore critical to identify any cases of yellow fever entering Australia and advise restrictions on travel to these areas of Queensland or isolation measures in areas with competent vectors if travel is unavoidable. This is to prevent local competent mosquitoes having an opportunity to obtain a blood meal and possibly transmit the virus, and in worst case scenario cause outbreaks.

To date there have been no notifications of travellers developing yellow fever following entry to Australia. The national notification system contains no recorded cases of yellow fever from its inception in 1991 to the present time. However, internationally there have been multiple reports of such events, some of which have occurred in recent times. This highlights the ever-present risk of importation of yellow fever from endemic regions through air travel. Ongoing transmission following such events has not been documented.

1.5 Requirement of surveillance system

The surveillance system needs to identify individuals that may have been exposed and later develop disease, both to allow early diagnosis, but also mitigate possible spread of yellow fever in Australia. Early detection of possible cases is critical to prevent spread and outbreaks in receptive areas such as large parts of Queensland where the principal vector *Aedes aegypti* mosquito is present. For overt disease upon arrival at the Australian border, there are other surveillance systems in place. Similarly, there are other systems to monitor for vector introductions.

2 OBJECTIVES OF EVALUATION

2.1 Purpose of evaluation

The evaluation was triggered by two events: the observation by the Department of Agriculture and Water resources (DAWR) of a large number of unprotected travellers arriving from yellow fever endemic areas during a one-month pilot study (requested by the Chief Human Biosecurity Officers); and the transition of the incoming passenger card to an electronic system. The one-month pilot study showed that for the whole of Australia there were 917 instances of travellers unable to present a valid Certificate despite indicating arrival from and time spent in a yellow fever endemic country (**Table 1**). This information is normally not collected, and there is a knowledge gap regarding the true magnitude of individuals at risk, the reason for travelling unprotected and whether these occurrences represent a significant public health risk, both in terms of personal risk and risk of outbreaks of yellow fever in Australia.

Table 1 Number of travellers arriving at international airports without a valid Certificate between mid-July and mid-August 2016.

International airport	Number of travellers	Cumulative %
Sydney	541	59.0
Melbourne	187	79.4
Brisbane	144	95.1
Adelaide	26	97.9
Darwin	17	99.8
Cairns	1	99.9
Perth	1	100
Canberra	0	
Gold Coast	0	
Townsville	0	
Total	917	

The purpose of the evaluation was to assemble information to address the knowledge gaps as mentioned above, and to assess the effectiveness and informative value of the system. Evaluation objectives were to:

- estimate the true number of unvaccinated travellers who arrive from countries considered by Australia to be yellow fever endemic;
- understand the reasons for travellers to not be vaccinated when visiting a yellow fever endemic region;
- describe the surveillance system;

- assess the attributes of the surveillance system;
- determine to what extent the surveillance system fulfils its purpose; and
- provide recommendations to inform the development of the eIPC and future public health policy on yellow fever.

As the operational aspects of the surveillance system are very simple, with immediate data usage and no requirement for data storage or analysis, the evaluation was more focused on the possible improvements by expansion of the system or adjustments of the current procedures. Therefore, the questions were designed to provide information on knowledge gaps rather than procedural gaps.

2.2 Stakeholders

I conducted the evaluation on behalf of the Australian Government Department of Health (DoH), with external stakeholders being Department of Agriculture and Water Resources (DAWR) and Home Affairs. The findings of the evaluation were also distributed to the State and Territory Departments of Health, who were represented in this project by the Chief Human Biosecurity Officers (CHBO) from each jurisdiction.

3 METHODS

3.1 Evaluation framework and system attributes definition

This evaluation was conducted using the *Updated Guidelines for Evaluating Public Health Surveillance Systems* published by the Centres for Disease Control and Prevention (CDC) which is based on the CDC's *Framework for Program Evaluation in Public Health*.⁽¹¹⁾ The evaluation includes assessment of the attributes described in **Table 2**.

Table 2 Attributes assessed in the CDC Guidelines. Data sources used to inform evaluation of the attribute are indicated in brackets.

Attribute	Definition
Simplicity	The simplicity of a public health surveillance system refers to both its structure and ease of operation. Surveillance systems should be as simple as possible while still meeting their objectives. (<i>OHP draft policy, DAWR work instruction</i>)
Flexibility	A flexible public health surveillance system can adapt to changing information needs or operating conditions with little additional time, personnel, or allocated funds. Flexible systems can accommodate, for example, new health related events, changes in case definitions or technology, and variations in funding or reporting sources. In addition, systems that use standard data formats can easily be integrated with other systems and thus might be considered flexible. (<i>Survey, OHP draft policy</i>)
Data quality	Data quality reflects the completeness and validity of the data recorded in the public health surveillance system. (<i>Survey</i>)
Acceptability	Acceptability reflects the willingness of persons and organisations to participate in the surveillance system. (<i>Survey</i>)
Sensitivity	The sensitivity of a surveillance system can be considered on two levels. First, at the level of case reporting, sensitivity refers to the proportion of cases of a disease (or other health-related event) detected by the surveillance system. Secondly, sensitivity can refer to the ability to detect outbreaks, including the ability to monitor changes in the number of cases over time. (<i>Survey, OHP draft policy</i>)
Positive Predictive Value	Positive predictive value (PPV) is the proportion of reported cases that actually have the health-related event under surveillance. (<i>Survey</i>)
Representativeness	A public health surveillance system that is representative accurately describes the occurrence of a health-related event over time and its distribution in the population by place and person. (<i>Survey, OHP draft policy</i>)
Timeliness	Timeliness reflects the speed between the steps in a public health surveillance system. (<i>OHP draft policy, DAWR work instruction</i>)
Stability	Stability refers the reliability (i.e. the ability to collect, manage, and provide data properly without failure) and availability (the ability to be operational when it is needed) of the public health surveillance system. (<i>OHP draft policy, DAWR work instruction</i>)

3.2 Survey to assess traveller perception of yellow fever vaccination

A paper-based anonymous survey in English was used to gather information from travellers regarding:

- Basic knowledge of yellow fever and mode of transmission
- Reason(s) for not having an International Certificate of Vaccination or Prophylaxis
- Reason(s) for not getting vaccinated
- Country(s) visited in the 6 days prior to the survey

No personal identifiable variables were collected. The survey is included as **Appendix 5B** in this chapter.

Travellers referred to a Biosecurity Officer were offered by the officer to participate in the survey before the traveller was provided verbal information regarding yellow fever and the yellow fever action card. As the survey was voluntary, the number of travellers that declined to participate or were unable to complete the survey due to language barriers was recorded to assess the total number of travellers offered to participate. No other information was recorded for these travellers.

The survey was administered by the Biosecurity Officers at the Sydney Kingsford Smith International airport and the Melbourne Tullamarine International airport over the three-month period of 1 August to 31 October 2017. On a regular basis the Biosecurity Officers scanned and emailed the completed surveys to the Border Health section, Office of Health Protection, Commonwealth Department of Health, where they were stored on a secure internal server. The Biosecurity Officers destroyed the original completed surveys.

3.3 Analysis of survey data

The analysis of the survey data was predominantly descriptive with only minor calculations as described below to support the evaluation of particular aspects of the surveillance system. Free form answers were grouped by themes and representative quotes are shown.

3.3.1 Definitions of true and false positive and true and false negative values

In the surveillance system under evaluation, the different case statuses were defined as described in **Table 3**.

Table 3 Definitions of true and false positives, and true and false negatives

Case status	Visited a yellow fever endemic country at least overnight within the past 6 days	Can show valid International Certificate of Vaccination or Prophylaxis	Has received yellow fever vaccination (only established by verbal communication)
True positive	✓	✗	✗
False positive 1	✗	✗	✗
False positive 2	✓	✗	✓
True negative	✓	✓	✓
False negative	✗ (traveller lies)	✗	✗

False positive 1 is the case where a traveller has been to Africa or South/Central America, but not visited a yellow fever endemic country. False positive 2 is the case where the traveller has been to a yellow fever endemic country and has been vaccinated, but is unable to show a valid certificate.

The data to assess the number of false negative (FN) cases were not available. It is possible travellers may not disclose visiting Africa or Central/South America or the Caribbean within the time period even if they have done so and, as an itinerary is not required to be viewed, it is very difficult to detect such instances of incorrect data. However, the assumption is that most travellers will take the entry process seriously and provide truthful answers. For the purpose of the evaluation I made the assumption that there are no false negative cases, and only true negative (TN) cases.

The false negative option of the traveller having a fake Certificate but has not been immunised is even more difficult to assess. Additionally, in this surveillance system the traveller would never be flagged to be asked the question.

3.3.2 Statistical measures

The above information was used to calculate the statistical measures of sensitivity and positive predictive value to evaluate the surveillance system (**Table 4**).

Table 4 Components for calculations of sensitivity and positive predictive value.

Detected by surveillance system	Disease present		Total
	Yes	No	
Yes	True Positive (TP)	False Positive (FP)	TP+FP
No	False Negative (FN)	True Negative (TN)	FN+TN
Total	TP+FN	FP+TN	

$$\text{Sensitivity} = \text{TP}/(\text{TP}+\text{FN})$$

$$\text{Specificity} = \text{TN}/(\text{TN}+\text{FP})$$

$$\text{Positive predictive value} = \text{TP}/(\text{TP}+\text{FP})$$

3.4 Standards for assessing the performance of the surveillance system

There is no official formalised policy for the surveillance system under evaluation. The requirement for surveillance and the legislative authority for its implementation are laid out as detailed in Section 4.2 of this chapter.

The Office of Health Protection in the DoH has a draft policy for the yellow fever surveillance, but it has yet to be made official. The operational aspects of the surveillance system at the border are defined in a work instruction by DAWR, *Yellow fever action cards – air pathway* (date published 11/05/2016). This document provides step by step instructions for the Biosecurity Officers. These documents were used to assess the performance of the surveillance system in relation to its defined purpose.

4 DESCRIPTION OF THE SURVEILLANCE SYSTEM

4.1 Purpose and objectives of surveillance system

The surveillance system serves to identify individuals that may have been exposed and later develop yellow fever, both to allow early diagnosis and management but also mitigate possible spread in Australia through movement advice to those potentially exposed and isolation of cases in areas where the competent vector is present.

In the DAWR work instruction the purpose is stated as defined in the *Entry Requirements Determination*, which more relates to the formal authority to conduct the surveillance, rather than stating the purpose or objectives of the surveillance system.

In the draft policy from OHP DOH the purpose is stated as: “*The purpose of this policy is to minimise the likelihood of the introduction and spread of yellow fever into Australia.*” The objective stated in the draft policy only relates to the objective of the policy document itself and does not mention any objective of the surveillance system.

4.2 Legal authority for data collection

Yellow fever is covered by the *WHO International Health Regulations 2005* (IHR): Annex 1, which relates to prevention of the international spread of disease by surveillance and border measures, and Annex 7, which relates to the requirement of vaccination against yellow fever.(9)

The collection of information and completion of the incoming passenger card is set out by the Australian *Migration Act 1958* and the *Migration Regulations 1994*.(12, 13) In Australia the requirement to carry an international vaccination certificate and the authority for a Biosecurity Officer to view the document is laid out in the *Biosecurity (Entry Requirements) Determination 2016*, under subsection 44(2) of the *Biosecurity Act 2015*.(14) Yellow fever is also considered a Listed Human Disease subject to the *Biosecurity (Listed Human Diseases) Determination 2016*, falling under subsection 42(1) of the *Biosecurity Act 2015*.

4.3 Case definition in surveillance system

Figure 3 shows the decision tree to determine that travellers are at risk of having contracted yellow fever when abroad. The flow chart also shows the plausible sources of false positives should the surveillance system function at sub-optimal levels.

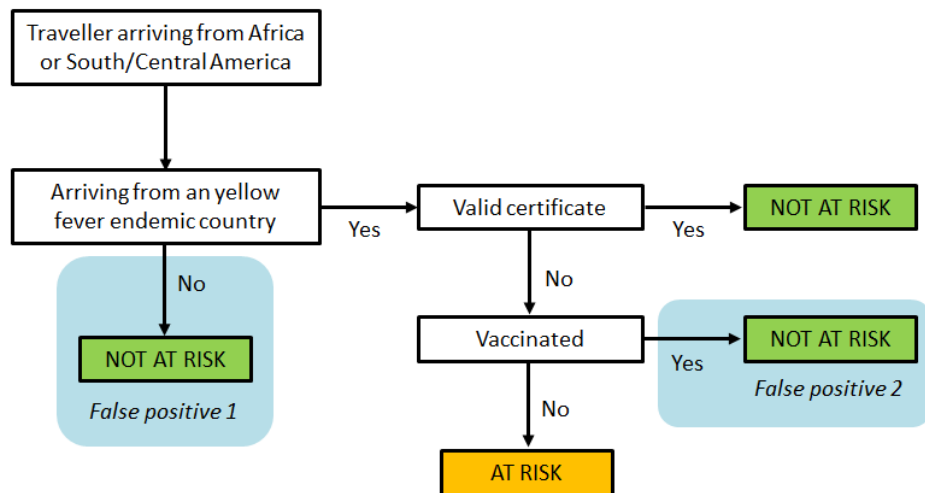


Figure 3 Decision tree to determine travellers at risk of yellow fever

An appropriate case definition of a traveller at risk would be:

Traveller arriving at the Australian border that:

- 1 *has been in a yellow fever risk country overnight or longer within the past 6 days*
and
- 2 *has not been immunised against yellow fever*

However, in order to be able to assess all possible factors for false positives, the case definition used in this evaluation was expanded to include all travellers being referred to a Biosecurity Officer, even if they did not visit a yellow fever endemic country. In this evaluation the following case-definition has been used:

Traveller arriving at the Australian border that:

- 1 *has been in Africa or South/Central America overnight or longer in the past 6 days*
and
- 2 *unable to produce a valid Certificate for yellow fever*

4.4 Population under surveillance

The population under surveillance is composed of all travellers over the age of 9 months arriving at the Australian international border.

4.5 Operation of the surveillance system

The physical activity of the surveillance system takes place at Australia's international border and shown in Figure 4. The Australian Border Force (Home Affairs, formerly Department of Immigration and Border Protection) processes the IPC and checks for the Certificate should it be

indicated. If the traveller is unable to produce valid proof of vaccination, they are referred to a Biosecurity Officer (Department of Agriculture and Water Resources) at the border, where the necessity of vaccination is underscored and information regarding yellow fever and the symptoms is provided.

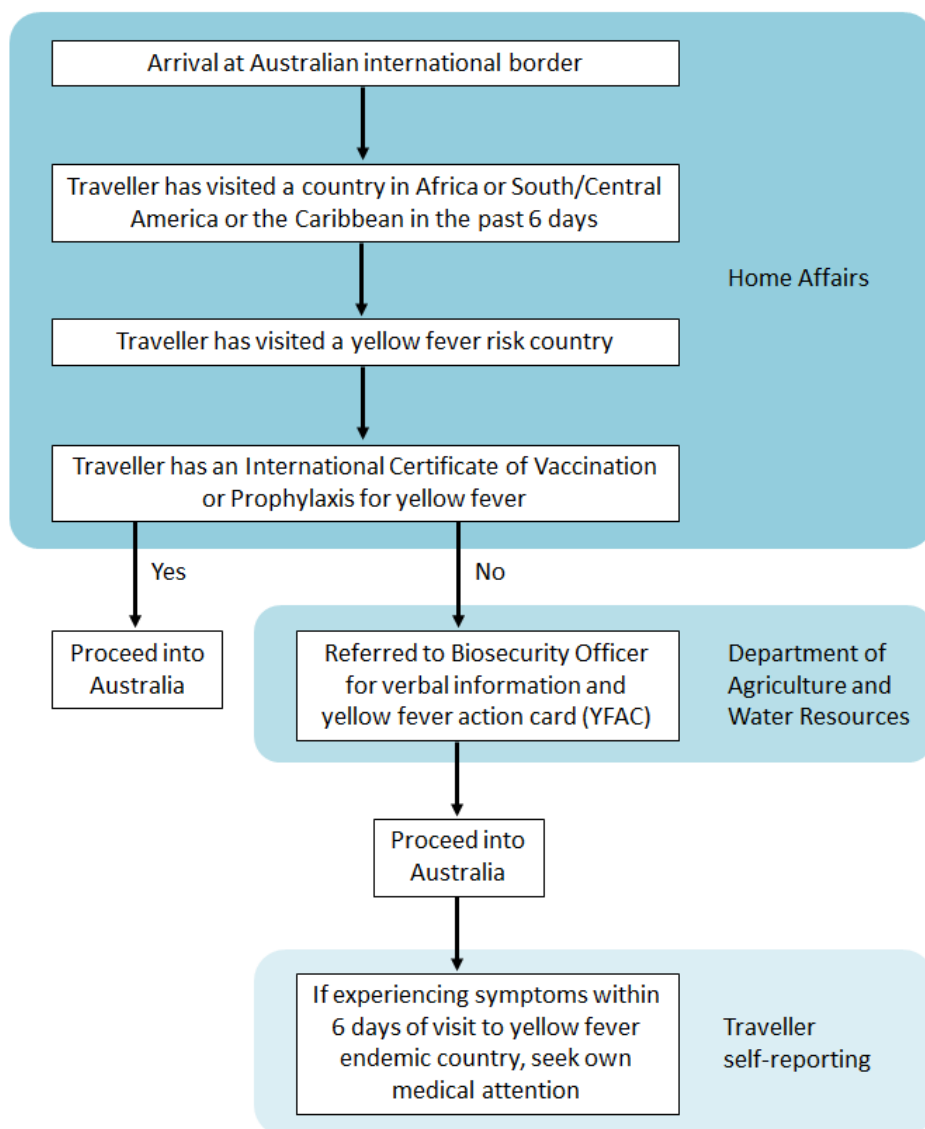


Figure 4 Flow-chart of the yellow fever surveillance system at the Australian border

4.6 Resources required to operate the surveillance system

Personnel involved in the surveillance system are Border Force Officers from Home Affairs and Biosecurity Officers from DAWR.

The personnel costs associated with the surveillance system are relatively minor. With a conservative estimate that a traveller will spend 5 minutes at the passport control (where also

the check for a Certificate occurs), and a monthly count of approximately 24,000 travellers arriving from Africa or South/Central America or the Caribbean, the cost is 2000 person-hours per month. However, only a small proportion of this activity is related to the surveillance system under review, and it could be argued that these person-hours should not be counted. A traveller that is unable to show a valid Certificate will spend a further 5 minutes receiving yellow fever information from the Biosecurity Officer. The one-month pilot study showed 917 such travellers arriving at the Australian border, resulting in 76 person-hours per month.

4.7 Data collection, storage and confidentiality

The collection and use of information is immediate. While the information contained on the Incoming Passenger Card is scanned and kept by Home Affairs indefinitely, for the purpose of the surveillance system under review, there is no further action after the passenger either has provided proof of a Certificate or received information regarding yellow fever from a Biosecurity Officer.

No data are stored for the purpose of the surveillance system, but the data on the IPC is stored for other purposes. The IPC contains personal details such as full name, date of birth, passport number and travel details as well as name and contact details of the stated emergency contact. Due to the sensitive nature of the information, the IPC are securely stored by Home Affairs. However, even if this information would be accessed, there are no details regarding the individual's medical details, such as yellow fever vaccination status, as this is only assessed verbally. If the passenger has overt yellow fever illness upon arrival to the Australian border, this is documented elsewhere.

4.8 Integration with other systems

As described above the system is carried out by officers from Home Affairs and DAWR. It forms part of the compulsory arrival procedure at the Australian international border. There are other surveillance systems that deal with overt cases of the listed human diseases, and these responses are triggered by other factors than those of the yellow fever surveillance system.

5 RESULTS

5.1 Overall travel volumes from areas of interest

Data from Home Affairs provided by the Australian Bureau of Statistics on Overseas arrivals and departures for 1 July to 31 October 2017 were used to extract travel volumes for the evaluation period, as shown in Table 5. Data are available at: <http://www.data.gov.au/dataset/overseas-arrivals-and-departures>

Data were extracted using the following fields and filters: *Long-term resident return; Long-term visitor arrival; Settler arrival; Short-term resident return; Short-term visitor arrival; Country of (Dis)Embarkation = countries in Africa or South/Central America or Caribbean; Travel mode = Air.*

Table 5 Arrivals to Australia from countries in Africa or South/Central America or Caribbean for the three months of the survey.

Category of traveller	August	September	October	Total
Long-term resident return	187	181	138	506
Long-term visitor arrival	756	722	869	2,347
Settler arrival	318	335	321	974
Short-term resident return	10,826	12,400	15,760	38,986
Short-term visitor arrival	8,604	9,310	10,130	28,044
Total	20,691	22,948	27,218	70,857

The above data are likely an underestimate of the volume of travellers that fulfil the criteria of having spent at least overnight in Africa or South/Central America or Caribbean in the past 6 days, as a proportion of travellers would have spent time (<6 days) in other countries before arriving in Australia, and as such have a port of embarkation that fall outside the above regions or have itineraries with non-linked flight bookings. However, in the absence of a good estimate of such a proportion, the above numbers were used in this evaluation.

To estimate the number of travellers that would be arriving at the Sydney and Melbourne international airports, either the filter “State/Territory of (Intended) Residence” in the above excel file could be used, or it could be calculated from the data from the one month snapshot that DAWR performed to assess the number of arrivals from yellow fever endemic areas that had no valid proof of vaccination (NSW and Vic had 80% of arrivals), see **Table 6**. The former might underestimate the number of travellers because it will not capture the ones that immediately travel domestically or declare that the bulk of their visit will be in a different state. The latter on the other hand, makes the assumption that the one-month pilot study was representative of all months, and that the general arrivals have the same distribution as the

individuals that arrive from yellow fever endemic areas without valid proof of vaccination. In this evaluation the conservative estimate of “State/Territory of (Intended) Residence” was used.

Table 6 Estimated travel volumes to Sydney and Melbourne international airports.

NSW and VIC arrivals only	August	September	October	Total
Total	20,691	22,948	27,218	70,857
State/Territory of (intended) residence NSW+Vic	12,409	12,113	16,275	40,797
Calculated proportion according to snapshot	16,553	18,358	21,774	56,686

5.2 Embarkation data for individuals fitting case definition

Over the three-month period of 1 August to 31 October 2017, a total of 1310 travellers met the case definition and were offered to participate in the survey. The survey was completed by 1103 (84.2%) travellers, 799 at Sydney international airport and 304 at Melbourne international airport. Of the remaining 207 travellers, 59 declined to participate and 148 were unable to participate due to language barriers.

If the survey had been offered in other languages than English and in an electronic format on a handheld device may have further improved the already good response rate. But due to the added challenges of obtaining accurate translations of the survey questions and interpretation of free text answers in a different language made this an unfeasible option. Similarly, to offer the survey in an electronic format would either require the Biosecurity Officers to have handheld devices on offer for travellers to use, or if the traveller would complete the survey online it would likely take much longer time and be more disruptive to the traveller.

There was a decline in numbers over the three months, with 536 surveys completed in August, 327 completed in September and 240 completed in October. This variation was mostly contributed to by decreasing numbers of arrivals to Sydney international airport, with 54%, 27% and 19% of the surveys collected in August, September and October, respectively. The distribution of surveys across the months was more consistent across the three months for Melbourne international airport (34%, 37% and 29%, respectively).

Using the observed travel volumes for New South Wales and Victoria in **Table 6**, the proportion of travellers fitting the case definition represented 4.3% (536/12,409), 2.7% (327/12,113), 1.5% (240/16,275) of all travellers from Africa or South/Central America/Caribbean, for the months of August, September and October, respectively.

5.2.1 Embarkation location by continent

At Sydney airport over the three months there were respectively 344, 167, and 128 travellers from South/Central America or the Caribbean, and 72, 44 and 18 travellers from Africa (**Figure 5**). For the same months, there were 66, 65 and 47 travellers from South/Central America or the Caribbean, and 38, 43 and 41 travellers from Africa arriving at Melbourne. At Sydney airport the majority of arrivals were from South/Central America/Caribbean (79-87%) while numbers were more evenly distributed at the Melbourne airport (53-63%). There was a decline in the number of travellers across the study period at the Sydney airport, despite an increase in travel volume during the period (both in terms of all destinations and yellow fever risk destinations). It is unclear why this occurred. A small number of travellers each month (15, 8, 6 respectively) did not disclose their port of embarkation.

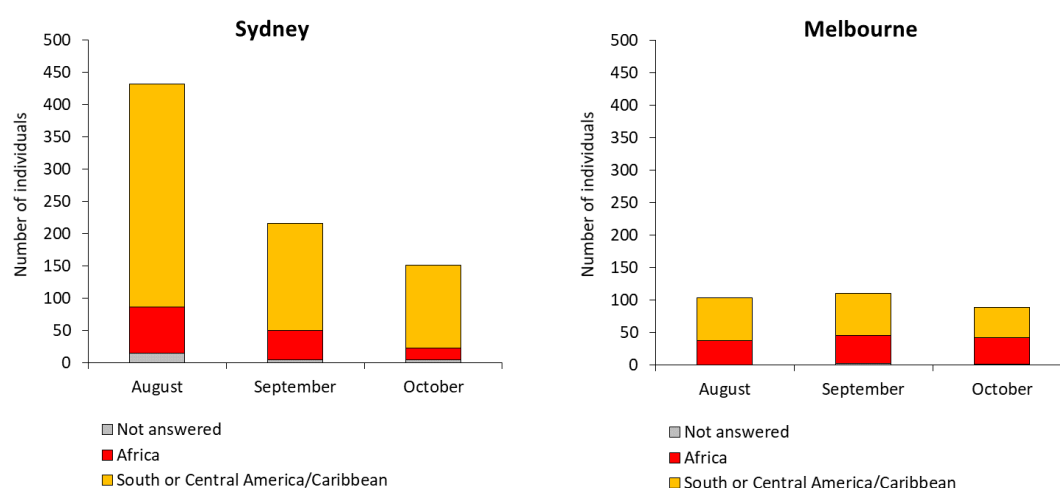


Figure 5 Number of travellers by continent of embarkation, month and airport

5.2.2 Embarkation location by country

Five countries represented 79% of countries visited in Africa: South Africa (30.5%), Ethiopia (17.7%), Kenya (13.5%), Nigeria (9.8%) and Sudan (7.5%) (see **Figure 6**). One person may have indicated visiting several different countries; this has been accounted for in the data below. With the exception of South Africa, the remaining four countries are considered by Australia to be yellow fever endemic.

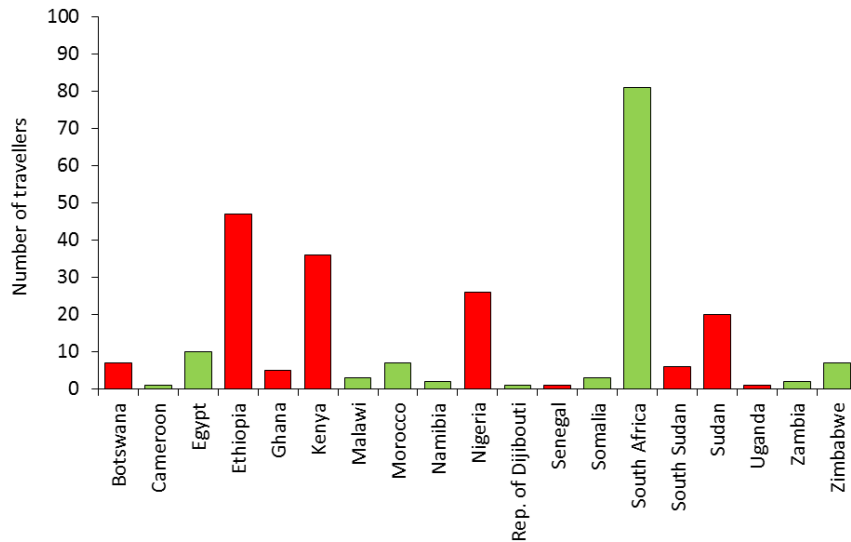


Figure 6 Port of embarkation from the African continent. Yellow fever risk countries are marked in red and non-endemic countries are marked in green.

Four countries were by far the most commonly stated countries of travel origin in South/Central America/Caribbean, representing 78% of countries visited: Brazil (22.4%), Peru (22.1%), Colombia (17.7%) and Argentina (15.9%), as shown in **Figure 7**. Parts of Peru and Brazil, and most of Colombia are considered by Australia to be endemic. Only the Misiones Province in Argentina is considered to be endemic.

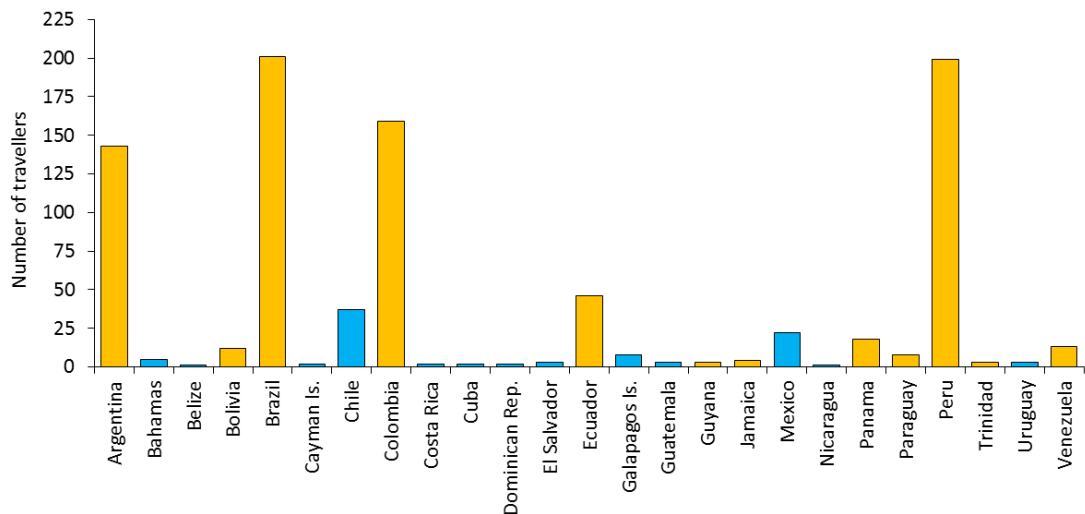


Figure 7 Port of embarkation from the South or Central American or Caribbean regions. Yellow fever risk countries are marked in yellow and non-endemic countries are marked in blue.

As can be seen from the data above there is a proportion of travellers that have not been to a yellow fever endemic country, in particular visiting Africa, and should not have been referred to the Biosecurity Officer. Of the 1103 completed surveys, 871 (79.0%) travellers visited countries

considered by Australia to be yellow fever endemic. Of the remaining 232, 193 (17.5%) should not have been referred, and 39 (3.5%) did not provide a port of embarkation. For all subsequent analysis only those travellers that have been to yellow fever risk countries (n=871) were considered. These travellers represented 2.1% (871/40,797) of all arrivals from Africa or South/Central America/Caribbean.

5.3 Reasons for not having a Certificate among travellers visiting a yellow fever risk country

Of the 871 travellers that had visited a yellow fever risk area and were unable to show a Certificate, 46.7% of the travellers stated they had not had a vaccination; this was 47.7% for South/Central America/Caribbean and 41.6% for Africa (**Figure 8**). Among the travellers that indicated they were vaccinated, the most common reason for not having a Certificate, was that they had lost or forgotten to bring it (31.7% and 38.7% respectively), followed by not being aware of the requirement that the Certificate should be shown (17.3% and 14.1% respectively). Out of the 871 responses for this question, 24 travellers stated they had not received a Certificate with their vaccination.

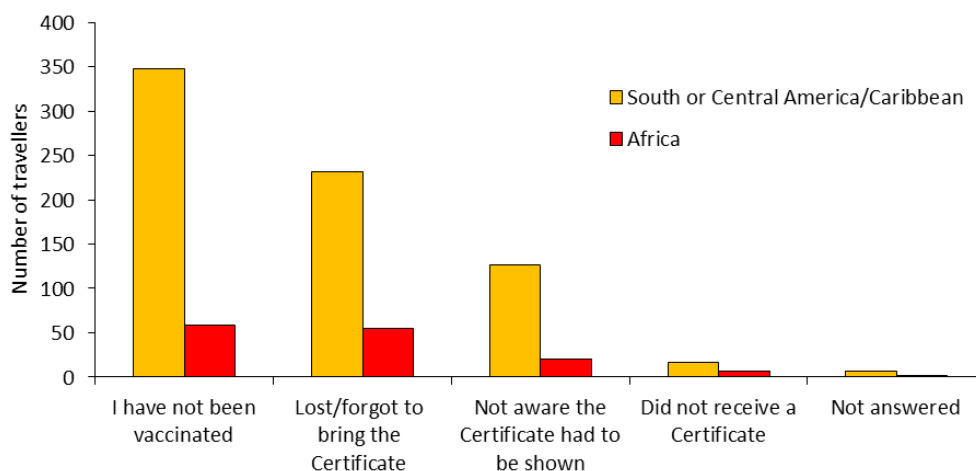


Figure 8 Reasons for not having a Certificate, by continent.

In total 407 individuals stated they were not vaccinated. According to the estimated arrival volumes for the three-month period (**Table 6**), these unvaccinated individuals represent 1% (407/40,797) of the travellers arriving at the Australian border from yellow fever endemic areas. When taking into account travel by one individual to multiple countries, there was a total of 444 instances of countries visited by unvaccinated travellers, detailed in **Figure 9** and **Figure 10**.

Of the 386 instances of visits to countries in South/Central America/Caribbean by unvaccinated individuals, almost a third (126; 32.6%) involved Peru. This was followed by Argentina at 88 (22.8%), Brazil at 71 (18.4%) and Colombia at 61 (15.8%). Of the 58 instances of visits to countries in Africa, most were to Ethiopia (23; 39.7%) and Kenya (18; 31.0%).

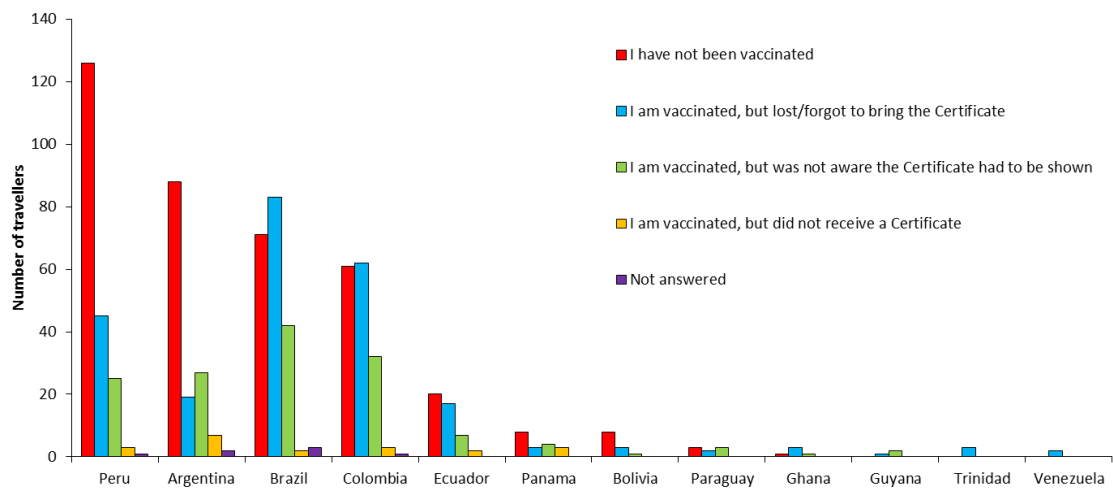


Figure 9 Reasons for not having a Certificate, South/Central America/Caribbean, by country.

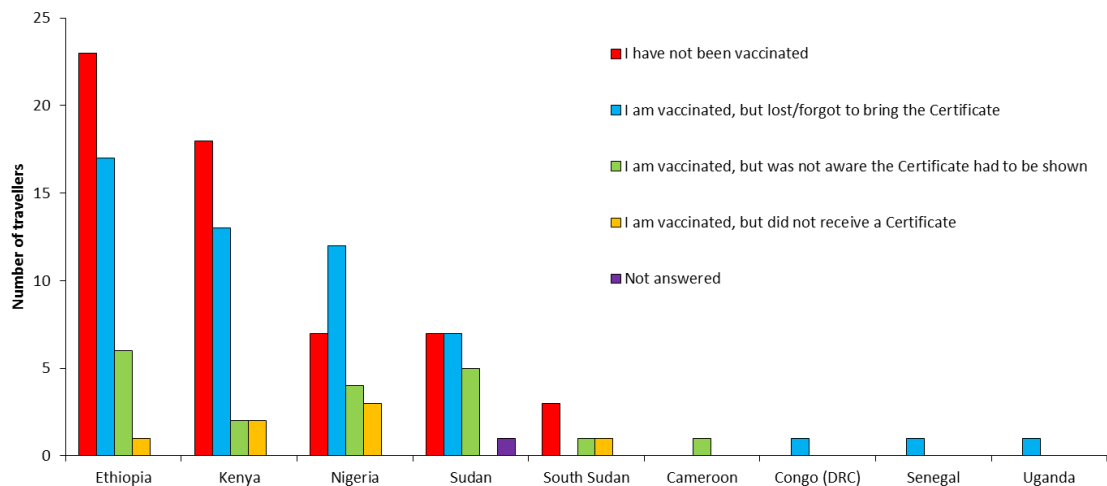


Figure 10 Reasons for not having a Certificate, Africa, by country.

Examples of the free-text answers provided for Question 3. Several of the aspects were captured in Question 4, and due to the layout of the questionnaire, respondents likely wrote the free form response for Question 3 prior to reading Question 4, which was on the back of the questionnaire. The quotes of answers below have been ordered into major topics.

Medical reasons:

- *"I was told people who are 70 years and above are not required to have yellow fever [vaccination]"* (Kenya)
- *"She is over the age she doesn't need it over 60 years old"* (Colombia)
- *"Undergoing chemo therapy – can't have any vaccinations"* (Kenya)

Expired certificate/vaccination:

- *"Have been vaccinated but certificate expired"* (Brazil)
- *"Provided to ABF at Primary line and not returned"* (Brazil)
- *"My vaccination expired more than 10 years ago"* (Brazil)
- *"I'm vaccinated but certificate expired"* (Colombia)

Not visited areas with yellow fever:

- *"I didn't think I need, because did not go to affected areas"* (Peru)
- *"I was told the city I went to was not an affected area"* (Brazil)
- *"There are no tropical disease where I was because it is too cold and too high (up in the Andes)"* (Bolivia)
- *"I only visited Sao Paulo on this trip. There is no yellow fever there"* (Brazil)

Advice regarding vaccination:

- *"Told on USA site not required"* (Colombia)
- *"Am flight crew – company advised we do not need for Brazil"* (Brazil)
- *"Not informed by travel agent"* (South Sudan)
- *"It was not required on the visa application form"* (Peru)
- *"The doctor advised it was not necessary for where I was going"* (Argentina)
- *"I have been in Lima city, and there are no cases of yellow fever there"* (Peru)
- *"No one advised me of this fact"* (Brazil)

Other:

- *"Never heard of the vaccine"* (Peru)
- *"Have had injection but it's stapled to old passport"* (Ecuador)
- *"I spend less than the occupational period in Sudan. I live in Khartoum"* (Sudan)

5.4 Reasons for not being vaccinated

There were 407 travellers in total that declared that they had not been vaccinated. Of these 34 only responded to the free text field in Question 4, and another 10 did not provide an answer to the reason for not being vaccinated.

Of the remaining 363 that provided answers, 64.2% stated they didn't know it was necessary, 17.4% had not vaccinated following advice from a medical professional, 7.2% had not vaccinated following advice from a travel agent, and 4.7% stated they could not afford or didn't have time to get vaccinated (**Figure 11**). Only 6.6% of non-vaccinated travellers had a medical exemption. In the breakdown by country the trends remain much the same. However, it is interesting to observe that advice against vaccination was more often received from travel agents in South/Central American countries (**Figure 12**) compared to those in Africa (**Figure 13**).

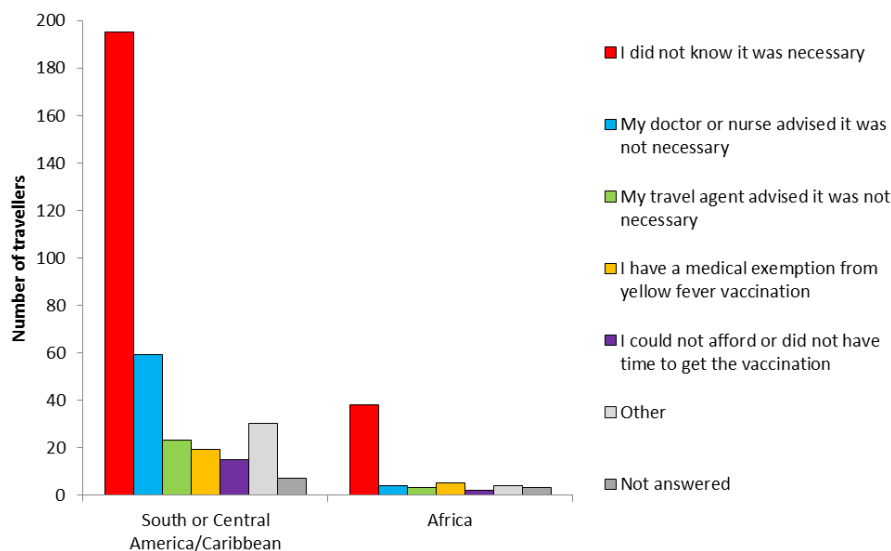


Figure 11 Reasons for not being vaccinated, by continent.

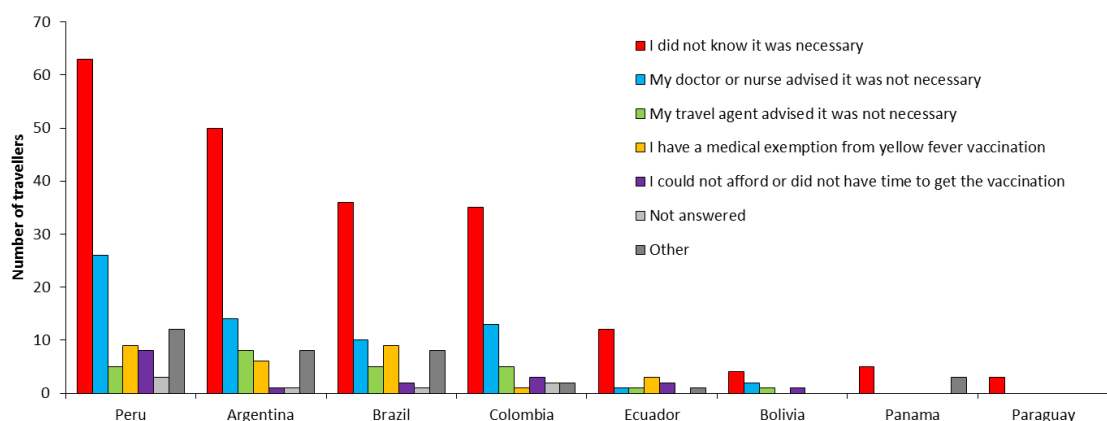


Figure 12 Reasons for not being vaccinated, South/Central America or Caribbean, by country.

Chapter 5 – Evaluation of yellow fever surveillance system

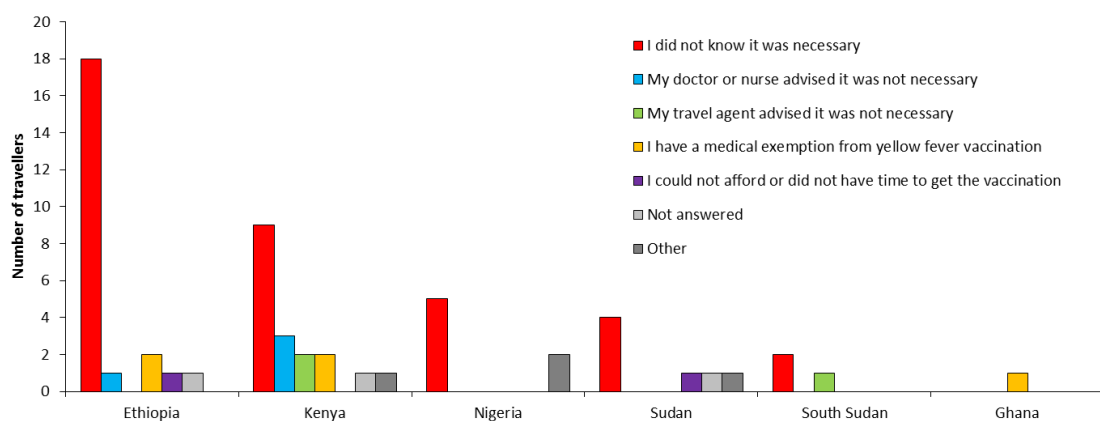


Figure 13 Reasons for not being vaccinated, Africa, by country.

Examples of the free-text answers provided for Question 4. The quotes of answers below have been ordered into major topics.

Vaccine hesitation:

- *"Sensitive to drugs"* (Brazil)
- *"I don't vaccinate"* (Peru)
- *"I do not consent to undisclosed ingredients in vaccines"* (Panama)
- *"I choose not to"* (Brazil)

Not visited areas with yellow fever:

- *"Live for 30 years in metropolitan cities in Ecuador and never known this is an issue. Problems could be in other areas"* (Ecuador)
- *"The places I went to don't have yellow fever (Lima, higher elevation than 2300m)"* (Peru)
- *"There are no cases of yellow fever in Lima"* (Peru)
- *"No need in Argentina"* (Argentina)

Advise not to vaccinate:

- *"Forgot to speak to Drs about vaccinations"* (Colombia)
- *"Not necessary on government website for our journey"* (Argentina)
- *"Google didn't advise necessary. Buenos Aires"* (Argentina)
- *"Internet and USH advisory wrote it is not necessary for Panama"* (Panama)

Other:

- *"I did not do it"* (Peru)
- *"Mosquito aware – long sleeve clothing and lots of bug off"* (Argentina, Brazil, Peru)
- *"Not compulsory"* (Panama)
- *"Knew it wasn't necessary to get back into Australia"* (Peru)
- *"My travel was unanticipated"* (Nigeria)
- *"Emergency visit – death in the family"* (Kenya)
- *"Didn't plan to visit country"* (Colombia, Peru)
- *"Clear of the symptoms"* (Brazil)

In summary, the countries for which travellers stated they did not visit areas with yellow fever were: Peru (8), Argentina (7), Brazil (4), Bolivia (1), Ecuador (1) and Panama (1).

Looking more closely at the 89 travellers that stated a medical professional or travel agent had recommended that vaccination was not necessary, 7 indicated recent travel to Africa, 82 indicated recent travel to South/Central America/Caribbean. When taking into account travel to multiple countries, there were a total of 98 instances of countries visited by unvaccinated travellers. The breakdown by country is shown in **Figure 14**. A high proportion of these were to Peru, where travellers are frequently stated that they only “visited urban areas” or “spent time at high altitude”. Similarly, some travellers from Argentina stated that they had only spent time in non-endemic areas. This may indicate that travellers had received advice appropriate for their travel plans.

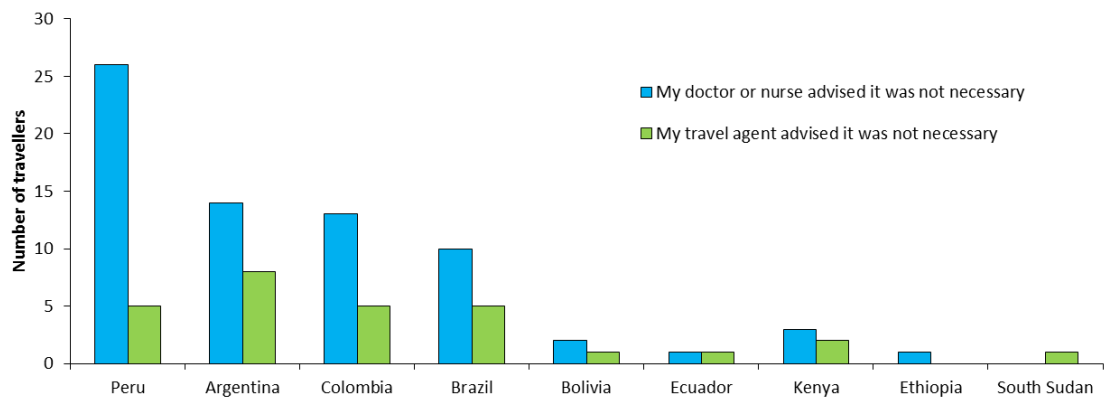


Figure 14 Medical professionals or travel agents advice against vaccination, by country of embarkation

5.5 Summary overview of results

A gradual breakdown of the results is shown in **Figure 15**.

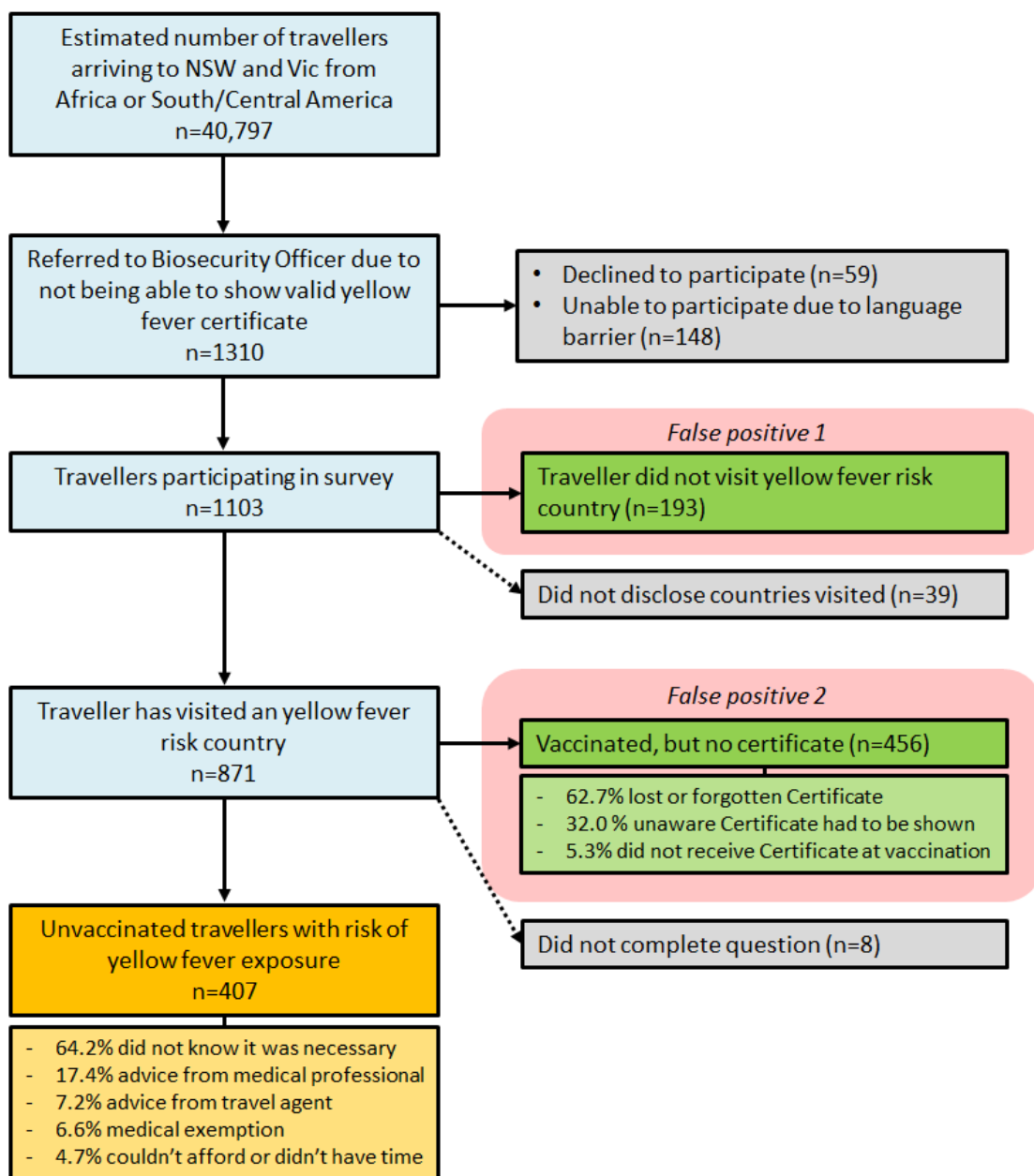


Figure 15 Summarised results from a three-month survey at Sydney Kingsford Smith and Melbourne Tullamarine international airports, showing that the number of travellers at risk of introducing yellow fever virus to Australia is approximately 135 travellers per month

5.6 Knowledge of yellow fever among unvaccinated travellers

The following analyses only considered unvaccinated travellers. The majority of unvaccinated travellers were aware that yellow fever was a serious disease, with 76.3% (45/59) and 81.2% (281/346) stating ‘yes’, from Africa and South/Central America/Caribbean, respectively.

Half (49.9%) of the travellers thought that yellow fever was transmitted by mosquitoes, as shown in **Figure 16**. The second most common response was that yellow fever was transmitted through a combination of contaminated food/water and mosquitoes (10.8%), followed by travellers believing that the transmission pathway was through contaminated food/water only (5.41%). 17% of the travellers stated “none of the above” and a further 1.7% did not respond to the question.

There were some differences between continents, with 51.2% of travellers from South/Central America/Caribbean stating mosquitoes as a transmission source, as opposed to 42.4% of travellers from Africa. 13.6% of travellers from Africa thought contaminated food/water was a transmission source, while only 4.0% of travellers from South/Central America/Caribbean stated this. In contrast, only 3.4% of travellers from Africa thought transmission involved both mosquitoes and contaminated food/water, while 12.1% of travellers from South/Central America/Caribbean thought this was the case.

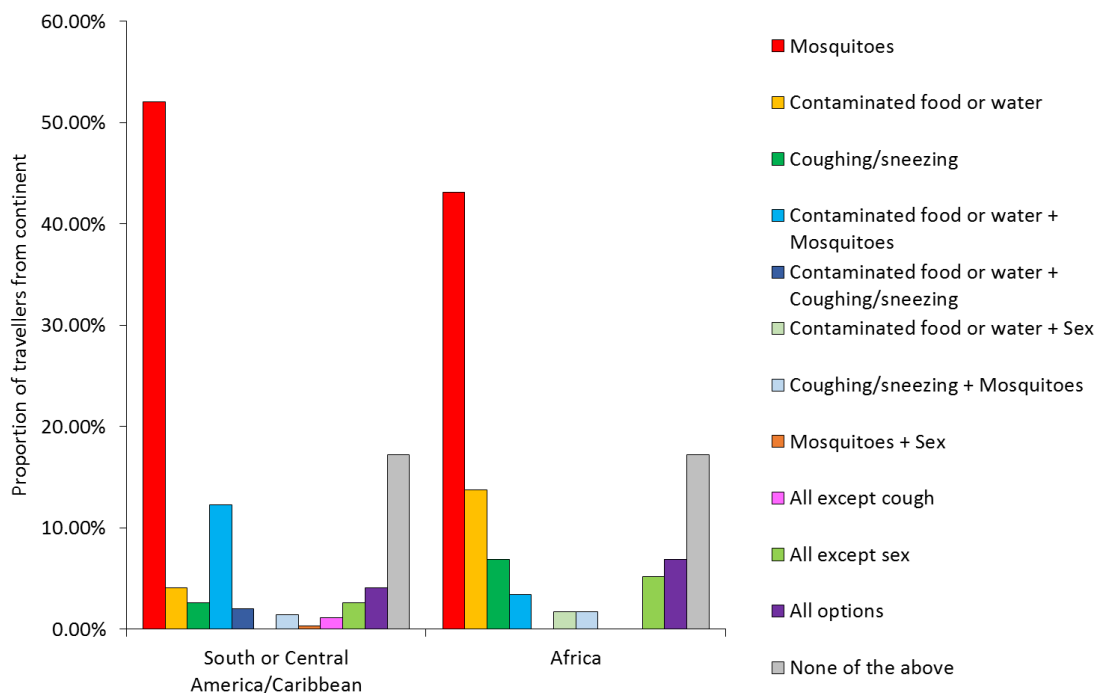


Figure 16 Knowledge of transmission pathways for yellow fever

6 SURVEILLANCE SYSTEM ATTRIBUTES

6.1 Simplicity

Definition: The simplicity of a public health surveillance system refers to both its structure and ease of operation. Surveillance systems should be as simple as possible while still meeting their objectives.(11)

Due to the integration in mandatory border procedures, immediate use of data collected and no requirement for data storage, the surveillance system is simple in operation. It is simple, both structurally and operationally, and to a large extent uses already established resources. The passport control must occur for every traveller and the check for a valid Certificate is a minor addition to this process. Relatively few of total travellers are directed to the Biosecurity Officer for further information. The system relies on few data sources, the first being a question on the IPC and the second a verbal query of valid proof of vaccination.

There is no ongoing storage or processing of the data collected. Furthermore, there is no follow-up beyond the interaction with the Biosecurity Officer and relies on the traveller themselves to report any illness in line with the information and YFAC provided.

Despite the simplicity it would be appropriate to have documentation of the procedure for the surveillance system, which would include the objectives, case definitions and advice required. This would also allow for a documentation trail to be established, such as documenting changes to the scope of the surveillance system to include of a previously non-endemic area that is experiencing an outbreak. Should in the future the electronic system be used to generate regular reports, thresholds and triggers to prompt a review of the system could be included.

There is no case definition *per se* stated in the DAWR work instruction, but the step by step instructions do identify travellers that are at risk of having been exposed to yellow fever and may not be appropriately immunised. While it is stated in the introduction that the traveller should be arriving from a yellow fever risk country, there are no checks for this in the step by step instructions. This may be explained by the fact that this check is conducted by Australian Border Force officers, and as such may be in their work instructions.

Recommendation 1: Publish a unified document from DoH, DAWR and Home Affairs that describes the objectives of the surveillance system, including: a case definition; advice to travellers regarding travel to areas in Queensland where the vector is present; and procedures for changing of the scope and geographical areas of interest.

6.2 Flexibility

Definition: A flexible public health surveillance system can adapt to changing information needs or operating conditions with little additional time, personnel, or allocated funds. Flexible systems can accommodate, for example, new health related events, changes in case definitions or technology, and variations in funding or reporting sources. In addition, systems that use standard data formats can easily be integrated with other systems and thus might be considered flexible.(11)

Due to the paper-based system of the Incoming Passenger Card, it is very difficult to add any questions and/or request additional information without a significant overhaul. A change in the question would involve printing new forms, collecting and ensuring that all old forms are replaced. This would be logistically challenging in a large country as Australia with multiple international ports of entry, and also financially costly. The transition to an electronic IPC system has the potential to solve a lot of problems. It would allow for rapid adaptation to new situations and would ensure consistency across jurisdictions.

There is a difference in the detail of the advice provided by sources such as Smart Traveller compared with the WHO recommendations provided by the Scientific and Technical Advisory Group on Geographical Yellow Fever Risk Mapping (GRYF). The latter details the specific regions in the countries known to be yellow fever endemic including elevation beyond which yellow fever is unlikely to be present, while the former in contrast only provides the traveller or a medical professional with general information of yellow fever risk in the country, but is arguably more timely and responsive to emerging outbreaks. The transition to an electronic system would allow greater flexibility to capture both detailed changes and emerging threat areas.

Recommendation 2: In the electronic IPC system, ensure that the list of countries considered to be endemic or high-risk can be easily adapted to new information.

6.3 Data quality

Definition: Data quality reflects the completeness and validity of the data recorded in the public health surveillance system.(11)

The entry process at the Australian border is likely to be taken seriously by most travellers, due to the serious consequences of providing false information. The information provided on the IPC can therefore be considered to be of high quality and completeness. This means that the first component of the case definition, that the travellers have visited potentially yellow fever

endemic area, is likely to be ascertained with a relatively high degree of certainty. It should be noted that a formal assessment of this has not been conducted as part of this evaluation.

However, the second part of the case definition - that the traveller has potentially had unprotected exposure to the infective agent - is much less precise. The fact that the traveller is unable to produce a valid proof of vaccination does not mean the traveller is at risk. In the absence of proof of vaccination, only a verbal confirmation of immunisation can be obtained, the validity of which is much more difficult to ascertain. From a procedural point of view, if the traveller is unable to show proof of vaccination, the follow up is the same regardless of the verbal assessment. As it stands now, while accurate, the data do not provide sufficient detail. Having a system that would allow the traveller to specify with greater detail their past travel history, would reduce the number of false positives associated with travellers having not visited a yellow fever risk country. This could easily be included as a feature in an electronic system.

From a public health point of view, it would be desirable to capture all travellers at risk, and to understand the reasons for the lack of immunisation. This would, however, be outside the scope of an operational system that sees a high volume of clients and needs to be streamlined with a high processing speed.

Recommendation 3: In the electronic IPC system, implement a series of selections allowing the traveller to state with greater detail their previous locations (currently only continent information is collected).

A suggested series of selections is outlined below:

1. Continent/large geographical region (e.g. Africa, South America, Central America, Caribbean)
2. Country(s) in the region selected above
3. Regions of particular interest (such as Galapagos Islands or Misiones Province) within specific countries

An algorithm in the software would allow automatic filtering of travellers that visited an at-risk country or region, and flag them for a check of a valid certificate of vaccination.

6.4 Acceptability

Definition: Acceptability reflects the willingness of persons and organisations to participate in the surveillance system.(11)

As the question to inform the first part of the case definition forms part of the compulsory entry process at the Australian border, travellers have little choice but to comply and the process is likely to be seen as inconvenient but acceptable for the traveller. The second part of the case definition is completed as a verbal communication at the passport control and is also likely to be perceived as an unavoidable routine measure.

Being identified as potentially non-immunised and singled out to receive yellow fever information, may be uncomfortable and cause anxiety in some travellers. This is both from the point of view of a worry stemming from being taken aside in an authoritarian situation, but also a worry of potentially having been exposed to a deadly disease while unprotected. Hence, this may lead some travellers to lie about their vaccination status. There would also be travellers that are frustrated over the additional process and time required, especially if they are immunised. The follow-up intervention, to receive additional information, has a relatively small impact on the traveller's journey and has no long-term requirements, making it likely more acceptable. The fact that out of the 1310 travellers offered the survey conducted as part of this evaluation, only 59 travellers (4.5%) declined to complete it, suggesting a high level of acceptability. An additional 148 travellers were unable to complete the survey due to language barriers, and it is unclear what proportion of these would have accepted to participate if they could.

Since the Certificate is now considered to be valid for the life of the individual, it would be possible that once the certificate has been sighted by the Australian Border Force officials, this information is entered and retained in the traveller's profile in electronic system (could be as easy as a tick-box). This would reduce the entry time for the traveller in the future and reduce the workload for the ABF officers. Such a feature should be applicable to both foreign and Australian nationals.

A whole system adoption of digital immunisation records could obviate the need for paper-based certificates of vaccination at the Australian border, at least for Australian nationals. Such a scenario is presented by Wilson *et al* (15), and could be applied to Australia, especially in the light of the recent move to the whole of life Australian Immunisation Register (AIR). Significant development of the AIR system would still be required to make such features a reality, and there

may be privacy issues with connected systems that need to be taken into consideration. Additionally, it should be noted that the requirement for the Certificate at some overseas borders will remain, thus necessitating a paper copy to be held by the traveller.

Recommendation 4: Once a valid certificate of vaccination has been sighted by ABF, this information is entered and retained in the traveller's profile in the electronic border security system.

Recommendation 5: Explore ways in which AIR information could be linked with the electronic immigration profile for Australian citizens.

6.5 Sensitivity

Definition: The sensitivity of a surveillance system can be considered on two levels. First, at the level of case reporting, sensitivity refers to the proportion of cases of a disease (or other health-related event) detected by the surveillance system. Secondly, sensitivity can refer to the ability to detect outbreaks, including the ability to monitor changes in the number of cases over time.(11)

One aspect of the sensitivity of the surveillance system can be defined as identifying all unimmunised travellers that have potentially been exposed to yellow fever within the incubation period, such that they if infected would develop symptoms while in Australia. The sensitivity is likely to be high for this surveillance system. This is in large part due to the fact that the assessment of is part of the standard entry procedure at the Australian border.

The calculation of the sensitivity becomes obsolete due to the fact that we, as stated in the methods, that we are assuming no false negatives, and hence all cases should be captured. For the sake of completeness, the formula is as follows:

$$\text{Sensitivity} = \text{TP}/(\text{TP}+\text{FN}) = \text{TP}/(\text{TP}+0) = 1 = 100\%$$

Another aspect of the sensitivity of a surveillance system is that it can detect outbreaks or changes in frequency of events under surveillance. In this aspect that surveillance system under review is not sensitive. This is because no data are recorded making assessments of time trends impossible. It can be argued that this is not required for the surveillance system to operate successfully. Should a traveller seek medical assistance and be diagnosed with yellow fever following entry to Australia, this information would be captured by epidemiologic surveillance systems such as the National Notifiable Diseases Surveillance System. From a public health point

of view the argument could be made that collecting and collating data on the number of individuals that are at risk of infection while travelling could be used to inform public health campaigns and identify if there are particular aspects of pre-travel vaccination promotion or advice that could be improved.

Recommendation 6: Once the electronic system is implemented, provide regular reporting to DoH allowing analysis over time which can be used to inform future public health campaigns and health policy changes.

6.6 Positive Predictive Value

Definition: *Positive predictive value (PPV) is the proportion of reported cases that actually have the health-related event under surveillance.*(11)

A true positive case was defined as a traveller that is unvaccinated and has visited a yellow fever risk country in the last 6 days. False positives include travellers referred to a Biosecurity Officer that had not visited a yellow fever risk country or had visited a yellow fever risk country in the last 6 days but was vaccinated.

Table 7 Positive predictive value calculation

Case status	Frequency
True positive	407
False positive	657
Incomplete embarkation information	39
PPV = TP / (TP+FP)	407/(407+657) = 0.383 = 38.3%

As can be seen from the calculation in **Table 7** the positive predictive value of the surveillance system is poor, with almost two thirds (62.7%) of the identified cases being false positives. There are two main reasons for the false positives: i) unvaccinated individuals who have travelled to non-endemic countries/regions, ii) vaccinated travellers that have lost or forgot their certificate of vaccination.

The first cause of false positives is the result of ABF officers not determining whether the traveller has visited a yellow fever risk country or not. This question should be asked at the primary line, prior to the Certificate check. In 193 instances this did not happen, and these travellers were unnecessarily referred to the Biosecurity Officer.

The second cause of false positives results from the traveller forgetting, having lost or not aware the certificate had to be shown. Some travellers were also unaware of the amendment of the *WHO International Health Regulations 2005* on the 11 July 2016, such that a Certificate became valid for the life of the vaccinated person. These travellers stated that they had been vaccinated but that the Certificate or vaccination had expired. Many of the older Certificates will have the 10-year expiry stated on the front.

The restriction imposed by some clinics that only the clinic that administered the vaccination can issue a new yellow fever Certificate has been viewed by some travellers who had lost their original Certificate as a hurdle to obtaining a replacement (anecdotal data from online travel forums). With the expansion of the Australian Immunisation Register (AIR) to become a whole of life register, it may be possible in the future for this to be used by any authorised yellow fever vaccination organisation to generate replacement Certificates. Currently the required information to issue replacement certificates is not available from the AIR. Vaccinations prior to 2016 are not captured in the AIR so this could only be used for future vaccinations. Significant development of the AIR system would still be required to make such features a reality. Furthermore, these features would have their own ethical considerations in terms of personal vaccination details being available to clinics where the person is not a patient.

In many instances a poor PPV would lead to an unacceptable misdirection of resources. However, in light of the potentially serious consequences of yellow fever outbreaks and introduction of the virus to vectors in Australia, and then relatively low-cost intervention carried out in response to the surveillance, it could be argued that the low PPV is acceptable especially if the sensitivity remains very high. Also, from the perspective of the traveller the intervention is not arduous, and only requires a relatively small amount of their time.

The situation would be different if a decision was made to perform active follow-up of the traveller for the entire incubation period, for instance through telephone or messaging checks on a regular basis, where it would be more important to allocate the resources accurately. The current system ultimately relies on the traveller to seek medical attention should they fall ill with the symptoms described in the YFAC, which may result in a delay and possible transmission opportunities. Given the lack of reports of yellow fever in Australia, a general expansion of follow-up procedures is not indicated and would not be economically feasible or desirable. The exception being to formalise the advice provided to travellers identified as at-risk regarding travel to areas in Queensland where the vector is present.

Recommendation 7: Evaluate the cost benefit of raising public awareness of the requirement to carry the Certificate, and that the vaccination and Certificate is now considered to be valid for life, and what countries are considered to be yellow fever endemic.

Recommendation 8: Explore ways in which the Australian Immunisation Record (AIR) could be used to generate new certificates to replace lost ones.

Also see recommendation 1 and 3.

6.7 Representativeness

Definition: *A public health surveillance system that is representative accurately describes the occurrence of a health-related event over time and its distribution in the population by place and person.*⁽¹¹⁾

The results of the evaluation show that the surveillance system is not representative of the occurrence of the health event (*“identifying all unimmunised travellers that have potentially been exposed to yellow fever within the incubation period”*) over time and its distribution in the population. This mainly due to two aspects, the first being the low PPV with a high degree of false positives, and the second being that no data is recorded for ongoing analysis of time trends.

See recommendations 3 and 5.

6.8 Timeliness

Definition: *Timeliness reflects the speed between the steps in a public health surveillance system.*⁽¹¹⁾

The Australian surveillance system for yellow fever can be said to be timely. The response to a positive case (*“identification of an unimmunised traveller that has potentially been exposed to yellow fever within the incubation period”*) is immediate, with the traveller being directed to a Biosecurity Officer to receive information regarding yellow fever. The referral to the Biosecurity Officer takes 5-10 minutes (depending on the airport layout) and the yellow fever information is provided in a time period of approximately 5 minutes. The greatest improvement to the timeliness would be a reduction in volume of travellers needing to see a Biosecurity Officer, which could be achieved if the number of false positives were reduced through previous recommendations 3, 7 and 8.

The formal part of the surveillance system terminates at this point, however a remaining aspect is the response of a traveller who subsequent to their entry into the country start experiencing symptoms of yellow fever.

The information provided verbally by the Biosecurity Officer and through the YFAC is intended to equip the traveller with sufficient knowledge to recognise the symptoms of yellow fever, seek medical attention and raise the possibility of yellow fever infection to the attention of the health professionals. As there have been no such instances recorded in Australia, there are no data to assess the timeliness of the health seeking behaviour of the travellers, and by proxy the effectiveness of the information provided.

6.9 Stability

Definition: Stability refers the reliability (i.e. the ability to collect, manage, and provide data properly without failure) and availability (the ability to be operational when it is needed) of the public health surveillance system.(11)

The low complexity, immediate use of data and integration with mandatory entry processes ensures stability of the surveillance component for yellow fever. The simplicity of the system means that there is no need for data storage, paper or electronic, nor a need to ensure ongoing and reliable storage of such data over time. The lack of an analysis step means that the data can be actioned immediately, and that the system can always be operational. The highly structured but simple process and the formulaic intervention in the form of the YFAC ensures that the system is consistent and stable.

7 PERFORMANCE OF THE SURVEILLANCE SYSTEM

7.1 Effectiveness

The effectiveness of the surveillance system can be viewed from the aspects of identifying and modifying risk behaviour. In the aspect of identifying all travellers that are at risk, the system is effective. It is unlikely to miss any travellers at risk of having been exposed to yellow fever since the current screening question on the IPC is very broad, resulting in no/few false negatives. The broadness of the question does lead to a poor efficiency (discussed below). However, the system is not effective in modifying risk behaviour due to the lack of details captured to assess the reasons behind non-immunised travellers. As previously mentioned, this surveillance system may not be the appropriate tool to obtain such details.

There has not been a single notification of yellow fever cases since the commencement of the National Notifiable Diseases Surveillance System. This makes it impossible to assess the effectiveness of the surveillance system in terms of preventing importation of cases of yellow fever, as it has never been tested. Overt yellow fever illness is detected by another surveillance system at the border.

7.2 Efficiency

The high proportion of false positives means there is an unnecessary work load on the system, meaning that it is not running with optimal efficiency. Resources are used to follow up individuals who have visited/arrived from a non-endemic country or area, or individuals who are vaccinated but did not have a Certificate. The first component can be addressed in the development of the electronic IPC by incorporating options that will capture visits to yellow fever risk areas with greater detail (as outlined in recommendation 3). The second component can be addressed through a suite of changes, including raising the public awareness of the Certificate and facilitate the generation of new Certificate to replace lost ones (outlined in recommendations 6 and 7). The follow up procedure for the surveillance system is relatively minor, both in terms of cost and time.

7.3 Usefulness

Not only is the surveillance system for yellow fever useful, but it is a requirement of the *International Health Regulations (2005)*, to which Australia is a signatory country. Due to the presence of the competent vector, *Aedes aegypti*, in North Queensland and part of Central and South Queensland it is critical that a non-immune individual who has been potentially exposed

to yellow fever in their incubation period is identified early to prevent travel to at risk areas and/or implement monitoring so that should a case become infectious further transmission can be prevented. Hence, the system is useful in contributing to reducing this risk by providing that early identification.

8 SUMMARY OF RECOMMENDATIONS

The evaluation of the Australian yellow fever surveillance system identified the following areas of proposed improvements.

1. Publication of a unified document from DoH, DAWR and Home Affairs describing the objectives of the surveillance system including a case definition, advice to traveller regarding travel to areas in Queensland where the vector is present, and procedures for changing of the scope and geographical areas of interest. (Rec.1)
2. The development and planned implementation of an electronic Incoming Passenger Card (eIPC) to provide opportunities to enhance the informative value of the yellow fever surveillance system. It is proposed that the eIPC would incorporate the following functionalities:
 - Easy adaptation and inclusion of changes to countries considered to be yellow fever endemic or high-risk. (Rec.2)
 - Implementation of a series of selections allowing the traveller to state with greater detail their previous locations (currently only continent information is collected). If a traveller is able to gradually provide more precise information, one source of false positives could be avoided. A suggested series of selections is outlined below:
 - Continent/large geographical region (e.g. Africa, South America, Central America, Caribbean)
 - Country(s) in the region selected above
 - Regions of particular interest (such as Galapagos Islands or Misiones Province) within specific countries

An algorithm in the software would allow automatic filtering of travellers that may have been exposed, and flag them for a check of a valid certificate of vaccination. (Rec.3)

- Subsequent to sighting by ABF of a valid certificate of vaccination, the information should be retained in the traveller's profile in the electronic border security system. (Rec.4)
- Once the electronic system is implemented, regular reporting to DoH would allow analysis over time, which can be used to inform future public health campaigns and health policy changes. (Rec.6)

3. Evaluate the cost-benefit of raising public awareness of the requirement to carry the Certificate, and that the vaccination and Certificate are now considered to be valid for life. (Rec.7)
4. The establishment of the whole of life Australian Immunisation Record (AIR) provides opportunity to expand its use. It is proposed to during the development of the AIR explore ways in which:
 - AIR information could be used to generate new certificates to replace lost ones. (Rec.8)
 - AIR information could be linked with the electronic immigration profile for Australian citizens (Rec.5).

9 DISCUSSION

As several aspects related to the specific evaluation components have been discussed in previous sections, the discussion here is more general in nature.

The data from the survey conducted as part of this evaluation shows that an estimated 2% of travellers from an approximate average of 160,000 per year arriving at Sydney and Melbourne international airports are flagged as potentially unvaccinated individuals at risk of having been exposed to yellow fever, but that more than half of these individuals were in fact immunised or did not visit yellow fever endemic areas. Only approximately one percent of travellers that indicated on their IPC that they have been overnight or longer in Africa or South/Central America or the Caribbean within the past six days (approx. 135 travellers per month) pose a risk of introduction and possible further transmission in North Queensland of Australia.

The perfect record held by Australia in terms of no yellow fever notifications since the commencement of the NNDSS could easily be interpreted as that the threat of yellow fever is low. However, the recent outbreak of yellow fever in Angola and the documented importations of 59 cases to the Democratic Republic of Congo, 11 cases to China, two cases to Kenya, one case to Mauritania (16-18); as well as 10 importations to Argentina, Chile, France, the Netherlands, Romania and Switzerland from the ongoing outbreak in Brazil (18, 19), highlights the risk of such complacency. It should be noted that all of the introductions to Europe were by unvaccinated travellers. Historically there have been other instances of importations such as two fatal cases in the USA returning from Venezuela (20) and Amazonas, Brazil (21), one fatal case in Belgium following a visit to the Gambia (22) and one case in the Netherlands of a traveller returning from Suriname (23). The increased volumes of rapid air travel elevate the risks for any nation or area with competent vectors. Regular outbreaks of dengue in North Queensland are prime examples of the ease by which vector borne viral diseases can be introduced by infected travellers into Australia (24, 25).

Yellow fever virus endemic areas are currently mostly rural and remote areas of Africa and South America, and therefore limit the number of Australian travellers that come into contact with the virus. However, the spread of YFV into coastal urban areas of Brazil shows this is not a static situation and has the potential to greatly increase the number of travellers potentially exposed. Furthermore, some countries will have particular geographic exceptions. While most of Argentina is considered to be YFV free, with only the Misiones Province being considered yellow fever endemic, this area harbours the Iguazu Falls, a highly popular tourist destination. Conversely, despite the country of Colombia being considered yellow fever endemic, the

commonly visited province of the Galapagos Islands, is not. This emphasises that an effective surveillance system must both capture detailed geographical information and be adaptable to changes in geographical spread of YFV. The increasing interest in exploring areas off the well-beaten track and the rising trend of adventure travel, means that there is an increased likelihood of Australian travellers coming into contact with the yellow fever virus even if it is restricted to remote locations.(26)

The Yellow Fever Action Card that is provided to non-immunised travellers that may have been exposed to yellow fever within the incubation period does not contain any advice on movement restrictions to, or precautions while in areas of Queensland with a competent vector. In the situation of an overtly ill passenger, presenting with classical yellow fever symptoms, such restrictions would undoubtedly be put in place to minimise the risk of further transmission. Whether it is justifiable or feasible to restrict the movements of asymptomatic and potentially non-infected travellers is less clear.

Similar to the situation of overt yellow fever disease, the monitoring of the introduction of potentially infected vectors is captured under a different surveillance system, than the one under evaluation here. Any aircraft or vessel that may cause the introduction of a vector species into Australia is subject to strict disinsection protocols, and permanent biosecurity monitoring zones are in place around all first points of entry for aircraft, vessels and goods into Australia. In addition, there is monitoring using mosquito traps at the ports of entry providing an active surveillance system. While possible that a competent vector may be introduced in areas of Australia where there currently are no competent vectors for yellow fever, it is unlikely that they would become established due to the response arrangements following a detection. Furthermore, should an infected vector be introduced, it is unlikely to cause disease outside the immediate bounds of the port of entry due to the limited radius of movement of mosquitoes, unless assisted by further vehicular travel. There have been isolated cases of disease attributed to transmission from introduced infected vectors to people with no compatible at-risk travel history. (27) In Australia such events have been documented in Darwin and Cairns. (28, 29) There have been no documented secondary cases or further transmission from such events.

Should the *Aedes aegypti* mosquito be eliminated from Australia (30), it would technically negate the requirement for yellow fever surveillance. However, elimination likely to only be successful in areas low vector density and unlikely to be achieved in large areas of North Queensland. Even in the hypothetical absence of a vector and a reservoir, and risk of transmission, the public health system has a responsibility for early identification and treatment

of any patient showing symptoms following entry to Australia. As a high proportion of the unvaccinated travellers were unaware of the risks, the most effective way of delivering the post-exposure public health measures remains through information and encouragement of health seeking behaviour.

There are a number of limitations to this study. Firstly, the scope of the evaluation was limited to only two jurisdictions. Although these airports were identified in the pilot study to account for 80% of the travellers referred to a Biosecurity Officer, there may be departure destinations or certain demographics groups not captured or well represented in these jurisdictions. Secondly, I make the assumption that travellers are truthful in their responses at the border. This may arguably be a stretch (given that there is a whole series of TV-shows dedicated to people not being truthful at the border), and the study may not have captured travellers that either lie about the vaccination history or the countries visited in past 6 days.

The surveillance system is inefficient due to a high proportion of false positive cases, which currently triples the amount of intervention work load required. Two main changes could reduce the number of false positives significantly. Firstly, the transition to an electronic IPC should allow for more appropriate level of detail with reference to the port of embarkation and countries visited. Secondly, a campaign to raise the awareness of the requirement of carrying the Certificate and that it is now valid for life, would further reduce the proportion of false positives but may not be cost effective.

10 CONCLUSION

The evaluation found the yellow fever surveillance system to be effective with regards to the objective of identifying arriving travellers at risk, but inefficient with a substantial number of false positives. These deficits could be addressed with improvements in two main areas, increased accuracy of the identification of at-risk cases, and adaptability to emergence of novel at-risk geographical areas. The transition to an electronic version of the Incoming Passenger Card provides an excellent opportunity to address both of these issues.

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APPENDIX 5A – Presentation for NT CDC conference

This talk was given at the Northern Territory CDC conference in Darwin, on the 14th of September 2018 following an invitation from the Northern Territory CHBO Dr Vicki Krause.

Chapter 5 – Evaluation of yellow fever surveillance system

**Australian Government
Department of Health**

**YOU SHALL
NOT PASS**

YELLOW FEVER VIRUS...

An evaluation of the surveillance system for yellow fever
at the Australian international border

Dr Patiyan Andersson
M.Phil. Applied Epidemiology Scholar
Border Health Section, Office of Health Protection
Australian Government Department of Health, Canberra

**Australian Government
Department of Health**

Yellow fever – disease and transmission

- Mosquito-borne viral acute haemorrhagic disease
- Flavivirus (dengue, Zika, JE)
- Incubation: 3-6 days
- Sudden fever, chills, headache, myalgia, nausea, vomiting, fatigue
- Severe disease (15-20%) – high fever, visible bleeding, liver failure with associated jaundice, kidney failure, cardiovascular instability
- 20-50% of cases with severe disease may die
- North Queensland have *Aedes aegyptii*

SYNATIC CYCLE
Aedes spp.
Haemaphysalis spp.
Sabethes spp.

URBAN CYCLE
Aedes aegyptii

14 September, 2018

**Australian Government
Department of Health**

47 yellow fever risk countries

Centers for Disease Control and Prevention (<http://www.cdc.gov/yellowfever/countries.html>)

Angola → DRC, China, Kenya, Mauritania
Brazil → Argentina, Chile, France, Netherlands, Romania, Switzerland

14 September, 2018

**Australian Government
Department of Health**

Border process for yellow fever

14 September, 2018

**Australian Government
Department of Health**

Purpose of evaluation

International airport	Number of travellers	Cumulative %
Sydney	541	59.0
Melbourne	187	79.4
Brisbane	144	95.1
Adelaide	26	97.9
Darwin	17	99.8
Cairns	1	99.9
Perth	1	100
Caribarra	0	
Gold Coast	0	
Townsville	0	
Total	927	

- Assess the performance of the yellow fever surveillance system
- Estimate the number of travellers posing a risk of yellow fever introduction into Australia
- Understand the reasons for travellers not vaccinating despite visiting a yellow fever risk country
- Provide recommendations for the development of the electronic incoming passenger card (eIPC)

14 September, 2018

**Australian Government
Department of Health**

Survey

Voluntary anonymous survey offered to all travellers referred to Biosecurity Officer:

- 3 months (Aug-Oct)
- Sydney Kingsford Smith airport
- Melbourne Tullamarine airport

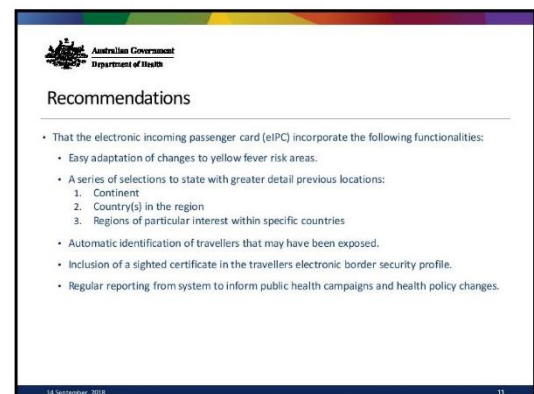
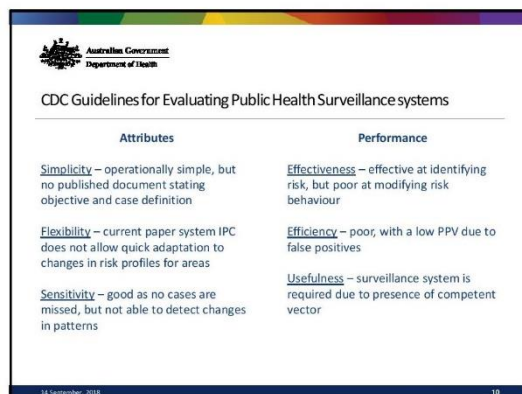
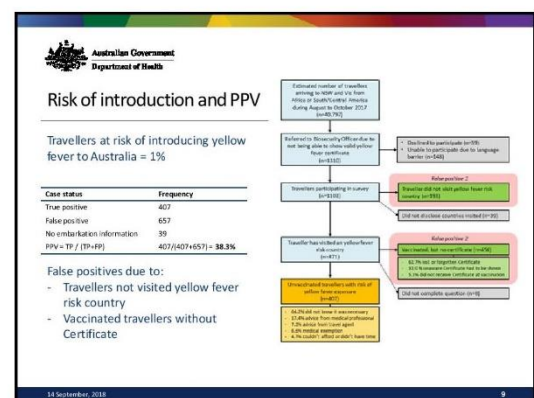
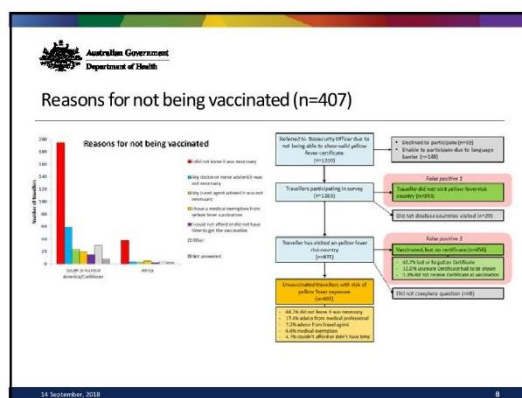
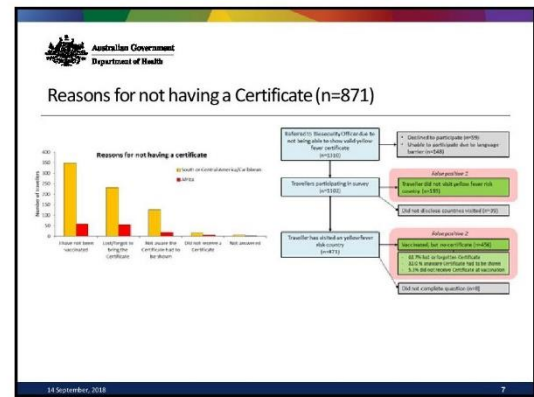
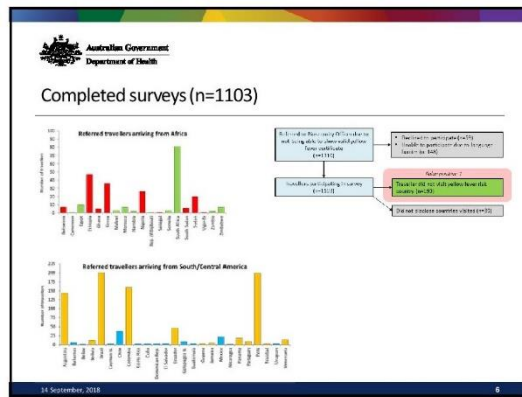
Question areas:

- Basic knowledge of yellow fever and mode of transmission
- Reason(s) for not having an Certificate of Vaccination
- Reason(s) for not getting vaccinated
- Country(s) visited in the 6 days prior to the survey

Noted number of travellers that:

- Declined to participate
- Unable to participate due to language barriers

14 September, 2018



Chapter 5 – Evaluation of yellow fever surveillance system



Recommendations

- Unified document that describes the objectives of the surveillance system, including a case definition and procedures for changing of the scope and geographical areas of interest.
- Evaluate the cost benefit of raising public awareness of the requirement to carry the Certificate, and that the vaccination and Certificate is now considered to be valid for life.
- **ASPIRATIONAL** - proposed to during the development of the AIR explore ways in which:
 - AIR information could be used to generate new certificates to replace lost ones.
 - AIR information could be linked with the electronic immigration profile for Australian citizens.

14 September, 2018

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Acknowledgements

- Rhonda Owen - Assistant Secretary, Health Emergency Management Branch
- Joel Willis - Director, Border Health section
- Border Health team
- Professor Brendan Murphy - Chief Medical Officer, Department of Health
- Chief Human Biosecurity Officers in each jurisdiction
- Biosecurity Officers - Department of Agriculture and Water Resources
- Dr Katrina Roper – ANU Supervisor

14 September, 2018

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7 October, 2018

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Case definition for at-risk traveller

Optimal	Used
• Traveller has been in a yellow fever risk country overnight or longer within the past 6 days	• Traveller has been in Africa or South/Central America overnight or longer within the past 6 days
And	And
• has not been immunised against yellow fever	• unable to produce a valid Certificate for yellow fever

14 September, 2018

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APPENDIX 5B – Yellow fever survey form

The anonymous voluntary survey was offered to all travellers referred to a Biosecurity Officer at the Sydney and Melbourne international airports between August-October 2017.



Australian Government
Department of Health

YELLOW FEVER SURVEY FORM

Dear Traveller,

You have been asked to complete this survey because you have indicated that you have visited a yellow fever risk country within the past 6 days, but are not able to show an International Certificate of Vaccination or Prophylaxis for yellow fever.

The intent of this survey is for the Australian Government Department of Health to understand the different reasons why travellers do not have a yellow fever vaccination or proof of vaccination certificate, to help inform future processes.

The results of this survey are anonymous and will not affect your continued travel in any way. Please do not include any personal details on the form.

Thank you for taking the time to complete this short survey. We wish you a pleasant onward journey.

Question 1

Are you aware that yellow fever is a severe disease that can be caught only in certain countries?

- ☐ Yes
- ☐ No

Question 2

Are you aware of how you can catch yellow fever?

- ☐ Contaminated food or water.
- ☐ Coughing/sneezing.
- ☐ Mosquitoes.
- ☐ Sex.
- ☐ None of the above

Question 3

Why do you not have an International Certificate of Vaccination or Prophylaxis (the Certificate) for yellow fever with you?

- ☐ I have not been vaccinated (*please go to Question 4*).
- ☐ I am vaccinated, but lost/forgot to bring the Certificate (*please go to Question 5*).
- ☐ I am vaccinated, but was not aware the Certificate had to be shown (*please go to Question 5*).
- ☐ I am vaccinated, but did not receive a Certificate (*please go to Question 5*).
- ☐ Other: _____

Question 4**Why did you not get vaccinated against yellow fever?**

- ☐ I have a medical exemption from yellow fever vaccination.
☐ I did not know it was necessary.
☐ My doctor or nurse advised it was not necessary.
☐ My travel agent advised it was not necessary.
☐ I could not afford or did not have time to get the vaccination.
☐ Other: _____

Question 5**What continent(s) and country(s) have you visited in the past 6 days?**

☐ South or Central America/Caribbean	☐ Africa	
☐ Argentina	☐ Angola	☐ Guinea
☐ Bolivia	☐ Benin	☐ Guinea-Bissau
☐ Brazil	☐ Burkina Faso	☐ Kenya
☐ Colombia	☐ Burundi	☐ Liberia
☐ Ecuador	☐ Cameroon	☐ Mali
☐ French Guiana	☐ Central African Republic	☐ Mauritania
☐ Honduras	☐ Chad	☐ Niger
☐ Galapagos Islands	☐ Congo, Democratic Republic of the	☐ Nigeria
☐ Guyana	☐ Congo, Republic of the	☐ Rwanda
☐ Jamaica	☐ Cote d'Ivoire (Ivory Coast)	☐ Senegal
☐ Panama	☐ Egypt	☐ Sierra Leone
☐ Paraguay	☐ Equatorial Guinea	☐ South Africa
☐ Peru	☐ Ethiopia	☐ South Sudan
☐ Suriname	☐ Gabon	☐ Sudan
☐ Trinidad	☐ Gambia	☐ Togo
☐ Venezuela	☐ Ghana	☐ Uganda
☐ None of the countries listed above: _____		

FOR OFFICIAL USE ONLY

Instructions for Biosecurity Officers of the Department of Agriculture and Water Resources.

1. Ask the traveller to complete the survey form before issuing any advice about Yellow Fever.
2. As completion of the survey is strongly encouraged but not mandatory, please make a note of the number of refusals so the total number of travellers offered the survey can be assessed.
3. Once the survey is completed, present the traveller with the Yellow Fever Action Card.
4. Scan and email the completed survey form within 7 days to humanbiosecurity@health.gov.au

Thank you for your assistance with this important work.

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CHAPTER 6

Evaluation of the traveller with illness checklist surveillance system for listed human diseases at the Australian border

**Australian Government Department of Health
Office of Health Protection**

“We live in a world at constant risk of public health emergencies. In our increasingly interconnected world, public health emergencies can affect anyone, anywhere”

Tedros Adhanom

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ABBREVIATIONS

ACT	Australian Capital Territory
DAWR	Australian Government Department of Agriculture and Water Resources
CHBO	Chief Human Biosecurity Officer
HBO	Human Biosecurity Officer
DoH	Australian Government Department of Health
LHD	Listed Human Disease
MERS	Middle East respiratory syndrome
NSW	New South Wales
NT	Northern Territory
PPV	positive predictive value
Q	Question
QLD	Queensland
The Act	Biosecurity Act 2015
TIC	Traveller with Illness Checklist
SA	South Australia
SARS	severe acute respiratory syndrome
TAS	Tasmania
UAE	United Arab Emirates
USA	United States of America
VHF	viral haemorrhagic fever
VIC	Victoria
WA	Western Australia

PROLOGUE

Study rationale

The traveller with illness checklist (TIC) system is a surveillance measure at the Australian border with the purpose of identifying people with signs of a listed human disease (LHD). The list currently includes: human influenza with pandemic potential; Middle East respiratory syndrome; plague; severe acute respiratory syndrome; smallpox; viral haemorrhagic fevers; and yellow fever. The TIC is administered by Biosecurity Officers at the Australian points of entry. When they identify a potential risk, they contact a Human Biosecurity Officer for further instructions. In a meeting of the Chief Human Biosecurity Officers (CHBO) concerns were raised regarding several unnecessary calls and perceived inconsistencies between jurisdictions. Summary data are neither routinely collected from the surveillance system nor analysed, and therefore it is not known how efficiently the system works. It should be emphasised that this evaluation did not seek to, nor was able to, assess the effectiveness of the TIC as a tool to detect LHDs. The purpose of the evaluation was to assess the operational process of the tool currently in use at the Australian border.

My role

My role was to review the TIC notifications collected from the first year of operation under the new *Biosecurity Act 2015*. I extracted the data and performed descriptive analysis and visualisation of the results. Data on travel volumes to each jurisdiction and ports of origin were also obtained from the Department of Home Affairs, as provided by the Australian Bureau of Statistics. The findings of my analysis were presented in a report for the Commonwealth Department of Health and subsequently distributed to the jurisdictions through the CHBOs.

Lessons learned

For being a relatively simple project, it identified several areas of improvement. I was amazed at how many ways a form can be completed incorrectly, despite having seemingly very clear instructions. For something as critical as screening for LHDs, there was a surprising variety in exactness of the details provided in many cases. It provided an insight into how the form could be misinterpreted and ways to minimise this occurring in the future.

Screening for LHD is complex, and several of these diseases have symptoms that are indistinguishable from many other diseases. This is compounded by the different needs and levels of risk between jurisdictions, as some will have more flights arriving from areas with higher risk of LHDs. This becomes a challenge for a unified system that is intended to operate Australia-

wide. It was therefore somewhat of a surprise that while data are collected, the information is not used for ongoing evaluation of the operation of the system.

After conducting the project, I have a better understanding of the legislation that governs the border operations and that the surveillance system is subject to. This includes the international obligations to screen for specific diseases, the operational aspects of both Australian officials and operators of aircraft/vessels arriving to the border, and the legislative process to make changes to aspects of the surveillance system, such as adding another LHD.

Public health implications

The project uncovered some concerns with the surveillance system as it currently operates. The aspect that underpinned most of these concerns was the poor data quality, with missing or erroneous data or decision making. The implications of this ranged from innocuous - where minor non-critical data were missing - to severe, where an assessment of risk was unable to be made due to missing data. Peculiar fluctuations in the frequency of TIC were also observed, possibly indicating TICs that were completely missing.

With regards to contact with HBOs the project identified several unnecessary calls. For some situations there were plausible reasons from a public health point of view for the Biosecurity Officer to inform the jurisdiction. However, the HBO is not the appropriate contact in such instances. This led to the recommendation that there needs to be an alternative pathway for the Biosecurity Officers to raise non-LHD communicable disease issues of public health concern, such as a *pro forma* email to a public health unit in the relevant jurisdiction.

The project also identified instances of missed cases of potential LHDs. This is a critical error, and in some cases thought to have been a consequence of misinterpretation of the TIC forms. To reduce the possibility of interpretative errors and to improve the data quality of the surveillance system, the overarching recommendation arising from the project was to transition to an electronic system. It is proposed that this system is an application-based system designed for use on secure tablet-style personal devices. The application would require compulsory completion of data, have an automatic decision tree and provide exact instructions for contacts, and incorporate a feature for referring non-LHD public health concerns.

Acknowledgements

Big thanks Rhonda Owen, Joel Willis and Susan Gavin for their supervision in this project. And thanks to Callum Mack for helping to dissect and discuss the findings of the study. I appreciate the advice from Anna Colwell with regards to the medical aspects of the project. Thanks also to

the Border Health team for all helping with random questions and for being a fun group to work with.

MAE core activity requirements

The MAE core activity requirements fulfilled in this project was: Evaluation of a surveillance system.

ABSTRACT

Background: The traveller with illness checklist (TIC) system is a surveillance measure at the Australian border with the purpose of identifying people with signs of a listed human disease (LHD). The list currently includes: human influenza with pandemic potential; Middle East respiratory syndrome; plague, severe acute respiratory syndrome; smallpox; viral haemorrhagic fevers; and yellow fever. The evaluation sought to assess the effectiveness and inter-jurisdictional consistency of the TIC surveillance system for LHDs at the Australian border over the course of the first year of operation under the *Biosecurity Act 2015*.

Methods: TICs submitted to the Department of Health from 1 July 2016 to 30 June 2017 were selected for review. Data from the TICs were extracted and collated in an Excel™ document for statistical analysis.

Results: A total of 533 TICs were submitted to the Department of Health over the study period. 47% of TICs were for travellers arriving from Singapore, Indonesia or Malaysia. For 31 of the 533 TICs the Biosecurity Officer contacted a Human Biosecurity Officer (HBO) for advice. Of these, 14 contacts were not indicated according to the information provided in the TIC. There were eight instances where an HBO was not contacted despite being indicated by the TIC. Both the sensitivity and positive predictive value were poor, at 68% and 54.8%, respectively. Queensland had the highest overall number of TICs (n=144). Western Australia and South Australia had the highest rate of TICs, 44.8 and 43.8 per million arriving travellers, respectively. Victoria had the highest number (n=13) and proportion (9%) of TICs resulting in an HBO contact. There were data quality issues identified, with 29% of the 533 TIC forms in some way incorrectly filled or incomplete. For 30 TICs crucial information was missing such that an assessment of risk could not be made. Western Australia and Queensland showed a slow uptake of new TIC versions.

Conclusions: A number of problems were identified with regards to the completion of the TIC form, which affected the data quality. There were also problems related to the decision process of the TIC, with both unnecessary HBO contacts, and instances of missed contacts. The evaluation found that a pathway for Biosecurity Officers to make notifications of non-LHD issues of public health importance is required.

Recommendations: A significant number of the problems identified in this evaluation could be resolved with the transition to an electronic version of the TIC. It is proposed that an application be developed for use on secure tablet-style personal devices. Suggested features include compulsory completion of questions, automatic triggering of HBO contact following the decision tree, automatic emailing of completed forms, and option to refer non-LHD information of public health interest to relevant public health units.

1 BACKGROUND

The increased frequency, ease and speed of international air travel poses some significant public health threats in terms of the spread of serious communicable diseases. Of main concern in Australia are the Listed Human Diseases (LHDs) as determined by the Director of Human Biosecurity, a list that as at 1 August 2018 consists of:

- Human influenza of pandemic potential
- Middle East respiratory syndrome (MERS)
- Plague
- Severe acute respiratory syndrome (SARS)
- Viral haemorrhagic fever in humans (VHF)
- Smallpox
- Yellow fever

To prevent the introduction and spread of LHDs in Australia, a range of human biosecurity activities are implemented pre-border, at the border and post-border. This proposal relates to activities at the latter two points.

The Australian Government Departments of Health (DoH) and Agriculture and Water Resources (DAWR) share the responsibility for the administration of the *Biosecurity Act 2015* (the Act), implemented on 16 June 2016.⁽¹⁾ Under the Act, ill travellers suspected of having an LHD, or of being exposed to an LHD, are assessed at the Australian border. An ill traveller, who is reported as ill by the crew of an incoming aircraft or vessel, or who declares being ill on arrival, will be interviewed by a Biosecurity Officer from DAWR. The Biosecurity Officer will administer a Traveller with Illness Checklist (TIC) form (**Appendix 6A**), which contains a series of questions to assess whether the traveller may be sick with an LHD. If the TIC indicates that the traveller may have an LHD, they will contact a Human Biosecurity Officer (HBO) in the appropriate jurisdiction. HBOs are medical professionals within jurisdictional health departments authorised to act on behalf of the Commonwealth in matters of human biosecurity. The HBO will determine what further actions are appropriate. A range of actions are available, such as: no action; advise to seek medical attention if certain symptoms occur; seek immediate medical attention; receive medication/treatment; contact precautions; travel restrictions; and isolation measures.

At the start of the project the surveillance system had been operating under the new *Biosecurity Act 2015* for a year, making it a suitable time point to assess the effectiveness and inter-jurisdictional consistency of the system. The evaluation would also provide an opportunity to investigate concerns regarding perceived unnecessary HBO contacts raised at the meetings of the Chief Human Biosecurity Officer committee.

2 METHODS

2.1 Study population and data source

The study population was composed of all travellers arriving at Australia's international border, who were administered the TIC. All TIC notifications submitted to DoH with assessment dates between 1 July 2016 and the 30 June 2017 were reviewed.

2.2 Travel volume data

Data on volume of arriving travellers were obtained from the Overseas Arrivals and Departures dataset provided by the Department of Home Affairs and hosted by the Australian Bureau of Statistics. The data were provided by financial year, with the 2016/2017 data used in this study. It is available at: <https://data.gov.au/dataset/5a0ab398-c897-4ae3-986d-f94452a165d7/resource/968a84fb-e4f4-4c0b-8359-e60adb8329d5/download/bp0022-oad-abs-revised-pivot-2016-17.xlsx>

2.3 Assessment of surveillance system attributes

Part of the evaluation was conducted using the *Updated Guidelines for Evaluating Public Health Surveillance Systems* published by the Centers for Disease Control and Prevention (CDC) which is based on the CDC's *Framework for Program Evaluation in Public Health*. (2)

The available data allowed assessment of four of the nine key system attributes, shown in **Table 1**. The remaining five attributes: simplicity, acceptability, representativeness, timeliness and stability, would require additional data to be collected. The findings from this study could be used to inform and target interviews of stakeholders in the system, such as HBOs and Biosecurity Officers, to evaluate the attributes of simplicity and acceptability. To evaluate representativeness, timeliness and stability I would propose an ongoing monitoring and analysis of the TIC data collected.

Table 1 Attributes assessed in the CDC Guidelines.

Attribute	Definition
Flexibility	<i>A flexible public health surveillance system can adapt to changing information needs or operating conditions with little additional time, personnel, or allocated funds. Flexible systems can accommodate, for example, new health related events, changes in case definitions or technology, and variations in funding or reporting sources. In addition, systems that use standard data formats can easily be integrated with other systems and thus might be considered flexible.</i>
Data quality	<i>Data quality reflects the completeness and validity of the data recorded in the public health surveillance system.</i>
Sensitivity	<i>The sensitivity of a surveillance system can be considered on two levels. First, at the level of case reporting, sensitivity refers to the proportion of cases of a disease (or other health-related event) detected by the surveillance system. Secondly, sensitivity can refer to the ability to detect outbreaks, including the ability to monitor changes in the number of cases over time.</i>
Positive Predictive Value	<i>Positive predictive value (PPV) is the proportion of reported cases that actually have the health-related event under surveillance.</i>

2.4 Data analysis

Analysis and descriptive statistics were done in Microsoft Excel 2010™.

2.5 Ethics and authorisation

The study was approved by the Australian National University Human Research Ethics Committee (protocol number 2017/375). Access to the completed and submitted Traveller with Illness Checklist documents held at the Department of Health was authorised by the Director of Human Biosecurity, the Commonwealth Chief Medical Officer.

3 RESULTS

3.1 Distribution of TICs in Australia over the investigation period

The numbers of TICs completed over the year generally follow the annual travel volume pattern, with peaks in January, April and September/October (**Figure 1A**). The proportion of TICs resulting in an HBO contact remained relatively consistent throughout the investigation period. Victoria, Queensland, Western Australia and New South Wales had the largest number of TICs and were the only jurisdictions with TICs resulting in HBO contacts (**Figure 1B**). Queensland had a markedly lower ratio of TICs with HBO contacts, compared with the three other jurisdictions (**Table 2**).

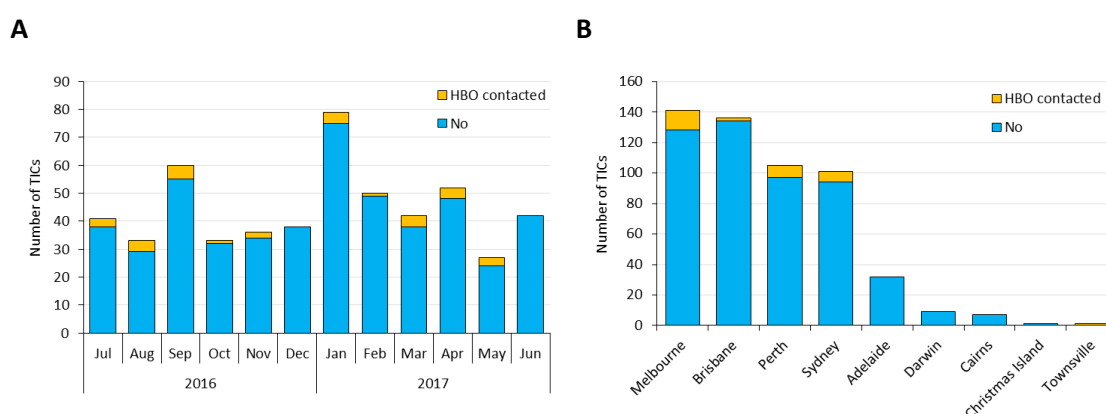


Figure 1 Overall number of TICs distributed by month (panel A) and by airport location (panel B).

Arrival data for each jurisdiction from 1 July 2016 to 30 June 2017 were extracted from the Home Affairs public dataset. The data were used for contextual purposes with totals for each jurisdiction presented in **Table 2** and the monthly breakdown used in **Figure 2**. Western Australia and South Australia had the highest rate of TICs, 44.8 and 43.8 per million arriving travellers, respectively. Despite having the highest travel volumes New South Wales had the lowest rate of TICs in the country.

Table 2 Number of TICs in relation to number of arrivals, by jurisdiction.

Location	Number of arrivals	TICs	TICs per million travellers	HBO contacts	Proportion of TICs with HBO contact
NSW	7,131,623	101	14.2	7	7%
VIC	5,049,121	141	27.9	13	9%
QLD	3,719,657	136 (144) [†]	36.6 (38.7) [†]	2 (3) [‡]	1% (2%) [‡]
WA	2,341,275	105	44.8	8	8%
SA	729,762	32	43.8	0	0
ACT	282,348	0	0	0	0
NT	206,576	9	14.5	0	0
TAS	167,706	0	0	0	0
Christmas Is.	N/A	1	0	0	0
AUSTRALIA	19,628,068	533	0	31	0

[†] First number is TICs from Brisbane airport, and number in brackets is with 7 additional TICs from Cairns and 1 TIC from Townsville.

[‡] First number is referred TICs from Brisbane airport, and number in brackets is with 1 additional referred TIC from Townsville.

3.2 Distribution of TICs by location over the investigation period

The patterns of TICs follow the travel volume pattern in most jurisdictions (**Figure 2**). There is an unexpected dip in the number of TICs from Perth international airport in October and November 2016, for which there is no apparent reason. It is possible that not all TICs completed during this period were submitted to DoH. From locations with low volume travel, the consistency with travel volume patterns is less apparent. In jurisdictions that had TICs resulting in HBO contact, the distribution of these events was even throughout the investigation period.

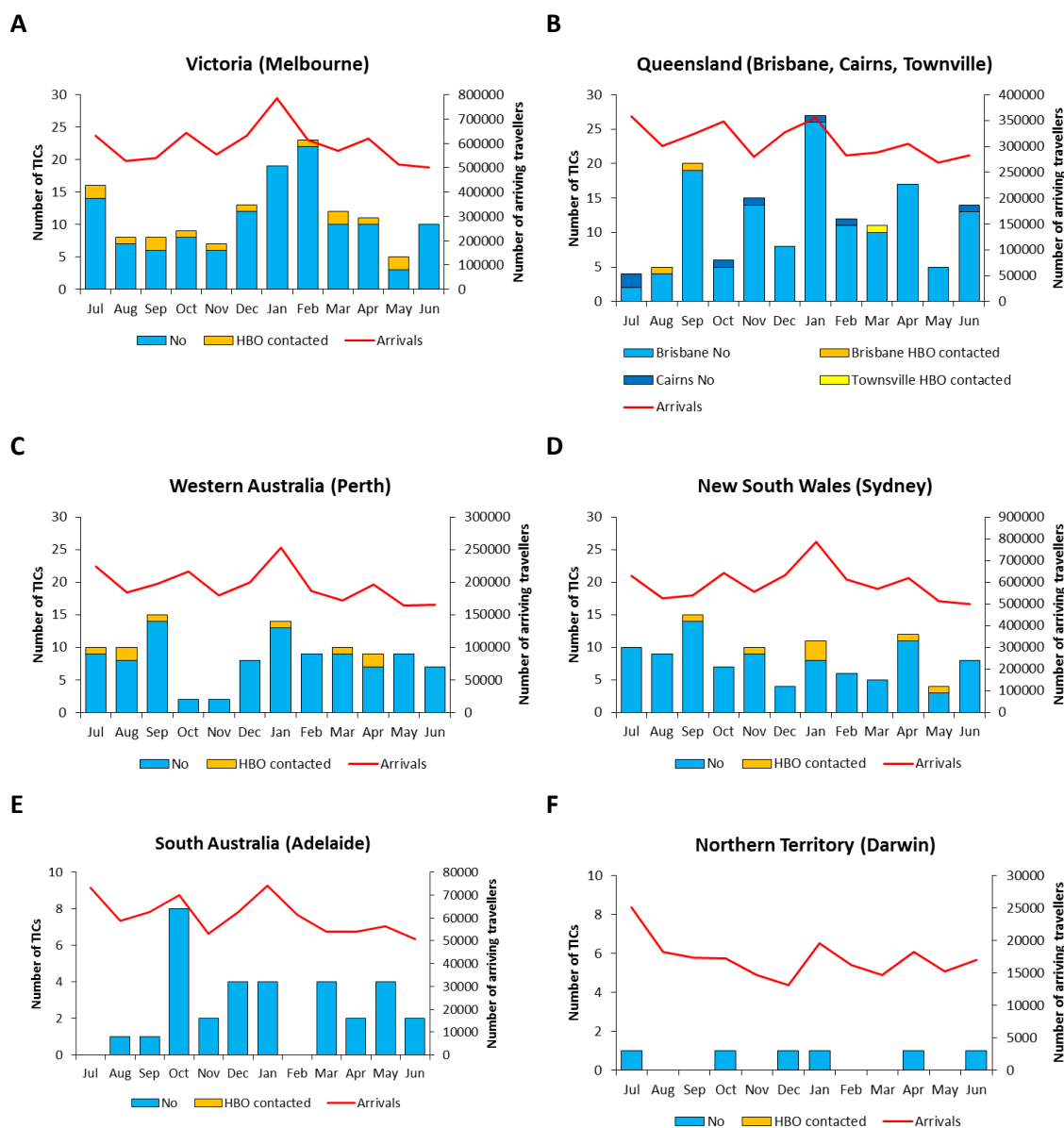


Figure 2 For each jurisdiction the number of TICs and number of TICs resulting in HBO contact are presented, together with the number of arriving travellers, by month in the investigation period 1 July 2016 to 30 June 2017. Jurisdictions are presented in decreasing order of number of TICs. Panel B includes data from airports in Brisbane, Cairns and Townsville. Please note the change in scale of the left-hand axis in panel E and F compared with panels A-D.

3.3 TICs and contacts with Human Biosecurity Officers

The Traveller with Illness Checklist is designed to provide a step-by-step process to assist a Biosecurity Officer in determining whether a HBO should be notified (**Appendix 6A**). A flow chart of the decision tree is presented in **Figure 3**.

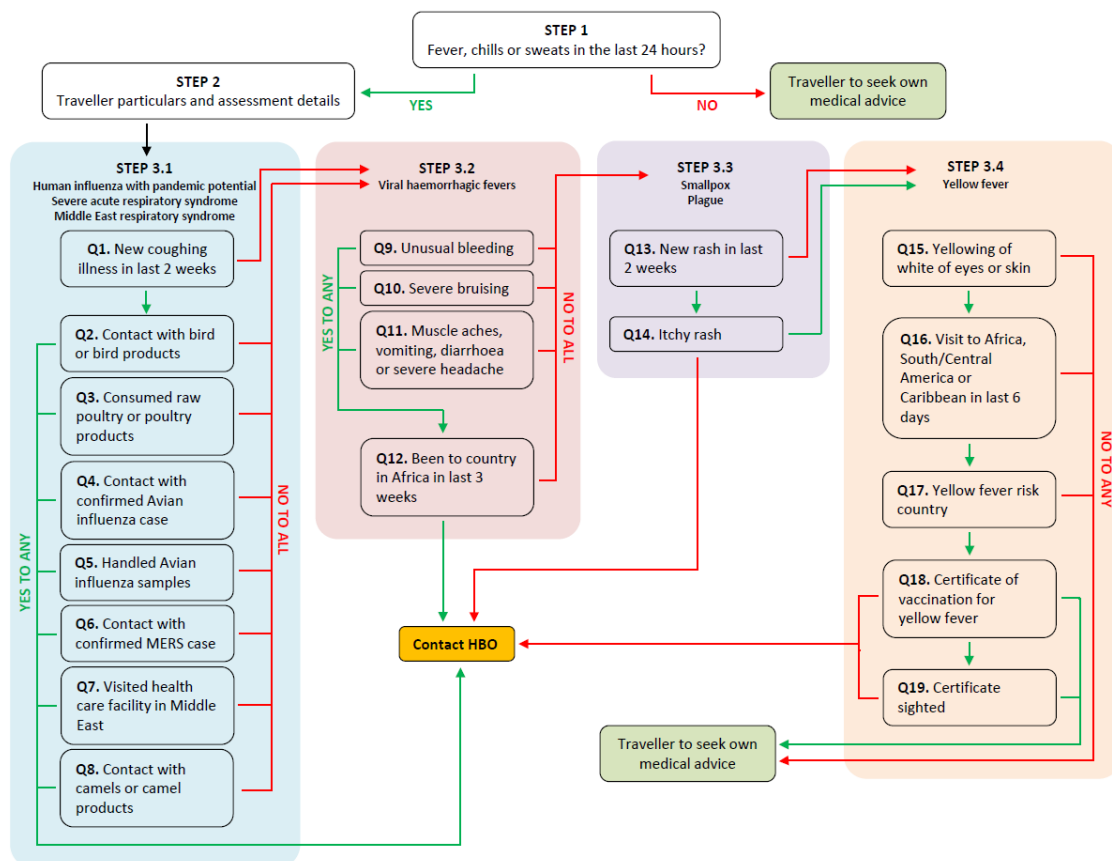


Figure 3 Decision tree for Traveller with Illness Checklist, based on version 10 (May 2016). Green arrows indicate “Yes” and red arrows indicate “No”. Stated at each step is the listed human disease(s) that the line of questions is aimed to screen for. Severe acute respiratory syndrome and plague do not have a specific line of questions but present with symptoms that would be captured by various questions in the TIC.

3.3.1 Instances where HBO was contacted

For the first year of operation under the Act, there were 31 instances where an HBO was contacted. In 17 cases the contact was indicated by the TIC and in 14 cases it was not, according to the TIC decision tree (summarised in **Table 3**). **Figure 4** shows that in Sydney and Melbourne airports the majority of referred TICs fell in the latter category.

For two of the cases in **Table 3**, it was appropriate, from a public health perspective, for the Biosecurity Officer to inform the jurisdiction of two active infections, typhoid fever and chikungunya fever. However, the HBO may not be the appropriate contact, and there is no immediate urgency warranting contacting the “on-call” medical officer as any follow-up (laboratory verification, advice to minimise spread) will be done during office hours the following day. For this evaluation these situations were discussed with a Medical Officer in the Medical and Scientific Advisory Unit, at DoH.

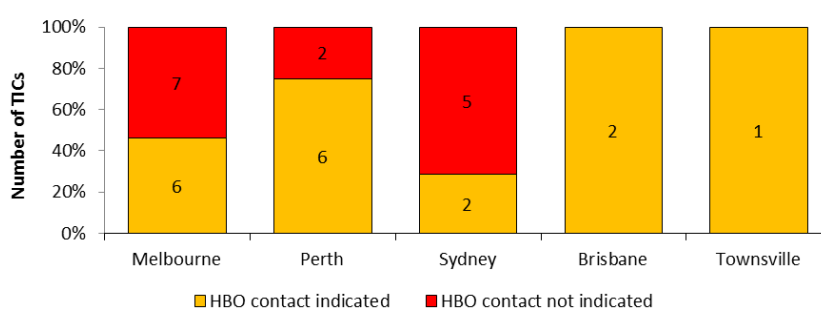


Figure 4 Proportion of TICs where HBO contact was indicated and not indicated, by jurisdiction. Number of TICs stated within each bar.

3.3.2 Instances where HBO should have been contacted

There were 8 instances where an HBO was not contacted despite the TIC indicating this course of action (**Table 4**). These instances are potentially serious as a traveller with an LHD could be missed. There were two instances where young passengers presented with non-itchy rash on torso, fever and headache, one of which also had a runny nose. The questions regarding rash (Q13 and Q14) are designed to capture smallpox, and while it is highly unlikely that there would be a case of smallpox presenting at the Australian border, if it did occur, it would be a result of deliberate release and critical to capture. The two passengers presenting here are more likely to have active measles infections, and although it is not an LHD, it is of public health interest and requires significant follow-up.

In three other cases, the Biosecurity Officer made the decisions that the non-itchy rash symptoms were innocuous (resulting from food allergy, bicycle riding or confirmation by parents

that it was normal for their child). In these cases, the Biosecurity Officer was probably correct. However, it is the role of the medically trained HBO to make this judgement, not the Biosecurity Officer at the border.

The five instances above, all relate to a positive response to Question 13 (new rash) and a negative response to Question 14 (*"Is the rash itchy?"*). This question, along with the two regarding yellow fever certificates (Q18 and Q19) are the only occasions where a negative response prompts the Biosecurity Officer to contact an HBO. This might be somewhat counterintuitive, particularly since for most questions a negative answer leads to the continuation of the questionnaire. The five instances above may have been accidental oversights by the Biosecurity Officers. With regards to the two yellow fever certificate related questions a negative response prompting an HBO contact is more intuitive.

The three remaining passengers indicated contact with birds or bird products which, in conjunction with a positive response to a new coughing illness (Question 1), indicates a possibility of influenza with pandemic potential. In two of these cases there was no response to Question 1, but according to the instructions of the TIC if the response is "No" to this question, the remaining questions of this step should be skipped. As they have been completed, one must presume a positive answer to Question 1.

3.3.3 Instances with crucial information missing

Thirty TICs were incomplete with regards to crucial information or questions such that an assessment of risk was not able to be made. It means that these passengers could potentially be carrying an LHD and pose a risk to Australia. While this is highly unlikely, it is undesirable to have a substantial number of TICs missing important information.

Table 3 Instances where HBO was contacted despite the TIC form not indicating this course of action. Statements within quotation marks were written on the TIC form by the Biosecurity Officer.

Airport	Symptoms	Age	Origin of travel	Yes to questions	Additional comments from Biosecurity Officer
Perth	"Just headache presently" "Joint pain"	69 years	Sydney (domestic)	Q11 (headache)	"Recently: 1 week in Thailand, 5 days in India" "Had scrub typhus about 5 years ago"
Perth	"Fever, vomiting, diarrhoea, lethargic, headache" "Severe pain – UTI treated" "Unable to walk – dizzy"	65 years	Singapore	Q11	"Several symptoms" written in Step 4, purpose of contact.
Melbourne	"Fever, vomiting"	2 years	China	None	"Ambo's coming to assess child and take him to hospital"
Melbourne	No information	27 years	Hawaii	Q11 and Q15	"Ambulance called"
Melbourne	"Fever" "Diagnosed as typhoid fever by Indonesian Dr"	24 years	Indonesia	None	"Name and phone number taken by Dr Cheng. Traveller to expect call from DHHS"
Melbourne	"Rash"	34 years	Jordan	Q13 and Q14	Only notes following the conversation with HBO. "Spent 2 weeks in Jordan. Has been on a camel in Jordan. Does have mosquito bites. Mild, only a few spots located (not blotchy or sweats). No fever, chills or sweats. No cold symptoms prior to rash developing. No vomiting or diarrhoea. No visit or contact with any hospitals or medical centres"
Melbourne	No information	57 years	Egypt	Q1 and Q11	Nil
Melbourne	"Rash"	29 years	Malaysia	Q13 and Q14	Nil
Melbourne	"Rash, fever"	4 years	Malaysia	Q13 and Q14	Nil
Sydney	"Fever" "Dr in India diagnosed Chikungunya fever"	54 years	India	Q11	"Alliance Insurance will Medivac patient to Armidale. Passenger will be hospitalised tomorrow in Armidale"
Sydney	"Chills, vomiting, diarrhoea"	22 years	Chile	Q11 and Q16 Visited Venezuela No yellow fever certificate	Final destination Gold Coast. Passenger had visited Venezuela and was not immunised against yellow fever. However, did not have any symptoms in Q15.
Sydney	"Advised influenza"	64 years	Singapore	Q1 and Q11	"Advised influenza, and that passenger had a H1N1 swab test done"
Sydney	"Fever, vomiting"	22 years	Nepal	Q11	Nil
Sydney	"Fever"	<1 years	Germany	None	Nil

Table 4 Instances where HBO was not contacted despite the TIC form indicating this course of action. Statements within quotation marks were written on the TIC form by the Biosecurity Officer.

Airport	Symptoms	Age	Origin of travel	Questions indicating HB contact	Additional comments from Biosecurity Officer
Perth	<i>"Fever, headache, runny nose"</i>	9 years	Singapore	Non-itchy rash on torso. (Yes to Q13 and No to Q14)	Underlined "severe headache" in Q11. <i>"Travelled on cruise (15 day) – visited Thailand, Malaysia, Singapore"</i>
Perth	<i>"Fever, chills, sweats, vomiting, diarrhoea"</i>	39 years	Indonesia	Non-itchy rash in groin. (Yes to Q13 and No to Q14)	<i>"Heat/sweat rash. Pushbike riding"</i> written on human outline in Q14.
Melbourne	<i>"Fever (>48h ago), weight loss (>48h ago), rash"</i>	4 years	Indonesia	Non-itchy rash on cheek and torso. (Yes to Q13 and No to Q14)	Assessment done on 11 th Sept 2016. <i>"When: 3rd nausea, stomach ache, vomiting, blood in stools. Lethargy and fever 39.2 on 8th. Weight loss and rash presented on face on 10th, has moved to torso."</i>
Melbourne	No information	3 years	New Zealand	Contact with birds or bird products. (Yes to Q1 and Q2) TIC also indicates an itchy rash.	<i>"Feeding"</i> written by Q2
Sydney	<i>"Fever"</i>	24 years	Singapore	Contact with birds or bird products. (Yes to Q2, presumably Yes to Q1 but not completed)	Nil
Brisbane	<i>"Fever"</i>	4 years	Singapore	Non-itchy rash around mouth. (Yes to Q13 and No to Q14)	<i>"Food allergy rash"</i> written on human outline in Q14.
Brisbane	<i>"High fever"</i>	1 years	Taiwan	Non-itchy rash on bottom. (Yes to Q13 and No to Q14)	<i>"Normal blanching red dots like dermatitis. Has suffered before + parents said is normal". "Started about 1hr into flight ~7 hrs ago. Father had been suffering bronchitis, tonsillitis + fever"</i>
Adelaide	<i>"Fever, vomiting"</i>	52 years	Indonesia	Contact with birds or bird products. (Yes to Q2, presumably Yes to Q1 but not completed) TIC also indicates a rash, but no response to whether it was itchy or not. (Yes to Q13, but no answer to Q14)	Nil

3.4 TICs and origin of travel

Nearly half (47%) of the TICs were completed for passengers arriving from Singapore, Indonesia or Malaysia (**Figure 5**). These three countries also accounted for 35% of the TICs resulting in HBO contact. It should be noted that several of the origins are travel hubs, Singapore and Dubai in particular but also Kuala Lumpur, and therefore these may represent a range of origins in turn. In only a very few circumstances was multiple origins stated on the TIC form, allowing trace back to the true point of origin of the travel. This means that the number of TICs may not necessarily reflect the risk profile of these transport hubs.

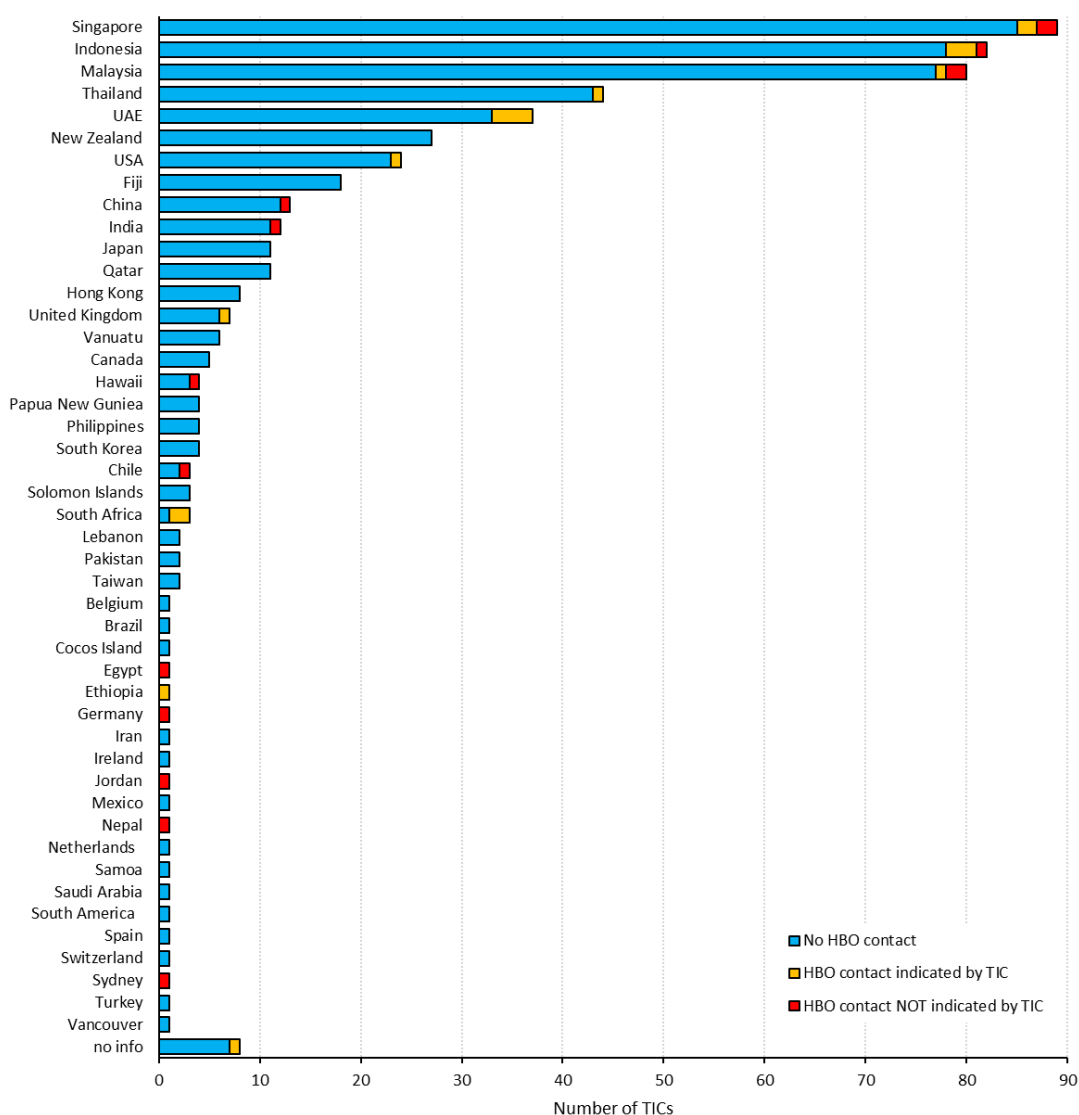


Figure 5 TICs according to origin of travel. Red bars indicate instances where HBOs were contacted without any indications. UAE = United Arab Emirates, USA = United States of America.

The individual jurisdictions display a generally similar pattern to the national pattern in **Figure 5**, with the top five countries being Singapore, Indonesia, Malaysia, Thailand and UAE (**Figure 6**). Victoria and Western Australia were dominated by a small number of countries, while for Queensland and New South Wales the TICs were distributed more evenly over a larger number of countries.

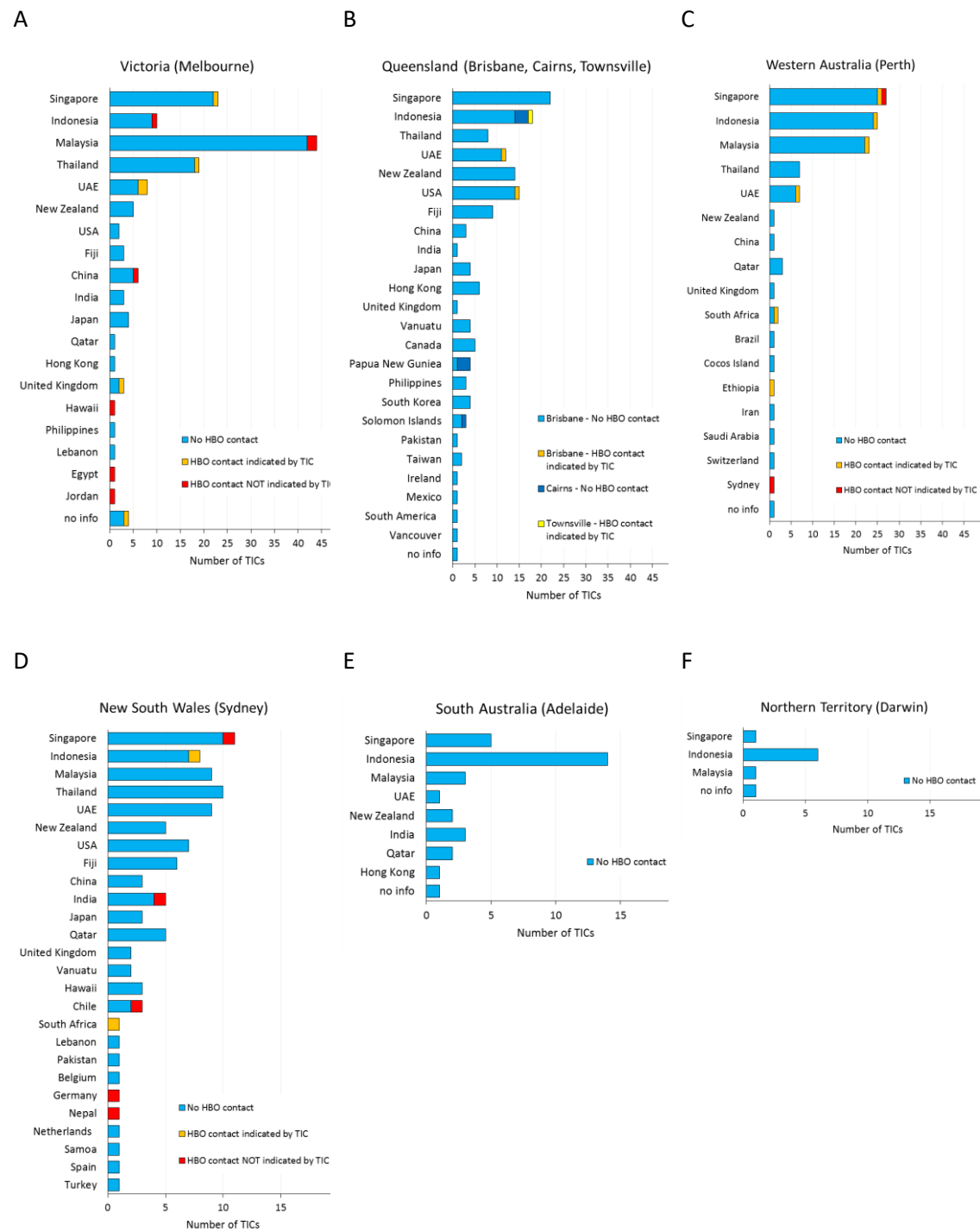


Figure 6 TICs according to origin of travel, by jurisdiction. Note change in scale of x-axis in panels D, E, F. UAE = United Arab Emirates, USA = United States of America.

In Queensland there is a notable absence of TICs from Malaysia, despite this jurisdiction having more than 100,000 arrivals per year from there (**Table 1** and

Figure 7). In all other jurisdictions (that had TICs) there were TICs generated for travellers from Malaysia. Even with conservative estimates of 5 per 100,000, one would expect 5 TICs during this period. Given that Queensland generally has relatively high rates of TICs compared with other jurisdictions, the rate would be expected to be even higher. The reason for this absence of TICs from Malaysia remains unclear.

As the number of TICs generated for travellers from a particular country may in part be due to the volume of travel from the country, the rate is more informative (**Table 5**). Despite having the highest number of arriving travellers of the five countries, Singapore has consistently moderate rates in all jurisdictions.

Figure 7 shows high rates of TICs for travellers from Indonesia at 16.4, 11.4 and 10.3 per 100,000 travellers, for South Australia, Northern Territory and Queensland. High rates were also observed for Malaysia in Victoria (11.4 per 100,000), and Thailand in Western Australia (9.8 per 100,000).

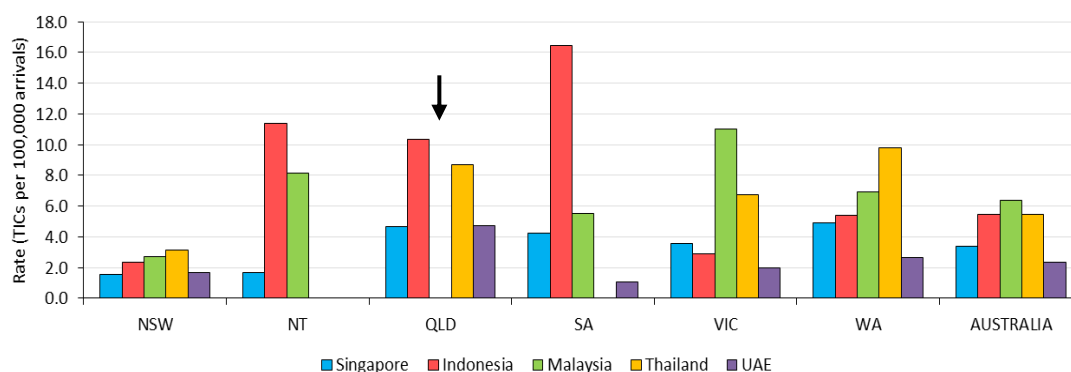


Figure 7 Rate of TICs for the countries resulting in the highest number of TICs. The black arrow indicates a notable absence of TICs from Malaysia in Queensland, despite a large number of arriving travellers from this country.

Table 5 Number of arriving travellers, number and rate of TICs for the five countries with the highest number of TICs. Rate expressed as TICs per 100,000 arriving travellers.

	Singapore			Indonesia			Malaysia			Thailand			United Arab Emirates		
	Arrivals	TICs	Rate	Arrivals	TICs	Rate	Arrivals	TICs	Rate	Arrivals	TICs	Rate	Arrivals	TICs	Rate
ACT	42,631	0	-	11,812	0	-	11,817	0	-	14,383	0	-	22,978	0	-
NSW	714,998	11	1.5	341,737	8	2.3	330,367	9	2.7	316,985	10	3.2	528,156	9	1.7
NT	58,687	1	1.7	52,629	6	11.4	12,242	1	8.2	1,992	0	-	5,895	0	-
QLD	469,585	22	4.7	173,932	18	10.3	107,517	0	-	92,269	8	8.7	255,026	12	4.7
SA	117,570	5	4.3	85,117	14	16.4	54,396	3	5.5	100,663	0	-	95,646	1	1.0
TAS	26,268	0	-	8,797	0	-	8,552	0	-	7,385	0	-	16,189	0	-
VIC	649,624	23	3.5	324,478	10	2.9	399,403	44	11.0	282,166	19	6.7	398,538	8	2.0
WA	548,796	27	4.9	461,403	25	5.4	332,747	23	6.9	71,655	7	9.8	263,655	7	2.7
Australia	2,628,160	89	3.4	1,477,906	81	5.5	1,257,094	80	6.4	801,911	44	5.5	1,586,090	37	2.3

3.5 Notifying entity

Operators of an arriving aircraft or vessel are granted positive pratique* automatically (division 4, section 48 of the Biosecurity Act 2015), but are subject to pre-arrival reporting procedures by exception (section 193 of the Biosecurity Act 2015).(1) This means that they must inform the airport or port of any ill travellers or deaths, and wait for pratique to be granted by a Biosecurity Officer or a Human Biosecurity Officer following an assessment (manual pratique process, division 4, section 49 of the Biosecurity Act 2015).(1)

In some instances, an ill traveller will go unreported, and is instead identified by other entities at the airport, such as the Australian Border Force or personnel in other areas of the airport or port. Adelaide and Perth airports had relatively high proportions of TICs that were notified by non-operator entities (**Figure 8**). Sydney and Melbourne airports have the largest travel volumes, and also have the best compliance with the pre-arrival reporting requirements. For the jurisdictions with smaller travel volumes the notifications were much more likely to be from a non-operator entity, although small number of TICs may influence this.

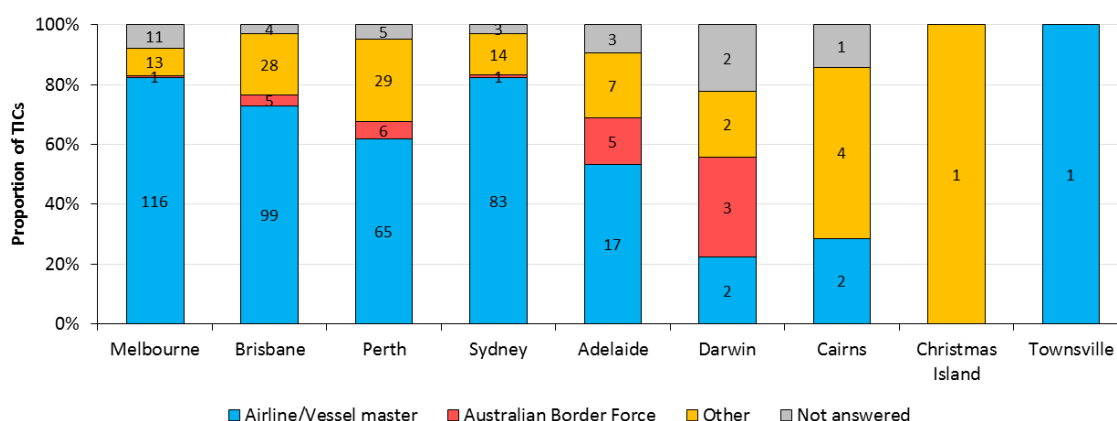


Figure 8 Entity that made the initial notification of the ill passenger to the Biosecurity Officer, as a proportion of all TICs in respective jurisdiction. As the number of TICs varied significantly between jurisdictions, stated inside each bar is the number of TICs the proportion represents.

* In the context of the Biosecurity Act 2015, pratique is the granting of permission to allow: any thing to be unloaded from or loaded onto the aircraft or vessel; or for any person to disembark from or embark onto the aircraft or vessel.

3.6 Versions of TIC used

Updates of the TICs are used to adapt the form to new situations and to clarify the content. Rapid adaptation of new versions is important to ensure high data quality and consistency across jurisdictions. Version 10 of the TIC was published and distributed in May 2016, and therefore all jurisdictions should have been using this version during the investigation period.

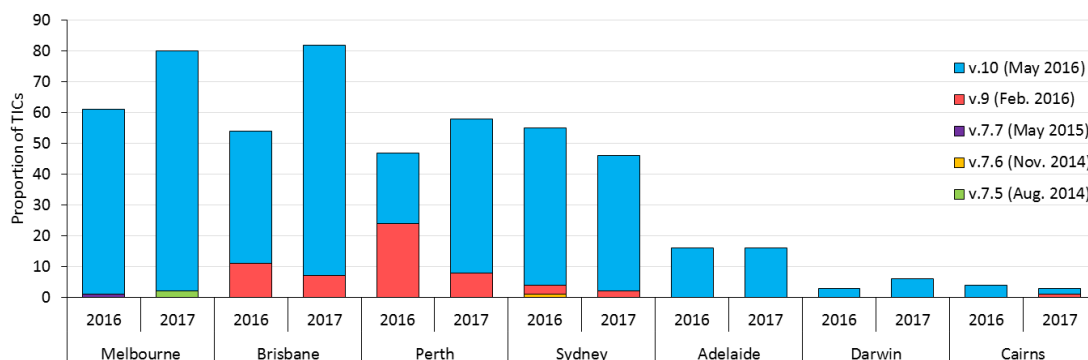


Figure 9 Version of TICs used, by jurisdiction and year. TICs completed for Townsville and Christmas Island are not shown (both used v.10)

However, as these are printed forms to be completed by hand, there may be a wish to “save the trees” and use up old printed forms before switching to the new forms. This behaviour was most evident in Perth, where more than half of the forms completed in July to December 2016 used the old version (**Figure 9**). Still in 2017 more than 10% of the TICs from Perth were on a superseded form. Brisbane showed a similar pattern of slow adaptation, but to a lesser extent. Sydney and Melbourne showed a more rapid uptake of new versions, with only a minor number of superseded forms. This shows the lack of flexibility of a paper-based system, as it takes a long time to get old versions out of the circulation, and it impacts on the ability of the system to quickly adapt to new threats, such as a pandemic. It also indicates a lack of standard operating procedure to effectively remove superseded versions from the system when new versions are released.

3.7 Incorrect completion of TIC form

Of the 533 TIC forms, 156 (29%) were in some way incompletely filled or incorrectly interpreted, resulting in poor data quality. While the form is completed by hand and results in occasional difficulties with legibility, the main issue was insufficient or missing data, or wrong decision-making. Included among the 156 forms are 11 TICs referred to HBO, 2 TICs that should have been referred to an HBO, and the 30 TICs where crucial information was missing, as described in section 3.3.3 of this chapter.

3.7.1 Assessment and passenger demographic details

A total of 125 (23%) TICs had missing data in the assessment and passenger demographics section. This included information such as location of assessment (88), name of reporting Biosecurity Officer (33), notifying entity (14), final destination (12), date of birth (10), origin of travel (8) or nationality (7).

The most common individual item to be incorrectly completed was the “Location of assessment” field. The intended information sought here is the name of the airport as this is the only field that subsequently will identify the geographical location where the assessment was conducted. In most cases when the information is insufficient or missing, it can be deduced from the flight number, email content, signature pane or email address. However, in some cases the Biosecurity Officer’s name or the scanner name had to be used, which requires a bank of previous forms to compare with.

Among the 533 completed TICs collected over the one-year period, 88 (17%) had insufficient or missing information to the field “Location of assessment”. Some of the alternative answers are listed below:

- “Primary line”	- “Gate 58 Aircraft”
- “Luggage carousel”, “Baggage hall”, “Baggage Hall – Carousel 1”	- “Plane”
- “Inspection benches”	- “Flight SQ215”
- “Customs – DOAWR position”	- “Seat 39A”
- “Pre primary Hall B”	- “Bay 61 – on aircraft”
- “Gate 8”, “Gate 76”, “Gate 78”, “Gate 83”	- “On board EK418 @ Bay 61”
	- “On board aircraft – seat 73C”

3.7.2 Problems with scanning of documents

One cause of missing information was missing pages in the scanned document due to single-sided scanning of double-sided original documents. A number of other issues were also observed with the scanned documents, such as low resolution, blank pages (double-sided scanning of single-sided documents) or pages scanned upside down. It would appear that the Biosecurity Officers do not always check the fidelity of the scanning. In worst case scenarios this rendered the scanned document unusable.

4 ASSESSMENT OF SURVEILLANCE SYSTEM ATTRIBUTES

The data extracted from the TICs only allow assessment of a selection of the system attributes used in the CDC *Updated Guidelines for Evaluating Public Health Surveillance Systems*.⁽²⁾

4.1 Flexibility

Definition: A flexible public health surveillance system can adapt to changing information needs or operating conditions with little additional time, personnel, or allocated funds. Flexible systems can accommodate, for example, new health related events, changes in case definitions or technology, and variations in funding or reporting sources. In addition, systems that use standard data formats can easily be integrated with other systems and thus might be considered flexible.⁽²⁾

Flexibility in the surveillance system is offered by production and distribution of new TIC forms from the DoH. This allows adaptation to new communicable disease threats or situations where additional information is required, such as the precautions in response to the 2014 Ebola outbreak in West Africa. The addition of questions to the TIC form can be introduced by the DoH in a timely manner, but the subsequent use relies on rapid uptake and implementation of the new TIC forms by the jurisdictions.

The evaluation observed that the uptake and implementation of new versions of TIC forms varied between jurisdictions (**Figure 9**). Western Australia and Queensland showed slow uptake, with 10% of completed TICs in 2017 using a form that had been superseded for more than 6 months. New South Wales and Victoria had a more rapid uptake, although the latter had two instances in 2017 where forms from 2014 were used, which had been superseded multiple times.

This aspect could be improved with a transition to an electronic format. In such a scenario the Biosecurity Officer would get a notification on their electronic device prompting them to update the application. Such a system would ensure conformity with regards to versions of the TIC and improve the reliability of the data collected. In the absence of an electronic system, adherence to the correct version of TIC could be improved by using a system where the forms are printed only at time of use, where the date stamp of the document must match the handwritten date. The drawback of such a system is the dependency on access to a functioning printer and reliable stocks of paper and toner.

4.2 Data quality

Definition: Data quality reflects the completeness and validity of the data recorded in the public health surveillance system.⁽²⁾

Of the two aspects of data quality, completeness was the most common issue, with the evaluation finding that 29% of the TIC forms submitted to DoH were missing data. This ranged from very minor omissions that would have little impact on the interpretation of the TIC, to more serious instances where whole pages of essential data were missing. These problems resulted from poor note taking and inattention when scanning the handwritten document. Missing data may lead to problems with identifying relevant jurisdictions of potential risk or contact tracing procedures. The details of these instances have been previously detailed in sections 3.7 and 3.3.3 of this chapter.

With regards to the validity aspect of the data quality, it was not without problems. The observation that 14 of the 31 TICs that resulted in contact with an HBO were not indicated by the information provided in the TIC questions the validity of the decision-making of the Biosecurity Officer. The evaluation showed the need for Biosecurity Officers to have a pathway for notification of non-LHD issues of public health importance. The validity aspect is also affected by the instances where Biosecurity Officer chose not to contact an HBO, despite the information in the TIC instructing this to be the appropriate response. In some instances, it could have been a result of misinterpretation of the decision tree following answers to questions (Question 14 in particular). In other instances, the Biosecurity Officer made a clinical decision, and while it was likely to be correct, is not within their professional role.

Both of the data quality aspects could be addressed by transition to an electronic format. A feature of the proposed application would be the compulsory completion of questions, where the Biosecurity Officer is unable to proceed before providing a response (“Don’t know” or “Not applicable” would be permissible options for some information). The application would have an automatic decision tree and prompt the Biosecurity Officer to call a HBO when indicated by the information provided. Upon completion of the form it would be automatically emailed to DoH, omitting the need for the Biosecurity Officer to correctly scan the document. Finally, at the end of the document, there would be a section allowing the Biosecurity Officer to raise concerns of non-LHD nature to the relevant public health authorities.

4.3 Sensitivity

Definition: The sensitivity of a surveillance system can be considered on two levels. First, at the level of case reporting, sensitivity refers to the proportion of cases of a disease (or other health-related event) detected by the surveillance system. Secondly, sensitivity can refer to the ability to detect outbreaks, including the ability to monitor changes in the number of cases over time.(2)

As the evaluation is assessing the functionality of the surveillance system, a positive is defined as a TIC that initiated contact with a HBO, rather than the detection of a LHD. The definitions used for the calculation of sensitivity and positive predictive value are outlined in **Table 6**.

Table 6 Definitions underpinning sensitivity and positive predictive value calculations.

	HBO contacted	HBO contact indicated by TIC	Number of TICs
True positive (TP)	✓	✓	17
False positive (FP)	✓	✗	14
True negative (TN)	✗	✗	494
False negative (FN)	✗	✓	8

$$\text{Sensitivity} = \text{TP}/(\text{TP}+\text{FN}) = 17/(17+8) = 68\%$$

Given the seriousness of the diseases target of the surveillance system, the estimated sensitivity at 68% needs to be improved. The fact that one third of potential LHD cases are not correctly assessed is a cause for concern and could be addressed in an electronic system with an automatic decision tree prompting the appropriate actions of the Biosecurity Officer.

The sensitivity when viewed in terms of monitoring changes to the data captured by the surveillance system could be improved. Implementation of a regular report of the data captured would allow DoH to monitor any changes over time, and investigate the factors influencing these changes. This would be facilitated by the use of an electronic format of the TIC, as these would be much simpler and less work intensive to compile into regular reports.

4.4 Positive predictive value

Definition: *Positive predictive value (PPV) is the proportion of reported cases that actually have the health-related event under surveillance.*(2)

The definitions used for the calculation of positive predictive value are stated in **Table 6**.

$$\text{PPV} = \text{TP}/(\text{TP}+\text{FP}) = 17/(17+14) = 54.8\%$$

The low PPV at 54.8% shows that the system is inefficient with a significant amount of resources being used unnecessarily. The resource in question is the time of the HBO (and the Biosecurity Officer). These unnecessary contacts are viewed particularly poorly when occurring out of office hours (anecdotally from CHBOs). It is unlikely that such calls would generate follow-up measures requiring additional resources. As with several of the other deficits in the system, the poor PPV could be improved by the use of an electronic system with an automated decision tree that assists the Biosecurity Officer by providing clear guidance.

5 DISCUSSION

Firstly, it should be emphasised that this evaluation does not seek to, nor is able to, assess the effectiveness of the TIC as a tool to detect LHDs. Mass screening for diseases at points of entry is notoriously difficult with a very low “hit” rate in relation to the resource requirements, with some historical initiatives resulting in no identified cases.(3-9) Even best-case scenario modelling suggests that screening processes will miss half of the actual cases.(10) Many systems, including the ones used in Australia, rely heavily on visual observation of ill travellers by flight crews or airport officials, or self-reporting of symptoms following in-flight announcements. As mentioned in Samaan *et al*, this may prove to miss a substantial proportion of travellers who did not hear or understood the announcement, or choose to not make a notification. (6) However, as previously mentioned, this is not the subject of the current evaluation. The purpose of the evaluation was to assess the operational process of the tool currently in use at the Australian border.

With close to 20 million travellers arriving at the Australian border each year, there is high probability of a range of communicable diseases being introduced. The purpose of the Traveller with Illness Checklist surveillance system is to identify passenger with diseases that have the potential to cause significant harm to human health. These diseases are specified in the *Biosecurity (Listed Human Diseases) Determination 2016* and currently include seven diseases: human influenza with pandemic potential; Middle East respiratory virus; plague; severe acute respiratory syndrome; small pox; viral haemorrhagic fevers; and yellow fever. When assessing the surveillance system, it is important to keep the above in mind. There are a plethora of pathologic conditions that may cause an arriving traveller to appear ill, which also may have to potential to spread further in the community following introduction to Australia, but are not LHDs, the target of the TIC. (11) The distinction is therefore between identification of LHDs and other communicable diseases of general public health interest. Diseases such as measles, typhoid fever or meningococcal disease, are of high interest to public health units in the jurisdictions as they may require significant public health follow up and contact tracing. Among the 14 of 31 TICs incorrectly referred to an HBO, there were instances where the contact was justified from a public health point of view. However, the HBO may not be the appropriate contact in these situations. This demonstrates the need for a separate mechanism through which a concerned Biosecurity Officer can notify a public health unit in the jurisdiction. This could easily be incorporated as a feature in an electronic version of the TIC, where an option is provided following the completion of the TIC allowing the Biosecurity Officer to send an email to the relevant public health unit.

In the instances where an HBO was contacted at Sydney and Melbourne airports, there were notable proportions (71% and 54% respectively) where contact was not indicated by the TIC. In a small number of cases this may have been warranted from a public health perspective (as discussed above), but for most instances these calls were unnecessary and increased the workload for the HBO. Such phone calls would be even less desirable outside office hours. The data suggest that a review of the internal procedures or additional training would be appropriate at these two locations. Conversely there were situations where the TIC indicated that an HBO should have been called, and the Biosecurity Officer chose not to. Some of these instances were deliberate, where the Biosecurity Officer made a medical judgement that the symptoms were innocuous, which is not desirable as they may not be medically trained. In other instances, these choices may have been the result of mistakes in the interpretation of the decision tree in the TIC. The fact that a negative answer in Question 14 triggers a HBO contact is arguably easy to miss, since up to that point only positive answers have been triggers. Most of these problems would be reduced by the introduction of an electronic version of the TIC, as the application would instruct the Biosecurity Officer what to do.

The rate of TICs completed in different jurisdictions ranged from 14.2 to 44.8 TICs per million travellers. A Biosecurity Officer will always attend and administer a TIC if there is a pre-arrival reporting of an ill traveller by an aircraft or vessel. The difference in rate of TICs observed may be influenced by a range of aspects: i) the culture of pre-arrival reporting of the aircraft/vessel operator, ii) a bona fide difference in risk for arrivals from areas where the LHDs are endemic iii) differences in vigilance and risk perception of airport staff or iv) the demographic of the travellers, e.g. age. There is anecdotal evidence that some budget airline companies have a low number of pre-arrival reporting despite arriving from risk countries. Whether this is due to inexperience or unfamiliarity with Australian requirements or a pressure to minimise turn around-times is unclear. There is a difference in risk between countries. It is much more likely that a traveller will be presenting with a disease if it is endemic or commonly causes outbreaks in the country from which they arrive (e.g. Ebola in Africa, MERS in the Middle East), than if the disease is never seen in the country of origin of travel. An increased vigilance or risk perception by staff at different airports may be indicated by a larger proportion of the notification coming from entities other than the pre-arrival reporting by the airline operators. This risk perception may in turn be affected by the demographic of the travellers arriving from particular points of origin (e.g. young adventure travellers, who are more likely to have visited areas off-the-well-beaten-path).

For some of the frequent points of origin there were marked differences in rates between the jurisdictions. For instance, the rates of TICs from Indonesia in New South Wales (2.3 per 100,000 arrivals) compared to those seen in South Australia (16.4 per 100,000 arrivals), Northern Territory (11.4 per 100,000 arrivals) and Queensland (10.3 per 100,000 arrivals) as shown in **Table 5**. Sydney airport had in general low rates for the top five ports of origins, compared with the three other jurisdictions. This may in part be explained by a lower proportion of TICs notified by non-airline entities. There may be differences in the experience of staff at the different airport, in particular those airports that are only part-time international airports (Adelaide and Darwin). There are also differences in the airline companies that operate into the respective airports, but as a consequence of small numbers especially when further stratifying by notifying entity, no reliable conclusions can be drawn from these data.

The majority of the problems identified with the TIC process in this evaluation would be resolved by transition to an electronic version of the TIC in an application-based format on secure personal devices. The number of secure personal devices required is likely to be relatively small and could form part of the “grab-kit” already used by Biosecurity Officers at the airports. The transition process will incur initial costs in the development of the application and the procurement of devices, but cost will be balanced by an increase in ease of use and reliability of the system as a whole.

There are some limitations to this study, mainly with regards to the lack of interviews with HBOs and Biosecurity Officers. The remarks from HBOs receiving, in their opinion, unnecessary phone calls were relayed through the CHBO committee, and no personal accounts from the HBOs obtained. The HBOs have a reactive role in the surveillance system being the very last component of the system. Interviews with the HBOs might at this stage not have yielded much additional information to that communicated by the CHBOs. I was not able to speak with Biosecurity Officers either to gauge their impressions of the process, which could have provided additional insight into the reasons for HBO contacts, the poor completion rate and concerns regarding the system. However, it was only through this evaluation that the relevant gaps to discuss in the system have been identified. Additionally, the fact that the Biosecurity Officers follow strict working instructions and operate under a different department of the government, adds a layer of inter-departmental political sensitivities to any interview process.

As the findings of the evaluation are disseminated to the CHBOs and DAWR this will trigger the necessary discussions and collection of the valuable information from the HBOs and Biosecurity Officers to further inform the improvements of the system.

6 RECOMMENDATIONS

The primary recommendation stemming from this work is that the TIC be converted to an electronic application, developed for use on secure tablet-style personal devices. It is suggested that the application include the following features:

- Each question must be completed before being able to move to the next.
- As much information as possible is auto-populated. For instance, the name of the Biosecurity Officer and the airport could be captured from logging in to the application or tablet.
- Upon completion (with or without HBO contact) the form is automatically emailed to DoH.
- When responses are such that HBO contact is indicated, a prompt automatically appears with appropriate HBO contact details.
- When HBO contact is prompted, a new section appears where the interaction and decisions can be documented.
- When completed and no HBO contact has been indicated, an option to refer non-LHD information of public health interest appears. It is suggested this takes the form of a *pro-forma* email with a section where the Biosecurity Officer states the concerns and the reason for referral. The email is automatically sent to the relevant public health unit in the jurisdiction.

While the electronic version is being developed, the following recommendations relating to the paper-based form are suggested:

- For Question 14 on the TIC form add “See below” in the “No” box, to guide the Biosecurity Officers attention to the instructions to contact a HBO.
- Articulate what information if required in the “Location of assessment” field (name of airport).
- Instruct all jurisdictions to cease using old versions (pre v.10) of the TIC form (i.e. implement proper version control procedures).
- Biosecurity Officers are to check the scanned document prior to sending to DoH.

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APPENDIX 6A - TRAVELLER WITH ILLNESS CHECKLIST FORM

Please note that this is a slightly updated version (v.13, August 2018) compared with the form used during the project period. Only significant addition to the previous version is the statement on page 1 beginning with “For assessment of ill travellers on aircraft only”

Traveller with Illness Checklist

Step 1: Determine if the person has had a fever, chills or sweats

Ask the ill traveller...

Have you had a fever, chills or sweats in the last 24 hours?

☐ Yes

If **NO** or **DO NOT KNOW** advise the traveller to seek their own medical advice.

If **YES**, continue to **STEP 2**

For assessment of ill travelers on aircraft only

DAWR Policy update as of 23 August 2018:

‘During the biosecurity assessment of an ill traveller on board an aircraft, the aircraft door must be in the closed (but not latched/locked) position’.

During the assessment of the ill traveller on board the aircraft, under Section 48 of the Biosecurity Act, the aircraft has not yet been granted pratique and it is a legislative requirement that the **operator of the aircraft ensures** that individuals **do not** disembark unless permission to do so is given by the attending biosecurity officer or human biosecurity officer.

Failure to do so may result in non-compliance action against the operator of the airline, *which may include a civil penalty of 120 penalty units.*

This policy update is to provide consistency to:

- operational staff
- airline operators, and
- prevent individuals from disembarking the aircraft prior to pratique being granted.

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Step 2: Collect information

Assessment details		
Location of assessment		
Date of assessment		
Was the assessment conducted:	☐ Face to face ☐ Over the phone (vessels only)	
Name Biosecurity officer(s)		
Department of Agriculture was notified of an ill traveller by:	☐ the Airline/Vessel Master prior to disembarkation from the vessel Name of Airline/ Vessel Master: _____ ☐ Australian Border Force ☐ Other If other, please specify: _____ Was non-compliance action against airline recorded? NB: a Non-Compliance Report Notification Form should be completed, where applicable ☐ Yes ☐ No	
What symptoms or information were provided with notification?		
Was a HBO/CHBO contacted?	☐ Yes Provide details at Step 4, page 7.	☐ No No details required.

III Traveller's personal particulars:	
Name (first name and surname)	
Gender	☐ Male ☐ Female ☐ Indeterminate/intersex/unspecified
Date of Birth (dd/mm/yy)	
Nationality	
Flight Number / Vessel Name	
Origin of flight/voyage	
Contact address in Australia	
Contact number in Australia	
Final destination in Australia	
Email address	

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Step 3: Establish if there are other symptoms

Please complete the entire checklist in full. All questions (as indicated) must be asked of the ill traveller and recorded.

Step 3.1: Cough

Ask the ill traveller...	Tick as appropriate		
1) Do you have a new coughing illness, which developed in the last 2 weeks?	☐ Yes ➤ Ask Questions 2 to 8		☐ No ➤ Go to STEP 3.2
2) Have you been in contact with any birds or bird products within the last two weeks (e.g. handling, slaughtering, defeathering, butchering, preparation for consumption)?	☐ Yes	☐ No	☐ Do not know
3) Have you consumed raw poultry or raw poultry products (including blood)?	☐ Yes	☐ No	☐ Do not know
4) Have you been caring for, speaking with, or touching a person who is a suspected, probable, or confirmed Avian Influenza case?	☐ Yes	☐ No	☐ Do not know
5) Have you handled samples (animal or human) suspected of containing Avian Influenza virus in a laboratory or other setting?	☐ Yes	☐ No	☐ Do not know
6) Have you been caring for, speaking with or touching a person who is a suspected or confirmed MERS case while they were ill?	☐ Yes	☐ No	☐ Do not know
7) Have you been in a healthcare facility (as a patient, worker or visitor) while in a country in the Middle East. (Tick appropriate country from list below):	☐ Yes	☐ No	☐ Do not know
☐ Saudi Arabia	☐ Egypt	☐ Iran	☐ Yemen
☐ Iraq	☐ Syria	☐ United Arab Emirates	☐ Bahrain
☐ Jordan	☐ Kuwait	☐ Qatar	☐ Oman
8) Have you touched camels or other bodily fluids, including having been coughed or sneezed on by a camel, or drunk raw camel milk or consumed camel meat in a country in the Middle East?	☐ Yes	☐ No	☐ Do not know

If YES to Questions 2, 3, 4, 5, 6, 7 or 8 immediately contact a Human Biosecurity Officer AND complete **STEP 4**;

OR

If NO or DO NOT KNOW to all of the above continue to **STEP 3.2**.

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Step 3.2: Bleeding and bruising

Ask the ill traveller....	Tick as appropriate	
9) Do you have any unusual bleeding, such as bleeding from the eyes or ears or nose?	☐ Yes	☐ No
10) Do you have any severe bruising?	☐ Yes	☐ No
11) Do you have any of the following symptoms: muscle aches, vomiting, diarrhoea or severe headache?	☐ Yes	☐ No

If **YES** to **any of** Question 9 **or** 10 **or** 11, go to Question

12; OR

If **NO** to Questions 9 **and** 10 **and** 11 continue to **STEP 3.3**.

	Tick as appropriate	
12) Have you been in any country within Africa* in the last 3 weeks?	☐ Yes	☐ No ➤ Go to STEP 3.3

* Not including Egypt

If **YES** to Question 12, immediately contact a Human Biosecurity Officer **AND** complete **STEP 4**;

OR

If **NO** to Question 12 continue to **STEP 3.3**.

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Step 3.3: Rash

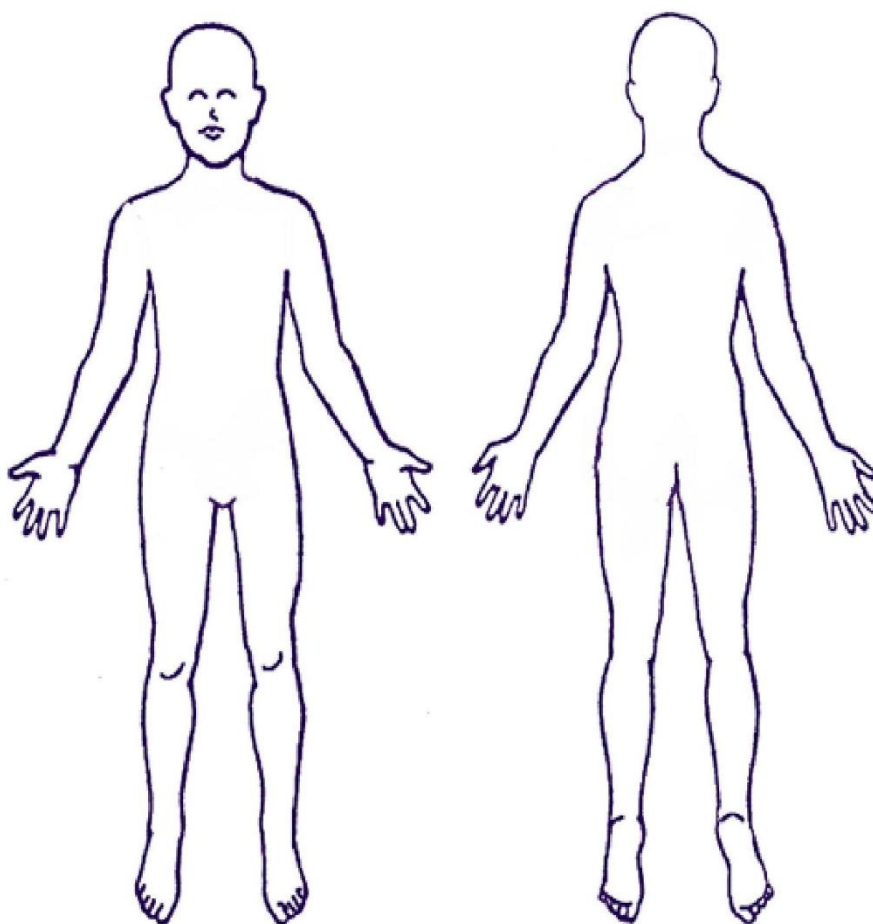
Ask the ill traveller...	Tick as appropriate	
13) Do you have a new rash which developed in the last 2 weeks?	☐ Yes ➤ Go to Question 14	☐ No ➤ Go to STEP 3.4
14) Is the rash itchy?	☐ Yes ➤ Go to STEP 3.4	☐ No

If **NO** to Question 14:

- Read the statement below to the ill traveller;
- Contact a Human Biosecurity Officer; **AND** Complete **STEP 4**.

The following statement is to be read out to the ill traveller:

I will also need you to confirm the location of the rash. Please mark the location of your rash by shading the appropriate area(s).



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Step 3.4: Yellow eyes and/or skin

Ask the ill traveller...	Tick as appropriate	
15) Have you, or anyone around you, noticed the whites of your eyes and/or skin has yellowed?	☐ Yes ➤ Go to Question 16	☐ No ➤ Advise person to seek own medical advice
16) Were you in Africa, South/Central America or the Caribbean within the previous 6 days (including transit)?	☐ Yes ➤ Go to Question 17	☐ No ➤ Advise person to seek own medical advice
17) Which country(s) did you visit?		
South or Central America/Caribbean	Africa	
☐ Argentina (Misiones province only)	☐ Angola	☐ Guinea
☐ Bolivia	☐ Benin	☐ Guinea-Bissau
☐ Brazil	☐ Burkina Faso	☐ Kenya
☐ Colombia	☐ Burundi	☐ Liberia
☐ Ecuador (excluding the Galapagos Islands)	☐ Cameroon	☐ Mali
☐ French Guiana	☐ Central African Republic	☐ Mauritania
☐ Guyana	☐ Chad	☐ Niger
☐ Panama	☐ Congo, Democratic Republic of the	☐ Nigeria
☐ Paraguay	☐ Congo, Republic of the	☐ Rwanda
☐ Peru	☐ Cote d'Ivoire (Ivory Coast)	☐ Senegal
☐ Suriname	☐ Equatorial Guinea	☐ Sierra Leone
☐ Trinidad	☐ Ethiopia	☐ South Sudan
☐ Venezuela	☐ Gabon	☐ Sudan
	☐ Gambia	☐ Togo
	☐ Ghana	☐ Uganda
☐ None of the countries listed above	☐ None of the countries listed above	

If **NONE of the countries listed above**, advise the person to seek their own medical advice.

Otherwise if a country(s) is selected from the above, **proceed to Question 18**.

	Tick as appropriate		
18) Do you have a valid Yellow Fever vaccination certificate?	☐ Yes ➤ Go to Question 19	☐ No	☐ Do not know

If **NO or DO NOT KNOW** to Question 18 immediately contact a Human Biosecurity Officer;
AND Complete **STEP 4**.

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Through observation...	Tick as appropriate	
19) Valid Yellow Fever vaccination certificate sighted?	☐ Yes Advise ill traveller to seek own medical advice	☐ No

If **NO** to Question 19 immediately contact a Human Biosecurity Officer; **AND** Complete **STEP 4**.

Step 4: HBO/ CHBO Contact Summary

To be completed in circumstances where a Human Biosecurity Officer (including the Chief Human Biosecurity Officer) is contacted regarding the ill traveller.

SECTION 1

(C)HBO Name:			
State / Territory:			
Time contacted:		Time advice received:	
Advice provided: ☐ Traveller to seek own medical advice. No Further information required ☐ Other (please specify) _____ _____ ☐ Further assessment required. ➤ Complete Section 2 & 3			

SECTION 2

Please complete the record of communications made during the administration of the Checklist.

CONTACT LOG		
Person contacted	Date and time	Purpose

SECTION 3

☐ (C)HBO detailed in Section 1 advised that: <i>"Duty of care for this traveller has been transferred to you as the relevant Human Biosecurity Officer"</i>	
☐ Traveller transferred by ambulance to _____ (name of hospital)	
☐ Traveller subject to a Human Biosecurity Control Order (HBCO) HBCO reference: _____	
Traveller referred to (please tick appropriate): ☐ Hospital ☐ GP ☐ Other	
☐ Traveller provided with a Yellow Fever Action Card	
☐ Other - please specify _____	

Once TIC is completed, scan and e-mail to humanbiosecurity@health.gov.au.

Please ensure all pages are scanned.

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CHAPTER 7

Teaching experience

Australian National University

“If you can’t explain it simply, you don’t understand it well enough.”

Albert Einstein

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ABBREVIATIONS

DALY	Disability Adjusted Life Years
LLF	Lessons from the Field
MAE	Master of Applied Epidemiology
YLD	Years of life lived with disability
YLL	Years of life lost to premature death

MAE TEACHING REQUIREMENTS

There are two teaching components in the MAE program. The first is to conduct a Lesson from the Field (LFF), which consists of preparing and delivering a lesson for 4-5 of our MAE peers on a topic that we have encountered in our projects. The lesson is usually composed of tasks that the other MAEs will complete in their own time and should take about 2-3 hours, followed a few weeks later by a teleconference where the lesson is run and the results and aspects of the tasks are discussed. The second teaching component is to prepare and deliver during the third course-block a lesson on a field epidemiology topic to the new first year MAE scholars.

1 LESSONS FROM THE FIELD

1.1 A burden of disease lesson

For my LFF component I chose to introduce my fellow MAEs to the wonderfully confusing world of burden of disease models. It was an area that I learned a lot about during my data analysis project and found to be useful when reading public health literature where these concepts are used. It was also a field of study that was not introduced during the MAE course work.

The burden of disease measure introduced was Disability Adjusted Life Years (DALY), which is commonly used in studies around the World. There are several approaches to estimating DALYs through modelling, each with its benefits and limitations. The main difference between models is the time-frame for which the burden is estimated and has a significant impact on the estimates produced. This also means that DALY measures estimated using different model approaches may not be directly comparable.

The problem is that in the literature it is rarely explicitly stated what burden of disease model is used. Instead, it is up to the reader to tease apart the methods section to determine the approach used. Therefore, the LFF would introduce and hopefully equip my fellow MAEs with a basic understanding to critically read burden of disease literature.

The LFF introduced the group to the general concept of DALYs and its components: years of life lived with disability (YLD) and years of life lost due to premature death (YLL). Three conceptual models were presented: incidence-based; pure prevalence-based; and a hybrid model, together with a brief calculation exercise for each. Finally, the group was provided with instructions and input data for a published and open source burden of disease calculator application from the European Centres for Disease Control and Prevention.

1.2 Lessons learned from the LFF

There were three main lessons that I learned from preparing and conducting the LFF. The first was how difficult it can be to provide precise instructions such that no misunderstanding can occur. This was highlighted in the DALY calculation exercise of the LFF, where I got a range of answers from the other MAEs, despite providing what I thought were very clear instructions and example calculations. I believe the reason for this is the fact that when you work extensively in a specific area, there are knowledge and logical bridges between concepts that you take for granted. I could have improved the instructions by doing a test run of the LFF on someone with little prior knowledge, before to sending it out.

The second lesson was to read the fine print of applications to be used. In the LFF I introduced the MAEs to a freely available burden of disease application. As the application was written in Java, I assumed compatibility with both PC and Mac platforms. This was not the case, and I should have checked this before sending out the LFF.

The final lesson was that I underestimated technology problems. The LFF was conducted using the Zoom teleconferencing application, and due to issues with WiFi access at the Department of Health, I had to use my mobile phone as a hotspot. I tested the connection and the planned demonstration of the application (as some MAEs had not been able to run it), and all worked well... until the 5 other people connected to the conference call. Everything slowed down, and in the end, I was unable to show the application. A classic IT failure that could have easily been avoided.

1.3 Feedback from follow-up survey of LFF

A brief electronic survey using SurveyMonkey was sent to gather feedback on the LFF and my performance from the other MAEs in the group. From the four persons that responded to the survey, the take-home messages from the responses were that one person thought the tasks were not clear or easy to understand, and that insufficient information and instructions had been provided. This person also thought the tasks too took long time to complete. The other three persons responded positively to the above areas. On the positive note was that all respondents thought the answers and explanations provided during the teleconference were easy to understand and that I displayed good knowledge of the subject.

In the free text field of what could be improved in the LFF, two responses were regarding confusion of how to perform the calculations in the Excel document, and another expressed a wish to have the application demonstrated. In response to this I prepared a recorded lesson for the group to view should they wish. I will keep the feedback in mind when I prepare similar tasks

in the future, and ensure that they are tested by people before use. This would be particularly important in teaching situations.

In the free text field for what had been learnt from the LFF, all respondents expressed that they appreciated having knowledge of DALYs and that there were different burden of disease models. One of the MAEs in the group mentioned that she has put the knowledge gained through the LFF to use when reading a publication on the burden of influenza. Overall, it could be concluded that the LFF was successful in as much as the respondents did benefit in spite of the issues, and that I learned a lot for future reference in regard to teaching technical items.

The LFF – instructions, questions and answers are provided at **Appendix 7A** and the calculation task with answers is provided in **Appendix 7B**.

2 TEACHING FOR THE FIRST YEAR MAEs

For the teaching component for the first year MAEs our cohort decided to introduce the students to skills that we had found useful during our first year in the program, but that were not normally included in the course block. Collectively as a cohort we decided on 5 topics, and divided up into groups, each preparing a 20-minute lesson. For such a short time, a lecture-based lesson would be the most effective, but as it was the last afternoon of an intense three week course block for the first years, we aimed to keep the lessons interactive.

My group - composed of Aurysia Hii, Sophie Phelan, Ximena Tolosa and myself - prepared a lesson on communication in the field while deployed. All four members of the group had been deployed overseas or had worked overseas prior to the MAE. We developed a scenario, where the first year MAEs had to distil a large volume of information and decide on the most relevant information to present in different situations.

The aim of the task was to highlight and make the students consider different circumstances when they may have to present information during a deployment. Not too uncommonly these instances will occur at short notice, where relevant information must be compiled quickly. The lesson was planned such that the students were put under time pressure, which also tested the group's team work capability and decision-making processes.

To evaluate the performance of the teaching sessions an electronic survey using SurveyMonkey was provided to the first year MAEs. There were three questions for each teaching session, with a five-grade scale: not of use; minimal use; neutral; useful; highly useful. The responses to the first question regarding the "Format of the session" were largely positive with most responses evenly distributed between "useful" and "highly useful", although two participants thought it was of "neutral" or "minimal use". The second question regarding "The presenters' style" also received mostly positive responses, again with two participants stating they were "neutral". Finally, the third question regarding "The session content" had positive responses, with the exception of two participants who were "neutral" and one that thought it was of "minimal use". In conclusion, the overall impressions of the session were positive. The participants also had opportunity to provide free form responses to "What they thought could be improved", where several participants expressed a desire to have had more time to have in-depth discussions about the topics, but also recognised the limited time available. In their free text answers, the participants expressed that they felt engaged, had learned something from the sessions and that they were impressed with the range of contents squeezed into a relatively short time period.

The lesson plan and scenario are detailed in **Appendix 7C** and the presentation slides are available in **Appendix 7D**.

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APPENDIX 7A – Lessons from the Field – Burden of disease models

Answers to the tasks in the LFF are provided in blue text in the boxes in the appendix.

Introduction to Burden of disease models

Zoom teleconference details:

Date: 15 May 2018

Time: 11am AEST / 9am AWST

Connection details: <https://uwa.zoom.us/j/951760140>

Instructions: The lesson will have two sections. First you will be introduced to the concept of measuring burden of disease (BoD) in a population, and the different approaches to estimating this. In this section you will calculate the burden of disease using three different models that each has a distinct view of the problem. In the second section you will use the publically available application from the Burden of Communicable Disease in Europe (BCoDE) project to estimate the burden of invasive pneumococcal disease (IPD) in Australia.

Learning objectives: By the end of this lesson you should be able to:

- Describe the measure Disability-Adjusted Life Years (DALY)
- Calculate DALYs using incidence-, prevalence- and hybrid-based BoD models
- Describe DALY measure from the three models
- Consider for which situations each model type is appropriate
- Use the BCoDE application from the ECDC to calculate DALYs for IPD

SECTION 1

Brief introduction to Disability-Adjusted Life Years (DALYs)

There are numerous ways to assess and express the burden that a particular disease has on a population. The principal goal for such estimates is to provide a summary and comparable measure of population health, suitable to inform policy decisions, allocation of resources and communication purposes. The Global Burden of Disease project has published estimates for 1990, 2010, 2013 and 2015. In Australia, the Australian Institute of Health and Welfare (AIHW) have published estimates for 2003 and 2011, with the 2015 report currently being prepared.

In this lesson we are going to focus on Disability-Adjusted Life Years (DALY) which is a commonly used summary measure. DALY quantifies health losses in years, and is composed by adding the number of Years Lived with Disability (YLD) and the number of Years of Lost Life (YLL) due to premature death. The YLD is calculated for each health state by multiplying the disability weight by the duration of the health state. Disability weights (DW) used are the result of extensive projects that assess people's perceptions of different health conditions, most commonly used DW are the ones from Global Burden of Disease project. The YLL is calculated as the remaining life expectancy at death.



Approaches to calculating DALYs

Walking into the office after a very relaxing holiday, you are greeted by an intense discussion among you colleagues. Turns out that your unit has been given the task of estimating the burden of invasive pneumococcal disease in Australia for the year 2015. However, there are different approaches to estimating DALY from the same data source, depending mainly from which perspective you look at the data and what purpose you want to use the estimate.

Your colleagues have not been able to settle on what approach to take, and have established a small training dataset to explore and discuss different perspectives of the problem. Now that you are back, they are all keen to convince you that their approach is best, and for you to be the judge.

Open the training dataset ([BoD.xlsx](#)). You find data for 10 patients over 8 years showing the disease, sequelae and age of the patient. The DALY estimate should be calculated for 2015.

Question 1. What additional data do you need to do these calculations?

Life expectancy

Disability weights for pneumonia, meningitis, septicaemia, hearing loss, cognitive disability, seizure disorder

Duration for pneumonia, meningitis, septicaemia, hearing loss, cognitive disability, seizure disorder

Hybrid based model

The first of your colleagues knock on your door. He suggests the use of a **Hybrid based model** to determine the burden of the disease of interest in 2015. Before you can object, he reassures you that this is a commonly used model and very intuitive, despite the ambiguous name. The model includes disability experienced in the time period of interest, and the deaths in the time period including future stream of life lost.

To calculate this you need to determine:

- amount of disability experienced in 2015 for each health state (YLD)

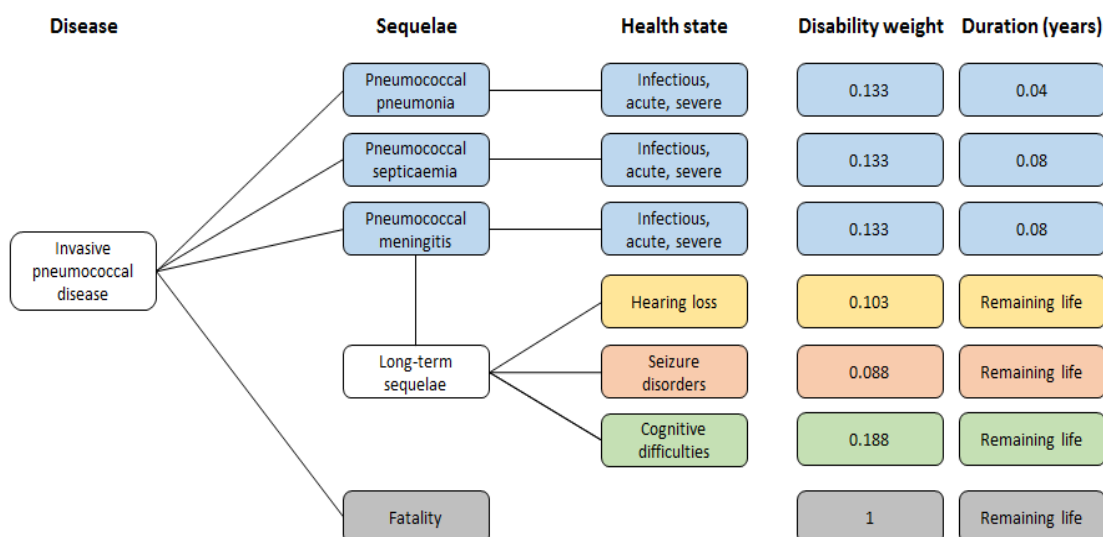
$$\text{YLD} = \text{disability weight}_{\text{acute disease}} \times \text{duration}_{\text{acute disease}} (\text{max 1 year})$$

$$\text{YLD} = \text{disability weight}_{\text{sequelae}} \times \text{duration}_{\text{sequelae}} (\text{max 1 year})$$
- the future life years lost due to death experienced in 2015 (YLL)

$$\text{YLL} = \text{each death in 2015} \times \text{remaining life expectancy}$$

Task 1. Complete the calculations for the Hybrid based model in the BoD.xlsx. Your colleague has kindly highlighted what cells to include and left some helpful bits of calculations.

For the training dataset assume a life expectancy of 84 years for all patients. Additional data required is provided below.



Question 2. Try to express the DALY measure that you have just calculated using the hybrid model?

The DALY provides an estimate of the amount of disability experienced in 2015 and the future years of life lost due to premature mortality in 2015.

Your colleague also had trouble finding a unified expression of this DALY measure. This is because the estimate measures YLD and YLL from different perspectives. The YLD measure considers disability in 2015 only, while the YLL measure includes the burden of the deaths into the future.

This may be a bit of a problem...

Pure Prevalence based model

You catch up with your second colleague over morning tea. Knowing that she very matter of fact and structured in her thinking, you hope she has a solution of the hybrid problem. She announces that a **Pure Prevalence based model** is the way to go. This model determines the burden of disability and death experienced in the exact time period of interest. To calculate this you need to determine:

- amount of disability experienced in 2015 for each health state (YLD)

$$\text{YLD} = \text{disability weight}_{\text{acute disease}} \times \text{duration}_{\text{acute disease}} \text{ (max 1 year)}$$

$$\text{YLD} = \text{disability weight}_{\text{sequelae}} \times \text{duration}_{\text{sequelae}} \text{ (max 1 year)}$$
- the amount of death experienced in 2015 (YLL)

$$\text{YLL} = \text{each individual experiencing death in 2015}$$

She emphasises that in order to be accurate the YLL need to include people whose life span would have included the time period of interest, should they not have died prematurely (e.g. if a person died at age 54 years, with a predicted life expectancy of 84 years, they would still be counted each year for the next 30 years).

Task 2. Complete the calculations for the Pure Prevalence based model in the BoD.xlsx. Your colleague has kindly highlighted what cells to include and left some helpful bits of calculations. Use the same life expectancy, disability weight and duration data as in Task 1.

Question 3. How would you express the DALY measure that you have just calculated using the pure prevalence based model?

The DALY provides an estimate of the disease states experienced in 2015, including disability and death.

Yes, it is a bit weird as nobody really experiences death, but the idea is that this person would still have contributed to society (for instance through working) if not for their premature death, and therefore it is still seen as a loss each year for the remaining life expectancy.

Question 4. Why is Patient 5's death not included in this model?

Patient 5 only had 2 years of life expectancy left when they died, and therefore would only be counted in the subsequent two years (2012 and 2013)

Incidence based model

At lunch time you meet up with your third colleague, the forward thinking one. He announces that because IPD is a communicable disease, an **Incidence based model** would be the most appropriate. He explains that this model takes into account both the effects of the initial infectious episode occurring in the time period of interest and any sequelae (downstream complications) associated with the initial infection, and the deaths in the time period including future stream of life lost.

To calculate this you need to determine:

- acute disease episodes experienced in 2015 and ongoing disability associated with these initial disease episodes (YLD)

$$YLD = \text{disability weight}_{\text{acute disease}} \times \text{duration}_{\text{acute disease}}$$

$$YLD = \text{disability weight}_{\text{sequelae}} \times \text{duration}_{\text{sequelae}}$$

- the future years of life lost due to death experienced in 2015 (YLL)

$$YLL = \text{each death in 2015} \times \text{remaining life expectancy}$$

Task 3. Complete the calculations for the Incidence based model in the BoD.xlsx. Again your colleague has kindly highlighted what cells to include and left some helpful bits of calculations. Use the same life expectancy, disability weight and duration data as in Task 1.

Question 5. How would you express the DALY measure that you have just calculated using the incidence based model?

The DALY provides an estimate of the disability (including deaths) experienced in 2015 and the future stream of disability (including deaths) associated with these events.

Having completed each of the model calculations you sit back a look at the data. You come to realise that you have not been given any information on what situation the model will be used for, and that this may have a big impact on which model you choose to go with. Before asking your supervisor, you try to envision a few situations where one model would be better suited than the others.

Task 4. Match the pairs of the most appropriate model with each of the situations below.

A. Estimating the impact of cardiovascular disease on the work force in 2015	1. Incidence based model
B. Inform decisions regarding allocation of funding for different vaccination programs	2. Hybrid based model
C. Assess the performance of a health care system	3. Pure prevalence based model

Enter alpha numeric matches:

A3, B1, C2

SECTION 2

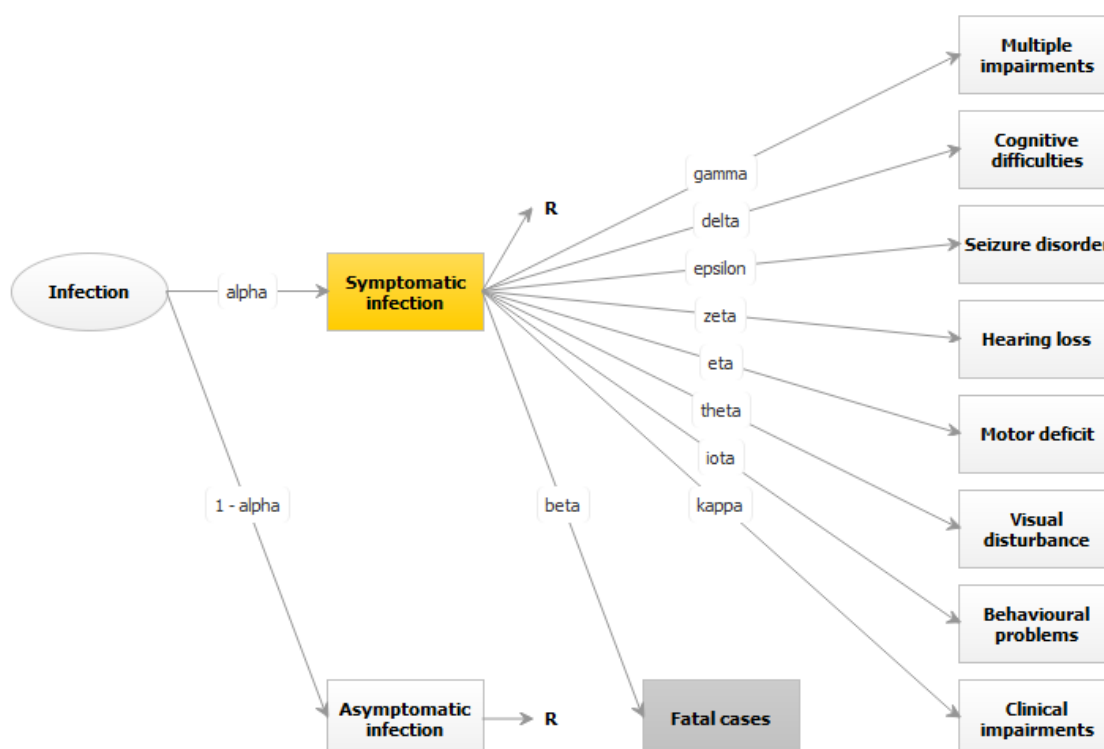
The real deal

Your supervisor is impressed with your team's efforts to explore several possibilities to address the problem. She explains that it is the intent of the Ministry of Magic Health to use the model to compare the effects of different potential vaccine intervention schemes. You discuss the different options of models and decide on using an incidence based model. She suggests that you check out a recent publication from the European Centre for Disease Control (ECDC) that describes a tool that may make your life easier.

The Burden of Communicable Diseases in Europe (BCoDE) tool

In 2017 the ECDC published a freely available software tool for estimating the burden of disease, after years of development. The tool is specifically adapted for communicable diseases, where incident cases of infectious diseases are linked with their potential sequelae in an outcome tree. Sequelae are included if there is an evidence-based causal relationship between the disease and the outcome. The input is incident cases with the remaining components modelled using transitional probabilities, which are informed by extensive literature reviews.

Below is the BCoDE model for IPD. In the model you have acute episodes of IPD (pneumonia, meningitis and septicaemia) which all go into the yellow square. Then you have a range of sequelae that may occur as a result of these acute episodes (mainly from the meningitis episodes). The input is incident cases on the left, and all the white squares (alpha, beta, gamma...) show what proportion of the cases (transition probabilities) will proceed to each of the health states (yellow or grey squares).



Task 5. Using the BCoDE tool you are to provide a DALY estimate of IPD for 2015 to be used as a baseline. All the necessary input data is available in the “BCoDE model input” tab in the BoD.xlsx file.

Download the BCoDE v1.4.zip from:

<https://ecdc.europa.eu/en/publications-data/toolkit-application-calculate-dalys>

Unzip the folder. You don't have to install anything as it runs as a stand-alone application and all the necessary libraries are included in the download package.

Instructions for BCoDE tool

1. Open [BCoDE.exe](#)
2. Click [Create models](#) on the left hand side menu
3. Tick the boxes for [Custom population](#) and [Invasive Pneumococcal Disease](#)
4. Click [Create models](#) on the top right hand side
5. Click [Edit model data](#) on the left hand side menu
6. Click the [Incidence data](#) tab along the top
7. Copy the [IPD 2015 incidence](#) data (select both female and male at the same time) provided in BoD.xlsx
8. In the BCoDE tool in the table [Average number of cases per year](#), right- anywhere in the table and choose [Paste as Constant](#). This should now be populated with your copied [IPD 2015 incidence](#) data.
9. Click [Apply changes](#) up the top
10. Click on the [Population data](#) tab along the top
11. Copy the [Estimated residential population 2015](#) data (both female and male) provided in BoD.xlsx
12. In the BCoDE tool in the table [Age distribution data](#), right-click anywhere in the table and choose [Paste as Constant](#).
13. Copy the [Life expectancy 2015](#) data (both female and male) provided in BoD.xlsx
14. In the BCoDE tool in the table [Life expectancy data](#), right-click anywhere in the table and choose [Paste as Constant](#).
15. Click [Apply changes](#) up the top
16. Click on the [Outcome tree](#) tab along the top.
17. Click on the white square labelled [beta](#). A pop-up window will... pop up.
18. Copy the [Case fatality rate](#) data (both female and male) provided in BoD.xlsx
19. In the new pop up window in the BCoDE tool in the table [Transition probability](#) right-click anywhere in the table and choose [Paste as Constant](#).
20. Click [Apply changes](#) up the top of the pop-up window
21. Close the pop-up window by clicking the “x” at the top right (just like normal)
22. Back in the BCoDE [Outcome tree](#) view, click [Apply changes](#) up the top

23. Click [Run models](#) on the left hand side menu
24. Click [Run simulation](#). A progress bar at the bottom will indicate when it's done.
25. Close the window by clicking [Close it](#).
26. Click on [View detailed results](#). Use this view to complete Task 4. If you hover over a cell, a window will show you additional metrics for the specific estimate.
27. Click on [View aggregated results](#). Explore the view and the graphs provided.
28. To save your model, click on [File](#) and [Save disease models](#). This way you don't have to repopulate all the fields when you want to return to your specific model at a later time.

Task 6. Populate the table (use the "...per year" figures).

	YLD	YLL	DALY
Acute infections	31.44	2699.16	2730.60
Sequelae	284.84	0.00	284.84
Total (all health outcomes)	316.28	2699.16	3015.44

Question 6. Describe the data you have generated above?

Acute IPD episodes contribute 31.44 years of disability and 2699.16 years lost to premature death, and the sequelae contributes an additional 284.84 years of disability. In total the estimated burden of IPD in 2015 is 3015.44 years lost to disability or premature death.

Congratulations, you have just produced a DALY estimate for IPD with the ECDC BCoDE tool, using Australian incidence data, population data and mortality data.

You are pleased with yourself, but...

Question 7. Do you think this model is accurate for the Australian setting? If not, why and what else would you take into consideration?

Aside from specific population and life expectancy data, accurate notification data and case fatality rates you need reliable data on transition probabilities in your country/area of interest

If incidence or mortality numbers are low, aggregating data over a number of years may also be more appropriate.

Further reading (nerd-scale indicates how far down the rabbit hole you want to go):

Excellent paper on burden of disease models and provided much inspiration for this LFF.

- Andrew Schroder. (2012) *Incidence, prevalence, and hybrid approaches to calculating disability-adjusted life years*. Population Health Metrics 10(9) 🧐

Below are a series of papers on the development of the ECDC BCoDE tool. Each paper describes a different aspect of the development: the first provides an over view of the problem and possible solution; the second goes more into the model, including the mathematical basis for the model; and the third paper describes the software tool.

- Mirjam Kretzschmar et al. (2012) *New methodology for estimating the burden of infectious diseases in Europe*. PLoS Medicine 9(4) 🧐
- Narie-Josee Mangen et al. (2013) *The pathogen- and incidence-based DALY approach: An appropriate methodology for estimating the burden of infectious diseases*. PLoS One 8(11) 🧐 🧐 🧐
- Supplementary files for this publication 🧐 🧐 🧐 🧐 🧐
- Edoardo Colzani et al. (2017) *A software tool for estimation of burden of infectious diseases in Europe using incidence-based disability adjusted life years*. PLoS One 12(1) 🧐 🧐 🧐

APPENDIX 7B – Lessons from the Field – Burden of disease models - calculations

Example calculations are provided in black. Calculation-tasks are indicated by red border, and answers are provided in blue text in the boxes in the appendix.

Chapter 7 – Teaching

HYBRID BASED BURDEN OF DISEASE IN 2015										YLD	YLL
	2010	2011	2012	2013	2014	2015	2016	2017	2018		
Patient 1			Pneumococcal meningitis + Hearing loss @ 64 years							$0.103 \times 1 = 0.103$	0
Patient 2	Pneumococcal pneumonia + Death @ 62 years									0	0
Patient 3					Pneumococcal septicaemia @ 4 years					0	0
Patient 4						Pneumococcal meningitis + Cognitive disability @ 5 years				$[0.133 \times 0.08] + [0.168 \times 1] = 0.199$	0
Patient 5		Pneumococcal pneumonia + Death @ 82 years								0	0
Patient 6						Pneumococcal meningitis + Death @ 80 years				$0.133 \times 0.08 = 0.011$	84-80=4
Patient 7				Pneumococcal meningitis + Seizure disorder @ 3 years						$0.088 \times 1 = 0.088$	0
Patient 8						Pneumococcal meningitis + Hearing loss @ 3 years				$[0.133 \times 0.08] + [0.103 \times 1] = 0.114$	0
Patient 9						Pneumococcal pneumonia @ 6 years				$0.133 \times 0.04 = 0.005$	0
Patient 10						Pneumococcal pneumonia + Death @ 2 years				$0.133 \times 0.04 = 0.005$	84-2=82
Total										0.525	86
DALY										>>>	86.525

PURE PREVALENCE BASED BURDEN OF DISEASE IN 2015										YLD	YLL
	2010	2011	2012	2013	2014	2015	2016	2017	2018		
Patient 1			Pneumococcal meningitis + Hearing loss @ 64 years							$0.103 \times 1 = 0.103$	0
Patient 2	Pneumococcal pneumonia + Death @ 62 years									0	1
Patient 3					Pneumococcal septicaemia @ 4 year					0	0
Patient 4						Pneumococcal meningitis + Cognitive disability @ 5 year				$[0.133 \times 0.08] + [0.168 \times 1] = 0.199$	0
Patient 5		Pneumococcal pneumonia + Death @ 82 year								0	0
Patient 6						Pneumococcal meningitis + Death @ 80 year				$0.133 \times 0.08 = 0.011$	1
Patient 7				Pneumococcal meningitis + Seizure disorder @ 3 year						$0.088 \times 1 = 0.088$	0
Patient 8						Pneumococcal meningitis + Hearing loss @ 3 years				$[0.133 \times 0.08] + [0.103 \times 1] = 0.114$	0
Patient 9						Pneumococcal pneumonia @ 6 year				$0.133 \times 0.04 = 0.005$	0
Patient 10						Pneumococcal pneumonia + Death @ 2 year				$0.133 \times 0.04 = 0.005$	1
Total										0.525	3
DALY										>>>	3.525

INCIDENCE BASED BURDEN OF DISEASE IN 2015										YLD	YLL
	2010	2011	2012	2013	2014	2015	2016	2017	2018		
Patient 1			Pneumococcal meningitis + Hearing loss @ 64 years							0	0
Patient 2	Pneumococcal pneumonia + Death @ 62 years									0	0
Patient 3					Pneumococcal septicaemia @ 4 year					0	0
Patient 4						Pneumococcal meningitis + Cognitive disability @ 5 year				$[0.133 \times 0.08] + [0.168 \times (84-5)] = 14.852$	0
Patient 5		Pneumococcal pneumonia + Death @ 82 year								0	0
Patient 6						Pneumococcal meningitis + Death @ 80 year				$0.133 \times 0.08 = 0.011$	84-80=4
Patient 7				Pneumococcal meningitis + Seizure disorder @ 3 year						0	0
Patient 8						Pneumococcal meningitis + Hearing loss @ 3 years				$[0.133 \times 0.08] + [0.103 \times (84-3)] = 8.343$	0
Patient 9						Pneumococcal pneumonia @ 6 year				$0.133 \times 0.04 = 0.005$	0
Patient 10						Pneumococcal pneumonia + Death @ 2 year				$0.133 \times 0.04 = 0.005$	84-2=82
Total										23.216	86
DALY										>>>	109.216

Input data for use in the BCoDE model

Estimated Resident Population 2015			Life expectancy 2015			IPD 2015 incidence			Case fatality rate		
	Females	Males		Females	Males		Females	Males		Females	Males
0	149,960	158,134	0	84.5	80.4	0	24	33	0	0.021	0.021
1-4	606,774	640,233	1-4	82.3	78.2	1-4	53	87	1-4	0.021	0.021
5-9	747,561	788,504	5-9	77.9	73.7	5-9	20	32	5-9	0.05	0.05
10-14	686,241	724,997	10-14	72.9	68.8	10-14	6	11	10-14	0.05	0.05
15-19	718,137	754,616	15-19	67.9	63.8	15-19	6	15	15-19	0.05	0.05
20-24	822,319	859,773	20-24	63	59	20-24	9	13	20-24	0.05	0.05
25-29	895,280	898,069	25-29	58.1	54.2	25-29	12	13	25-29	0.05	0.05
30-34	879,065	875,193	30-34	53.2	49.4	30-34	18	29	30-34	0.05	0.05
35-39	789,525	785,555	35-39	48.3	44.6	35-39	31	28	35-39	0.05	0.05
40-44	837,491	819,072	40-44	43.5	39.9	40-44	38	42	40-44	0.05	0.05
45-49	796,162	768,727	45-49	38.7	35.2	45-49	35	40	45-49	0.05	0.05
50-54	791,206	769,904	50-54	34	30.7	50-54	53	57	50-54	0.05	0.05
55-59	736,692	710,741	55-59	29.4	26.3	55-59	55	64	55-59	0.05	0.05
60-64	654,825	629,304	60-64	24.9	22	60-64	59	63	60-64	0.05	0.05
65-69	583,757	573,559	65-69	20.6	18	65-69	51	72	65-69	0.136	0.136
70-74	434,260	416,395	70-74	16.4	14.2	70-74	54	50	70-74	0.136	0.136
75-79	332,461	298,201	75-79	12.5	10.7	75-79	48	59	75-79	0.136	0.136
80-84	251,121	198,492	80-84	9.1	7.7	80-84	39	45	80-84	0.136	0.136
85 and over	297,120	171,358	85 and over	4.3	3.8	85 and over	57	59	85 and over	0.136	0.136

Population from: ABS Estimated resident population, 2015

Life expectancy from: ABS Life tables, States, Territories and Australia, 2013-2015

IPD data from: IPD Public dataset 2009 to 2016 from Commonwealth Department of Health NNDSS

Case fatality rate: Estimated average from IPD Annual reports

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APPENDIX 7C – Lesson for first year MAEs – Scenario and lesson plan

Communicating in complex environments in public health

Learning objectives

- **Understand** your role as a Field Epidemiologist investigating an outbreak within the context of a complex, fast evolving, humanitarian emergency.
- **Practice** communicating to different audiences as a part of your role as Field Epidemiologist.
- **Apply** your epidemiological skills in order to understand the outbreak and prioritise information
- Tailor your message to effectively communicate relevant epidemiological knowledge of the outbreak to key stakeholders in the outbreak investigation

Introduction:

- Introduce the session: Why is communication to different stakeholders an important skill as an epidemiologist working in a complex environment in public health?
- Who are some of the stakeholders in an outbreak investigation and what information do they require?
- Introduce the **scenario** and **task**.

Scenario: You are the Field Epi on deployment to a post disaster zone: a cholera outbreak following a tsunami in a coastal urban centre in a Western Pacific country. You will need to communicate and translate epidemiological knowledge to a wide variety of audiences in your role as a Field Epi in order to control the outbreak.

Task: The class will be divided into three groups. Each group will be allocated to communicate to a different stakeholder in the outbreak response.

Your task in the group is to select the top 3 most important messages to communicate from our Outbreak Info Sheet. If you can think of an important message you will need to communicate that wasn't on the Outbreak Info sheet, note that as well. Each group will have 5 minutes to discuss within themselves, and then we will report back and have a group discussion for 10 minutes.

Lesson Plan (20 min total time)

Timeline	Allocated time	Task
0-3 min	3 min	Introduction
4-5 min	2 min	Allocate class into the three stakeholder groups. Read out our Outbreak Info Sheet.
6-10 min	5 min	Group work
11-20 min	10 min	Discussion

- SCENARIO -

UPDATE 16/02/2018

Western Region, Districts 1-4.

Background

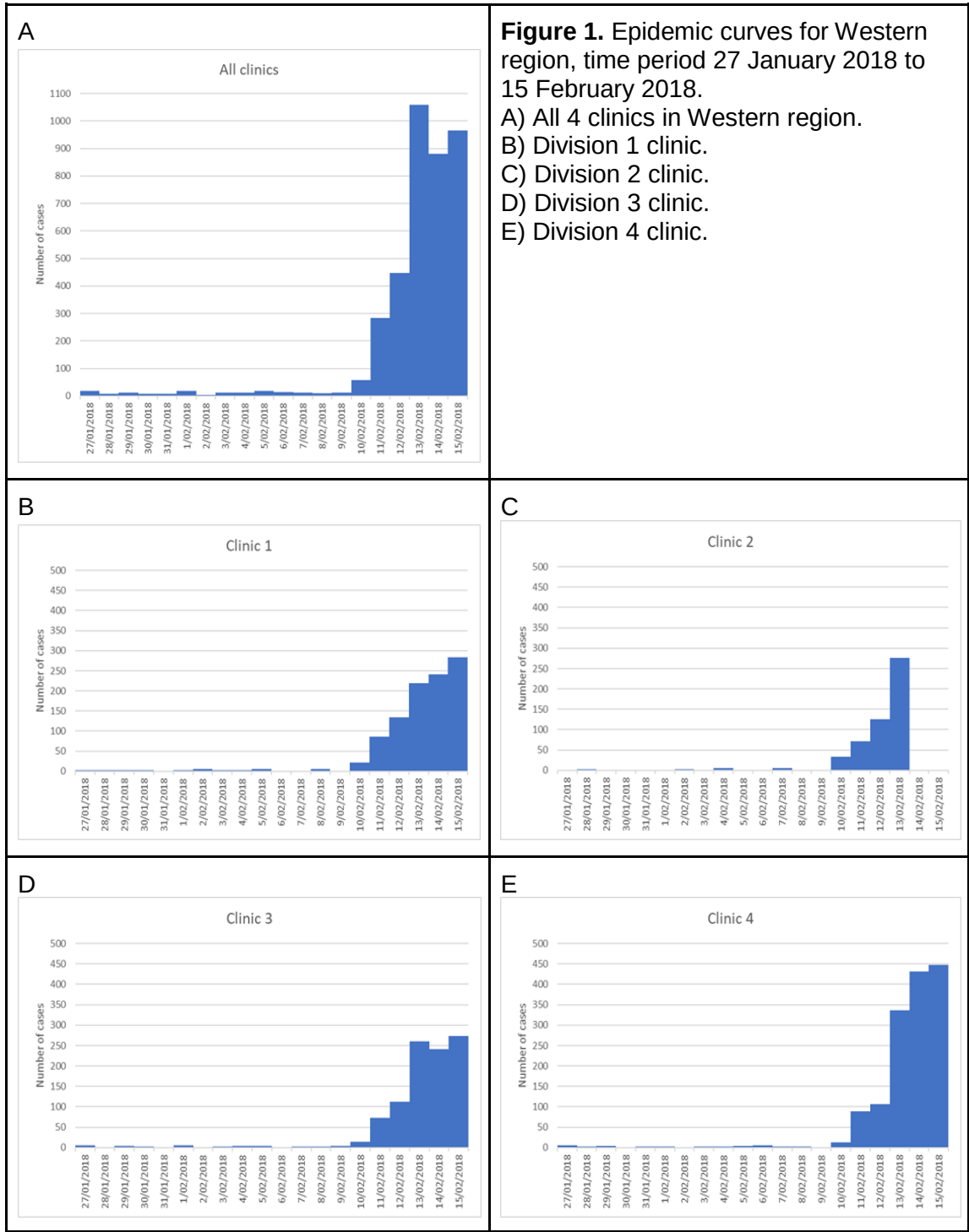
- The tsunami that hit the Western region of the island on the 26 January 2018 caused widespread destruction of infrastructure and services.
- Country officials estimate there are 23,000 residents in the affected area, with an additional influx of 6,000 people into the region from rural areas.

Epi-update

- Minor cholera outbreaks occur annually in the region during the wet season. An increase in cholera cases were noted at the end of epidemiologic week 6 (5 – 11 February), with the weekly average of 58 cases exceeding the baseline weekly average by more than 2 S.D.
- As of the 16 February 2018 there have been 3859 suspected cases of cholera and 189 deaths (CFR 4.9%) in the four districts of the Western region following the tsunami event, with 3694 suspected cases and all 189 deaths occurring in the past 6 days. The case definition used for suspected cholera is: Any patient with acute watery diarrhoea, defined as 3 or more loose stools in the past 24 hours.
- Current attack rate is 13.3%, with children under 5 years representing 29.3% of suspected cases.
- On the 15 February there was laboratory confirmation of 5/8 specimen (collection on 29 and 30 January, 2,6 and 7 of February) testing positive for *Vibrio cholerae* O139.
- The clinics in the 4 districts of the Western region are operating at or near maximum capacity. On the 15 February 2018, clinic 1 reported 245 suspected cases, clinic 3 reported 274 suspected cases and clinic 4 reported 447 cases (**Figure 1**). No report has been received from clinic 2 since 13 February. The report from clinic 4 state they are unable to cope with the increased volume of cases and request urgent assistance to open more dedicated cholera wards.

Other

- Oxfam's WASH teams report high bacterial failure rates in stored drinking water in the temporary camp in district 4, and logistical problems with distribution of cholera prevention kits.
- Concerns have been raised regarding ritual contact with deceased individuals during burial ceremonies, and advice sought regarding appropriate interventions. Burial teams report no problems for districts 1, 3 and 4, but the team in district 2 are raising concerns with the current burial location, and possible contamination of water table in the aftermath the tsunami.



STAKEHOLDER: Daily Interagency Situation Report Meeting

ROLE: You are the LEAD Field Epi presenting at a daily interagency Sit Rep meeting with ALL other stakeholders (WHO, MSF, Red Cross, in country Ministry of Health, UNHCR). The Interagency Sit Rep meeting is a daily 20 min meeting used to disseminate information and coordinate the response from all agencies involved.

TASK: What are the three most important statistics/messages you would need provide at the meeting and how you would communicate this? Note that you only have 3 minutes to provide your update.

KEY MESSAGES

- 1.
- 2.
- 3.

In general, how would you communicate these messages?

STAKEHOLDER: Handover to the next field epi

ROLE: You are the LEAD Field Epi about to finish deployment and need to provide a handover to your replacement.

TASK: What are the three key pieces of information you would need to provide your replacement. How would you communicate this?

KEY MESSAGES

- 1.
- 2.
- 3.

In general, how would you communicate these messages?

STAKEHOLDER: Field epi discussing data collection with local clinic staff

ROLE: As the field epi, you notice that one clinic (clinic 4) has stopped reporting data. You have heard that the clinic staff don't see the importance of extra reporting, it is a burden and is not as important as treating patients.

TASK: What are three strategies you could implement to communicate the importance of reporting data in a timely way and what information do you think would be important to provide?

KEY MESSAGES

- 1.
- 2.
- 3.

In general, how would you communicate these messages?

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APPENDIX 7D – Lesson for first year MAEs – Lesson slides

Communicating as a Field Epi during Public Health Emergencies



Learning objectives

1. **Understand** your role as a Field Epidemiologist investigating an outbreak within the context of a complex, fast evolving, humanitarian emergency.
2. **Communicate** to different audiences as a part of your role as Field Epidemiologist.
3. **Work** and **deliver** relevant information under time pressure.

Scenario

You are the Field Epi on deployment to a post disaster zone. **There has been a cholera outbreak following a tsunami in a coastal urban centre in a Western Pacific country.**

Today, you have three stakeholders that you need to communicate to:

1. Interagency members at daily Situation Report meeting
2. Data collectors at local health care clinic
3. Your incoming replacement Field Epi (another GOARN volunteer)

Lead Field Epi presenting at a daily interagency Situation Report meeting

1. Recent data (24 hours)
2. Any problems? Eg increase in cases in clinic 4 (they have asked for help), no reporting from clinic 2.
3. In-country situation (is there still an influx of people?)

Method: short talk, use PowerPoint/whiteboard to assist if available

Field Epi discussing data collection with local clinic staff (who have stopped reporting)

1. Ask what is going on, and discuss what additional support would be helpful
2. Explain the significance of the outbreak in terms of how it is affecting their local area (local stats so far), and how important their data is in contributing to the bigger picture of solving the outbreak.
3. Develop a feedback loop so they can see how their data is contributing to the big picture (ie brief 1 page epi report disseminated among health care clinics)

Method: Arrange a field visit to discuss in person. Be aware of cultural faux pas!

Handover to the next Field Epi

1. Contact details of MoH, WASH, etc people you were dealing with
2. Explain what stage the work is at
3. Hard and soft copies of all documents

Method: meet in person, connect over email prior if possible, leave soft/hardcopy backups if you can.